ANALYSIS OF ALTERNATIVES

Public Version

Legal name of applicant(s):	*Swords Laboratories, (Trading as Bristol-Myers Squibb Cruiserath Biologics) (BMS)*
Submitted by:	*Swords Laboratories, (Trading as Bristol-Myers Squibb Cruiserath Biologics) (BMS)*
Substance:	*4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO)*
Use title:	*Industrial use of the substance as a surfactant in the purification of the biopharmaceutical drug Orencia, used for the treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis and Adult Psoriatic Arthritis.*
Use number:	*1*

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LIST OF ABBREVIATIONS

4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated
4-tert-OP	4-(1,1,3,3-tetramethylbutyl)phenol
AoA	Analysis of Alternatives
BDS	Biological Drug Substance
BMS	Bristol-Myers Squibb
CHO	Chinese Hamster Ovary
CRO	Contract Research Organisation
CSR	Chemical Safety Report
DNA	Deoxyribonucleic Acid
ECHA	European Chemicals Agency
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GPS	Global Product Development and Supply
HMW	High Molecular Weight
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
L	Litres
mL	Mililitre
nm	Nanometre
pI	Isoelectric Point
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals
RNA	Ribonucleic Acid
R&D	Research and Development
S/D	Solvent/Detergent
SVHC	Substance of Very High Concern
µg/mL	microgram per millilitre

VI	Viral Inactivation
w/w	Percentage Weight of a Substance of the Total Weight at a Specified Temperature
WFI	Water For Injection
f [redacted]	f [redacted]

DECLARATION

We, Swords Laboratories (trading as Bristol-Myers Squibb Cruiserath Biologics) (BMS) request that the information blanked out in the "public version" of the Analysis of Alternatives is not disclosed. We hereby declare that, to the best of our knowledge as of today, **17th 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:

Noel Heaney

Date, Place:

17-MAY-2019
CRUISERATH.

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1. SUMMARY

1.1. The Applicant

Swords Laboratories, Trading as Bristol-Myers Squibb Cruiserath Biologics (BMS), is part of a global pharmaceutical company headquartered in the USA. BMS has several primary manufacturing and Research & Development (R&D) facilities located throughout the world. The company has invested significantly in facilities in the EU including a new state of the art manufacturing facility in Cruiserath, Dublin, Ireland. The Cruiserath site hosts a Multi-Product Cell Culture (MPCC) biologics manufacturing facility within the BMS network. The new facility will produce multiple therapies for the company's growing biologics portfolio. The MPCC holds [redacted] 15,000 L cell culture bioreactors. The facility will initially manufacture a single product at a time and eventually move to several product campaigns per year. The Cruiserath site, hereafter 'the Applicant' is using the substance 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, hereafter '4-tert-OPnEO', in the purification process of a Biological Drug Substances (BDS).

1.2. The Applicant's Products

The site commenced its operations with the manufacture of the first BDS, nivolumab in 2018. Nivolumab is a monoclonal antibody used to treat a wide range of different cancers. This process does not require the use of 4-tert-OPnEO in the purification step. In 2020, BMS will transfer the second BDS product to Cruiserath for commercial manufacture. The second product, Orencia which is the brand name for the BDS abatacept. Abatacept is a fusion protein that is used to treat patients with Rheumatoid Arthritis with specific indicators as well as Juvenile Idiopathic and Adult Psoriatic Arthritis. The BDS represents the most common type of biologic therapeutic agents that have been developed in recent years to target specific autoimmune diseases, cancer and infectious agents. Biologics are complex, sensitive molecules and changes to the manufacturing process may have significant impacts on the quality and safety of the final drug products.

1.3. Viral inactivation in Biopharmaceutical Processes

As biopharmaceuticals are produced using biological cell lines and complex raw materials, they are inherently susceptible to adventitious infection from viruses. As such, stringent guidelines are in place to ensure that pharmaceutical products from biological sources do not pose a threat to patient safety. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have established guidelines for viral safety of biotechnology products. Chemical inactivation of enveloped viruses using detergents at optimal conditions of pH, temperature and time is a common approach and a critical step in downstream purification processes for many biologics, particularly those that are derived from mammalian cell lines. Incubation with a suitable detergent causes the viral cells to lyse and release their genetic material thereby prohibiting further replication. Detergents offer a good alternative to other viral inactivation technologies where the protein molecules are pH or heat sensitive. 4-tert-OPnEO is widely used in the viral inactivation step of protein purification as it is an efficient and long-established viral inactivation agent and its detergent properties do not impact protein quality.. Within the EU the EMA regulates the safety of biologic drugs under the Pharmacovigilance Directive 2001/83/EC and Regulation 726/2004 sets out the necessary procedures for receiving marketing authorisations for medical products, including biologics. Within the regulatory framework manufacturers of biologic therapeutics must demonstrate efficient viral inactivation and removal from the drug products before clinical trials can be initiated.

1.4. Identification of Possible Alternatives

4-tert-OPnEO has been used for many years by BMS in its US facilities as an effective viral inactivation agent that does not impact protein quality in the abatacept manufacturing processes. There are few validated methods for viral inactivation in use in the production of biopharmaceutical products. During the development of abatacept, the Applicant carried out studies on alternative viral inactivation techniques. These studies demonstrated that the molecule was very sensitive to process changes associated with alternative techniques, such as low pH or heat treatment impacting product quality namely causing protein aggregation. Aggregation is a potential source of impurities in the final BDS and must be demonstrated to be within regulatory ranges before product release therefor these methods were not considered as possible alternative to 4-tert OPnEO. The Applicant focused efforts on finding a potential alternative detergent (surfactant) that could provide comparative viral inactivation and maintain the quality of the abatacept molecule. Through literature review of supplier information, academic literature and patent databases, eleven potential alternative surfactants were identified for initial screening.

1.5. Substitution effort

The Applicant has contracted a third party specialist laboratory to carry out laboratory studies on potential alternatives in viral inactivation process. Detergents with low or no hazardous properties were selected over those with hazardous properties. A final short list of ten detergents was developed as the starting point for initial screening studies. Each detergent was trialled against a model virus in an Applicant designed laboratory study to assess effectiveness of the alternative detergents in viral load reduction. Of the initial list of eleven, nine progressed to the initial screening phase. Seven potential alternatives demonstrated viral inactivation capability with some demonstrating comparative viral inactivation with 4-tert-OPnEO. Potential alternatives that are listed under approved patent applications for viral inactivation were not shortlisted for further assessment due to potential constraints on their future use. The top three performing potential alternatives will advance to further viral inactivation studies including expansion of the viral test panel and demonstration of process stream clearance for the detergent. The current estimated timeframe for the completion of the supporting studies is two years. If the Applicant is successful in finding an alternative with comparable viral inactivation capabilities that does not impact product quality, the full substitution program will commence. The entire substitution program encompassing supplier and material validation, process re-design, clinical trials, plant validation, and regulatory approvals is estimated to take twelve years after the Sunset Date.

The Applicant is therefore seeking an Authorisation with a 12-year review period to allow for the identification and complete substitution of 4-tert-OPnEO from the viral inactivation step of the abatacept BDS manufacturing process.

2. ANALYSIS OF SUBSTANCE FUNCTION

2.1 Substance Identification

The substance within the scope of this AoA is identified as the Annex XIV entry number 42 [1] for 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated covering well-defined substances and UVCB substances, polymers and homologues (4-tert-OPnEO). The entry does not include an EC or CAS registry number. The descriptor available is the IUPAC name mentioned above and the molecular formula $(C_2H_4O)nC14H_{22}O$.

In the Annex XV dossier identifying the substance as a Substance of Very High Concern (SVHC) [2], the substance is identified in by the structural formula shown in Figure 1 below.

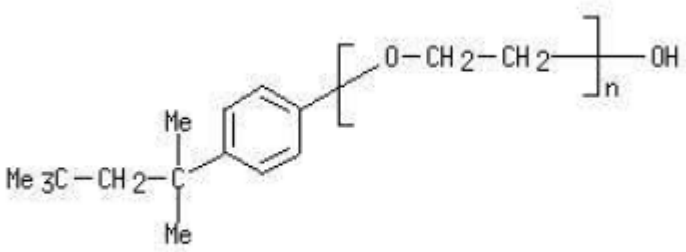

Figure 1. Annex XV dossier structural formula for 4-tert-OPnEO

2.1.1 Annex XIV Substance Details

4-tert-OPnEO covering well-defined substances and UVCB substances, polymers and homologues were identified substances meeting the criteria of Article 57(f) of Regulation (EC) 1907/2006 [3] due to their endocrine disruption properties for which there is scientific evidence of probable serious effects on the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of article 57 of REACH.

Table 1. Annex XIV substance details

Entry Nr.	Name	Intrinsic properties referred to in Article 57	Latest Application Date	Sunset Date
42.	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated [covering well-defined substances and UVCB substances, polymers and homologues] EC No: - CAS No: -	Endocrine disrupting properties (Article 57(f) - environment)	4th July 2019	4th Jan 2021

2.2 Scope of the Analysis of Alternatives

2.2.1 The Applicant

Swords Laboratories, Trading as Bristol-Myers Squibb Cruiserath Biologics (BMS) is part of a global pharmaceutical company headquartered in the USA. It has several primary manufacturing and Research & Development (R&D) facilities located throughout the world. The company has invested significantly in facilities in the EU including a new state of the art manufacturing facility in Cruiserath, Dublin Ireland. The Cruiserath facility is a Multi-Product Cell Culture (MPCC) biologics manufacturing facility within the BMS network. The new facility will produce multiple therapies for the company's growing biologics portfolio. The MPCC holds [redacted] 15,000 L cell culture bioreactors. The facility will initially manufacture a single product at a time and eventually move to several product campaigns per year. The Cruiserath site, hereafter 'the Applicant' is using 4-tert-OPnEO in the purification process of a Biological Drug Substances (BDS).

