PUBLIC VERSION OF THE
SOCIO-ECONOMIC ANALYSIS

Legal name of applicants:	Janssen Vaccines & Prevention B.V. Janssen Biologics B.V.
Submitted by:	EPPA S.A. on behalf of the applicants
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-octylphenol ethoxylates) (4-tert-OPnEO) (OPnEO)
Use title:	OPnEO is used as a lysing agent for the permeabilization of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Its use allows the selective elimination of enveloped adventitious viruses and is compatible with the chemical needed to control the host cell DNA precipitation in next process step
Use number:	1

CONTENTS

LIST OF ABBREVIATIONS

AIDS = Acquired Immune Deficiency Syndrome

AoA = Analysis of Alternatives

API = Active Pharmaceutical Ingredient

ART = Antiretroviral Therapy

BCG = Bacillus Calmette-Guérin Vaccine primarily used against Tuberculosis

CSR = Chemical Safety Report

DSP = Downstream Process

DNA = Deoxyribonucleic Acid

DTP = Diphtheria, Tetanus, Pertussis

EBIT = Earnings Before Interest and Tax

ECDC = European Centre for Disease Prevention and Control

ECHA = European Chemicals Agency

ED = Endocrine Disruptor

EEA = European Economic Area

EU = European Union

EUROSTAT = Statistical Office of the European Union

GDP = Gross Domestic Product

HA = Hemagglutinin

HIV = Human Immunodeficiency Virus

HPV = Human Papilloma Virus

J&J = Johnson & Johnson

JVP = Janssen Vaccines & Prevention B.V.

kg = Kilogram

L = Litre

LLOQ = Lower Limit Of Quantification

LOD = Limit Of Detection

MAA = Market Authorization Application

MVA = Modified Vaccinia Ankara

mm^3 = Cubic Millimetre

NPV = Net Present Value

PrEP = Pre-Exposure Prophylaxis

QALY = Quality Adjusted Life Years

RAC = Committee for Risk Assessment

R&D = Research and Development

REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals

RSV = Respiratory Syncytial Virus

SEA= Socio-Economic Analysis

SEAC = Committee for Socio-Economic Analysis

UNAIDS = Joint United Nations Programme on HIV/AIDS

USP = Upstream Production Process

WHO = World Health Organization

w/v = Weight by Volume

µg = Microgram

DECLARATION

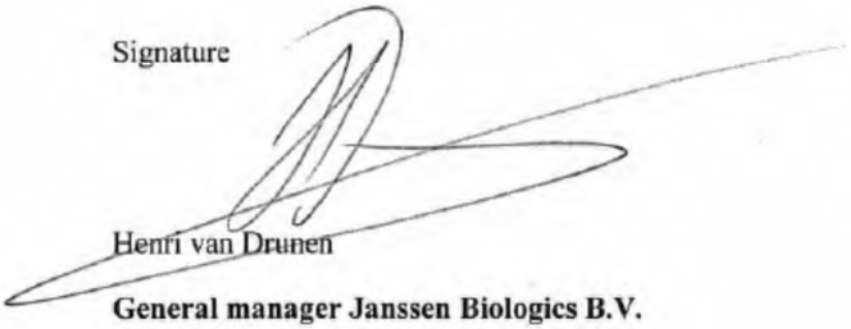
We, *Janssen Vaccines & Prevention B.V.* and *Janssen Biologics B.V.*, request that the information blanked out in the "public version" of the Socio-Economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (13 May 2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature 

13 May 2019, Leiden (NL)

Bart van Zijll Langhout

Director Janssen Vaccines & Prevention B.V.

Signature 

13 May 2019, Leiden (NL)

Henri van Drunen

General manager Janssen Biologics B.V.

GLOSSARY

Term	Explanation
AdVac® technology	Proprietary vaccine technology that uses adenovirus as vectors for introducing and expressing genes in human cells.
PER.C6®	Cell line that is suitable for the production of adenoviruses. The PER.C6® cell line is proprietary to Janssen
PIN platform	Process Intensification is a concept that was implemented in Janssen Vaccines' adeno-based vaccine development in 2012-2013 to augment the virus production. The consequence was that the amount of OPnEO used per vaccine dose was reduced approximately [redacted].

1. SUMMARY OF SOCIO-ECONOMIC ANALYSIS

OPnEO [4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated] was added to Annex XIV of the European Union's (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC) No 1907/2006 due to its classification as endocrine disruptor (ED), because of the suspected endocrine disrupting properties of its biodegradation product octylphenol. The sunset date for OPnEO is 4 January 2021.

Based on the scientific knowledge available to date, no eco-toxicological threshold can be derived because there is no scientific consensus on what this threshold should be. Therefore, an authorization can be granted if there are no suitable alternatives and if the socio-economic benefits of using Triton OPnEO outweigh the risks to human health and the environment. However, as it will be shown, concerning the use highlighted in this application for authorization, all risks are more than adequately controlled during the substance's lifecycle (zero emission).

Janssen is a worldwide group of pharmaceutical companies and is part of Johnson & Johnson (J&J, Health Corporation based in the USA). Janssen has several R&D centers in Europe and the US. Janssen is developing treatments in five important therapeutic areas: cardiovascular and metabolic diseases; immunology; infectious diseases and vaccines; neuroscience; oncology.

The applicants of this application for authorization are Janssen Vaccines & Prevention B.V. (hereafter JVP) and Janssen Biologics B.V.,[1] both based in Leiden, The Netherlands. JVP is one of Janssen's R&D centers. Regarding the link between the applicants and the production plant: Janssen Biologics B.V. is the owner and manager of certain production facilities, whereas JVP is performing vaccines R&D. Clinical trial materials are produced by JVP. As products enter late clinical stage and commercial, production will be transferred to the Vaccine Launch Facility at Janssen Biologics B.V. In case of the products in scope of this authorization, commercial production will take place at Janssen Biologics B.V.

The applicants are currently planning to use 270 kg (0.27 tons) of OPnEO per year for the production and development of adeno vectors vaccines. OPnEO will act as an active cell-lysing agent for the permeabilization of the host cell membrane and the release (extraction) of adenovirus particles.

The commercial production of the vaccines requiring OPnEO is expected to start in [redacted] after a total development period of up to two decades. The applicants are applying for an authorization to use OPnEO in the future because there are no technically suitable substitutes to date, as shown in the Analysis of the Alternatives (AoA).

As a consequence, in the event of authorization not being granted ("non-use" scenario), the applicants will not be able to launch the production of the vaccines requiring the use of OPnEO in Leiden as planned, but with considerable delay, as detailed in the AoA.

[1] JVP is a pharmaceutical company founded in 2000 and based in Leiden, The Netherlands (formerly known as Crucell Holland B.V.). Crucell Holland B.V. was acquired by Johnson & Johnson (J&J) in 2011. Janssen is used as the branding name for all pharmaceutical companies owned by J&J.

In addition, the development of new vaccines addressing new emerging diseases for which there is no medical alternative on the market will be jeopardized.

In terms of socio-economic benefits to the society of the continued use of OPnEO, the monetized residual risk for the environment is *zero*, because there will be no OPnEO emission from the plant in Leiden, as reported in the CSR. This finding will not change during the whole period of an eventual granted authorization. This means that there are no benefits for the European society to be considered from refusing this application for authorization, but only costs.[2] Conversely, the total costs (i.e., lost benefits) for the European society from refusing the authorization would be *at least* [redacted] **(public range: 1-10 billion EURO)** over 15 years after the sunset date. We have also assessed the "non-use" scenario with conservative assumptions to show the robustness of this finding.

Specifically, the main costs for the European society coming from delaying the launch of the vaccines currently in development at JVP are:

- The loss of business (calculated by using EBIT) from the production of vaccines in the EEA due to the delay of introducing the vaccines in the market;
- The adeno vector vaccine technology allows to design potential vaccines for which there is no alternative available yet. This benefit will be also compromised.
- The employees currently working in Leiden would become redundant, as well as the future employees would lose the possibility of being immediately employed in the plant located in Leiden; in addition, satellite companies would be affected;
- Many people will lose the possibility to use the vaccines for the treatment or the prevention of the target diseases. In this SEA the focus is on the HIV preventive vaccine, as a case study, also because this is one of the most likely vaccines in the portfolio of the applicants to be first in entering the European market ([redacted]). This is intended to show the benefits of having this vaccine available according to the current development timelines, which would prevent a considerable economic burden for the EEA (and worldwide) society. Of course, once considering all vaccines planned to be brought to market by the applicants, the total benefits will be greatly magnified.

In line with SEA findings – which show that the benefits of the "applied for use" scenario outweigh its costs to the society (which is actually zero) – the applicants are applying for an authorization to use OPnEO for 15 years. Based on the results of the SEA and the potential benefits of the vaccines to the EEA and worldwide, the applicants should be granted the authorization to use OPnEO in the production of vaccines, in accordance with the article 60(4) of REACH.

[2] Throughout this SEA a "." separates units from decimals, whereas a "," indicates thousands and millions.

2. AIMS AND SCOPE OF SEA

2.1. Aims and scope of SEA

OPnEO [4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated] was added to Annex XIV of REACH under entry 42, with a sunset date on 4 January 2021. After this date the substance cannot be placed on the EU market or used in the EU unless an authorization has been granted.

In the case of OPnEO, the application for authorization has to be submitted under the Socio Economic Analysis (SEA) route foreseen under REACH, as the substance is considered to be without a safe threshold (being an ED). When the application is submitted under the SEA route, an authorization can only be granted if there are no suitable alternatives to OPnEO for the use in question and the costs (the risks to the environment) are outweighed by the benefits of the continued use. However, as the risks are more than adequately controlled, there will be no emission into the environment of OPnEO during the production of the vaccines.

The aim of this SEA is to assess the lost benefits (*whereas the costs are equal to zero*) to the society in the event of authorization not being granted to the applicants. In line with the Costs and Benefits Analysis (CBA) methodology, this SEA has covered all the relevant impacts (health, environmental, economic, social and wider economic impacts).

The substance use has been defined in the following way:

"OPnEO is used as a lysing agent for the permeabilization of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Its use allows the selective elimination of enveloped adventitious viruses and is compatible with the chemical needed to control the host cell DNA precipitation in next process step."

On the basis of the projected demand for vaccines for the coming 15 years, the applicants are applying for the authorization to use 270 kg (0.27 tons) per year of OPnEO for its production in Leiden, The Netherlands. The supplier has not been decided yet, as the recent inclusion of OPnEO in the REACH Annex XIV has also affected vendors. This quantity will be used in the manufacturing process of vaccines because there is no technically suitable substitute to date, as shown in the Analysis of the Alternatives (AoA).

From a geographical point of view, the focus of this SEA is on the EEA. However, when assessing all possible impacts in the "non-use" scenario, the analysis has been qualitatively extended, when needed, to other EEA companies as well as to non-EEA countries, as vaccines will be sold and used worldwide.

In line with the ECHA guidance on the preparation of the Socio-Economic Analysis (2011),[3] this report aims to assess and quantify (when feasible) all the relevant impacts

[3] ECHA (2011): Guidance on the preparation of socio-economic analysis as part of an application for authorisation, Reference: ECHA-11-G-02-EN, available at: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

expected in the "non-use" scenario (i.e., refused authorization). All the impacts will be discounted at 4% discount rate. All monetized values have been adjusted to a base year, which is 2021 (the year of the sunset date). The identification of the most likely non-use scenario (delaying the launch of vaccines) and the assessment of the related impacts are based on information provided by the applicants and no third parties have been interviewed.

2.2. Definition of "applied for use" scenario

2.2.1 Company profile and the future production of vaccines

JVP (formerly known as Crucell Holland B.V.) is (based in The Netherlands) specialized in the development of vaccines. J&J acquired Crucell Holland B.V. (which was renamed a couple of years later to Janssen Vaccines & Prevention) in 2011 after which several marketed products were discontinued. Since 2015, no revenue has been reported for JVP. Only R&D expenses and investments have been reported. The facilities in Leiden (both applicants) are the focal point for vaccine process development and vaccine drug substance manufacturing. Only clinical trial materials are produced so far by JVP. As soon as products enter the commercial phase, they will be transferred to the Janssen supply chain organization. In case of the products in scope of this authorization, commercial production will take place at Janssen Biologics B.V. (part of the Janssen Supply Chain organization), which is the other applicant of this application for authorization.

The applicants are applying for a future use so that the "applied for use" scenario (baseline scenario) is the future use of OPnEO in the manufacturing process of vaccines. The starting date of the commercial production is foreseen at the beginning of [redacted] but the selling of these products is expected to be at least one year later, after the formal granting of a license.

The applicants will use OPnEO for producing vaccines by using AdVac® technology. The AdVac® technology is based on the development and production of adenovirus vectors which are gene carriers. The AdVac® technology allows the induction of robust and sustained humoral and cellular immune responses (CD4 and CD8 cells), which is considered to be critical to achieve protection in "difficult fields" (e.g., HIV and RSV). The AdVac® technology together with another production technology (PER.C6®), can be used to develop vaccines against infectious diseases. The PER.C6® in combination with the PIN technology (viz., manufacturing technology that was developed to use the cell-line) allows to obtain high yields with lower costs (viz., intensified production process allows substantial increase in volumetric productivity, [redacted]).

Currently there are Ad26-based virus products in preparation for vaccines against diseases that are listed below.

Table 1. Portfolio overview of the vaccines in the pipeline requiring OPnEO in their production processes

Target	Product
RSV	RSV junior
	RSV senior
HPV	
HIV	Px (preventive)
	Tx (therapeutic)
Ebola	Filo mono
Ebola (Zaire, Sudan) and Marburg	Filo multi
Zika virus	Zika
Influenza	UNIFLU

The applicants have multiple targets (viz., pathogenic viruses causing viral diseases) from which they can generate multiple vaccines, as shown in Table 1. All the above-listed vaccines can have multiple Ad26-based and additional components ([redacted]) and are in different stages of development. Some of them are still in early R&D phase (viz., discovery and pre-clinical trials). Some others are in more advanced stages such as in human safety and immunogenicity trials (phase I and phase IIa); or close to efficacy trials (phase III), [redacted] (phase IIb trial is ongoing).

Vaccines are products often with lower profit margins than other biological APIs, for example monoclonal antibodies. [redacted]

Competitors may provide vaccines against the same viruses but with a different production process. [redacted] (we will focus specifically on the HIV preventive vaccine as a case study when we assess the social impacts).

The additional information below is briefly explaining the market dynamics behind the development of the vaccines of the concerned diseases.

RSV

RSV is a leading cause of respiratory infections in paediatrics and older adults (older than 60 years), with a worldwide high-unmet public health need for a vaccine. JVP is developing RSV vaccines for paediatrics and older adults based on an Ad26 vector [redacted]

Supported by current preclinical and phase I clinical results, [redacted] combines the advantages of the Ad26 platform (safety and induction of sustained immune responses) with a best-in-class immunogen. The vaccine entered in clinical phase II for both paediatrics and older adults at the end of 2017. JVP aims to launch a vaccine for older adults in the US in [redacted] and in Europe by [redacted] which will significantly reduce the disease burden in this population.

HPV

HPV is the most common sexually transmitted infection. High-risk HPVs have a global prevalence of 10-13% in the population and are well known for their causative role in cervical cancer. In addition, they play an important role in vulvar vaginal (60%), anal (40%), penile (40%), and oropharyngeal (50%) cancers.