2.2.2 Description of the drug substance produced using 4-tert-OPnEO by the Applicant

The Applicant has recently completed construction of a multimillion Euro, state of the art Bio-pharmaceutical processing plant located at Cruiserath, Dublin, Ireland. The facility is dedicated to the production of biologic drugs to treat Arthritis and life limiting illnesses such as cancer. In 2018, the site commenced its first commercial production of the biologic drug OPDIVO which is the brand name for the BDS, nivolumab. The drug is used to treat several types of cancer such as melanoma and advanced non-small cell lung cancer.

A second process is currently in technology transfer (commenced in 2018) for the manufacture of abatacept BDS, the process is already established at another BMS site that is located outside of the EU.

Nivolumab and abatacept are biological products. Biological products differ from traditional small molecule drugs in that they are large, complex molecules manufactured using a biological process, employing mammalian cells that extracellularly express the product of interest. Nivolumab does not require the use of 4-tert-OPnEO in the purification process.

2.2.3 Description of the substance function within Applicant's use

Viral Safety in Biotechnological processes

A biopharmaceutical is a pharmaceutical drug product manufactured in, extracted from or semi-synthesised from biological sources. Products include vaccines, blood, blood components, gene therapies, tissues, monoclonal antibodies and recombinant therapeutic proteins.

Owing to the origin of the molecules, regulatory requirements exist to ensure that adventitious contamination of the biologic components is risk assessed and well controlled for each production process. One such control requirement is viral inactivation to remove any potential risk of viral contamination of the product as detailed in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, guide Q5A (ICHQ5A)[4].

As biopharmaceuticals are produced using cell lines and complex raw materials, they are inherently susceptible to adventitious infection from bacteria and viruses. As such, stringent guidelines are in place to ensure that pharmaceutical products from biological sources do not pose a threat to patient

safety. Both the U.S. Food and Drug Administration (FDA) [5] and the European Medicines Agency (EMA)[6] have established guidelines for viral safety of biotechnology products with some harmonisation achieved through the ICH. Recent reports of contamination of bulk harvests, adventitious virus contamination of manufacturing environments and even a marketed vaccine product have demonstrated the vulnerability of all pharmaceutical/biopharmaceutical operations [7]. Fortunately, to date, biopharmaceuticals produced in recombinant cell lines have had an excellent safety record; there has been no reports of iatrogenic illness due to the transmission of a pathogenic virus through administration of these products.

Viral safety measures must consider that virus particles may be either enveloped with a lipid bi-layer or non-enveloped, Figure 2[8]. The lipid bi-layer of the enveloped virus particle renders these viruses more difficult to disrupt that non-enveloped type. Mechanisms that are efficient viral inactivators for non-enveloped virus have no impact on enveloped virus particles. Therefore, more than one method of clearance is required to ensure complete viral safety of biological products.

Technical function of 4-tert-OPnEO

Chemical inactivation using 4-tert-OPnEO of enveloped viruses using detergents is a common approach and a critical step in downstream purification processes for many biologics, particularly those that are derived from mammalian cell lines. 4-tert-OPnEO is a non-ionic surfactant; non-ionic surfactants have uncharged and hydrophilic headgroups attached to their hydrophobic tails. They are considered mild surfactants as they break protein-lipid, lipid-lipid associations, but not protein-protein interactions, and most of them do not denature proteins. This is an important point when selecting a detergent for viral inactivation in biopharmaceutical process; it must be an effective agent that does not have an adverse impact on the target protein integrity (i.e. does not denature the target protein). 4-tert-OPnEO surfactants are considered to be efficacious viral inactivation agents and are widely used as such in the biopharmaceutical processing [9]. Non-ionic detergents and mild surfactants are capable of breaking protein-lipid and lipid-lipid links, but do not interrupt protein-protein interactions. Such non-ionic detergents act by inserting their hydrophobic tails into the hydrophobic region of the lipid bilayer that surrounds the virus. This disrupts the viral envelop, causing release of the viral genetic information, and therefore, inactivation of the virus. The use of non-ionic detergents precludes charge-based interactions with the target protein and prevents denaturing of the target therapeutic protein.

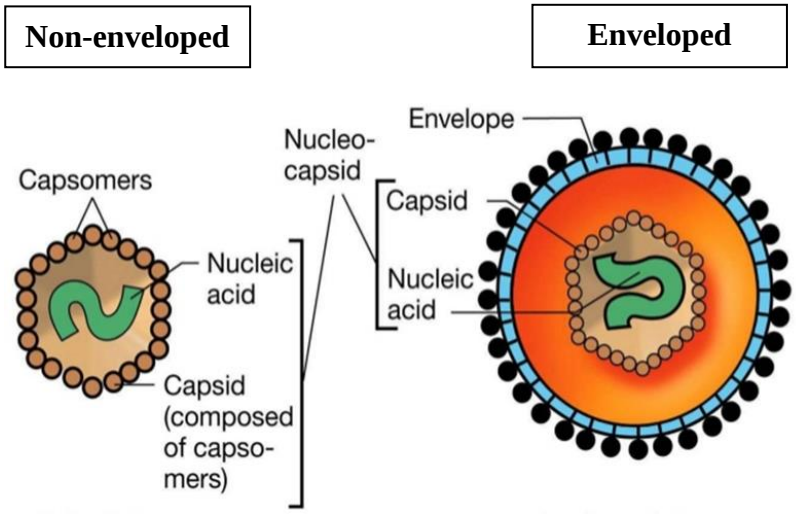

Figure 2. Enveloped and non-enveloped virus particle

2.2.4 Applicant's viral safety strategy

All quantitative viral assays are limited in their ability to detect low levels of virus; therefore, no single approach is able to ensure safety. Confidence in the process to clear virus cannot typically be determined by directly testing the product itself, but from demonstrating the capability of the purification process to both inactivate and remove virus. Generally, the three major approaches to ensure viral safety of a biopharmaceutical product are (i) selecting and testing cell lines and raw materials for the absence of viral contaminants products [10],[4], (ii) assessing the capability of the purification process to clear any infectious virus, (iii) testing the product at appropriate steps to confirm the absence of contaminating viruses.

The ICHQ5A guidelines supply definitions for viral clearance, viral removal, and viral inactivation. These are listed below:

> *Viral Clearance*: Elimination of target virus by removal of viral particles or inactivation of viral infectivity.
>
> *Viral Removal*: Physical separation of virus particles from the intended product
>
> *Viral Inactivation*: Reduction of virus infectivity caused by chemical or physical modification

The Applicant uses a number of different mechanisms to satisfy the regulatory expectation for viral safety of its biologics. Within the EU, the EMA mandates that viral clearance studies are performed by the manufacturer before drugs are launched for clinical trials. The guidance sets out the quantification of Log Reduction Value (LRV) where LRV = $-log_{10}$ [virus product]/[virus lead/feed]. To claim viral clearance within a process, the manufacturer must demonstrate an LRV≥ 1. For all of the products manufactured by the Applicant at least a viral clearance safety factor per dose for patient safety is demonstrated. This is achieved currently for abatacept through a combination of viral inactivation completed with detergent (4-tert-OPnEO), virus removal by chromatography steps and viral clearance by nanofiltration. It is important to note however that no single approach is sufficient, and it is only through a combination of risk assessment, controls and viral clearance steps that an acceptable level of assurance can be reached.

During the process design for the manufacture of abatacept, the Applicant considered its existing processes (in US) and relevant virus clearance data. Therefore, the Applicant subsequently developed and designed its viral safety strategy based on Regulatory guidelines, ICH Q5A[4], experience with other processes, available literature, and industry practices.

The Applicant evaluated the downstream process for viral load reduction by spiking model viruses to show viral clearance, removal or inactivation of several logs of viral infectivity across the various downstream steps. Such studies provide assurance that viral contaminants introduced by starting materials or materials employed during manufacturing are not transferred and are appropriately removed during the manufacturing process.

The Applicant will use 4-tert OPnEO in the viral inactivation step to produce abatacept starting in 2020.Therefore, the Applicant is seeking an Authorisation for:

Industrial use of the substance as a surfactant in the purification of the biopharmaceutical drug Orencia, used for the treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis and Adult Psoriatic Arthritis.

Considerations for substitution of 4-tert OPnEO in viral inactivation step

Proteins by their nature are susceptible to variations within the processing parameters and operational conditions. Proteins are also susceptible to raw material variability within the process such as the use of surfactants and solvents. Viral inactivation is therefore specifically designed and maintained at optimal operating conditions in order to safeguard the integrity of the protein.
A viral inactivation step must be specifically designed to provide a final BDS that meets the regulatory expectation for viral removal while ensuring the quality of the final product is maintained.

Criteria for substitution of 4-tert-OPnEO

Any potential alternative (substance or technique) must meet the following criteria:

- Meet the regulatory expectation for viral inactivation within the Applicant's process including orthogonal approach to inactivation [4].
- Maintain the quality of the purified protein, in particular minimise the level of aggregation and maintain these levels within the EMA regulatory specification limits. Protein aggregates are any physically associated or chemical linked non-native species of two or more monomer protein molecules[11].Therapeutic proteins can aggregate during manufacturing, shipping and storage. Aggregation levels are a concern for BDS molecules as they can have an adverse immune response in patients that may affect safety and efficacy of the drug [12], [13].
- Have reduced adverse impact on human health and the environment as compared to 4-tert-OPnEO.
- Must be commercially available, with no Intellectual Property (IP) constraints and must be economically feasible.

2.3 Description of the Manufacturing Process for Abatacept

The manufacturing process of biopharmaceutical products is typically divided between upstream and downstream steps. The process is presented schematically in Figure 3 below and is briefly described. A more detailed description is provided in the Chemical Safety Report (CSR) (as part of this application). The use of 4-tert-OPnEO is limited to the viral inactivation step which is part of the downstream process.

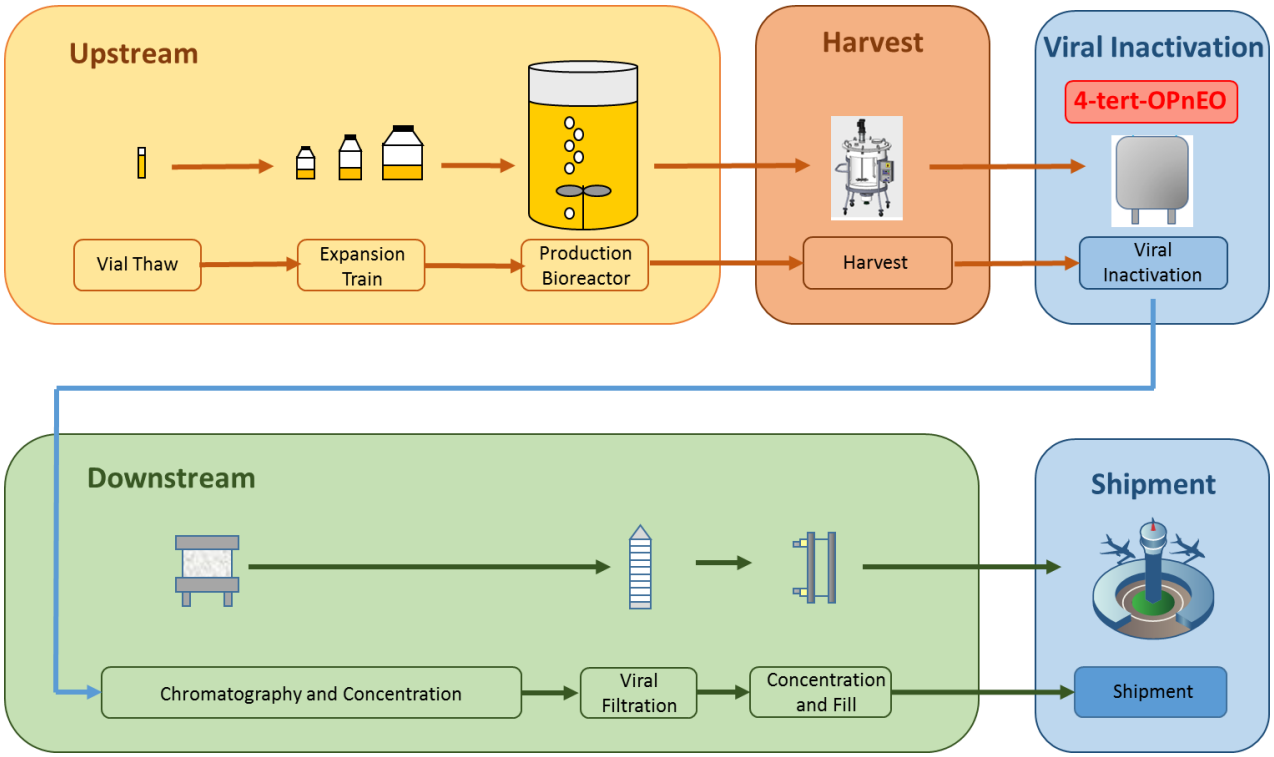

Figure 3. Abatacept purification process flow

(source the Applicant)

2.3.1 Upstream Process

The abatacept protein is a genetically engineered fusion protein, which is produced by Chinese Hamster Ovary (CHO) cell lines. The upstream process is initiated with thawing of a working cell bank vial. The culture is propagated in a series of shake flasks, cell bag bioreactors and seed bioreactors. The final stage inoculum culture is transferred to the production bioreactor where the cells extracellularly express the protein. The production bioreactor is harvested based on cell culture duration via centrifugation, and filtration.

2.3.2 Downstream Process

The downstream process involves the viral inactivation step, where the abatacept protein is incubated with the 4-tert-OPnEO solution for a defined time period to allow for complete viral inactivation. The protein is purified through a series of chromatography steps and the detergent is removed and purified harvest is filtered to its final state.

2.3.2.1 Viral Inactivation- critical process parameters

Following preparation and storage, the initial concentration of 4-tert-OPnEO solution is transferred to the harvest suite and placed on load cells. Outlet tubing from the bag system is welded onto the harvest vessel via an aseptic tubing pigtail for buffer/solution additions. The 4-tert-OPnEO solution is added to the harvest vessel using a peristaltic pump by monitoring the weight of the tote on load cells. The final 4-tert-OPnEO concentration in the harvest vessel is achieved by diluting the initial solution with Water For Injection (WFI). The process parameters for the viral inactivation step for abatacept are listed in Table 2.

Table 2. Viral inactivation process parameters

Process variable	**Setpoint/target**	**Acceptable range**
b % 4-tert-OPnEO quantity (w/w of pH adjusted harvest)	**b** %	**b** %
Incubation Temperature	N/A	°C
Incubation Time	N/A	**b**

2.3.2.2 Additional purification and viral clearance steps

The viral inactivated pool is subsequently purified using a chromatography step, see Figure 4. The affinity column is equilibrated prior to loading the viral inactivated pool. During the loading, the viral inactivated pool is filtered in a stainless-steel filter housing. The column undergoes a series of washing steps following loading and prior to elution. The abatacept molecule is subsequently eluted from the column. Two subsequent polishing chromatography steps are performed, both of which are considered virus removal steps in the abatacept process. The product is then buffer exchanged by diafiltration prior to viral filtration.

Viral Filtration

Viral filtration is carried out using nanofiltration. Any disposable single-use components will be treated as hazardous waste at the Cruiserath facility. The reader is referred to section 9 of the Chemical Safety Report (CSR) for more information on waste management.

Figure 4. Abatacept purification affinity chromatography step

The schematic displays the chromatography purification steps and is credited to the Applicant

3. ANNUAL TONNAGE

The annual consumption of 4-tert-OPnEO in the purification process for abatacept at the Cruiserath facility is presented in Table 3, use quantities are estimated to be in the range of d (1-3 tonnes/yr.) tonnes per year from validation in 2020 to commercial production 2021 to 2032.

Table 3. Estimated tonnage of 4-tert OPnEO in use by the Applicant to end of requested review period

Year	Tonnes/yr.
2020 (Validation)	**d (1-3)**
2021-2032 (Commercial Production per year)	**(1-3)**

4. IDENTIFICATION OF POSSIBLE ALTERNATIVES

In order to assess potential alternatives to 4-tert-OPnEO in the abatacept manufacturing process, the Applicant must consider the duplicate requirements of efficient viral inactivation and maintaining the integrity and quality of the BDS. Further the Applicant must consider the sustainability of supply of any potential alternative in accordance with regulatory requirements for biopharmaceutical production.

4.1 List of Possible Alternatives

In the biopharmaceutical sector, there are few validated viral inactivation methods in use. Several techniques that are used widely in other manufacturing processes are not appropriate for use with the Applicant's BDS given the complex structures and sensitive nature of the protein molecules. For the purpose of this AoA, the Applicant has completed an assessment of all known techniques that were considered within the review of potential alternatives under the following categories:

1. known alternative techniques to chemical viral inactivation
2. novel or new alternative detergents to 4-tert-OPnEO viral inactivation

4.1.1 Description of known viral inactivation techniques

Viral inactivation of BDS proteins is a delicate balance between fulfilling the regulatory requirements for removing any potential contaminating virus and maintaining the integrity and quality of the purified proteins.. Traditional methods in use within the biopharmaceutical sector include solvent/detergent, detergent only and low pH. Other less commonly used methods include heat treatment and UV irradiation. The Applicant's wider organisation has many years' experience in the use of viral inactivation techniques relevant to biopharmaceutical BDS manufacturing processes. Table 4 below provides a summary of known techniques, their mode of action and potential for use by the Applicant in the abatacept process. Suitability for use takes account of the fact that the BDS is a complex protein that can be easily disrupted by mechanical, physical and chemical agents.

Table 4. Summary of possible alternatives to 4-tert-OPnEO viral inactivation

Technique or method category	Mode of action	Applicant experience/assessment
Acidic pH inactivation	Many viruses are denatured rapidly when exposed to low pH conditions.	Low pH inactivation is in use in other Applicant BDS processes and trials have been completed with abatacept
Heat treatment/ Pasteurisation	Pasteurisation or high heat processing method used to sterilise aqueous solutions by thermally destabilising the intermolecular interactions between virus capsid proteins and/or the integrity of the lipid bilayer of enveloped viruses, thereby resulting in a loss of virion capsid structural integrity and virus infectivity.	High heat inactivation is not in use in other Applicant BDS processes, trials have been completed with abatacept
Radiation treatment/ UV Inactivation	UV inactivation of viruses results from the formation of dimers in RNA and DNA. Once the DNA or RNA is dimerised, the virus particles cannot replicate their genetic material which prevent them from spreading.	UV inactivation is not in use in other Applicant BDS processes, trials have been completed with abatacept
Chemical treatment Solvent/Detergent	S/D treatment inactivates enveloped viruses by disrupting the lipid membranes of enveloped viruses while leaving proteins intact. The solvent creates an environment in which the aggregation reaction between the lipid envelope and the detergent occurs more efficiently. Once the lipid interactions are interrupted the detergent will cause the virus cell to lyse and lose infectivity.	Solvent/Detergent treatment is in use in other Applicant BDS processes, trails with S/D are not currently planned as it is anticipated that the environment would cause disruption to the BDS molecule
Chemical treatment Detergent only	Effective viral inactivation can be achieved solely with detergents such as 4-tert-OPnEO. Lipid interactions are interrupted when exposed to detergents and the virus can no longer survive without its intact lipid coat.	Detergent only methods using 4-tert-OPnEO in use in abatacept and other Applicant BDS processes, alternative detergents under trial with abatacept
Mechanical Filtration/nanofiltration	Nanofiltration is a technique that is designed to remove viruses specifically by size exclusion and is suitable for both enveloped and non-enveloped viruses.	Filtration and nanofiltration are already in use in the Applicant's process but is not a standalone method to demonstrate safety.