Despite the successfully marketed prophylactic vaccines by competitors – Gardasil, Cervarix, and Gardasil 9 – a large group of men and women remain at risk of developing HPV related cancers, both oral and genital. Many men and women in their thirties and older have not been vaccinated. Several companies are evaluating therapeutic vaccines in phase I and II studies, with a focus on high-risk groups such as women with high-grade cervical intraepithelial neoplasia (CIN2/3), cervical cancer, or other HPV-related cancers.

JVP believes that an improved efficacy will be delivered by targeting the virus earlier in the disease process, before the stage of high-grade neoplasia. In addition, with the inclusion of the HPV [redacted] antigen in JVP vaccine, which is expressed [redacted], JVP is in a unique position for this early intervention approach.

HIV

A detailed description of HIV is deferred to in Section 3.4.1, in which a case study is presented.

ZIKA virus

ZIKA is an infectious disease which when acquired during pregnancy can lead to severe handicaps or development challenges in children born from this pregnancy and even to miscarriages. JVP is developing a vaccine to be administered in teenager and adults based on an Ad26 vector based on the [redacted] protein of the ZIKA virus [redacted].

Supported by current preclinical and phase I results, [redacted] combines the advantages of the Ad26 platform (safety and induction of sustained immune responses) with a best-in-class immunogen.

Ebola monovalent

Ebola is one of the deadliest infectious diseases known to mankind. When an outbreak occurs, up to 50% of the infected people could die. At this moment there is no Ebola vaccine

licensed and there is a need for vaccines used in outbreak situations as well as for broader protection of healthcare workers and others as currently demonstrated in The Democratic Republic of Congo. JVP is developing a vaccine for this disease. The final regimen consists of an Adeno and an MVA vaccine component.

Current clinical studies support that JVP vaccine gives a high immune response and has a good safety profile. JVP is in the process of filing a registration dossier with the authorities.

Filo Multi

The filovirus family has a number of members of which the Ebola Zaire virus mentioned above is one. Janssen is also working on a multivalent vaccine to cover three strains (two Ebola species Zaire and Sudan and the Marburg virus) that aims to prevent the three most commonly seen filovirus infections.

The applicants' current studies show that this combination of antigens is able to give an immune response in humans.

Influenza (UNIFLU)

Influenza (flu) is a well-known infectious disease. Due to the incomplete protection of the current available vaccines, yearly still thousands of people die because of the flu. Likewise, the flu virus changes from year to year which can result in incomplete coverage of traditional seasonal flu vaccines. JVP is developing a vaccine, which will be universal in coverage, to be administered to adults and elderly as first groups of interest. The final vaccine will most likely be a complex mixture of Adeno, [redacted] and [redacted].

Current preclinical studies show that this combination could be very advantageous to become the first Universal Flu Vaccine, meaning that yearly updates as with the current vaccines or mismatch (not the right antigens present in the vaccine) will no longer occur. [redacted]

2.2.2 Supply chain

Supplier of OPnEO

OPnEO will be preferably sourced as a 10% "ready to use" viscous solution. No further dilution will be done at Leiden. [redacted] is the current supplier of OPnEO and Janssen is investigating a number of suppliers for future use. The applicants expect that, to cover the peak market demand for all vaccines in the pipeline, 270 kg (0.27 tons) of OPnEO will be needed per year.

Manufacturing of vaccines by the applicants

The use of OPnEO dates from at least 2005 (e.g., Goerke et al., 2005).[4]

There are several methods for manufacturing vaccines. The choice of the method depends heavily on the antigen, the method of immunization (i.e., how the antigen is presented) and the expected immune response. The method with adenovirus particles is based on the presence of DNA that codes for the antigen in the virus genome of the viral pathogen (e.g., HIV virus), a transgene. This transgene is expressed after administration of the vaccine. The vaccines for which the authorization is required are based on these (currently Ad26) viral particles. Other methods can be the use of DNA directly, the use of protein directly or otherwise, or other components. Regarding those new vaccines, the applicants have no additional knowledge outside of public domain of what exact processes their potential competitors adopt and whether they use OPnEO for their vaccine manufacturing.

In general, the method of the virus particles does not only give good humoral responses (antibody titers against the antigen), but also good T-cellular immune responses. The applicants are working on vaccine candidates that are considered to become first in class or best in class for the related diseases.

Ad26 particles are specifically only produced in PER.C6® cells [redacted]. After a PER.C6® cell is infected by an Ad26 particle, the PER.C6® cell starts producing more Ad26 particles. The vaccine is composed of Ad26 particles with a specific piece of DNA that codes for a specific antigen. The expression of the antigen in the receiver of the vaccine triggers the immune response.

These Ad26 particles must be extracted from the PER.C6® cells by a controlled permeabilization. This is accomplished with OPnEO used as a lysing agent (detergent). After several purification steps the active pharmaceutical ingredient (also called drug substance) is ready for being formulated in the drug product (vaccine to be administered).

Use of OPnEO in the production process

What follows is the description for the currently anticipated commercial process. One bag containing OPnEO is connected to a bioreactor at the end of viral production. After establishing this closed connection, the solution of OPnEO is pumped from the bag into the bioreactor. The final concentration of OPnEO in the bioreactor liquid is then [redacted]. After incubation, the subsequent process step (DNA precipitation) is initiated. Any liquid waste is disposed via the BioKill system for decontamination.

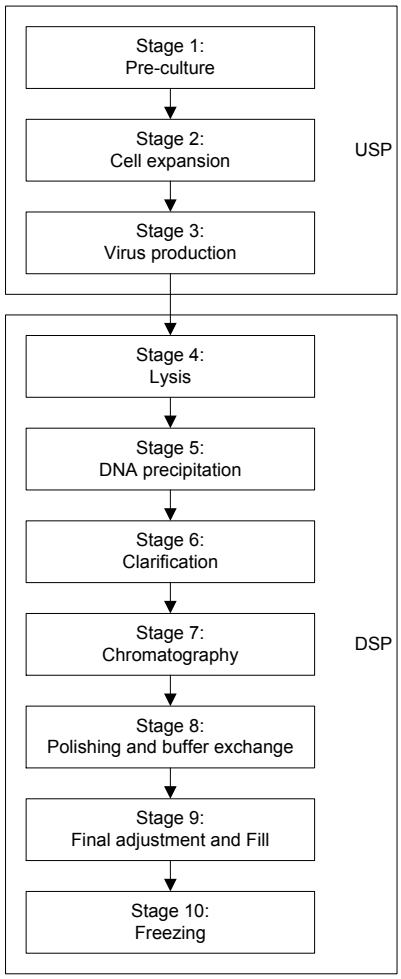
All solid waste (including empty bags containing OPnEO remainders) will be captured and disposed in hospital containers (for hazardous medical waste). All liquid waste will be thermally decontaminated and collected in a tanker truck. Both solid and liquid waste streams are sent off-site to a certified waste handler for incineration. Direct contact of workers with OPnEO (which is already in a closed system) will be also avoided by the usage of personal protection equipment and training. OPnEO is removed from the Drug Substance

[4] Goerke et al., 2005. Development of a Novel Adenovirus Purification Process Utilizing Selective Precipitation of Cellular DNA. Biotechnology and Bioengineering 91(1), 12-21.

(API) in several purification steps and that the removal is controlled via process validation. OPnEO in the final Drug Substance (API) is below the limit of quantification.

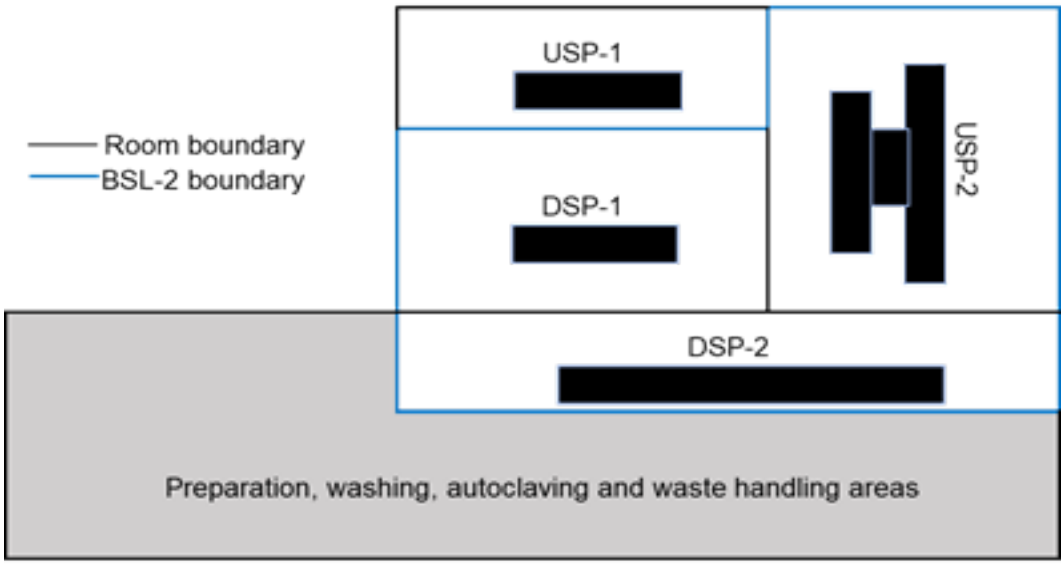
Given the special properties of OPnEO, its use is indispensable for the production of these vaccines as, to date, no potential alternatives (described in the AoA) are ready from both economical and technical viewpoints.

Figure 1. Overview of the production process of vaccines at the applicants' plant.[5] **OPnEO is used in stage 4 (lysis) of the production process.**



[5] USP and DSP stand for upstream process and downstream process, respectively.

Figure 2. Schematic overview of production facility process and BSL-2 envelope. OPnEO is used in the same production steps that need a biological containment, facilitating the capture of waste stream containing OPnEO.



From a biological safety point of view strict (well defined) measures are in place to contain the virus. In this case the same measures are containing the OPnEO as well. OPnEO is added and removed in process steps that require biological containment (i.e. within the BSL-2 boundary depicted in Figure 2). The BSL-2 area is segregated from other parts of the facility and the outside world, by using pressure cascades, leak tight floors, and separate air handling. This segregation includes dedicated waste streams as well.

2.2.3 Brief economic data

To date the applicants do not yet sell the vaccines that will be produced in Leiden. However, according to the applicants' sales plan, the Leiden plant's expected average global market share (from sales) will be [redacted] for the produced vaccines. The applicants do not expect to sell other Ad26-based products than vaccines to be produced by using OPnEO. There are also other products in the portfolio ([redacted]) that are non-Ad26 based and do not use OPnEO in their process. However, the Ad26 portfolio is the largest part.

As of year-end 2018, the applicants have [redacted] people employed in total in the plant: [redacted] people working directly in the plant and [redacted] people working in support functions for the plant. Over the coming few years, the applicants will ramp up from clinical production to commercial scale production in the plant by hiring additional staff. The total people involved (both directly and in support of the plant's operations) are expected to rise to [redacted] for the years 2019 and 2020, to [redacted] in 2021 (reference year for this SEA). From 2022, the employment will be stable at around [redacted] people for all the relevant time period under analysis (up to 2035: 15 years from the beginning of year 2021).

JVP has already invested approximately [redacted] EURO in vaccine R&D after the acquisition in 2011. In addition, over [redacted] EURO has been invested in CAPEX to create launch capabilities and infrastructure. One has to recall that so far no commercial production has occurred yet. The plant, being in an R&D phase, has not generated any revenue. Additional investments are also on-going.

2.3. Definition of "non-use" scenario

The AoA concludes that a suitable alternative to OPnEO in the manufacturing process of vaccines that would be able to replace the functions of OPnEO without adversely affecting the plan to market the vaccines has not yet been found. Furthermore, it is highly unlikely that an alternative will be validated by the sunset date. Without using OPnEO, the applicants are unable to have a controlled lysis step (stage 4 of the production process shown in Figure 1). This means that the applicants will not be able to produce vaccines using the AdVac® process without using OPnEO. A different compound will potentially influence the virus particle release, efficacy, residual impurities, and product stability. Moreover, as outlined in the AoA, the whole substitution process to an alternative requires 15 years beyond the sunset date.

The applicants have a unique position with respect to their competitors in the unique capabilities of their platform process. For example, for the Ebola vaccine, the applicants were able to produce two million regimens during the 2014 outbreak in West Africa ([redacted]). This is believed to significantly outpace competition.

In case of a refused authorization for using OPnEO, it can be foreseen that some vaccines will not be available as planned (see also the case of the HIV preventive vaccine, which will be further discussed later in the case study in Section 3.4), and others will be available only in a limited quantity.

On the basis of the considerations mentioned in the AoA, the most likely "non-use" scenario in the event of no authorization being granted is a 7-year delay in the launch of the first product by the applicants.

2.4. Information for the length of the review period

The substitution of OPnEO will require an estimated time period of 15 years, as detailed in the AoA. This is due to specific constraints the applicants have to face. Specifically, those related to the vaccine production in general (ensuring the same level of qualification, quality, and manufacturability) and those related to the applicants' specific production platform:

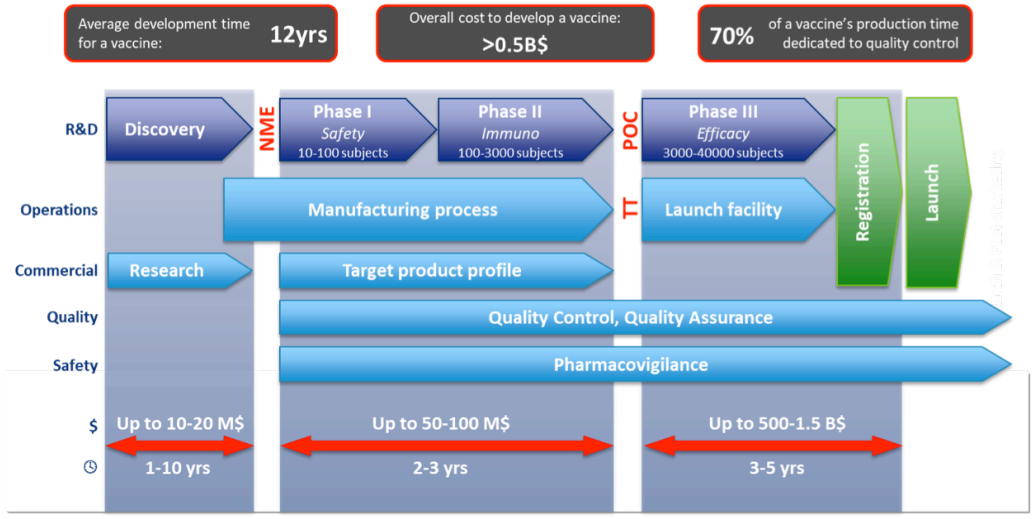
- The lysis with OPnEO provides a controlled permeabilization step minimizing host cell DNA levels;
- It eliminates lipid enveloped viruses from the process;
- Many compatibility issues (e.g., interaction with domiphen bromide; effect on disposable manufacturing equipment) to be overcome by an alternative substance;
- The uniqueness of the platform itself and the fact that the applicants own this platform.

The uniqueness of OPnEO relates to its capacity to extract only the adenoviruses particles, and at the same time the majority of the cell content remains inside the cell. A major change in the lysis, and therefore in the vaccine quality, will be a significant regulatory variation requiring clinical comparability in addition to all process validation and characterization activities. The substitution will affect the planned launch dates of the vaccines, as indicated in the AoA, with an expected delay of seven years, while impacting human health. The vaccines in question are intended for large-scale production as well as for some vaccines being exported to developing countries.