4.2 Description of the efforts made to identify possible alternatives

4.2.1 Research and Development- Past studies

The Applicant has many years of experience in the development of viral inactivation strategies for its biological processes. Each strategy requires specific experience, evaluation and confirmatory studies to understand the range of acceptable results and to develop the critical process parameters that can impact the results of virus inactivation as well as the quality of the protein molecule. Within some of the BDS processes the Applicant uses combinations of viral inactivation techniques to best suit the

process and the specific BDS molecule. As part of the development of abatacept, the Applicant carried out initial laboratory studies using alternative techniques to detergent treatment to verify the best strategy for both the production process and the molecule. Non-chemical viral inactivation alternatives (low pH, thermal, and UV irradiation) were evaluated for the abatacept BDS. These studies, described in the subsequent sections, concluded that these methods are not feasible substitutes for viral inactivation in the purification process for abatacept due to the impact on the biochemical and biophysical properties of the molecule.

Low pH treatment and assessment studies

When exposed to an acidic pH, many viruses will become denatured rapidly. Acidic pH inactivation of virus is an efficient and validated technique that is currently in use by the Applicant for some of its existing commercial drug substances. Viral inactivation using low pH conditions was evaluated during the process characterisation for the abatacept manufacturing process. The Applicant conducted a laboratory study that utilised a product pool maintained at a low pH compared to a neutral pH adjusted product pool as a control. Both product pools were held at ambient conditions for a defined time period. The observed product pools shown in Figure 5.A (low pH) and Figure 5.B (neutral pH) show that the level of aggregates significantly increased for the low pH product pool versus the neutral pH adjusted pool. The protein aggregation is expected due to crossing the pI (Isoelectric Point) of the molecule, therefore low pH viral inactivation is not a viable alternative to the use of 4-tert-OPnEO by the Applicant in abatacept due to the increased formation of aggregates. Protein aggregates are known to cause immune responses in animal studies and clinical work, therefore a majority of biological drug substances/products measure aggregation prior to releasing the molecule for human use [14].

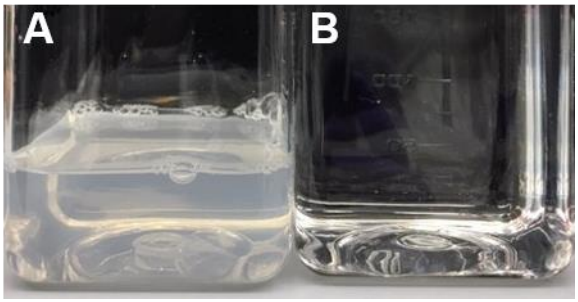

Figure 5. Low pH study with abatacept

Conclusion on suitability of low pH treatment

Low pH conditions are not compatible with the Applicant's drug molecule. Acidic pH treatment for the viral inactivation steps of the abatacept manufacturing process is not considered further as an alternative to the use of 4-tert OPnEO in viral inactivation of its BDS molecules.

Heat and Ultraviolet treatment and assessment studies

- Heat: Pasteurisation, typically used in the food manufacturing sector to kill viruses, bacteria and other infectious agents, also has some limited applications within the biopharmaceutical sector for viral inactivation. Such viral inactivation processes were originally developed for the production of human albumin and can be an effective method if the target proteins being purified are more thermally resistant than the viruses being inactivated [15]. Pasteurisation thermally destabilises the intermolecular interactions between virus capsid proteins and/or the

integrity of the lipid bilayer of enveloped viruses, thereby resulting in a loss of virion capsid structural integrity and virus infectivity.

- Ultraviolet light irradiation: The UV inactivation of viruses results from the creation of nucleic acid dimers in DNA and RNA. Studies have shown that short wave UVC light was found to be the most effective. In particular, wavelengths between 200 and 280 nm are germicidal and affect the double-bond stability of adjacent carbon atoms in molecules including pyrimidines, purines and flavin. Thus, UV inactivation of viruses results from the formation of dimers in RNA (uracil and cytosine) and DNA (thymine and cytosine). Once the DNA or RNA is dimerised, the virus particles cannot replicate their genetic material which prevent them from replicating [16].

During the abatacept molecule development, methods of protein degradation were intentionally applied to the molecule in a forced degradation study to understand the impact of different types of typical degradation pathways including UV irradiation and temperature. The abatacept BDS was subjected to an elevated temperature for extended periods of time. The BDS was then evaluated using assays for structural and/or functional alterations. After exposing the abatacept BDS under these conditions, there was an 80-fold increase in aggregate content which is significantly above the product specification limit. In a separate study abatacept BDS was exposed to e UV radiation at ambient conditions for 1 hour, resulting in a 25-fold increase in aggregate content. If the drug substance has an aggregate content higher than product specification upper limit the product cannot be released for use. Exposure to thermal and UV environments not only caused increased protein aggregation, but also impacted bioactivity of the molecule, thus negatively impacting the overall quality of the product.

Conclusion on suitability of heat and UV treatment

Studies have demonstrated that the abatacept molecule is sensitive to UV exposure. The temperature ranges for thermal inactivation of potential viruses are also outside of the range required for the production process that safeguards protein integrity. Heat treatment and UV irradiation are not considered further as potential alternatives to the use of 4-tert OPnEO in viral inactivation of the Applicant's BDS molecules.

Filtration and Nanofiltration

While references are made in the literature to filtration as a viral inactivation/removal method, it is widely used as part of the orthogonal strategy rather than a standalone method of virus removal. The Applicant is currently using a filtration step as part of the abatacept virus removal process but in accordance with the requirements it is a complimentary method.

Overall Conclusion on Alternative techniques

The Applicant reviewed the known alternative techniques to 4-tert-OPnEO use in viral inactivation as listed in Table 4. Past R&D studies carried out during the development of the abatacept process concluded that low pH, UV and high temperature treatment are not suitable potential alternatives for viral inactivation of the abatacept molecule. Furthermore, filtration methods are considered complementary rather than a replacement for a chemical viral inactivation step. The use of solvent/detergent is considered to be limited due to the anticipated impact on the protein. Consequently, the Applicant has focused its efforts on the assessment of alternative detergents that could provide comparative viral inactivation to 4-tert-OPnEO. This was deemed to represent the greatest potential for success whilst being the least disruptive with respect to variations within the operational parameters of the current purification process.

4.2.2 Research and Development – On-going studies

The Applicant has developed a comprehensive R&D plan for the identification and evaluation of potential alternative detergents to the use of 4-tert-OPnEO in viral inactivation. A dedicated team of researchers was established to carry out the R&D program. The R&D activity is included within a larger substitution and phase-out plan for 4-tert-OPnEO from its viral inactivation process. The full plan is presented below, and the individual steps are described in further detail in so far as they are relevant to this AoA.

1. **Potential alternatives, identification evaluation and selection**

    a. development and refinement of a list of potential alternatives
    b. initial technical feasibility studies
    c. full scale technical feasibility studies

2. **Potential alternative supply sustainability assessment**

3. **Scale up and technology transfer including clinical trials**

4. **Process validation**

5. **Regulatory filing and approval, post clinical trials**

1. Potential alternatives evaluation and selection

a. development and refinement of list of potential alternatives

The Applicant's R&D scientists with experience in BDS production processes completed an initial literature review for potential alternative detergents. The review was focused on detergents referenced in the literature as being efficient viral inactivation agents or used in membrane protein purification or in fermentation processes in addition to those with low or no environmental toxicity. The review resulted in the identification of potential alternatives from across academic literature, in supplier product information and in patent applications focusing specifically on the development of new methods for viral inactivation using alternatives to 4-tert-OPnEO [17], [18].

4-tert OPnEO is a non-ionic surfactant therefore choosing non-ionic surfactants in the first instance was deemed an appropriate method for initial identification. Surfactant type was considered a primary criterion in developing the initial list.

- Non-ionic surfactants (detergents) have uncharged and hydrophilic headgroups. They are considered 'mild' surfactants as they break protein-lipid and lipid-lipid associations, but do not impact protein-protein interactions. Most non-ionic detergents do not denature proteins. The literature reports that non-ionic glycoside surfactants as being used in membrane protein studies, with reference to their optimal choice in membrane protein research as they are non-denaturing to the proteins being isolated [19]. Furthermore, these glycosides are not classified as hazardous for the environment or for human health. Other non-ionic surfactants identified included mixtures, polymeric glucosides and polysorbates.

- Zwitterionic surfactants contain hydrophilic headgroups. Their positive and negative charges are in equal numbers, resulting in zero net charge. They are often considered 'harsher' surfactants than the non-ionic. The list contains two zwitterionic surfactants, reported in the literature as being non-denaturing and used in protein studies to solubilise proteins. One of the Zwitterionic detergents is reported in the literature as a potential viral inactivation agent.

- Anionic surfactants were not considered as part of the this AoA as it was anticipated that these would be too harsh and incompatible with the Applicant's BDS.

Table 5 provides the initial list of eleven identified potential alternatives surfactant type developed by the Applicant.

Table 5. Initial list of potential alternatives to 4-tert-OPnEO

Potential alternative name (trade name)	**CAS number**	**Surfactant type**
Octyl-β-D-Glucopyranoside ([redacted])	29863-26-8	Non-ionic
n-Decyl-β-D-Maltopyranoside ([redacted])	82494-09-5	Non-ionic
n-Dodecyl-β-D-Maltopyranoside ([redacted])	69227-93-6	Non-ionic
Lauryldimethylamin-oxide ([redacted])	1643-20-5	Zwitterionic
n-Dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate ([redacted])	14933-08-5	Zwitterionic
Polyalkylene glycol ([redacted])	9003-11-6	Non-ionic
n-Decyl β-D-glucopyranoside ([redacted])	68515-73-1/110615-47-9	Non-ionic
n-Decyl β-D-glucopyranoside ([redacted])	68515-73-1	Non-ionic
2-((1-((2-ethylhexyl)poly-oxy)poly-propan-2-yl)oxy)ethanol ([redacted])	164366-70-7	Non-ionic
Polysorbate 80 ([redacted])	9005-65-6	Non-ionic
Polyglycol ([redacted])	903-11-6	Non-ionic

b. Initial feasibility: Assessment of viral inactivation capability of shortlisted alternatives.

The second step of the alternative selection and evaluation phase was the completion of initial laboratory feasibility studies to ascertain the capacity of the identified potential alternatives to inactivate viruses in a laboratory setting. The Applicant engaged a specialist Contract Research Organisation (CRO) in 2018 to carry out viral inactivation assessment studies on the shortlisted alternatives at dedicated facilities. A viral inactivation study was performed using each of the potential alternatives to assess the substitution potential of the identified alternative surfactants against one model virus [redacted]. Any alternative that was deemed to meet an equivalent level of viral load reduction to the existing process using 4-tert-OPnEO would potentially progress to the next stage of feasibility assessment.

Study design:

The Applicant designed and conducted a study to assess the effectiveness of each of the shortlisted alternatives. Of the eleven listed in Table 5 above, one potential alternative was not progressed to the lab testing as the supplier could not provide sufficient sample for test and it was therefore excluded from further assessment. An additional alternative was added to the study panel later and as such results were pending at the time of this AfA submission.

Harvested cell culture was incubated with spiked [redacted] virus. Each of the shortlisted alternatives was evaluated at two concentrations of the detergent Critical Micelle Concentration (CMC) and

maintained at [redacted] (temp range 1-20°C). Samples were taken at specified time intervals and tested for viral load.

Conclusion on viral inactivation of shortlisted surfactants

The initial viral inactivation studies were not carried out on the abatacept molecule but using a standard reference cell culture mAb derived harvest material to determine viral inactivation capabilities in the first instance. Viral inactivation effectiveness was reported as Log Reduction Value (LRV); an achieved LRV [redacted] was considered acceptable by the Applicant to demonstrate initial viral inactivation capacity of the potential alternative.

Initial viral inactivation studies demonstrated effective viral inactivation with the spiked virus for some of the identified potential alternatives. The results, presented in Table 6 , allowed the Applicant to refine the selection for potential large-scale technical feasibility within the abatacept process. A pass indicates an acceptable LRV in at least the one concentration of surfactant. Following analysis, one potential alternative, [redacted] was eliminated from the potential alternatives list as the manufacturer informed the Applicant that it would not be commercially available. One potential alternative [redacted] was under test at the time of submission.

Table 6. Results on initial viral inactivation studies with potential alternatives

Potential alternative name (trade name)	CAS number	Viral inactivation study Pass = Applicant accepted value Fail = Not accepted
[redacted]		

Hazard and availability screening

Before full scale assessment trials for potential substitution commenced, the Applicant verified that the potential alternatives were capable of meeting the Applicant's requirement for low or no environmental impact and that the potential alternatives are considered available for future assessment and use, those under IP constraints from approved patent applications were not

progressed. Table 7 below summarises the results of the screening steps of the identified potential alternatives.

Table 7. Summary of initial feasibility and hazard screening of potential alternatives

Potential alternative name (trade name)	CAS number	Viral inactivation study result (Pass of Fail)	Environmental hazard classification
g			

Conclusions on alternative identification, screening and initial technical feasibility

From the initial list of eleven potential alternatives, ten progressed to initial feasibility assessment at the CRO. One potential alternative was not available in sufficient quantity for test and was therefore eliminated on the basis that the Applicant could not be assured of future supply. From the initial CRO studies, two potential alternatives failed to demonstrate adequate viral inactivation capacity and are therefore excluded from further consideration. Of the remaining seven potential alternatives that demonstrated acceptable viral inactivation capacity, the Applicant has selected the three top-ranked potential alternatives based on performance and availability of future supply. Potential alternatives with IP constraints from approved patent applications were not progressed. One potential alternative g will be considered further pending the results of the on-going initial feasibility studies. Table 8 below summarises the four shortlisted candidates and ranks them according to performance in initial feasibility studies.

Table 8. List of alternatives proposed for further assessment after initial screening

Alternative ranking	Substance Name
g	

4.2.1.3 Substitution effort taken by the Applicant if an authorisation is granted

From the screening and initial feasibility viral inactivation assessment, the top-ranked candidates from Table 8 have been chosen for further assessment to establish which if any can act as a suitable alternative to 4-tert-OPnEO. The process is discussed further in section 5 of this AoA. The alternative selection was based on performance, environmental risks and availability of the alternatives including any approved patent or IP rights. The following is a summary of the stages of the substitution program following alternative identification that will be executed by the Applicant and completed during the requested review period if an Authorisation is granted.

1c. Full scale technical feasibility

For each of the shortlisted potential alternatives, further viral inactivation studies will be initiated with the CRO only where it has been concluded that there is no potential IP constraints owing to existing patent applications. These studies will be carried out with a wider virus panel to verify viral inactivation capability. Once initiated, studies are anticipated to take one year to complete. It is more efficient and cost effective for the Applicant to include all potential alternatives in a single study. In parallel the Applicant must assess the potential impact of each of the alternatives on the abatacept molecule to ensure product quality requirements can be maintained. Should the Applicant be successful in finding a suitable alternative after the second feasibility studies, the next phases of the substitution program will be initiated.

Substitution activities post research and development studies

A summary of the target timeline for implementation of a technically feasible alternative following completion of R&D activities is provided in Figure 6 and is described further below.

The target timeline is dependent on

(1) determining a viable alternative that may be selected from the shortlisted candidates outlined in Table 8 without impacting the product quality and efficacy

(2) production of the selected alternative is commercially sustainable routinely meeting Applicant material quality specifications as well as supply demands.

(3) regulatory approvals on any new or novel alternative to viral inactivation are granted

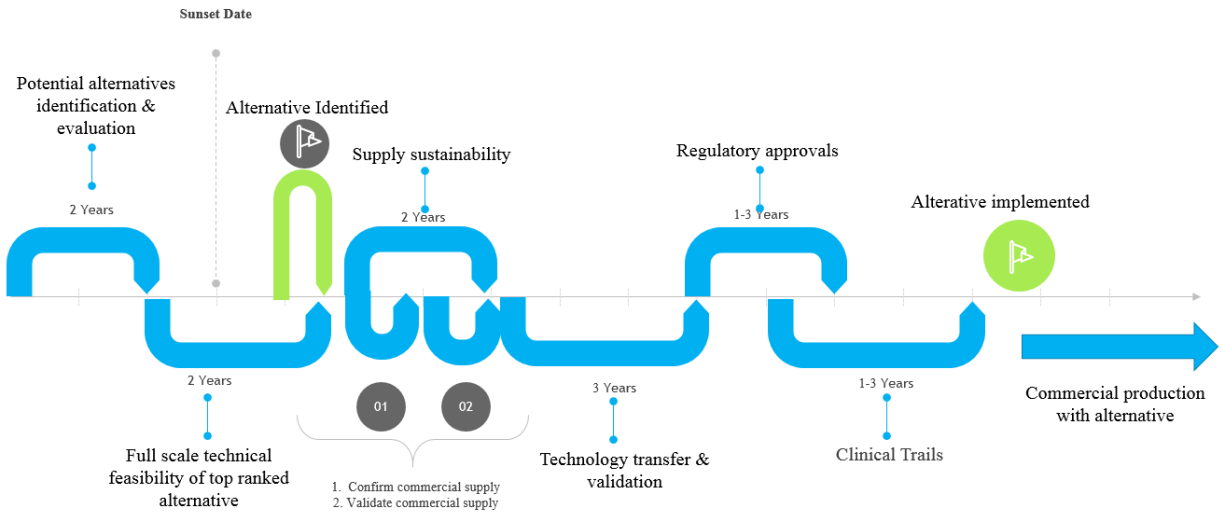

Figure 6. Estimated timeframe for substitution post identification of a tehncially feasbile alternative

Should these studies fail to find a suitable alternative, the Applicant must start the process again and look to other potential alternatives to commence viral inactivation studies. The Applicant will start with those that were identified in the original assessment and perform further literature review for any newly developed methodologies.

3. Potential alternative supply sustainability

Following identification and selection of a suitable alternative, the alternative substance and the supplier will be further evaluated to ensure an alternative surfactant has a sustainable commercial supply of pharmaceutical grade with consistent quality and stability as well as a supply chain that meets the requirements of the Applicant's quality systems. The assessment also includes the verification of appropriate and adequate REACH registration for the alternative by the chosen supplier or by the Applicant.

Supplier and potential alternative surfactant quality validation is estimated to take two years to complete, one year to confirm there is commercial supply and a second year to validate the commercial material.

Once the potential alternative supply is fully validated the process moves to the next phase.

4. Technology transfer & process validation at the Applicant's site

Following the successful completion of R&D studies, the substitute must be validated within the Applicant's own production process. A pilot study will be conducted primarily to demonstrate scalability of the new process and to provide flexibility for the study design. This activity estimated to take three years to complete, would be followed by technology transfer of the process into the commercial facility and scale-up to large-scale equipment.

The abatacept process is currently planned for commercial validation at the Cruiserath site in 2020, changes cannot be made to the production process during validation and startup of commercial production during this time. If a successful alternative is identified, a second validation campaign would have to be executed at commercial scale to validate the new process with the alternative detergent. Technology transfer and process validation is estimated to take three years once the alternative is identified and supply and quality confirmed.