Based on the above arguments and in line with the conclusions reported in the AoA, the applicants request an authorization for the future use of OPnEO in the manufacturing of vaccines for 15 years, starting from the sunset date (2021). This request is based on the following considerations:

- For the time being no viable alternative to OPnEO has been identified *with equal performance*;
- The change is in an early stage in the platform process (stage 4 of Figure 1) potentially affecting all consecutive steps;
- Changes late in the development are only achievable with additional efforts, potentially resetting complete development cycles;
- Each single vaccine product already in the pipeline will be impacted by the substitution of OPnEO and will require additional resources (time, money) to have a replacement implemented;
- Even if a both technically and economically viable alternative to OPnEO were to become available, it would take more than 12 years to develop and to validate a manufacturing process that would lead to vaccines with equal quality and safety standards. Any new viral inactivation method will have to be assessed and approved. The timeline reported in the AoA demonstrates that it would require 15 years. Additional time should be taken into account because a new marketing authorization could be required. However, the substitution activities are already ongoing.

Figure 3. Typical timeline for vaccine development



- The applicants' investment cycle is demonstrably long: main machinery and equipment will need to be changed every 13 years; buildings have an amortization period of 30 years.
- The adoption of an alternative will require specific administrative measures. In particular, the revalidation of the production process and re-approval of market authorizations by regional and national medicine agencies. This is a significantly costly process: the experience of the applicants' regulatory affairs department is that worldwide license updates cost [redacted] EURO for monoclonal antibodies (in the event the implementation of the OPnEO replacer is done after licensing), though updates in a limited number of markets are cheaper than that. Taking the assumption that vaccines require the same amount of money one should multiply this value with the current product portfolio (at least those products that have started Phase II).
- There will be no risk of introducing OPnEO to the environment, as shown in the CSR, and the socio-economic benefits are high. This costs-benefits balance will not change in the next two decades.

Therefore, the applicants believe that any review (or more correctly in this case, substitution) period shorter than 15 years would not be sufficiently long for identifying a viable alternative, developing and testing the impacted process steps, and completing the transition to an OPnEO free process. A review (substitution) period shorter than 15 years would potentially delay the introduction into the market of several vaccines that are in the pipeline, if the re-application will take resources that would be used for the development, validation, and implementation of the new process not using OPnEO. A 15-year authorization will prevent a disruption in the supply chain of vaccines and help to protect the health of people in the EEA and worldwide. Thus, the applicants are strongly convinced that a long

review (substitution) period of 15 years is appropriate and justifiable, as all criteria that are laid out by ECHA (2013) are fulfilled.[6]

The applicants are also asking for a 15-year review (substitution) period for the following reasons, making this application for authorization an exceptional case. Indeed, as the CSR shows, the additional requirements for being granted a review period longer than 12 years, as set by ECHA (2017),[7] are also fulfilled:

- For applications for non-threshold substances, the applied risk management measures and operational conditions should be appropriate and effective in limiting the risks and it should be clearly demonstrated that the level of excess lifetime *cancer* risk is:
    - below $1x10^{-5}$ for workers and
    - below $1x10^{-6}$ for the general population.

Although OPnEO is not included in Annex XIV as carcinogenic but ED (and not even an ED for humans), the CSR clearly shows that there is no risk for the environment because all risks will be adequately controlled with no emission from the production process.

- The analysis of alternatives and the third-party consultation on alternatives should demonstrate without any significant uncertainties that there are no suitable alternatives for any of the utilizations under the scope of the use applied for and that it is highly unlikely that suitable alternatives will be available and can be implemented for the use concerned within a given period, which is longer than 12 years.

We strongly believe to have fulfilled also this second requirement, as the AoA shows.

The applicants would like to conclude this sub-section by recalling that the European Union in one of its recent documents (G/TBT/N/EU/407; Ref. Ares(2017)1311554 - 14/03/2017) has stated:[8] *"The EU is also aware of the concerns of the pharmaceutical industry about the length of authorisation periods in relation to the long timelines that are required for development of innovative pharmaceutical products as well as for the necessary clinical trials and the regulatory approval of such products."*

The applicants conclude this sub-section by highlighting the activities to reach zero emissions. The applicants, after some preliminary internal discussions, have informally

[6] ECHA (2013), Setting the Review Period when RAC and SEAC Give Opinions on an Application for Authorisation (SEAC/20/2013/03), available at: https://echa.europa.eu/documents/10162/13580/seac_rac_review_period_authorisation_en.pdf

[7] ECHA (2017), REACH Authorisation - Criteria for Longer Review Periods (CA/101/2017). Available at: https://echa.europa.eu/documents/10162/13580/ca_101_2017_criteria_longer_review_period_afa_en.pdf/4cda0778-02c3-c949-f1c2-6deb1622a754

[8] http://ec.europa.eu/growth/tools-databases/tbt/en/search/?tbtaction=get.comment&Country_ID=EU&num=407&dspLang=EN&comment_num=4&lang_id=EN&basdatedeb=&basdatefin=&baspays=HUN&baspays2=HUN&basnotifnum=30&basnotifnum2=&bastypepays=&baskeywords=

committed to invest up to [redacted] EURO (worst case calculations) to have a production process with zero emissions. However, after the implementation has started and it is in progress, it has become clear to the applicants that the CAPEX investment needed to reach zero emissions would require [redacted] EURO [redacted] (this is the finding from the feasibility study).

In these zero-emissions activities are involved: 2 PhD's, 2 Master's, and 8 Bachelor's. The core team involved in the OPnEO replacement program is composed by 4 PhD's: experts in the fields of Downstream Processing, Analytical Development (assays), Analytical Development (product characterization), and Drug Product Development. All of them have multiple years of pharmaceutical experience. Work packages are planned by the core team and executed in their respective departments. All combined hours dedicated by the four core team members plus additional departmental hours for 2018 and the expected hours for 2019 and 2020 are equivalent to over 5 Full-Time Equivalent (FTE). Each year an assessment will be performed on the status of the replacement project and the FTE needs for oncoming years.

[redacted] was hired as a consultancy firm to perform the feasibility study (for [redacted] EURO) and the basic design ([redacted] EURO). [redacted] His charged hours add to [redacted] EURO for the feasibility study and around [redacted] EURO for the basic design.

3. ANALYSIS OF IMPACTS

3.1. Environmental impacts

As shown in Sections 9 and 10 of the CSR, the production process is a closed system operating under controlled conditions. Hence, no emission of OPnEO will be registered from the production at the applicants' plant, and all waste streams containing OPnEO will be collected and incinerated. Therefore, there is no risk for the environment (and therefore there is no negative impact to be assessed) from granting the authorization for using OPnEO for the production of vaccines, as described in the present application for authorization.

3.2. Health impacts

The assessment of the impacts of the use of OPnEO on workers' and general population's human health is not relevant for this application, as the reason for authorization is the concern for the environmental compartment. The substance is used under controlled conditions. No contact with the substance will occur during normal operation. In addition, a range of measures has been put into place based on the biohazard of the process. These risk mitigation measures are aimed to prevent human exposure to viruses and are therefore also more than sufficient to address risks to humans of exposure to OPnEO.

The health impacts on potential people who could benefit from the use of the vaccines in the future are deferred to Section 3.4 (social impacts).

3.3. Economic impacts

The direct cost of a refused authorization is represented by the loss of the contribution to the EEA economy of the production of vaccines in Leiden, estimated in the applicants' business plan. As a refused authorization of this application will be equivalent to the case of a temporary stop of the development and future production, the relevant economic measure to quantify the impact is given by EBIT. Monetization (net present values, NPV, with 4% discount rate) of the economic impacts (EBIT) is reported below, regarding the delay of seven years of introducing vaccines into the market.

Table 2. The applicants' sales and EBIT (from the business plan) in million EURO

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Sales	[redacted]										
- Costs of goods sold	[redacted]										
- Other expenses linked to the production of vaccines	[redacted]										
- Depreciation	[redacted]										
+ Non-operating income	[redacted]										
= EBIT	[redacted]										

Year	2032	2033	2034	2035
Sales	[redacted]			
Costs of goods sold	[redacted]			
Other expenses linked to the production of vaccines	[redacted]			
+ Non-operating income	[redacted]			
Depreciation	[redacted]			
EBIT	[redacted]			

The monetization (net present values, NPV, with 4% discount rate) of the economic impacts (EBIT) over 15 years is equal to [redacted] EURO (applied for use scenario). Delaying the production with seven year implies a reduction of the economic benefits due to the discounting of future values. This loss is equal to $1-(1+4\%)^{-7}= 0.24 = 24\%$. This means that delaying seven years is equivalent to a loss in NPV over 15 years of EBIT of 24% with respect to the amount related to the applied for use scenario that would start to be accounted in 2021 instead of 2028. Hence, the monetized negative economic impacts due to a refused authorization is equal to *at least* 24% ([redacted]). **(public range: 1-10 billion EURO)**

It is likely that the delay of several years will negatively affect also the competitive position of the applicants in the market of vaccines in the EEA causing an even worse

economic impact on the EBIT. However, the monetization is limited here to only that 24% that is easily foreseeable.

In addition, the applicants will lose the value of the investments already done, because most of these investments are specific to the AdVac® production process (in addition the investments in Leiden already made are depreciated without returns) and would not be able to be retrofitted and could only be sold in the market for a fraction of their value. In the case these investments will not be used, their amortization will continue.

As already reported in Section 2.4, the adoption of an alternative will require the revalidation of the production process and re-approval of market authorizations by regional and national medicine agencies. This is a significantly costly process: the license updates cost [redacted] for monoclonal antibodies (in the event the implementation of the OPnEO replacer is done after licensing). Taking the assumption that vaccines require the same amount one should multiply this value with the current product portfolio (at least those products that have started Phase II clinical trials). Because of the uncertainty related to these license updates costs, we prefer not to consider them in a quantitative way, but to mention them in a qualitative fashion later when we summarize all impacts (Section 4).

In case of refusing the authorization, satellite activities would also lose the possibility to contribute to the economy created by the applicants. Indeed, some vaccine productions at the applicants' plant will be collaboration efforts with other partners (e.g., [redacted]) as well as the filling operation of Drug Product that is planned in [redacted], and the testing activities performed by a number of contractors in the EEA. Additionally, the suppliers of raw materials and disposables used in the production process would be impacted, a large part of which is supplied by companies within the EEA (e.g., [redacted]).

3.4. Social impacts

This section summarizes the main expected social impacts of the "non-use" scenario. The most important ones are the following:

- The number of people affected by a delay of seven years for several preventive or therapeutic vaccines. As a case study, we focus on the HIV-1 preventive vaccine, being among the most advanced in terms of development; therefore likely to be approved by regulatory authorities and made available in the EU market;
- Secondly, the unemployment associated with the dismissal of workers in the applicants' production plant.

With a refused authorization, satellite activities' employment (e.g., [redacted] or [redacted]) is likely to be negatively affected. The same negative impact is expected for the employment in the suppliers of raw materials and disposables; some of them are companies from the EEA (e.g., [redacted]).

The applicants do not expect negative social impacts from changes in working conditions, job satisfaction, training and skill development, and social security within the

whole organization. However, as detailed below, a negative feedback effect could be also in place among the whole organization as a consequence of the refused authorization. However, the applicants are not in a position to judge whether these additional potential negative social impacts would happen in satellite activities.

3.4.1 Reduction of medical treatments (vaccines)

The estimated year in which the applicants will bring the commercial products (vaccines) to market, if approved by regulatory authorities, are subject to changes depending on the outcome of development activities. Current estimates are:

- Ebola monovalent vaccine: [redacted]
- RSV senior preventive vaccine: [redacted] in Europe
- HIV-1 preventive vaccine: [redacted] in Europe

For the other vaccines in development, time to market is beyond [redacted]:

- Zika virus preventive vaccine
- RSV junior preventive vaccine
- Filovirus multivalent preventative vaccine
- HIV therapeutic vaccine
- HPV therapeutic vaccine
- Influenza (UNIFLU) preventive vaccine

Depending on disease epidemiology and unmet medical need, some of these vaccines would be more important for developing countries (i.e., Ebola Zaire and Zika virus) but the other vaccines (i.e., RSV, HPV, Influenza, and HIV) would serve the whole world, therefore also the EEA countries.

The substitution of the current non-ionic detergent OPnEO is certain to affect all of these currently planned launch dates even for vaccines foreseen for a launch beyond [redacted]. Namely, the substitution of OPnEO will set back the launch date of these vaccines by a number of years, as demonstrated in the AoA. Such a delay would be impactful for millions of potential beneficiaries of these vaccines around the world. Hence, the request of the applicants is to be allowed to continue using OPnEO to respect the timeline for the production of the vaccines already in the pipeline, while the applicants work at substituting OPnEO in its production processes and ensure qualification, quality, and manufacturability of the processes and the vaccines.

Here we try to frame a simple logic approach on how to quantify *the minimum* costs of refusing the authorization. The focus is on the HIV preventive vaccine, which may be produced and brought to the market in the near future ([redacted]). However, the same logic approach would also apply to the assessment of the other vaccines. This means that the quantified costs we are going to estimate in this sub-section are clearly an underestimation of the total costs of not granting the authorization to the applicants to use OPnEO in its

production to bring to the market the above-listed vaccines. However, the focus on the HIV preventive vaccine will allow us to show the *minimum* order of magnitude of the social costs of refusing an authorization.

From the review of the scientific literature on the benefits of vaccines, it is clear that vaccines and vaccination programs provide to the society both direct (narrow, medical) and indirect (broad) benefits, although the vast majority of the literature focuses on the direct ones, such as a better health and lower health care costs.[9]

The estimation of indirect (broad) benefits is much more complex. They are related to, among others, health-care productivity gains, and other (very) long-run effects such as economic growth, macroeconomic stability, educational performance, cognitive development, and herd immunity (e.g., Belli et al., 2005; Bloom et al, 2004).[10] For example, Ozawa et al. (2012) try to provide a comprehensive and systematic review of these benefits.[11] Scholars have attempted to estimate the indirect benefits with sophisticated models, both static and dynamic ones, including differential equations and agent-based simulations. When the complexity of models rises, the parameter-space uncertainty also plays a fundamental role in obtaining reliable estimations. A benefit of simple models is the capacity of interpretation.

Jit et al. (2015),[12] in their systematic review of the literature show less clear evidence for these indirect benefits and macroeconomic gains of vaccines, with mixed results for the causal pathway.[13] These broader/indirect benefits originating from the introduction of vaccines also depend of socio-economic conditions of countries before the introduction of vaccines. At the same time, Jit et al. (2015) present that there is strong evidence that vaccines contribute to narrow/direct benefits. Because including broader indirect benefits would increase the complexity and uncertainty of estimations, we will focus our calculations further in this section on the direct benefits of vaccines, which will lead to a conservative estimation of the total societal benefits.

In 2009, WHO, referring to vaccines, declared: "with the exception of safe water, no other modality, not even antibiotics has had such a major effect on mortality."[14] It is clear that the concerned vaccines for which the applicants are planning to start the commercial production in the coming years are in high demand worldwide.[15] With the exception of influenza and HPV related diseases, none of the disease in the applicants' vaccine portfolio is vaccine preventable yet (RSV, HIV, Ebola and filovirus diseases, Zika). For some, there is no specific approved treatment available (Ebola, Zika, RSV). HIV, despite the availability of antiretroviral drugs, is a life-long condition.