5. Regulatory filing and approval

In accordance with the requirements of biopharmaceutical production, a prior approval supplement (PAS) or a Type II variation [20] for the abatacept product will be submitted to the appropriate markets to seek regulatory approval for the changes in the downstream process. The approval application must account for any change in the detergent used in addition to a confirmation of the capability of the alternative to act as a suitable viral inactivation agent, this would be confirmatory viral inactivation studies. As such, since the potential alternatives that have been shortlisted have not been filed by the Applicant previously there is a degree of uncertainty as to how regulatory bodies may react to any new or novel approaches to viral inactivation methods in a biologic medicinal product. Novel methods may result in longer processing times, additional requests for data by the regulatory bodies or potentially a rejection of the approval. The regulatory filings cannot start until after the process validation has commenced, according to the theoretical timeline this is estimated to take thirteen months. However, given the uncertainties this could extend to two years. Regulatory approval requires a significant investment by the Applicant to validate and verify the scalability of any substitution. In addition, the there is a potential that human clinical trials would be required to support the filing.

6. Clinical trials

Given the scale of the process change, if a 'new' or unvalidated detergent was used in the viral inactivation combined with the sensitivity and structural complexity of the abatacept molecule, it is likely that the agency (EMA or other regulatory agency) may request clinical data to support a filing submission for the new process with the alternative detergent. It is anticipated that clinical trials will take two to three years from patient enrollment to final readout, assuming that the material required for the clinical studies is already generated. Regulatory approval for process changes such as this will vary depending on the markets. For the major markets such as US and EU, approval may be given within a year, whereas for the rest of world markets it may take up to three years to file and receive marketing approvals.

Conclusions on the substitution effort

The successful substitution of 4-tert-OPnEO from the abatacept process is dependent on the completion of on-going R&D studies to verify that a technically feasible alternative can act comparatively to 4-tert-OPnEO in viral inactivation step without negatively impacting the Applicant's BDS quality. Further to verification of the technical feasibility of any alternative, the substitution will be constrained further by regulatory approvals, potential alternative supply sustainability and operational scale-up requirements for technology transfer and validation of the Applicant process at site. Finally, the change in the process will require marketing authorisation submission and approval and may also require the completion of repeat clinal trails.

The Applicant therefore requests a review period of 12 years for the identification, evaluation and validation of a suitable alternative to 4-tert-OPnEO in the viral inactivation step for the purification of abatacept BDS and for the submission and approval for marketing authorisations for Orencia.

4.2.3 Data searches

For the identification of potential alternatives, the Applicant carried out internet searches of following available information on substances/surfactants using the following keywords:

- Viral inactivation
- Environmentally friendly detergents
- Product quality
- Protein stability

The review resulted in the identification of potential alternatives that was developed into the shortlist from academic literature, in supplier product information, and in patent applications focusing specifically on the development of new methods for viral inactivation using alternatives to 4-tert-OPnEO [17], [18].

To refine the search for potential alternatives based on low or no impact to the environment, the Applicant reviewed hazard classifications of the potential alternatives under Annex VI of the CLP Regulation [21] and reviewed the US EPA safer choice database.

The US EPA Safer Choice database [22] provides a list for consumers and industrial users of chemicals to seek alternatives that are considered' safer' for the environment based on classification

The Annex XV dossier [2] for the identification of 4-tert-OPnEO as an SVHC was also consulted for information on potential alternatives.

ECHA public dissemination site of registered substances [24] was also consulted for any information on potential alternatives and uses in the EU.

CHemSec Marketplace [23] a tool developed by ChemSec to facilitate the interaction between chemical suppliers and users to enhance substitution was used to determine if commercial alternatives to 4-tert-OPnEO were available.

Potential alternatives physical chemical and hazardous properties were assessed using the following databases:

ECHA public dissemination site [24] including the C&L notification inventory and registration dossiers.

Annex VI to the CLP regulation [21]

ECHA PACT list [25] of substances potentially subject to Regulatory Risk Management Measures

SIN List by ChemSec [26]

PubChem [37]

Supplier website [27], [29]

5. SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

The Applicant has completed initial laboratory based studies on alternative viral inactivation techniques and has concluded that alternative surfactants to 4-tert-OPnEO in the viral inactivation step of the purification process of the abatacept BDS is the most appropriate potential means for successful substitution. Literature review of public, academic sources and patents identified eleven potential alternative non-ionic and zwitterionic detergents.

Initial feasibility studies on viral inactivation capacity, assessment of potential IP and review of hazardous properties resulted in the development of a shortlist consisting of four potential alternatives that have been progressed for further feasibility assessment in accordance with the Applicant's substitution program as outlined in section 4.2.2 of this AoA. This section provides details on each of the shortlisted potential alternatives and provides an assessment of their technical and economic feasibility and availability for substitution.

5.1 Alternative No. 1 g

5.1.1 Substance identification and properties

Alternative No. 1, g, is a non-ionic detergent. g g are used widely in membrane protein purification processes as surfactant properties are mild and do not denature the proteins being purified. Table 9 below provides details of the identification of Alternative No. 1.

Table 9. Alternative No. 1 Substance identification and properties

Substance name(s)	IUPAC name (s)	EC/CAS number
g		

Source [24],[37]

5.1.2 Technical feasibility of Alternative No. 1

According to the literature, studies on g g at preserving the protein's properties. In addition, g larger hydrophilic group confers higher solubility in water [27]. Alternative No. 1 was identified as a possible alternative to 4-tert-OPnEO as it is reported in the literature as being used in membrane protein purification processes [28]. The purification and study of membrane proteins is challenging as membrane proteins must be purified and extracted while retaining their native conformation.

Initial viral inactivation studies demonstrated that Alternative No. 1 provided an acceptable level of viral inactivation in the laboratory assessment. However, further assessment will be required to be completed to verify the viral inactivation effectiveness of Alternative No. 1. In addition, the Applicant must assess the impacts of the change in detergent on the stability and bioactivity of the abatacept

molecule. It is therefore not possible to conclude on technical feasibility of Alternative No. 1 at this point.

Conclusion and requirements to make Alternative No. 1 technically feasible
In order to confirm that Alternative No. 1 can act as a technically feasible alternative to 4-tert-OPnEO further viral inactivation studies at both laboratory and larger scale will be required to be conducted to verify initial results on reduction of viral load in test conditions. The Applicant will proceed with viral inactivation studies with an expanded model virus panel to verify the results on the initial assessment and to ensure wide viral inactivation capacity for a number of non-enveloped viruses. In parallel, the Applicant will conduct viral inactivation studies using the abatacept molecule to confirm that Alternative No. 1 does not have any impact on the bioactivity and quality of the protein molecule in accordance with regulatory requirements for the production of biopharmaceuticals. These studies are in the planning stage and will commence with the chosen third party laboratory before the Sunset Date.

5.1.3 Economic feasibility of Alternative No. 1

The estimated costs that would be incurred from the substitution of 4-tert-OPnEO to Alternative No. 1 provided, can be considered applicable to all of the shortlisted alternatives. The cost categories are described below.

1. Research and development: R&D represents a significant investment towards finding an alternative. Viral inactivation studies required for regulatory approvals are known to cost in the region of € [redacted] million for a single process. This is estimated based on previous experience of the Applicant from abatacept and other processes. The current viral inactivation laboratory studies being undertaken is estimated at € [redacted] million. This work will involve numerous viral inactivation studies that examine the impact of alternatives on the abatacept process, examined under a diverse range of conditions and using a variety of costly input material.

2. Plant adaptation: Once the alternative is proven, scale-up and process validation including facility fit modifications such as automation, electronic batch records and vessel hardware changes will be required to accommodate the alternative in the downstream process. Once the facility fit modifications have been completed, the process will be scaled-up into the large-scale. Given that the process wouldn't have been scaled up to manufacturing-scale previously, full scale development batches will be required for equipment and process trials at manufacturing scale. Process validation batches will then be executed to demonstrate the new process can be successively scaled-up and that the process can deliver consistent product quality at the manufacturing scale. It is estimated that plant adaption, scale-up and validation could cost upwards of € [redacted] million.

3. Clinical trials: A significant potential cost associated with substitution would be incurred if the Applicant is required to undertake any repeat clinical trials of the abatacept drug following substitution. Since clinical trials have already been conducted, the Applicant can estimate a potential € [redacted] million cost for repeat trials. This cost is uncertain as it is not known how the regulatory authorities would view a new or novel viral inactivation method for biological drug production in this complex process. The cost will only be incurred at the time a suitable alternative has been identified and proven in both the laboratory and manufacturing scale studies as well as following confirmation that an alternative is considered available and sustainable.

3. Regulatory filing. Regulatory submissions will be required for marketing approval for the use of an alternative in all the various markets that abatacept is currently licenced within. Submission costs alone are estimated at € [redacted] million for a single filing.

4. Raw Material: As part of the initial assessment study, the Applicant conducted a preliminary cost assessment of the short-listed alternatives against the cost of 4-tert-OPnEO. Some of the shortlisted alternative surfactants at laboratory scale (cost/L) were greater than for 4-tert-OPnEO. As part of the supply and sustainability assessment, the Applicant will conduct a full cost assessment of potential alternative surfactants. The Applicant however would not be able to accept a cost increase of for example 10-fold as it would not be acceptable to pass this cost onto patients. Costs associated with the REACH registration of any of the potential alternatives will also be included in the supply sustainability assessment. The Applicant has completed many REACH registrations to date therefore costs for this activity are well understood.

In summary, estimated costs for substitution of 4-tert-OPnEO from the abatacept process are significant. The capital investment in plant adaptation and validation will be completed only after a suitable and validated alternative has been chosen. Other potential costs associated with the future use of the alternatives could arise through IP constraints but any cost estimate at this stage would be speculative. Should any alternative raw material cost prove unsustainable, the Applicant will move to another shortlisted alternative.

Substitution of 4-tert-OPnEO is considered economically feasible for the Applicant over the course of the requested 12-year review period.

Table 10 below summarises the estimated costs for Alternative No. 1.

Table 10. Summary of estimated costs for substitution

Cost item	**Estimated cost (€)**
Research & Development	[redacted] million (1-2 million)
Plant adaptation & process validation studies	[redacted] million (20-80 million)
Clinical trials *	[redacted] million (2-6 million)
Regulatory filing	[redacted] million (0.5-5 million)
Total estimated	[redacted] million (23 – 95 million)

* Applicable if repeat trials are required

5.1.4 Reduction of overall risk due to transition to Alternative No. 1

Table 11 below provides a comparison of the hazard classification of Alternative No. 1 with 4-tert-OPnEO and its degradation compound 4-Octyl Phenol (4-tert-OP).

Alternative No. 1 does not hold a harmonised classification and labelling in Annex VI to CLP[21] nor has it been registered in the EU[24]. There are notified classifications on the C&L inventory[24] of not classified. The supplier Safety Data Sheet (SDS) was used as the basis for the comparative hazard assessment. The 4-tert-OPnEO hazard classification was also taken from the supplier SDS. 4-tert-OP does have a harmonised classification and labelling [21] and this was used as a basis for the comparative assessment.

Table 11. Comparative C&Ls of Alternative No. 1 with 4-tert-OPnEO and 4-tert-OP

Hazard Classification	Substance		
	g [redacted]	**4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO)**	**4-(1,1,3,3-tetramethylbutyl)phenol** EC 205-426-2 CAS 140-66-9
Endocrine disruption	Not Classified	Endocrine Disrupting properties-environment (degradation to 4-tert-OP)	Endocrine Disrupting properties-environment
Physicochemical	Not Classified	Not Classified	Not Classified
Human health	Not Classified	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute toxicity oral 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318)
Environmental	Not Classified	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)
Source	Supplier SDS [29]	Supplier SDS [29]	Annex VI to CLP [21] index number 604-075-00-6

Alternative No. 1 is not classified as hazardous[29]. It is not listed on ECHAs Candidate list [30], PACT list [25] of substances subject to regulatory risk management assessment or on ChemSec SIN list [26]. As a conclusion, a comparative assessment of the hazard profiles of 4-tert-OPnEO and 4-tert-OP to that of Alternative No. 1 demonstrates that the overall risks to human health and the environment after transition to the alternative would be reduced with the endocrine disruption risk being eliminated completely.

5.1.5 Availability of Alternative No 1.

The Applicant identified two potential suppliers of the substance for lab scale quantities during the initial feasibility assessment. However, as part of the substitution plan, the Applicant must conduct a full evaluation of any potential alternative to ensure sustainable commercial supply with consistent pharmaceutical quality and stability as well as a supply chain that meets the requirements of the Applicant's quality systems. The substance is not registered according to REACH within the EU, the Applicant will conduct an assessment of registration requirements and will plan for possible registration should Alternative No. 1 prove successful in scale up studies. Finally since the substitution of Alternative No. 1 would also require regulatory approval from EU authorities [6] the Applicant concludes that Alternative No. 1 cannot be considered available for substitution, currently.

In order for Alternative No.1 to become available, the Applicant must conduct supply sustainability assessment including REACH registration requirements. Should a commercially available source be identified that meets pharmaceutical grade requirements, the alternative will be selected for scale up. Should scale up studies conclude that the alternative can act comparably to 4-tert-OPnEO in viral inactivation process without impacting the abatacept BDS, regulatory approvals will be sought for the substitution in the abatacept process.

5.1.6 Conclusion on suitability and availability for Alternative No. 1

In order for the Applicant to confirm technical feasibility of Alternative No.1, further viral inactivation studies must be conducted both at laboratory and at manufacturing scale in order to ensure effective viral inactivation that meets the current regulatory requirements. The Applicant will also need to complete studies with the abatacept molecule to confirm that the molecule is not impacted by the change in surfactant. Therefore, is it not currently possible for the Applicant to conclude on technical feasibility until all studies have concluded.

While the Applicant has identified two potential suppliers at laboratory scale. a full quality and supply sustainability assessment will need to be completed on the material and on the supplier. This assessment will take place after technical feasibility has been confirmed and is estimated to take two years to complete. Finally, any change in the production materials or in the viral inactivation step will be subject to re-validation and re-approval by the regulatory bodies. Therefore, the Applicant concludes that the substance is not currently available for substitution. Substitution of 4-tert-OPnEO with Alternative No. 1 would result in a reduction in overall risk to the environment and to human health.

5.2 Alternative No. 2 [redacted]

[redacted] also known as [redacted] is an [redacted] zwitterionic detergent, with [redacted]. It is one of the most frequently-used detergent of this type [31]. Like other [redacted] detergents it is antimicrobial, being effective against common bacteria such as S.*aureus* and E.*coli* [32]. However, it is also non-denaturing and may be used to solubilise proteins. Table 12 provides details of substance identification.

5.2.1 Alternative No. 2 Substance identification and properties

Table 12. Alternative No. 2 Substance identification and properties

Substance name(s)	IUPAC name (s)	EC/CAS number
[redacted]		
Sources [29],[37]		

5.2.2 Technical Feasibility of Alternative No. 2

Alternative No. 2 is a zwitterionic detergent used to solubilise proteins and to study the conformation and molecular interactions of macromolecules. It has been reported in literature as being an effective viral inactivation agent for enveloped viruses [33].

Initial viral inactivation assessment carried out by the CRO for the Applicant, showed that Alternative No. 2 provided acceptable LRV in the model studies. However, technical feasibility of Alternative No. 2 cannot be concluded until further planned studies are conducted including expanded viral inactivation studies and assessment of the impact of Alternative No. 2 on the abatacept molecule.

Conclusion and requirements to make Alternative No. 2 technically feasible

In order to confirm that Alternative No. 2 can act as a technically feasible alternative to 4-tert-OPnEO further viral inactivation studies at both laboratory and manufacturing scale will be required to be conducted to verify initial results on reduction in viral load. The Applicant will proceed with viral inactivation studies with an expanded model virus panel to verify the results on the initial assessment and to ensure wide viral inactivation capacity for a number of non-enveloped viruses. In parallel, the Applicant will conduct viral inactivation studies using the abatacept molecule to confirm that Alternative No. 2 does not have any impact on the bioactivity and quality of the protein molecule in accordance with regulatory requirements for the production of biopharmaceuticals. These studies are in the planning stage and will commence with the chosen laboratory before the Sunset Date.

5.2.3 Economic feasibility of Alternative No. 2

The costs associated with the potential substitution of 4-tert-OPnEO with Alternative No. 2 will largely be based on the same activities as have been identified for Alternative No. 1 (section 5.1.3).

The total estimated cost for the substitution of 4-tert-OPnEO is € [redacted] million. The Applicant concludes that the substitution is economically feasible over the cou f the requested 12-year review period.

5.2.4 Reduction of overall risk due to transition to Alternative No. 2

Table 13 below provides a comparison of the hazard classification of Alternative No. 2 with 4-tert-OPnEO and its degradation compound 4-tert-OP.

Alternative No. 2 does not hold a harmonised classification and labelling in Annex VI of CLP [21].It has been registered in the EU, the registered C&L is presented in Table 13. The 4-tert-OPnEO hazard classification was taken from the supplier SDS and the OP from Annex VI to CLP [21].

Table 13. Comparative C&Ls of Alternative No. 2 with 4-tert-OPnEO and 4-tert-OP

Hazard Classification	**Substance**		
	[redacted]	**4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO)**	**4-(1,1,3,3-tetramethylbutyl)phenol** EC 205-426-2 CAS 140-66-9
Endocrine disruption	Not Classified	Endocrine Disrupting properties-environment (degradation to 4-tert-OP)	Endocrine Disrupting properties-environment
Physicochemical	Not Classified	Not Classified	Not Classified
Human health	Skin Irritant 2 (H315) Eye Damage 1(H318) Acute oral Tox 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute toxicity oral 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318)
Environmental	Aquatic Acute 1 (H400) Aquatic Chronic 2 (H411)	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)
Source	ECHA [24] [29]	Supplier SDS [29]	Annex VI to CLP [21] index number 604-075-00-6

The comparative assessment demonstrates that the main difference between 4-tert-OPnEO and Alternative No. 2 is that the latter does not have any endocrine disrupting properties associated with the substance or its degradation products. It is not listed on ECHAs Candidate list [30], PACT list [25] of substances subject to regulatory risk management assessment, ChemSec SIN list [26].

As a conclusion, a comparative assessment of the hazard profiles of 4-tert-OPnEO and 4-tert-OP to that of Alternative No. 2 demonstrates that the transition to the alternative would reduce the risk through the endocrine disrupting properties being eliminated completely. Alternative No. 2 does have hazard classifications that will need to be fully assessed. The Applicant will complete a full risk

assessment on the use of the substance with respect to its hazard classification prior to any introduction to their processes.

5.2.5 Availability of Alternative No 2.

The Applicant secured laboratory scale quantities for the initial feasibility studies from two suppliers. However, as part of the substitution plan, the Applicant must conduct a full evaluation of any potential alternative to ensure sustainable commercial pharmaceutical grade supply with consistent quality and stability as well as a supply chain that meets the requirements of the Applicant's quality systems. As part of this process, the Applicant will complete an assessment of the potential REACH registration requirements for future use of Alternative No. 2.

Alternative No. 2 is listed in a patent application [17] describing the potential to act as an effective viral inactivation agent. Therefore, until the Applicant has assessed and concluded that the substance use is not currently restricted by intellectual property rights of this patent application, it is concluded that Alternative No. 2 cannot be considered available for substitution by the Applicant at this point.

5.2.6 Conclusion on suitability and availability of Alternative No. 2

In order for the Applicant to confirm technical feasibility of Alternative No. 2, further viral inactivation studies must be conducted both at laboratory and at full scale in order to ensure effective viral inactivation that meets the current regulatory requirements. The Applicant must also complete compatibility studies with the abatacept molecule to confirm that the molecule is not impacted by the change in surfactant. Therefore, is it not currently possible for the Applicant to conclude on technical feasibility until all planned studies have concluded.