[9] Bloom, D.E., 2015. Valuing Vaccines: Deficiencies and remedies. Vaccine 33, Supplement 2, B29-B33.

[10] Belli, P.C., Bustreo, F., Preker, A., 2005. Investing in Children's Health: What Are the Economic Benefits? Bulletin World Health Organization 83, 777-784; Bloom, D.E., Canning, D., Jamison, D.T., 2004. Health, Wealth and Welfare. Finance Development 41, 10-15.

[11] Ozawa, S., Mirelman A., Stack M.L., Walker, D.G., Levine O.S., 2012. Cost-Effectiveness and Economic Benefits of Vaccines in Low- and Middle-Income Countries: A Systematic Review. Vaccine 31, 96-108.

[12] Jit, M., Hutubessy, R., Png, M.E., Sundaram, N., Audimulam, J., Salim, S., Yoong, J., 2015. The Broader Economic Impact of Vaccination: Reviewing and Appraising the Strength of Evidence. BMC Medicine 13, 209.

[13] Nevertheless, as a general rule in statistical analysis, the absence of evidence does not imply the evidence of absence of these causal pathways relating vaccines to broader benefits.

[14] WHO, 2009. State of the World's Vaccines and Immunization. 3rd ed. Geneva.

[15] PDVAC meeting 2018: https://www.who.int/immunization/research/meetings_workshops/pdvac_june18/en/.

We assume that these vaccines are all cost-effective for EEA governments and, in turn, will be introduced in their national health-care systems as soon as possible.

This section continues, as previously mentioned by focusing on the HIV preventive vaccine, as a sort of case study. It is widely accepted that an effective prophylactic HIV-1 vaccine has the potential to control the spread of this infection globally and could play a pivotal role in the so-called "HIV prevention toolbox" (Fauci, 2017).[16] Indeed, despite 30 years of investment in research to develop a preventive vaccine against HIV-1, the availability of a panel of preventive tools such as condoms, male circumcision or pre-exposure prophylaxis by antiretroviral drugs, and tremendous progress in the treatment of HIV, one can observe the insufficient decrease of the number of new cases each year (incidence) and a constant rise in the number of people living with this virus (prevalence). To date no HIV-1 preventive vaccine exists.

A prophylactic (preventive) vaccine is the cheapest and most effective way of avoiding infectious diseases (Bloom, 2015).[17] Historically, vaccines have eradicated, eliminated or strongly reduced the consequences of catastrophic infectious diseases (Roush, 2007).[18] Despite these successes, six of the top ten global health threats are still directly linked to infectious diseases highlighting the need to pursue development and manufacturing of innovative vaccines against unmet medical needs (WHO, 2019).[19] In addition, unlike many drugs, vaccines bring potential benefits also to people that do not get vaccines through herd protection: sufficient immunization coverage can halt the transmission of a virus or a bacterium (Bloom, 2015).[20] Adamson et al. (2017) provide the first systematic review of the literature on the cost-effectiveness of an HIV vaccine and conclude that many research studies show that HIV vaccines would be cost-effective.[21]

HIV is one of the human diseases with the highest fatality rate (up to 90%) if untreated. As just a matter of comparison, Ebola has a 50% fatality rate if untreated. To be more precise, HIV is not lethal per se but people are killed by connected diseases such as respiratory ones, due to the immunodeficiency originated by HIV (i.e., AIDS). Having HIV, without adopting any therapy, weakens humans' immune system, destroying the white blood cells (leukocytes, especially the depletion of CD4+ T helper cells) that protect against infectious diseases. This creates risks from the so-called opportunistic infections, which are serious infections that take advantage of the compromised immune system, though these infections are less common and less severe in healthy people. For instance, opportunistic infections are: tuberculosis, hepatitis C, toxoplasmosis, and cryptococcal meningitis. Yet, having HIV makes even common infections, like common flu, harder to treat (if HIV reaches the advanced status of AIDS), by generating potentially severe complications and even the death of ill people.

[16] Fauci, 2017. An HIV Vaccine Is Essential for Ending the HIV/AIDS Pandemic. Jama 2017.
[17] Bloom, D.E., 2015. Valuing Vaccines: Deficiencies and remedies. Vaccine 33, Supplement 2, B29-B33.
[18] Roush, JAMA, November 14, 2007—Vol 298, No. 18
[19] WHO, Ten Threats to Global Health in 2019. Available at: https://www.who.int/emergencies/ten-threats-to-global-health-in-2019
[20] Bloom, D.E., 2015. Valuing Vaccines: Deficiencies and remedies. Vaccine 33, Supplement 2, B29-B33.
[21] Adamson, B., Dimitrov, D., Devine, B., Barnabas, R., 2017. The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review 1, 1-12.

HIV can only be transmitted through the following biological fluids: blood, sperm, vaginal secretions, and breast milk. To simplify, we do not take into consideration the "vertical" transmission from mother to new-born child via the breast milk (this is a source of underestimation for the assessment).[22] The HIV infection happens when one of these biological fluids of a seropositive person (i.e., infected with HIV) comes in contact with the bloodstream of a healthy person. Therefore, beside breastfeeding, HIV can be transmitted through, for example, unsafe sex (e.g., not using a condom).

The HIV field has been through major therapeutic advancements since the virus was first isolated, with implementation of antiretroviral therapy, which has in most cases turned a fatal disease into a lifelong condition. These treatments require lifelong administration and can be impaired by variable compliance, the relatively frequent development of resistance of the virus to antiretroviral therapies, and geographically variable access (Ghosn et al., 2018).[23]

Therefore, the benefits (at least the narrow/direct ones) of eradicating HIV are clear. One has also to notice that people who are infected with HIV are treated by the society as having a stigma, which translates in different types of discrimination. For example, study results show that some people living in Eastern European countries might not buy products from a shopkeeper infected with HIV.[24]

When a HIV-1 preventive vaccine is ready to be introduced into the market, it is very likely that there will be strong support for its practical implementation into national health-care systems. Similar arguments also apply for the other concerned vaccines (e.g., Ebola, Zika virus).

In 2017, 25,353 people were newly diagnosed with HIV in 30 of the 31 countries of the EU/EEA according to the report published jointly by ECDC and the WHO Regional Office for Europe in 2018.[25] Sex between men remains the predominant mode of HIV transmission reported in the EU/EEA and heterosexual transmission is the second mode of transmission. While the overall EU/EEA trend appears to have declined slightly during the last decade, contrasting trends are seen at national level with a number of countries still experiencing an increase in new cases.[26] The current increasing trends indicate that EU/EEA is not on track to meet the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) targets; achieving the target would require a decline in estimated new infections of 74% by 2020,[27] showing that not only strengthening of current prevention strategies is needed but also an HIV preventive vaccine.

What follows is a series of paragraphs that can be considered as the building blocks to estimate the minimum number of people negatively affected by the refused authorization to the applicants and the relative monetization of this negative social impact.

[22] The mother-new-born-child transmission rate can be up to 45% in case no measure is taken (http://www.who.int/hiv/topics/mtct/en/).
[23] Ghosn, J., Taiwo, B., Seedat, S., Autran, B., Katlama C., 2018. HIV. The Lancet 392 (10148), 25-31.
[24] http://www.unaids.org/en/resources/documents/2018/2018-global-aids-update-slides-part2
[25] https://ecdc.europa.eu/sites/portal/files/documents/hiv-aids-surveillance-europe-2018.pdf.
[26] https://ecdc.europa.eu/sites/portal/files/documents/hiv-aids-surveillance-europe-2018.pdf
[27] https://ecdc.europa.eu/sites/portal/files/documents/hiv-aids-surveillance-europe-2018.pdf

DISCLAIMER

The applicants would like to note that they take a case example to illustrate on what could be the minimum potential benefits of having the HIV vaccination. To simplify the assessment, the following have not been taken into account:

- **No loss in productivity of infected people;**
- **No potential HIV transmission between newly infected people and their sexual partners;**
- **The lack of benefit of herd immunity;**
- **No healthcare resource utilization as part of the direct cost of treatment (such as hospitalization and office visits; hospitalization may be an important component when patient progress into AIDS).**

ELIGIBLE POPULATION AND RISK

Janssen aims to develop an HIV-1 preventive vaccine that protects adults and adolescents from infection with diverse HIV-1 strains circulating globally.

Early sexual debut provides more risks over time for adolescents to be exposed to HIV-1, especially where higher risk partners or multiple partners are involved and use of other preventive measures is less likely. The prospective prophylactic HIV-1 vaccine should therefore aim to prevent HIV-1 infection in children before they become sexually active.

The choice of this lower age cut-off (9 years) for vaccination is based on the following considerations:

- As early sexual debut increases the risk of exposure to HIV-1 and because the WHO defines puberty as 10 years or older, vaccination prior to the onset of puberty and possible sexual debut lessens the risk that it could encourage risky behaviour;
- The vaccination regimen takes 12 months to administer;
- 9 years is the lower age cut-off for prophylactic human papillomavirus (HPV) vaccines and could potentially allow co-administration (subject to demonstration of the absence of interference), thereby increasing the likelihood of uptake

It is acknowledged that, for the age range of 9 to 18 years old, vaccination will be adapted to the country specifications. However, for the matter of this case study, we focus the economic assessment on adolescents (i.e., 10-19 years old, as defined by WHO)[28] and adults (for this case study, people aged 20+).

[28] http://www.who.int/topics/adolescent_health/en/

Eurostat reports for 2017 that in the EU-28 there were 53,612,047 adolescents (sum of the two age groups 10-14 and 15-19).[29] In 2017, the EU-28 population was 511,373,278.[30]

For the adolescents, we use the statistics for the general population. We know from a recent report of The European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe that the 2016 incidence rate of HIV in the EU/EEA was 5.9 per 100,000.[31].

If we apply this incidence rate of 5.9 per 100,000 to the number of adolescents in the EU-28 (53,612,047), then we obtain an estimate for the whole EU-28 of 3,163 (rounded to units) cases of adolescents infected with HIV per year without any available medical treatment. However, it is unlikely that adolescents younger than 15 years are sexually active. Then, we decide to reduce this estimate accordingly (nevertheless, this is also a source of underestimation following the conservative approach). Hence, we use the ratio between adolescents aged 15-19 and adolescents aged 10-19 to multiply the estimate of 3,163. Eurostat reports that in 2017 adolescents in the EU-28 aged 15-19 were 27,106,174.[32] Therefore, we take into account the following potential HIV cases for the adolescents: 3,163 times 27,106,174/53,612,047 = 1,599 (rounded to units).

The Eurostat's projection for the EU-28's population growth rate is 1.7 % from 2016 to 2080.[33] This is equivalent to a constant annual rate of growth that is pretty close to zero (less than 0.03%). Hence, we do not consider any growth rate to be applied to the eligible population for our assessment (this is a source of underestimation, though negligible, of HIV cases).

We further assume a uniform distribution across the whole EEA of potential people as target of being infected with HIV. Namely, we assume a "representative" country (covering the whole EEA). This is done to simplify the assessment.

As the relevant geographical area for REACH is the EEA (not the EU-28), we correct for this fact as follows. From the EU-28 population in 2017 (511,373,278) we include the populations in 2017 of Iceland (338,349), Liechtenstein (37,810), and Norway (5,258,317).[34] Therefore the 2017 EEA population is equal to 517,007,754. We use the ratio (511,373,278 + 338,349 + 37,810 + 5,258,317)/511,373,278 = 1.01101832309666 to adjust (by linear extrapolation once the three EEA non-EU-28 countries are included) the cases of adolescents derived above: 1,599 times 1.01101832309666 = **1,616** (rounded to units).

We close this building block of the model by taking into account the remaining EEA population, that is the adults. From the 2017 EU-28 population (511,373,278)[35] we subtract all people aged 0-19:

25,820,664 (people aged lower than 5),

[29] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjangroup&lang=en
[30] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjangroup&lang=en
[31] https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf
[32] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjangroup&lang=en
[33] http://ec.europa.eu/eurostat/statistics-explained/index.php/People_in_the_EU_-_population_projections
[34] https://ec.europa.eu/eurostat/en/web/population-demography-migration-projections/data/main-tables
[35] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjangroup&lang=en

27,331,233 (people aged 5-9), and
53,612,047 (adolescent aged 10-19),[36]

Therefore, we arrive to 404,609,334. Hence, the cases of adults in the EEA infected with HIV per year without any available medical treatment are equal to: 5.9/100,000 times 404,609,334 times 1.01101832309666 = **24,134**.

PRE-EXPOSURE PROPHYLAXIS

Although it has been shown that the pre-exposure prophylaxis (PrEP) is highly effective against HIV (almost 100% effectiveness),[37] it is not widespread in Europe. "PrEP in Europe" claims that comparing to PrEP access for high risk population in Europe and in the US: "*in Europe just under 3000 people are currently receiving PrEP through the healthcare system in France and up to 150 in Norway*".[38] Therefore, PrEP has a negligible impact in the EEA. For this reason we do not reduce the cases of HIV per year as derived above.

EFFECTIVENESS OF A PREVENTIVE VACCINE

The effectiveness of a preventive vaccine depends on many factors and trying to consider all of them would lead to an analysis well beyond this SEA's scope. The main considerations one can take into account are the **efficacy** of the vaccine and the **immunization coverage** over time among the eligible population.

IMMUNIZATION COVERAGE

How many eligible people would be vaccinated? The immunization coverage that the national health-care systems are able to obtain every year is influenced by many factors, such as financial constraints, migration, skepticism of vaccine programs, and "vaccine hesitancy" (Doherty et al., 2016).[39] All of these factors yield to a vaccination gap, especially during the first years after the introduction of vaccines into the market (no mass vaccination). This has been common for all diseases and the related developed vaccines.

For example, WHO published the worldwide coverage for many diseases, which goes from as low as 13-45% (rotavirus) to as high as 78-96% (DTP) or 83-96% (BCG), with the difference within the immunization coverage ranges for the same disease due to the level of development of the countries.[40]

Here we assume an average [redacted]% **(public range *to avoid reverse calculation*: 1-10%)** of immunization coverage per year for both adolescents and adults. Namely, we

[36] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjangroup&lang=en
[37] https://www.cdc.gov/hiv/research/biomedicalresearch/prep/index.html
[38] http://www.prepineurope.org/en/who-is-the-prep-in-europe-initiative/the-prep-situation-in-europe/
[39] Doherty, M., Buchy, P., Standaert, C.G., Prado-Cohrs, D., 2016. Vaccine Impact: Benefits for Human Health. Vaccine 34, 6707-6714.
[40] http://apps.who.int/gho/data/node.main.A824?lang=en

assume that [redacted]% of adolescents and adults in the EEA will vaccinate every year starting form the first year in which the HIV preventive vaccine will be launched to the market ([redacted]).

The applicants assume that the vaccine will reach a plateau of maximum coverage after around [redacted] years from the introduction of the HIV preventive vaccine, namely a maximum coverage of [redacted]% at the peak year ([redacted]% times [redacted]).

Of course, the immunization coverage is strictly related to the number of doses that are available in the EEA market. For the time being we assume that the whole demand (based on the assumptions adopted so far) for vaccines coming from the EEA population will be entirely satisfied. This is done only for simplifying the calculations without affecting the final finding to be derived at the end of this section. Indeed, we notice that the more cases of immunized people are estimated now, a lower percentage of these cases will be considered later. We will come back on this issue later, when the potential production capacity of the applicants will be taken into consideration.

EFFICACY OF THE HIV PREVENTIVE VACCINE

Regarding the HIV preventive vaccine, the efficacy will be estimated from controlled clinical trials, because one cannot observe ex-post exposure to the virus in real-life conditions with the vaccine that is in routine use. This is the case because the HIV preventive vaccine is not on the market yet.

To date, only one experimental HIV preventive vaccine (not the vaccine to be produced by the applicants) went through a first phase III clinical trial in Thailand (RV144 study).[41] This clinical trial has shown an efficacy of the HIV preventive vaccine in humans of 31.2% over three years (e.g., Rerks-Ngarm et al., 2013).[42] This is also the only positive (although not sufficient to license for public use) result in efficacy available to date. This HIV experimental vaccine was compounded by a canarypox viral vector (ALVAC-HIV) and the Env subunit protein gp120 (AIDSVAX B/E). ALVAC-HIV and AIDSVAX B/E were manufactured by Sanofi Pasteur and Genentech (a US biotechnology corporation, subsidiary of the Swiss multinational Roche), respectively. This vaccine candidate does not use the adenovirus serotype 26 (Ad26) vector, which is the one proposed by the applicants with its technology. An important difference from the competitors lies in the design of the transgene that is a mosaic construct with env and GP proteins from different clades.

A clade C gp120/MF59 version of ALVAC-HIV (collaborators: Sanofi Pasteur and GlaxoSmithKline) is currently evaluated in South Africa in a phase IIb/III clinical trial (NCT02968849; known as Uhambo study) with the estimated study completion date in 2021.

[41] In total only six vaccine candidates (and four vaccine regimens) have been tested for clinical efficacy since the discovery of HIV more than 30 years ago.

[42] Rerks-Ngarm, S., Paris, R.M., Chunsutthiwat, S., Premsri, N., Namwat, C., Bowonwatanuwong, C., Li, S.S., Kaewkungkal, J., Trichavaroj, R., Churikanont, N., de Souza, M.S., Andrews, C., Francis, D., Adams, E., Flores, J., Gurunathan, S., Tartaglia, J., O'Connel, R.J., Eamsila, C., Nitayaphan, S., Ngauy, V., Thongcharoen, P., Kunasol, P., Michael, N.L., Robb, M.L., Gilbert, P.B., Kim, J.H., 2013. Extended Evaluation of the Virologic, Immunologic, and Clinical Course of Volunteers Who Acquired HIV-1 Infection in a Phase III Vaccine Trial of ALVAC-HIV and AIDSVAX B/E. Journal of Infectious Diseases 207, 1195-1205.

Nevertheless, the last evidence (July 2018), based on the HIV experimental vaccine to be produced by the applicants, shows that the efficacy is 67% in rhesus monkeys.[43] This is a clear improvement in the efficacy rate from the first phase III clinical trial in Thailand (RV144 study). This phase I/IIa clinical trial (NCT02315703) has assessed the mosaic adenovirus serotype 26-based HIV-1 vaccine candidates in 12 clinics around the world (i.e., Rwanda, South Africa, Thailand, Uganda, and USA).[44] All vaccine candidates have shown favorable safety and tolerability. JVP's mosaic Ad26/Ad26 [redacted] boost vaccine (no previous testing of this candidate in ClinicalTrials.gov) gave the best results in terms of a robust humoral and cellular immunogenicity responses in healthy humans and rhesus monkeys, with similar kinetics, durability, magnitude, and phenotype. Therefore, this specific vaccine regimen has been advanced to the currently running phase IIb clinical trial (NCT03060629; known as Imbokodo study) to assess clinical efficacy in women in sub-Saharan Africa (i.e., Malawi, Mozambique, South Africa, Zambia, Zimbabwe), with the estimated study completion date on 2022. The key difference of the Ad26-based (Ad26.Mos.HIV) vaccine to be produced by the applicants is its mosaic inserts to obtain global market coverage against all clades of HIV-1 (clade B is the most prevalent one in Europe). Every geographical region of the world is characterized by the prevalence of a specific clade. The mosaic version of the HIV vaccine is a new concept for developing a worldwide effective vaccine against HIV.

Being the vaccine of the applicants in phase IIb clinical trial, we do not know whether it will reach the target for the licensure as expressed in the Target Product Profile ([redacted]% **(public range: 35-100%)** efficacy) of the applicants. For this reason we are going to apply a reasonable probability of success of 50% for the assessment (even split of probability between pass and fail) of the [redacted]% efficacy expressed in the target product profile.[45] This means that for our purpose we use a "discounted" efficacy rate of [redacted]% times 50% = [redacted]%.

HIV CASES PER YEAR THAT COULD BE AVOIDED THE FIRST YEAR

Considering both the assumed immunization coverage rates as well as the efficacy of the HIV preventive vaccine, we can estimate what is relevant for this SEA, the number of people in the EEA that the HIV preventive vaccine produced by the applicants could avoid but which avoidance would be delayed if the authorization were to be refused:

- Adolescents: 1,616 times [50% times [redacted]%] times [redacted]% = **28** (rounded to units)
- Adults: 24,134 times [50% times [redacted]%] times [redacted]% = **422** (rounded to units),

[43] Barouch, D.H., Tomaka, F.L., Wegmann, F., …, 2018. Evaluation of a Mosaic HIV-1 Vaccine in a Multicentre, Randomised, Double-Blind, Place-Controlled, Phase 1/2a Clinical Trial (APPROACH) and in Rhesus Monkeys (NHP 13-19). Lancet, July 21, 392 (10143), 232-243.

[44] HIV-1 is the common type of HIV. HIV-2 is less common (almost completely found in Africa) and relatively less dangerous.

[45] Although 50% might seem somewhat too high, we prefer to err toward the conservative side.

in which the first value stands for the number of concerned people in each EEA population category, [50% times [redacted]%] stands for the "discounted" Target Product Profile efficacy rate of the HIV preventive vaccine to be produced by the applicants, and the third percentage ([redacted]%) stands for the assumed coverage rate per year, differentiated by target population.

MARKET INTRODUCTION

The date of introduction after the release of a vaccine differs by country. Here, to simplify, we assume that all EEA countries will introduce the HIV preventive vaccine in the same year (viz., we are adopting the assumption of an EEA "representative" country). And this specific year is [redacted] (i.e., we assume that there will be an immediate introduction, given the society's high demand for a preventive vaccine against HIV).

DELAY DUE TO A REFUSED AUTHORIZATION

If the authorization is not granted, the time to market of the vaccines to be produced at the applicants' facility in Leiden will be extended. Activities to replace OPnEO in the process are detailed in the AoA and include identification of possible alternatives, testing in the applicants' complex production process, testing of the final product for comparability and stability, and regulatory steps to implement a process change in a highly complex regulatory environment. In case of a refused authorization, the applicants estimate that at the minimum the launch of the HIV vaccine would be postponed of seven years, as well as the launch of the other vaccines (Ebola, Zika, HPV, RSV, Influenza, and HIV therapeutic) will be likewise pushed forward by a similar time delay with respect to their currently planned market launches.

Hence, we are going to calculate how many cases of HIV cases would not be avoided among the eligible population in the EEA because of the refused authorization, which will yield to a delay of seven years in introducing the HIV preventive vaccine in the EEA health-care systems.

ANTIRETROVIRAL THERAPY

HIV can be suppressed by a combination of at least three antiretroviral therapy (ART) drugs. Current ART drugs do not provide a cure for HIV but, unlike drugs of two decades ago, strongly reduce the viral replication under a risk threshold, so as HIV is not able to compromise the immune system and AIDS status is avoided.[46] WHO reports that people using ART "*can enjoy healthy, long and productive lives.*"[47] Similar statements can also be found in ECDC documents.[48]

[46] Nevertheless, one cannot disregard the negative facet of ART. Namely drugs are expensive and have many side effects, as well as there exists potentiality for developing drug resistance for some people.
[47] http://www.who.int/en/news-room/fact-sheets/detail/hiv-aids
[48] https://ecdc.europa.eu/sites/portal/files/documents/HIV%20treatment%20and%20care.pdf

ECDC's estimations show that about 29% of people infected (both diagnosed and undiagnosed) with HIV in the EU/EEA who could receive the benefits from ART are still not receiving it; social and administrative barriers to obtain an ART are behind this gap.[49] However, only 89% of people receiving an ART in the EEA are virally suppressed.[50]

By using these statistics, we assume that [100%-29%] times 89% = 63% people infected with HIV will use ART and will not end up to the AIDS status during their life. Conversely, 37% [=100%-63%] will progress to the HIV advanced stage of AIDS during their life (29% of people not taking ART as well as 8% [=37%-29%] people taking ART without a successfully viral suppression).

The HIV-to-AIDS conversion can take 2-15 years.[51] We assume that for the 29% (HIV cases without any treatment) the conversion will happen after 8 years (rounded average between 2 and 15 years). Next, for the other 8% (HIV cases taking ART but without success) we reasonably assume that the conversion will happen after a longer period, which we set to 12 years (rounded average between 8 (previous derived average) and 15 years).

QUALITY ADJUSTED LIFE YEARS

To estimate the magnitude of loss in consumer surplus (i.e., the social impact of refusing the authorization to the applicants), the concept of Quality Adjusted Life Years (QALY) can be adopted. We apply a QALY-adjusted factor for ill people, as detailed below, and calculate the difference with the scenario in which the applicants will obtain the authorization to use OPnEO, characterized by the fact that all targeted people have a QALY = 1 for every life year, in case they were healthy.[52] This will allow estimating the total loss in terms of QALY.

The literature provides indications on how to convert QALY in monetary terms. An overview of the topic is given by ECHA (2015).[53] The studies cited in this ECHA report yield values of £10,000 - £70,000 per QALY (where £ stands for British pound). The WHO has suggested to use the following equation to calculate the cost-effectiveness of an intervention: one QALY = GDP per capita (of a given country).[54] We follow the suggestion of WHO. Regarding the GDP per capita, we consider the European average (viz., the available EU-28 datum), which was 29,900 EURO for the year 2017.[55] Being the QALY reference value (as suggested by the WHO) within the interval based on the review presented in the ECHA report (viz., range £10,000-£70,000 = range 11,568 EURO-80,979 EURO; exchange rate of

[49] https://ecdc.europa.eu/sites/portal/files/documents/HIV%20treatment%20and%20care.pdf
[50] https://ecdc.europa.eu/sites/portal/files/documents/HIV%20treatment%20and%20care.pdf
[51] http://www.who.int/en/news-room/fact-sheets/detail/hiv-aids
[52] QALY = 1 is the value of one life year *without* the disease for one person.
[53] ECHA (2015): Quantification and Valuation of the Human Health Impacts of Chemicals Based on Quality and Disability-Adjusted Life-Years, available at: https://echa.europa.eu/documents/10162/13639/report_qualy_daly_en.pdf/f8c20060-8e7d-4b87-9e0c-64ba2999e63d (p. 61).
[54] Walker, D.G., Hutubessy, R., Beutels, P., 2010. WHO Guide for Standardization of Economic Evaluations of Immunization Programmes. Vaccine 28, 2356-2359.
[55] http://ec.europa.eu/eurostat/tgm/refreshTableAction.do;jsessionid=9ea7d07e30dd3bf0a52b9a8a474c872db039e243c026.e34OaN8Pc3mMc40Lc3aMaNyTa3eQe0?tab=table&plugin=1&pcode=tec00001&language=en

18 April 2019) we stick with the WHO approach to monetize one QALY. Notice the 29,900 EURO is smaller than the average as calculated between the minimum (£10,000) and the maximum (£70,000) of the interval presented in the ECHA report (viz., £40,000 = 46,289 EURO; exchange rate of 18 April 2019). Therefore, the 29,900 EURO (year 2017) can be considered a conservative estimation, but it also avoids the extremism toward the conservative side for estimates, such as that of applying the lower bound of the interval in the ECHA report (£10,000). For the sake of comparison, to be precise, one should actualize the value of £40,000 from 2015 to 2017. This will just slightly put a wider wedge between 29,900 EURO and the average of the interval in the ECHA report and, in turn, slightly yielding to an addition to the pragmatic and prudential approach we aim to. By the way, the same report at p. 61 also states that *"[v]ia survey research, most methods of aggregating the data resulted in values of a QALY of between £18,000 - £40,000"*, which is also in line with our derived reference value. We will adjust this reference value of 29,900 EURO by taking into consideration that it will be applied to assess QALY starting from the year [redacted]. Therefore, we "actualize" (viz., toward the future) 29,900 EURO from 2015 to [redacted].

Price Adjuster from 2015 to [redacted]

To adjust 29,900 EURO from the year 2015 to the year [redacted], the value is multiplied by a price adjuster. We take the geometric average (average annual growth) from the last five years of EUROSTAT's available GDP deflator (Q1, seasonally and calendar adjusted) for the EU-28 area:[56]

2013Q1: 103.92
2014Q1: 105.21 (year-on-year growth: 1.01241339)
2015Q1: 108.18 (year-on-year growth: 1.02822926)
2016Q1: 108.48 (year-on-year growth: 1.00277316)
2017Q1: 107.81 (year-on-year growth: 0.99382375)

We assume that prices will continue to raise in the future from 2015Q1 (central year in the 5-year interval used) to [redacted]Q1 to the same derived average annual growth: [redacted]Q1 values equal to 2015Q1 times (1.00922959)[redacted] = 2015Q1 times [redacted] (rounded up).

Therefore, multiplying 29,900 EURO per the price adjuster derived above yields [redacted] EURO (= 29,900 EURO times [redacted]). This value will be used later to monetize the estimated total loss in terms of QALY the society would face in case of a refused authorization.

Developing countries are not considered for the monetized impact of the social damage from a refused authorization, but they will experience not only morbidity but a higher mortality rate, too, among their populations. We would like to stress again that, although the focus of this SEA is on the EEA, the monetized impact we are going to

[56] Available at: https://sdw.ecb.europa.eu/browseTable.do?node=9691222

assess is just the tip of the iceberg with respect to the social (qualitatively described) impacts the whole world would face in the event of a refused authorization. In 2017 there were 1.8 million new HIV infections worldwide (of which 1.6 million were adults),[57] the vast majority of which was in developing and third-world countries (66% in sub-Saharan countries).[58] Yet, the high population growth in sub-Saharan Africa is high, this means that, the absolute number of (young) people living there with HIV will raise over time.

Without any treatment, the average survival with HIV/AIDS is about 10 years, having previously assumed that HIV will convert, on average, after 8 years without treatment. This means that people will survive after having acquired the AIDS status only for additional two years because AIDS will allow the opportunist diseases to attack the human body fatally (QALY=0). We reasonably assume that the two additional years of survival after the HIV-to-AIDS conversion also applies to the case taking ART without a successfully viral suppression (viz., the death will happen after 12+2 years). The loss in QALY, for each person per year, will be simply given by 1-QALY, with 0<=QALY<1.

Moving from theory to practice, we need to put some explicit numbers attached to QALY. To do so, we make reference to the epidemiological literature. Specifically, we adopt the findings from the much-cited review of the literature on HIV health status of Holtgrave and Pinkerton (1997), as re-adapted by the Australian Government's Department of Health.[59] Their findings are reported below in Table 3.[60] We have used Australian data because they were readily available and also because the level of development of Australia is not much different from that of EEA.

[57] http://www.unaids.org/en/resources/fact-sheet;
http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides

[58] http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides

[59] Holtgrave, D.R., Pinkerton, S.D., 1997. Updates of Cost of Illness and Quality of Life Estimates for Use in Economic Evaluations of HIV Prevention Programs. JAIDS, 16, 54-62.

[60] Table 3 has been slightly adapted (in terms of presentation; no change to the QALY values) from that of the Australian Government's Department of Health, which also makes reference to Holtgrave and Pinkerton (1997). http://www.health.gov.au/internet/publications/publishing.nsf/Content/illicit-pubs-needle-return-1-rep-toc~illicit-pubs-needle-return-1-rep-5~illicit-pubs-needle-return-1-rep-5-3

Table 3. Loss in QALY due to HIV infection

Disease Stage	Description	Loss in QALY Value
Early HIV Disease – undiagnosed	HIV infection with CD4 count above 500/mm^3, unaware of HIV serostatus	**0.06** (QALY=0.94)
Early HIV Disease – diagnosed	HIV infection with CD4 count above 500/mm^3, aware of HIV serostatus and no antiretroviral therapy	**0.13** (QALY=0.87)
Progressive HIV Disease – undiagnosed	HIV infection with CD4 count below 500/mm^3, unaware of HIV serostatus	**0.10** (QALY=0.90)
Progressive HIV disease – diagnosed	HIV infection with CD4 count nadir below 500/mm^3 and commenced on antiretroviral therapy	**0.24** (QALY=0.76)
AIDS	AIDS as defined by clinical condition	**0.38** (QALY=0.62)

The loss in QALY values are referred to each single year of the remaining life after having contracted HIV. We will assign the relevant value of the loss in QALY at the end of each lived year. In yellow, we have highlighted the four situations of loss in QALY that are adopted in the assessment.

DIAGNOSIS

WHO reports that,[61] *"HIV infection is often diagnosed through rapid diagnostic tests (RDTs), which detect the presence or absence of HIV antibodies. Most often these tests provide same-day test results, which are essential for same day diagnosis and early treatment and care."*

We assume that all cases of HIV will be diagnosed within the first year of infection. Therefore, we assume that the ART will start immediately (and well before AIDS develops) and continues indefinitely. This is coherent with what ECDC reports: in most countries ART starts in less than a month after a confirmed diagnosis of being HIV positive.[62]

LOSS IN QALY FOR THE FIRST YEAR OF DELAY ([redacted])

We assume that in the EEA the average age of the "representative" eligible adult person who could use the HIV preventive vaccine and at risk of being infected with HIV is 37 years (this is in line with what is reported by the ECDC/WHO's HIV/AIDS Surveillance in Europe 2017 report).[63] Life expectancy at birth in the EU-28 (assumed the same for the EEA) was 80.6 years in 2015.[64] Hence, this "representative" person is assumed to be born [redacted] and we set for him a reasonable life expectancy at birth lower than the

[61] http://www.who.int/en/news-room/fact-sheets/detail/hiv-aids
[62] https://ecdc.europa.eu/sites/portal/files/documents/HIV%20treatment%20and%20care.pdf
[63] See p. x and p. 7. of the report available at: https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf
[64] http://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics

current one, namely at 73 years (i.e., 7.6 years lower than the current life expectancy at birth).[65] This implies that in case the "representative" person will be infected with HIV will live, *at maximum* (excluding mortal cases), for another 36 years with a reduced QALY for each remaining year of life. In case the "representative" person will die, we will assign a loss in QALY equal to 1 (1-QALY, with QALY = 0) for the remaining years that could be lived (up to 73 years).

For the adolescents, we take the average of 17 years of the 15-19 age range. Namely, the "representative" adolescent is assumed to be born [redacted], with a life expectancy at birth in [redacted] of 79.1 for the EU-28 (assumed the same for the EEA), which we round to 79.[66] This implies that in case the "representative" adolescent will be infected with HIV will live, *at maximum* (excluding mortal cases), for another 62 years with a reduced QALY for each remaining year of life.

DURATION OF THE IMMUNIZATION

Once the cycle of vaccination is complete (**full regimen with four vaccinations with one dose of Ad26 vaccine each**), the prevention of HIV **is expected to last for** [redacted] **(public range: 1-10 years)**, according to the applicants. We assume – to simplify the analysis without affecting the final finding to be derived at the end of this section – that the same people who vaccinated will redo the vaccination cycle every [redacted] years so as to have a continuous immunization over time. [redacted]

As already stated before, the more cases of immunized people are estimated now, a lower percentage of these cases will be considered later. We will come back on this issue later, when the potential production capacity of the applicants will be taken into consideration.

LOSS IN QALY OVER THE YEARS

We discount future values of QALY (or, for our purpose, the loss in QALY) at the standard rate of 4%. Then we multiply the sum of discounted QALY per the reference monetized value for 1 QALY, as derived before.

From the whole above discussion, it follows that in case of a refused authorization, the EEA society will experience a welfare loss in terms of QALY that can be accounted as follows.

[65] The value for the EU-28 is not, of course, available for the year [redacted]. Values for single countries range from [redacted] years. We take the average of these two extreme values and rounded to units. http://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics

[66] http://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics

Adolescents.

63% of 28 HIV cases = 17 (rounded to units)

Years	1 (= [redacted])	2-62
Loss in QALY per year	0.06	0.24

Present value (4% discount rate): 5.30

29% of 28 HIV cases = 8 (rounded to units)

Years	1 (= [redacted])	2-8	9-10	11-62
Loss in QALY per year	0.06	0.13	0.38	1

Present value (4% discount rate): 16.02

8% of 28 HIV cases = 3 (remaining cases: 28-17-8)

Years	1 (= [redacted])	2-12	13-14	15-62
Loss in QALY per year	0.06	0.24	0.38	1

Present value (4% discount rate): 14.77

Therefore, the impact for adolescents is monetized as follows:

(17 x 5.30 + 8 x 16.02 + 3 x 14.77) x [redacted] EURO = [redacted] **(public range: 1-10 million) EURO** (rounded).

Adults.

63% of 422 HIV cases = 265 (rounded to units)

Years	1 (= [redacted])	2-36
Loss in QALY per year	0.06	0.24

Present value (4% discount rate): 4.36

29% of 422 HIV cases = 122 (rounded to units)

Years	1 (= [redacted])	2-8	9-10	11-36
Loss in QALY per year	0.06	0.13	0.38	1

Present value (4% discount rate): 12.13

8% of 422 HIV cases = 35 (remaining cases: 422-265-122)

Years	1 (= [redacted])	2-12	13-14	15-36
Loss in QALY per year	0.06	0.24	0.38	1

Present value (4% discount rate): 10.87

Therefore, the impact for the adults is monetized as follows:

(265 x 4.36 + 122 x 12.13 + 35 x 10.87) x [redacted] EURO = [redacted] **(public range: 50-100 million) EURO** (rounded).

Monetization over years.

The monetization we have presented above is only for the first year ([redacted]) without the availability of the HIV preventive vaccine. According to the discussion and assumptions we have provided above, we have to consider that this estimated infected people would repeat for other six years. As already stated, future values are discounted with 4% discount rate.

Therefore, the sum of the monetized impacts derived above is equal to [redacted] **(public range: 100-200 million)** EURO. Multiplying this sum for seven subsequent years is equivalent to multiplying by 6 (with 4% discount rate):[67]

[redacted] EURO x 6 = [redacted] **(public range: 500-750 million)** EURO

Hence, we can conclude that the monetized total loss **in terms of QALY** for the whole EEA society due to the refusal of the authorization (continuing to assume that the whole EEA demand for the HIV preventive vaccine will be entirely satisfied) is equivalent to [redacted] **(public range: 500-750 million)** EURO.

LIFETIME TREATMENT COSTS

[67] Using excel function =PV(4%,7,-1,0,0), which yields the value 6.00.

Besides the loss in QALY, the infected people who take ART drugs create an economic burden for the national health-care systems during their lifetime. From the analysis above one has that:

Adolescents.

17 people x 22.80 (= 62 remaining life years with 4% discount rate[68]) x
x 6 (= 7 years without vaccine with 4% discount rate) = 2,325.60

3 people x 10.56 (= 14 remaining life years with 4% discount rate[69]) x
x 6 (= 7 years without vaccine with 4% discount rate) = 190.08

Adults.

265 people x 18.91 (= 36 remaining life years with 4% discount rate)
x 6 (= 7 years without vaccine with 4% discount rate) = 30,066.90

35 people x 10.56 (= 14 remaining life years with 4% discount rate)
x 6 (= 7 years without vaccine with 4% discount rate) = 2,217.60

Summing up all the derived values yields to 34,800.18. This is the value to be multiplied by the average annual treatment costs related to the ART taking.

Treatment costs vary among countries in the EEA. In a recent document, the ECDC reports available data for 24 EEA countries for the year 2016 (though three countries reported values for 2014).[70] The ART cost per patient per year ranged from 1,000 EURO (Slovakia; year 2014) to more than 20,000 EURO (Germany). We take the average across all these EEA countries and because of 21 countries out of 24 reported values for 2016; we consider this derived average as of 2016. This average is equal to 9,214.29 EURO (rounded). We then multiply this average by [redacted], to adjust the average from 2016 to [redacted] price level ([redacted]). Then, we obtain that the adjusted average annual treatment costs are equal to [redacted] **(public range: 9,000-15,000)** EURO (rounded).

Therefore, the economic burden for the national health-care systems of the whole EEA due to the refusal of the authorization is equivalent to:

[redacted] **(public range: 9,000-15,000)** EURO x 34,800.18 = [redacted] **(public range: 300-400 million) EURO** (rounded).

SUMMARIZING THE FINDINGS DERIVED SO FAR

We conclude this analysis by reporting the sum of the two monetized impacts:

[68] Using excel function =PV(4%,62,-1,0,0), which yields the value 22.80.
[69] Using excel function =PV(4%,14,-1,0,0), which yields the value 10.56.
[70] https://ecdc.europa.eu/sites/portal/files/documents/HIV%20treatment%20and%20care.pdf

- Total loss in QALY ([redacted] **(public range: 500-750 million)** EURO)
- Treatment costs ([redacted] **(public range: 300-400 million)** EURO)

The total is equal to [redacted] **(public range: 800-1,150 million)** EURO. We additionally discount (at 4%) this value for [redacted] years to bring it to from [redacted] to 2021 (reference year): [redacted] **(public range: 800-1,150 million)** EURO/(1 + 4%)[redacted] = [redacted] **(public range: 800-1,150 million)** EURO (rounded).

Nevertheless, there are many other aspects – some of which we have mentioned at the beginning of this sub-section – that would magnify the monetized impact. We just recall here four important sources of magnification:

- **Loss in productivity of infected people;**
- **The potential HIV transmission between newly infected people, who have been considered above, and their sexual partners;**
- **The lack of benefit of herd immunity;**
- **Healthcare resource utilization as part of the direct cost of treatment (such as hospitalization and office visits; hospitalization may be an important component when patient progress into AIDS).**

THE APPLICANTS' PRODUCTION CAPACITY AND EXPORTS

So far we have assumed that the whole EEA demand for the HIV preventive vaccine will be totally satisfied by the applicants. To address this issue we need to know how many doses of HIV vaccine will be available from the applicants' annual production over the seven years of delay due to the refused authorization. To make the analysis easier, we consider the estimated doses at the end of the seven-year period.

In the plant in Leiden the applicants make the API (Drug Substance) but this needs to be formulated and potentially mixed with other vaccine components. Table 4 shows the estimation over time of the vaccine doses to be sold that can be made from produced API (Drug Substance batches), as estimated by the applicants.

Table 4. Sale forecasts of doses of the HIV preventive vaccine (Drug Product)

Year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doses HIV Px Ad26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The vaccine produced is meant primarily for being exported outside the EEA (on average: [redacted]% across 7 years after the sunset date; estimates of the applicants). The cost component for this high-volume vaccine to be used in poor countries is crucial. An

alternative that dramatically increases the cost is sure to reduce the viability of these low-cost products and will result – quite literally – in deaths around the globe that could have been prevented. We maintain the focus on the EEA countries, which are the main scope of this SEA. This also allows us to neglect the cost-effectiveness factor, which is assumed to be fulfilled in all EEA countries, being all developed countries with less financial constraints for the national health systems with respect to developing countries. This is also in line with the empirical literature on the cost effectiveness (e.g., Adamson et al. 2017).[71] Hence, on average [redacted]% of the total annual sales of HIV Px Ad26 vaccine produced by the applicants will be available to the EEA population across the 7-year period ([redacted]). Therefore the doses that will be available in the EEA market over [redacted] period are equal to: [redacted]% times [redacted] doses = [redacted] **(public range: 10-50 million)** doses (rounded to units).

POTENTIAL FUTURE COMPETITORS OF THE APPLICANTS

We would need to know how many doses of HIV preventive vaccines non-EEA future competitors (either with or without using OPnEO) and EEA future competitors (without using OPnEO or using OPnEO if the competitor will obtain a similar authorization from ECHA for doing so) will be able to produce during the period in which the applicants could produce but will not be able to due to the refused authorization. As the reader can easily understand, obtaining these pieces of information is practically impossible for the applicants, being competitors' strictly confidential commercial and strategic information. Therefore, it is not possible to predict with certainty how the *worldwide* market of vaccines will be at the end impacted in case of a refused authorization. And, in turn, to which extent the delay in the market introduction of the HIV preventive vaccine could be filled by vaccines provided by the applicants' competitors.

In general terms, the market of vaccines is not competitive, with only a few key companies having the lion's share of the world market. Nevertheless, from the scientific literature and the register for clinical trials (https://clinicaltrials.gov), it is clear that to date only one trial has been carried out in phase III by testing two experimental vaccines (ALVAC-HIV and AIDSVAX B/E) manufactured by Sanofi Pasteur and Genentech, respectively. The HIV preventive vaccine to be manufactured by the applicants is currently running a phase IIb trial. [redacted] This is also indirectly confirmed by the last report of Access to Medicine Foundation indicating the announcements done by pharmaceutical companies in 2017 in the scope of the 2017 Access to Vaccines Index.[72] Only J&J is reported as having announced good new findings for the HIV vaccine development.

Nevertheless, the only HIV preventive vaccine under advanced clinical trial covering clade B (the type of HIV-1 that is mostly present among the EEA population) is the one

[71] Adamson, B., Dimitrov, D., Devine, B., Barnabas, R., 2017. The Potential Cost-Effectiveness of HIV Vaccines: A Systematic Review 1, 1-12.

[72] https://accesstomedicinefoundation.org/media/atmf/A-look-back-on-a-year-of-announcements-by-vaccine-companies.pdf

manufactured by the applicants, being it a mosaic version encapsulating all types of HIV-1. Hence, we assume that the only HIV preventive vaccine that can be used in the EEA will be that manufactured by the applicants, at least for the first decade after [redacted]. This is so because to date no other advanced-phase clinical trials are running to test HIV preventive vaccines.[73] And it will be impossible to see a situation in which another company (a newcomer) could launch to the market an HIV preventive vaccine in, for example, [redacted]. This is so because the total time to run all phases of a clinical trial and to bring a vaccine to the market can easily be more than 20 years (viz., extreme cases for developing a vaccine: typhoid, 105 years; polio, 47 years).[74] A company alone, on average, invests in time 10-12 years (e.g., HIV efforts at Janssen vaccines originate from 2003). In short, if there will be a potential partial shortage in the HIV preventive vaccine, then this potential shortage will only involve non-EEA markets, which is not the focus of the assessment at hand.[75]

THE EEA DEMAND AND APPLICANTS' SUPPLY

Each person to be vaccinated needs four doses containing Ad26 vaccine to complete a full regimen in 12 months. [redacted]

In 7 years, to cover the whole EEA demand [redacted], one would need the following number of doses. For the adolescents and the adults, we have the following annual fraction (assuming that they will get vaccinated by the end of each year):

- Year 1: 5% (4 vaccinations/shots)
- Year 2: 5% (4 vaccinations/shots)
- Year 3: 5% (4 vaccinations/shots)
- Year 4: 5% (4 vaccinations/shots)
- Year 5: 5% (4 vaccinations/shots)
- Year 6: 5% (4 vaccinations/shots) [redacted]
- Year 7: 5% (4 vaccinations/shots) [redacted]

This means that in 7 years one would need the following vaccine doses:

[73] https://www.avac.org/sites/default/files/infographics/HVAD2018_VaxTrialsPipeline.pdf; https://www.avac.org/sites/default/files/infographics/yearsAheadHIVpreventionResearch_july2018.pdf
[74] https://www.avac.org/infographic/time-develop-vaccine
[75] If competitors in non-EEA markets have a sufficient excess capacity, then there could be no partial shortage because they should be able to take the applicants' non-EEA market shares.

35% of the number of adolescents in the EEA (53,612,047 times 1.01101832309666) times 4 doses = 75,883,867 doses (rounded up to units)

+

[redacted]

This is equal to [redacted] **(public range: 50-100 million)** doses.

For the adults with an assumed annual coverage of [redacted]%, we similarly end up to:

35% of the number of the adults in the EEA (404,609,334 times 1.01101832309666) times 4 doses = 572,694,431 doses (rounded up to units)

+

[redacted]

This is equal to [redacted] **(public range: 500-1,000 million)** doses.

Summing up all these doses (over 7 years) from the potential EEA demand is equal to [redacted] **(public range: 550-1,100 million)** doses.

As a last step of this monetization exercise, we need to account for the supply-to demand ratio: [redacted] **(public range: 10-50 million)** doses divided by [redacted] **(public range: 500-1,000 million)** doses. Therefore we consider only this fraction (about [redacted]%) of the estimated monetized benefits (with the whole EEA demand satisfied) of having the authorization, which is equal to [redacted] **(public range: 10-50 million) EURO** (rounded to units).

CONCLUDING REMARKS

We hope to have convinced the reader that the monetized social impacts coming from the HIV preventive vaccine ([redacted] **(public range: 10-50 million) EURO**), which have been detailed above, are of a sufficient order of magnitude to support the approval of the request of the authorization for using OPnEO for 15 years (requested review/substitution period), also considering that there will not be any emissions of OPnEO from the applicants' production process.

OTHER VACCINES IN THE PIPELINE

Nevertheless, as a source of magnification of the estimated benefits, the reader should bear in mind that the applicants will also produce other vaccines (see Section 2.2.1 for

details), which will be also able to reduce the associated costs for the health care system coming from the hospitalization and medicaments to cure the affected people.

Although some of these vaccines are mostly relevant for developing countries, RSV is also important for the EEA and is at the same level of development of the HIV preventive vaccine.

To show the order of magnitude of this severe disease, we recall that 160,418 RSV cases have been detected in 15 EU/EEA member states in the period 2010-2016 (Broberg et al., 2018).[76] RSV is the main cause of hospitalization for children, especially in the first year of life. As highlighted by the Center for Diseases and Control Prevention (CDC), *"[v]irtually all children get an RSV infection by the time they are 2 years old. Most of the time RSV will cause a mild, cold-like illness, but it can also cause severe illness",* (e.g., bronchiolitis and pneumonia).[77] In addition RSV is an annual hidden epidemic among older adults (especially those older than 60 years), as the disease is often misdiagnosed because the symptoms of RSV and Influenza are nearly indistinguishable and there are no licensed treatment to incentivize specific diagnostics. Therefore the burden of RSV for health-care systems is underestimated.

Qualitative assessment for RSV senior vaccine

Respiratory Syncytial Virus (RSV) is recognized as a significant cause of respiratory infection in adults. Individuals at the highest risk of severe RSV disease include adults aged 60 years and older, the immunocompromised, and persons with underlying heart or lung conditions. There is currently no vaccine or treatment available, and a vaccine is needed to prevent this annual epidemic.

RSV: overview of the disease

RSV is a common seasonal virus that affects the lungs and airways of 64 million children and adults every year. There are two strains: Group A and Group B. In temperate locations of the Northern and Southern Hemispheres, RSV tends to peak in winter months (although limited data exist in the Southern Hemisphere). In the tropical zone, RSV peak timing was more diverse than in temperate regions (Pangesti, et al., 2018; Sullender, 2000).[78]

RSV disease can be contracted by anyone (Bont, 2009).[79] It is spread from person to person through large-particle respiratory droplet transmission or direct contact (i.e. handshake). RSV can also be transmitted by indirect contact.

[76] Broberg, E.K., Waris, M., Johansen, K., Snacken, R., Penttinen, P., European Influenza Surveillance Network, 2018. Seasonality and Geographical Spread of Respiratory Syncytial Virus Epidemics in 15 European Countries, 2010 to 2016. Euro Surveillance 23(5): 17-00284. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2018.23.5.17-00284

[77] https://www.cdc.gov/rsv/high-risk/infants-young-children.html

[78] Pangesti, K.N.A., Abd El Ghany, M., Walsh, M.G., Kesson, A.M., Hill-Cawthorne, G.A., 2018. Molecular Epidemiology of Respiratory Syncytial Virus. Rev Med Virol. Mar;28(2); Sullender, W.M., 2000. Respiratory Syncytial Virus Genetic and Antigenic Diversity. Clin Microbiol Rev. Jan;13(1):1-15.

[79] Bont, L., 2009. Paediatr Respir Rev. 10 Suppl 1, 16–7.

RSV is generally a mild and self-limiting infection, with symptoms similar to a common cold. However, RSV can cause lower respiratory illness in infants and elderly and cases of severe disease or death in at-risk patient groups:

- premature babies, children < 2 years of age with congenital heart or chronic lung disease, and children with compromised immune systems are at greatest risk of severe disease (Borchers et al., 2013);[80]
- in older adults, particularly among nursing home residents, severe pneumonia can result from RSV infection (Bawage et al., 2013);[81]
- patients with compromised immunity or underlying heart or respiratory conditions.[82]
- adults at the highest risk for severe RSV infection include older adults, especially adults who are ≥ 60 years old or those with underlying conditions such as immunosuppression, and chronic heart or lung disease (e.g., asthma, chronic obstructive pulmonary disease [COPD]). In these populations, RSV can lead to more serious conditions such as pneumonia, increase of severity of symptoms for people with asthma and COPD and congestive heart failure.

RSV prevention tools

Despite being recognized as a human pathogen for 59 year, there is no vaccine or effective antiviral treatment currently available. A monoclonal antibody, RSV F mAb palivizumab, is recommended for only a subset of high-risk infants.

Unmet need in Europe

The full burden of diseases caused by RSV has historically been unclear for two reasons:

- the disease caused by RSV is clinically indistinguishable from disease caused by influenza virus (Falsey, et al., 1995; Falsey, et al, 2005);[83]
- insensitive testing methods, and no urgent need to develop such methods in the absence of treatment or vaccine.

In the Northern Hemisphere, RSV affects nearly 100% of infants by the of age 2 years (Borchers et al., 2013).[84] The health burden in the senior population is underestimated due to

[80] Borchers, A.T., et al. Clin Rev Allergy Immunol. 2013;45:331–79.
[81] Bawage, S.S., et al. Adv Virol 2013;2013:595768.
[82] Available at: http://www.cdc.gov/rsv/
[83] Falsey, A.R., Cunningham, C.K., Barker, W.H., Kouides, R.W., Yuen, J.B., Menegus, M., Weiner, L.B., Bonville, C.A., Betts, R.F., 1995. Respiratory Syncytial Virus and Influenza A Infections in the Hospitalized Elderly. J Infect Dis. Aug;172(2):389-94; Falsey, A.R., Hennessey, P.A., Formica, M.A., Cox, C., Walsh, E.E., 2005. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med. Apr 28;352(17):1749-59.
[84] Borchers, A.T., et al. Clin Rev Allergy Immunol. 2013;45:331–79.

under diagnoses but considered to be a hidden worldwide epidemic. In the USA it was estimated that RSV infections result in approximately 177,000 hospitalizations and 14,000 deaths per year (Falsey, et al. 2005).[85] Hospitalization costs in the US alone exceed USD 3.5 billion.[86] RSV-attributable disease is high in UK adults, particularly in older adults, with an average of 487,247 GP episodes, 17,799 hospitalizations, 8,482 deaths attributable to RSV respiratory disease per season in the UK in adults aged 18 years and older (Fleming et al., 2015).[87]

Indication and target population

The applicants aim to develop an RSV vaccine offering protection against clinically significant RSV disease in adults aged 60 years and older, including those with underlying heart or lung conditions. The target population is adults aged 60 years and older.

RSV senior preventive vaccine production capacity

The applicants are developing, qualifying and scaling up the manufacturing process of RSV vaccine to be able to produce the adequate number of doses at launch. The plant in Leiden has been built (inaugurated in 2018) for this purpose.

Potential future competitors of the applicants

RSV vaccine development for older adults has been marked by the recent failure of two vaccine candidates that are based on a non-stabilized RSV F protein. Our vaccine components also rely on the RSV F immunogen but differ from failed candidates because our antigen design has introduced [redacted]. The most potent neutralizing antibodies (NAbs) elicited during natural RSV infection target the F protein in its [redacted].

Other RSV vaccines currently in development are:

- **GSK** has initiated a phase I/IIa study in healthy adults and older adults with a recombinant preF protein alone and in combination with their $AS01_B$ or $AS01_E$ adjuvant.
- **Pfizer** has initiated a phase I/IIa study in healthy adults and older adults with a recombinant preF protein alone or with an undisclosed adjuvant.

[redacted]

[85] Falsey, A.R., Hennessey, P.A., Formica, M.A., Cox, C., Walsh, E.E., 2005. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med. Apr 28;352(17):1749-59.

[86] Amand, C., Tong, S., Kieffer, A., Kyaw, M.H., 2018. Healthcare Resource Use and Economic Burden Attributable to Respiratory Syncytial Virus in the United States: A Claims Database Analysis. BMC Health Services Research BMC Series – Open, Inclusive and Trusted 18:294.

[87] Fleming, D., et al. BMC Infect Dis 2015;15:443.

RSV cases per year that could be avoided

The goal of the vaccine is to prevent the clinically significant RSV disease in adults aged 60 years and older. If broadly used in this population, it could prevent a substantial part of GP visits, hospitalizations and deaths attributable to RSV in senior.

3.4.2 Unemployment

As mentioned above, the applicants will have to put in stand-by its production of vaccines in the "non-use" scenario for seven years. Thus, the assumption of temporary (frictional) unemployment is justifiable.

In the non-use scenario [redacted] **(public rage: 10-100)** people (mainly located close to the applicants' plant in Leiden) would lose their job as a result of the refused authorization. This is the case because this entire staff will be redundant given the downsizing of the operations that will take place. For this assessment we focus on the employment in 2021, which is the first year of the time period that has been considered for this SEA. Although The Netherlands has a low long-term unemployment with respect to other EEA countries (4.1%),[88] it is clear that the impact on the unemployment from a refused authorization, especially at the local level (Leiden local area), would be important. Unfortunately, in the short-run, frictional unemployment is always present in job markets.

As workers at the applicants' plant are usually high skilled, they would compete in the labour market with low levels of unemployment. Hence, the duration of unemployment is expected to be shorter than the average duration. We will take into account this fact, by assuming that high-skill workers will need 50% less time to find a job with respect to the average duration of the unemployment, which is calculated in detail below and will be applied for the assessment of the unemployment impact on low-skill workers instead.

For the assessment, we consider the average pre-tax (gross amount, including the employer's social contributions) worker compensation for the applicants' employees.[89] We proceed as suggested by both the ECHA document on the evaluation of the unemployment (SEAC/32/2016/04)[90] and the paper of Dubourg (2016)[91] endorsed by ECHA. Therefore:

- We know from the applicants that each high-skill worker working in the plant is paid approximately [redacted] EURO gross per year fully loaded (including the employer's social contributions), whereas each low-skill worker is paid

[88] http://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Unemployment_rates,_seasonally_adjusted,_February_2018_(%25)_F2.png

[89] Pre-tax worker compensation is equivalent to the social value of labour output and takes into consideration the income taxes paid by workers as well as the employers social insurance contribution.

[90] ECHA (2016). The Social Cost of Unemployment. Available at: https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25

[91] Richard Dubourg, 2016. Valuing the Social Costs of Job Losses in Applications for Authorization. The Economics Interface Limited.

approximately [redacted] EURO gross per year fully loaded (including the employer's social contributions). We take these annual pre-displacement gross wages into account;

- [redacted] people are expected to lose their job in 2021 (start of the production);
- Using Table A7 (column G, considering that we take into consideration the gross wage *including the employer's social contributions*) in Dubourg's paper, the total social costs of unemployment in The Netherlands is equal to 1.99 (value adjusted by Dubourg for considering The Netherlands) times the annual gross salary.[92] This is a reasonable rule of thumb derived in Dubourg's paper, which is endorsed by ECHA in its document SEAC/32/2016/04;
- Table 5 present the statistics from Eurostat (data for 2018Q1) on the average duration of the unemployment for both men and women with the age of 25-64 years in The Netherlands. The age group of 25-64 years has been considered the most representative because the broad majority of the applicants' workers enter with higher education being high-skill workers who completed high school or a bachelor (university) degree.[93]

Table 5. Duration of unemployment

Duration Grouping	Thousand units	Proportion (A)	Assumed duration (B)	Weighted average (A*B)
Less than 1 month	13.2	0.048263254	0.5	0.024131627
From 1 to 2 months	52.0	0.190127971	1.5	0.285191957
From 3 to 5 months	38.8	0.141864712	4.5	0.638391204
From 6 to 11 months	43.4	0.158683729	8.5	1.348811697
From 12 to 17 months	27.7	0.101279707	14.5	1.468555752
From 18 to 23 months	11.4	0.041681901	20.5	0.854478971
From 24 to 47 months	46.0	0.168190128	35.5	5.970749544
48 months or over	41.0	0.149908592	48	7.195612416
Total	273.5	1		**17.785923168 months**

As already explained above, we consider only 50% of the average duration calculated above (8.892961584 months) for high-skill workers, whereas we use the whole value for the average duration of temporary unemployment for low-skill workers.

As of year-end 2018, the applicants' plant has already [redacted] people in total: [redacted]. As all of the [redacted] employees of the plant carry on technical functions, we consider them as high-skill workers. [redacted]

[92] This value is greater than 1 because it takes into account the following components: lost wage, costs of job searching, recruitment costs, scarring costs (i.e. the impact of unemployment status on future wages and employment possibilities), and leisure time (which is a benefit and therefore subtracted from the previous components).

[93] Data extracted from http://appsso.eurostat.ec.europa.eu/nui/show.do?wai=true&dataset=lfsq_ugad

[redacted] are low-skill workers. We assume that this proportion will hold also in the future, when the plant's employment will expand. This means that we assume that in the year [redacted] will be low-skill workers, who will be directly or indirectly be involved in the applicants' production plant. We round this value [redacted]. Therefore this implies that the remaining [redacted] workers will be considered as high-skill workers.

Hence, the social costs of employment due to a refused authorization are given by:

[redacted] EURO x [redacted] people x 1.99 x 8.892961584/12 months = [redacted] **EURO (rounded)**

[redacted] EURO x [redacted] people x 1.99 x 17.785923168/12 months = [redacted] **EURO (rounded)**

Therefore the total monetization for the unemployment of the [redacted] **(public range: 10-100)** people described above is equal to [redacted] **(public range: 1-10 million) EURO (rounded)**.

In addition to this monetized impact, we also want to highlight the potential broader organization impact of refusing the authorization for which the applicants are applying. The applicants rely on the AdVac® technology with several products in the pipeline based on the production process that will be used in the applicants' plant. Specifically Janssen Vaccines & Prevention B.V. is directly built on AdVac®; whereas Janssen Biologics B.V. is built on monoclonal antibodies, nonetheless part of this second applicant's organization will rely on the work coming from the vaccine franchise.

Some of these products are already in the late-stage clinical development with the existing process, and the applicants expect these products to come to the market in the timeframe [redacted]. The long-range financial plan for the applicants' business strongly depends on the revenue from these products. Not receiving the authorization would pose large risks, including the survival of the applicants' business, which could impact about [redacted] employees in R&D, production, commercial, and other functions.

Of course, the employment dynamics for these additional [redacted] workers is difficult to forecast. However, we would like to state that among these [redacted] people around 95% are high-skilled, with a wage [redacted] EURO gross per year fully loaded (including employer's social contribution) used for the monetization above for high-skill workers who completed only high school or at most a bachelor's degree. This is so because these [redacted] high-skill workers are university-educated having acquired master degree or even PhD (35% of JVP employees hold a Ph.D.). For these [redacted] people the applicants pay, on average, [redacted] EURO gross per year fully loaded (including employer's social contribution).

It is not an impossible scenario in which all of these [redacted] people are dependent on the success of the applicants' products. The applicants' top two products in terms of commercial potential and three top products in terms of soonest launch to the market depend on the process as currently designed, and if they had to be cancelled or take multi-year delay, then there is a real possibility that R&D for vaccines within J&J organization will be cancelled. The applicants have been spending around [redacted] EURO per year as an organization, without obtaining anything in terms of revenue. All depends on the fact that in the [redacted] the applicants' research efforts will succeed into commercially successful

products. Without the process involving OPnEO, the project for the launch of an HIV preventive vaccine as well as the other concerned vaccines could cease to exist (including [redacted] invested in R&D to date). The probability for having such a negative wider scenario for the applicants' organizations depends most on whether the applicants could redesign the process without OPnEO within a short timeframe and with a minimal impact on the product (details on the substitution plan requiring 15 years are provided in the AoA). It might be possible that the applicants could continue with only a few years of delay, but that is difficult to estimate before the creation of the data on the replacement project and the comparability of material produced with such a replacement of OPnEO. However, the replacement, as shown in the AoA, has a non-negligible probability to require a very long timeframe (which could be well beyond the 15-year review/substitution period the applicants request with this application for authorization) because of the real possibility to repeat clinical trials [redacted]

Given the availability of all necessary data, we provide here the monetization of the negative social impact from the unemployment of these additional [redacted] people:

[redacted] EURO x [redacted] people x 1.99 x 8.892961584/12 months = [redacted] **EURO (rounded)**

[redacted] EURO x [redacted] people x 1.99 x 17.785923168/12 months = [redacted] **EURO (rounded)**

Therefore, the total monetization for the unemployment of these [redacted] people described above is equal to [redacted] **EURO (rounded)**. We remain, however, agnostic on which weight to put on this monetized estimation. We have provided these additional monetization values only for the sake of completeness of the analysis, but we will not add them up with the other monetized impacts to be taken forward.

For the production process in the plant, the applicants rely on a complex supply chain of custom designed and produced disposable products as well as custom media and buffers. Approximately, [redacted]% of the production cost is raw materials; therefore, the applicants estimate that potential impacts to the incoming chain are on the same order of magnitude as the employees working at the applicants' plant ([redacted] people), at least as a general-equilibrium feedback effect in the long run. The applicants are not in a position to monetize these additional employment impacts on upstream suppliers. Therefore, the applicants limit themselves to this qualitative description, avoiding any speculative monetization, given the uncertainty faced in providing a reliable estimation on these additional negative social impacts.

3.5. Wider economic impacts

During the seven years of delay, due to the refusal of the authorization, there could be some companies outside the EEA that could gain market share. This would worsen the competitiveness of the applicants, which are both based in the EEA. And, in turn, a negative macroeconomic effect of a refused authorization would be associated with a worsening of the

European trade balance due to potential increased imports (as long as there will be companies able to supply the concerned vaccines).

Although there could be some additional negative macroeconomic impacts, due to the refusal of authorization, associated with broader benefits of having vaccines in the market (as already discussed in Section 3.4.1), these impacts are likely to be limited.

However, all of these impacts are just the tip of the iceberg of the negative wider economic impacts.

Europe is a key player in the worldwide production of vaccines. Indeed, 86% of all produced vaccines in the EU by Vaccine Europe members are exported outside the EU, with more than half (54%) of export going to humanitarian groups. The focus is on the populations in third-world and developing countries, which could have the concrete possibility to use the vaccines to be produced by the applicants. The reference for these countries is mainly for HIV, Ebola, and Zika virus. As it has been already shown with the above case study (Section 3.4.1) on the HIV preventive vaccine to be produced and marketed in the EEA, it is likely that a quantification of the costs of refusing an authorization for non-EEA countries would be immensely greater than that for the EEA.

It is worthwhile to add that a world free of, for example, Ebola and Zika virus is also very favorable for the EEA, because none can exclude a future pandemic in the EEA of these two diseases.

4. COMBINED ASSESSMENT OF IMPACTS

4.1. Comparison of impacts and distributional impacts

When analysing all the impacts in the "non-use" scenario, the monetization of the environmental risks (associated with the use of OPnEO) represents a benefit to the society, but this is zero, because of zero emissions, whereas the economic, wider economic, and social impacts are the expected costs of a refused authorization. The following table aims to summarize all the monetized impacts derived in the previous sections.

Table 6. Overview of the monetized impacts

Type of impacts expected in the "non-use" scenario	**Stakeholder/region impacted**	**Over 15 years** **Values in EURO**
Benefits for the avoidance of the environmental risk that might be linked to the use of OPnEO during the production of vaccines at the applicants' plant	Environment, mainly that around the area where the plant is located	0.00
[redacted] **(10-100)** people working in the applicants' plant would lose the possibility to have a job (frictional unemployment)	Workers in The Netherlands (most of them likely to live not far from Leiden)	-[redacted] **(1-10 million)**
Social costs related to the reduction of medical treatments (*specifically HIV preventive vaccine, used as a case study*)	EEA population	*At least* -[redacted] **(10-50 million)**
Loss of EBIT from the production of vaccines in the EEA due to the delay of introducing the commercial products into the vaccine markets	Society (EEA): city of Leiden (The Netherlands) and the local economy in which the plant is located	-[redacted] **(1-10 billion)**
Net costs of a refused authorization	**The EEA society**	***At least*** -[redacted] **(1-10 billion)**

Note: the symbol "+" is used for benefits in the "non-use" scenario and the symbol "-" for the costs.

In addition to the above impacts, we have qualitatively highlighted the following negative impacts for the EEA society due to a refused authorization:

- Loss of business opportunities for satellite activities (and employment) generated by the applicants' production;
- An additional loss in EBIT from the likely worsening of he competitive position of the applicants in the market of vaccines in the EEA, due to the delay of several years in introducing the vaccines into the market;
- The applicants will face a waste of the investments already done, because these investments will become useless, being not able to be retrofitted or sold in the market;
- There could be the possibility that the adoption of an alternative will require the revalidation of the production process and re-approval of market authorizations by regional and national medicine agencies. The license updates cost at least [redacted] for monoclonal antibodies (in the event the implementation of the OPnEO replacer is done after licensing). Taking the assumption that vaccines require the same amount one should multiply this value with the current product

portfolio (at least those products that have started phase II clinical trials). Although the applicants know the minimum costs for these license updates, they prefer not to take into consideration them in a quantitative way, because of the uncertainty related to whether they will be faced or not (viz., these updates costs are not expected if the implementation of the OPnEO replacer is done before a previous filling);

- Satellite activities would also lose the possibility to obtain gain from the economy created by the applicants. Some vaccine productions at the applicants' plant will be collaboration efforts with other partners. Yet, companies within the EEA supply a large part of disposables;
- We have also highlighted in Section 3.4.2 the potential broader organization impact of refusing the authorization. Not receiving the authorization would pose large risks, including the survival of the applicants' business, which could impact about [redacted] employees in R&D, production, commercial, and other functions. As the employment dynamics for these additional [redacted] workers is very difficult to forecast, we remain agnostic on the likelihood of this impact and the real people out of those [redacted] will be affected at the end from a refused authorization. We limit here to report that in case all [redacted] workers will become redundant, the monetized economic cost for the EEA society has been estimated to be more than [redacted] EURO. Given the uncertainty, we have preferred not to add this monetized impact to the other impacts as reported in Table 6. Yet, the applicants rely on a complex supply chain of custom designed and produced disposable products as well as custom media and buffers. Approximately, [redacted]% of the production cost is raw materials; therefore, the applicants estimate that potential long-run impacts to the incoming chain are on the same order of magnitude as the employees working at the applicants' plant;
- The applicants will also produce other vaccines. Some of them are also important for the EEA society, for example: RSV vaccine, HPV vaccine, and Universal flu (UNIFLU) vaccine. The benefits deriving from these vaccines will greatly magnify the positive social impacts accounted in Section 3.4.1.

4.2. Uncertainty analysis

With zero emissions, there is no risk to be considered for costs of granting the authorization.

For what concerns the estimated costs of not having available in [redacted] the preventive HIV vaccine (Section 3.4.1), one could use for the periods after 30 years a lower discount rate. As suggested by the ECHA guidance on the SEA (2011, p. 170), "*If the impacts are likely to occur over a long period of time, it is recommended to include in the sensitivity analysis a discount rate scheme that allows for a falling rate after 30 years.*"[94] Hence, one

[94] ECHA (2011): Guidance on the preparation of socio-economic analysis as part of an application for authorisation, Reference: ECHA-11-G-02-EN, available at: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

could use for sensitivity the use of a declining discount rate (smaller than 4% for period over 30 years). This will magnify the negative impacts of a refused authorization, which have been already assessed.

Anyway, because there is zero cost for the EEA society from granting the authorization, any more restrictive assumptions that could be alternatively adopted (e.g., on the social costs of unemployment, loss of value added, produced doses of the HIV preventive vaccine) will not change in any way the main result: the benefits of granting the authorization are and remain larger than costs, which are actually zero.

We conclude this section by providing some statements on the cost-effectiveness ratio. This is relevant because OPnEO is an ED substance as required by SEAC (SEAC/37/2017/03). However, in this application for authorization there will be no release of OPnEO to the environment. This implies that the cost-effectiveness ratio (based on releases quantity of OPnEO) of refusing the authorization is, mathematically speaking, (+) infinity, because we are going to divide the sum of all benefits of allowing to use OPnEO by zero. Namely, it is not possible to identify any "switching value" for any potential variations in input variables. We leave the reader to decide whether and how it is necessary to vary input variables used in this SEA. However, as already said, any variation is not going to change – in any manner – the key finding of this SEA: the costs of not granting the authorization (in absolute value) will be always much greater than benefits (which are actually zero).

As an alternative way of presenting this situation with zero release, we are going to provide here an alternative cost-effectiveness ratio, not formally required by SEAC for applications for authorization, but that we think of it as a useful tool in showing the huge costs of not granting the authorization to the applicants. Namely, instead of considering the releases (which are zero), we consider the quantity requested of OPnEO over 15 years (the effective quantity will be lower than that for many years; 270 kg/year is the peak demand). This is equal to 15 years times 270 kg/year = 4,050 kg. Therefore, one can conclude that not granting the authorization is equivalent to destroy *at least* a potential monetized benefit for the EEA of more than [redacted] **(public range: 0.2-2 million)** EURO/kg ([redacted] EURO divided by 4,050 kg) of OPnEO *requested* (viz., not released) by the applicants (we said "at least" because this is in addition to the many qualitative costs we highlighted in this SEA coming from not granting the authorization). At the same time there is no cost for the environment because of the zero-emission production process. In addition, the applicants would like to highlight that 4,050 kg over 15 years is a truly worse-case scenario; in reality it will take many years before 270 kg of OPnEO usage is reached.

5. CONCLUSIONS

The applicants are applying for an authorization to use OPnEO in the production process of different types of vaccines because there are no technically suitable substitutes so far. This SEA, as a part of the authorization application, has analysed all the main impacts expected in the "non-use" scenario.

There will be no benefit for the EEA society (over 15 years) in case of a refused authorization. Conversely, the total costs for the European society would be *at least* [redacted] **(public range: 1-10 billion EURO)** over 15 years.

Given the above considerations, we believe that the applicants should be granted the authorization in accordance with the article 60(4) of REACH. Based on the above arguments and in line with the conclusions reported in the AoA, the applicants request an authorization for 15 years, starting from 2021 because, as this application for authorization has shown, all criteria laid out by ECHA (2013)[95] and ECHA (2017)[96] are fulfilled.

ANNEX I – JUSTIFICATIONS FOR CONFIDENTIALITY CLAIMS

Blanked out item	***Page number***	***Justification for confidentiality***
Year of initial commercialization of a vaccine	*7, 10*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details on a supplier	*13*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Values of total impacts	*8,24,56*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Other information to avoid reverse calculations	*42, 43, 45*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Launch dates of vaccines + other information to avoid reverse calculations	*8, 12, 31, 33, 35, 37, 38, 39, 40, 41, 42, 43, 44, 48, 51, 55*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Main competitors and related information	*11, 43*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Concentration of OPnEO in the bioreactor	*14*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Market shares	*16*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Number of workers	*16*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Figure 2	*16*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Vaccines in the portfolio	*16, 23*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*

[95] ECHA (2013), Setting the Review Period when RAC and SEAC Give Opinions on an Application for Authorisation. Available at: https://echa.europa.eu/documents/10162/13580/seac_rac_review_period_authorisation_en.pdf

[96] ECHA (2017), REACH Authorisation - Criteria for Longer Review Periods (CA/101/2017). Available at: https://echa.europa.eu/documents/10162/13580/ca_101_2017_criteria_longer_review_period_afa_en.pdf/4cda0778-02c3-c949-f1c2-6deb1622a754

Amounts of investments	*17, 21, 52*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details of the production process	*17, 52*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Cost of a license	*19, 23, 54*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details of contracts with consultants	*21*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Value of sales and EBIT	*22*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Satellite activities	*23*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Number of doses produced	*42, 43*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Exported quantity of vaccines	*42*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Duration of a vaccine	*38, 44*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Information on a vaccine boost	*38, 44, 45*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Assumption on the annual coverage to avoid reverse calculations	*30, 31, 32, 33, 45*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Paid salaries	*49, 50, 51, 52*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Number of employees	*49, 50, 51, 54, 55*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details on proteins	*48*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details on the PIN platform	*6, 10*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Details on the business	*51, 54, 55, 56*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Efficacy of a vaccine	*32, 33*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*

Information on a clinical trial	*11, 13*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Components of a vaccine	*11, 12, 13, 14, 32*	*The information is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*