While the Applicant has identified two potential laboratory scale suppliers for the substance, full quality and supply sustainability assessments will need to be completed on the material and on the supplier. This assessment will take place after the feasibility has been confirmed and is estimated to take two years to complete. In addition, the Applicant must conduct an assessment on any possible constraints on the future use of the substance that may apply to intellectual property rights of the patent owner. Finally, any change in the production materials or in the viral inactivation step will be subject to re-validation and re-approval by the regulatory bodies. Therefore, the Applicant concludes that the substance is not currently available for substitution.

Substitution to Alternative No. 2 would result in a reduction in overall risk to the environment through the elimination of the endocrine disrupting properties.

5.3 Alternative No 3. [redacted]

Alternative No 3 is a [redacted] non-ionic surfactant that is reported to be biodegradable with low aquatic toxicity [34] to supplier information these surfactants are used in cleaning applications [35]. Table 14 provides details of the substance identification.

5.3.1 Substance identification and properties

Table 14. Alternative No 3. Substance identification and properties

Substance name(s)	IUPAC name (s)	EC/CAS number
[redacted]		
Source [24],[34], [35]		

5.3.2 Technical feasibility of Alternative No. 3

Alternative No. 3 was chosen by the Applicant as it met the criteria for low toxicity to the environment. Initial viral inactivation assessment carried out by the CRO for the Applicant showed that Alternative No. 3 provided acceptable viral inactivation in the model studies conducted. Technical feasibility of Alternative No. 3 cannot be concluded until further planned studies are conducted including an expanded viral panel and an assessment of the impact of Alternative No. 3 on the abatacept molecule is concluded.

Conclusion and requirements to make Alternative No. 3 technically feasible

In order to confirm that Alternative No. 3 can act as a technically feasible alternative to 4-tert-OPnEO further viral inactivation studies at both laboratory and manufacturing scale will be required to be conducted to verify initial results on reduction in viral load. The Applicant will proceed with viral inactivation studies with an expanded model virus panel to verify the results on the initial assessment and to ensure wide viral inactivation capacity for a number of non-enveloped viruses. In parallel, the Applicant will conduct viral inactivation studies using the abatacept molecule to confirm that Alternative No. 3 does not have any impact on the bioactivity and quality of the protein molecule in accordance with regulatory requirements for the production of biopharmaceuticals. These studies are in the planning stage and will commence with the chosen laboratory before the Sunset Date.

5.3.3 Economic feasibility of Alternative No. 3

The costs associated with the potential substitution of 4-tert-OPnEO with Alternative No. 3 will largely be incurred from the same activities as have been identified for Alternative No. 1 (section 5.1.3). The total estimated cost for the substitution of 4-tert-OPnEO is € [redacted] million. The Applicant concludes that the substitution is economically feasible over the course of the requested 12-year review period.

5.3.4 Reduction in overall risk due to transition to Alternative No. 3

Alternative No.3 was chosen by the Applicant owing to low toxicity for the environment. Table 15 below provides a comparison of the hazard classification of Alternative No. 3 as compared with 4-tert-OPnEO and its degradation compound 4-tert-OP.

Alternative No. 3 does not hold a harmonised classification and labelling in Annex VI of CLP [21]The presented C&L is from the suppliers SDS[29]. The 4-tert-OPnEO hazard classification was taken from the supplier SDS and the OP from Annex VI to CLP [21].

Table 15. Comparative C&Ls of Alternative No. 3 4-tert-OPnEO and 4-tert-OP

Hazard Classification	**Substance**		
	g [redacted]	**4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO)**	**4-(1,1,3,3-tetramethylbutyl)phenol** **EC 205-426-2** **CAS 140-66-9**
Endocrine disruption	Not Classified	Endocrine Disrupting properties-environment (degradation to 4-tert-OP)	Endocrine Disrupting properties-environment
Physicochemical	Not Classified	Not Classified	Not Classified
Human health	Eye Irritant 2 (H319)	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute toxicity Oral 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318)
Environmental	Not Classified	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)
Source	Supplier SDS [29]	Supplier SDS [29]	Annex VI to CLP [21] 604-075-00-6

As a conclusion, a comparative assessment of the hazard profiles of 4-tert-OPnEO and 4-tert-OP to that of Alternative No. 3 demonstrates that the transition to the alternative would reduce the risk through the endocrine disrupting properties being eliminated completely. The Applicant will complete a full risk assessment on the use of the substance with respect to its hazard classification prior to any introduction to their processes.

5.3.5 Availability of Alternative No. 3

Alternative No. 3 is a general-purpose surfactant and is commercially available. A supplier of laboratory scale has been identified by the Applicant. However, as part of the substitution plan, the Applicant must conduct a full evaluation of any potential alternative to ensure sustainable commercial pharmaceutical grade supply with consistent quality and stability as well as a supply chain that meets the requirements of the Applicant’s quality systems.

Alternative No. 3 is listed in an old patent application [17] describing the potential to act as an effective viral inactivation agent. Therefore, until the Applicant has assessed and concluded that the substance use is not currently restricted by intellectual property rights of the patent application, it is concluded that Alternative No. 3 cannot be considered available for substitution by the Applicant at this point.

5.3.6 Conclusion on suitability and availability of Alternative No 3

In order to verify Alternative No. 3 as a technically feasible alternative to 4-tert-OPnEO further viral inactivation studies are required to be completed. The availability of Alternative No. 3 may be limited or constrained by a patent application therefore it is not considered available for substitution by the Applicant at this point. The Applicant will complete further viral inactivation studies using Alternative No.3 if it is concluded that there are no IP constraints and will subsequently carry out supply and sustainability assessments.

Substitution to Alternative No. 3 would result in a reduction in overall risk to the environment through the elimination of the endocrine disrupting properties.

5.4 Alternative No. 4 [redacted]

Alternative No. 4 is a [redacted] non-ionic surfactant. It is widely reported to be used in biochemical a [redacted] ising proteins, isolating nuclei from cells in culture[36] emulsifying and dispersing substances in medicinal and food products. Table 16 provides further details on its identification.

5.4.1 Alternative No. 4 Substance identification

Table 16. Alternative No. 4 Substance identification

Substance name(s)	IUPAC name (s)	EC/CAS number
[redacted]		
Source [24],[29],[37]		

5.4.2 Technical feasibility of Alternative No.4

Alternative No. 4 is referenced in the literature for use in efficient viral inactivation of medicinal products derived from human plasma.[redacted] Alternative No. 4 was not included in the initial feasibility studies carried out by the CRO however studies are now planned with the model virus. Technical feasibility of Alternative No. 4 therefore cannot be concluded until viral inactivation studies have completed, and comparative viral inactivation efficiency has been met. In addition, it may be necessary to evaluate Alternative No. 4 with a suitable solvent.

Conclusion and requirements to make Alternative No. 4 technically feasible

Should Alternative No. 4 provide acceptable results in the initial viral inactivation studies, it will be added to the R&D schedule with potential Alternatives 1,2 and 3 for studies on an expanded virus panel and parallel studies on the abatacept molecule. These studies are planned to commence before the Sunset Date.

5.4.3 Economic Feasibility of Alternative No. 4

The costs associated with the potential substitution of 4-tert-OPnEO with Alternative No. 4 will be the same as have been identified for Alternative No. 1 (section 5.1.3). The total estimated cost for the substitution of 4-tert-OPnEO is € [redacted] million. The Applicant concludes that the substitution is economically feasible over the course of the requested 12-year review period.

5.4.4 Reduction in overall risk due to transition to Alternative No. 4

Alternative No. 4 was chosen by the Applicant owing to low toxicity for the environment. The substance does not hold a harmonised classification and labelling but is notified to the C&L inventory

[24] as not classified. As can been seen from the comparative assessment, presented in Table 17 a substitution of 4-tert-OPnEO with Alternative No. 4 would result in a reduction in risk for human health and the environment and the elimination of endocrine disruption properties.

Table 17. Comparative C&Ls of Alternative No. 4 with 4-tert-OPnEO and 4-tert-OP

Hazard Classification	**Substance**		
	g [redacted]	**4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO)**	**4-(1,1,3,3-tetramethylbutyl)phenol** **EC 205-426-2** **CAS 140-66-9**
Endocrine disruption	Not Classified	Endocrine Disrupting properties-environment (degradation to 4-tert-OP)	Endocrine Disrupting properties-environment
Physicochemical	Not Classified	Not Classified	Not Classified
Human health	Not Classified	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute toxicity Oral 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318)
Environmental	Not classified	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)	Aquatic Acute 1 (H400) Aquatic Chronic 1(H410)
Source	Supplier SDS [29]	Supplier SDS [29]	Annex VI to CLP [21] 604-075-00-6

5.4.5 Availability of Alternative No. 4

Alternative No. 4 is a general-purpose surfactant and is assumed to be commercially available. A supplier of laboratory scale has been identified by the Applicant. However, the Applicant must complete full assessment of the supply of pharmaceutical grade that meets the regulatory and quality standards. Alternative No. 4 is also listed on an old patent application [17] investigating the potential to act as a viral inactivation agent and therefore the Applicant must assess any potential constraints imposed by the patent application before the Alternative can be considered available for substitution.

5.4.6 Conclusion on suitability and availability of Alternative No. 4

In order to verify Alternative No.4 as a feasible alternative to 4-tert-OPnEO, the Applicant must complete initial viral inactivation studies with the CRO in accordance with the studies conducted on Alternatives 1,2 and 3. Should Alternative No. 4 provide acceptable viral inactivation results at laboratory scale further studies will be initiated with the expanded virus panel and parallel studies with the abatacept molecule.

The availability of Alternative No. 4 may be limited or constrained by listing on an old patent application therefore it is not considered available for substitution by the Applicant currently. The Applicant will complete further viral inactivation studies using the Alternative and carry out supply

and sustainability assessment. Furthermore, since the potential substitution of 4-tert-OPnEO with Alternative No. 4 will be subject to regulatory approval prior to marketing of the drug, the Applicant concludes that Alternative No. 4 is not currently available for substitution.

Substitution to Alternative No. 4 would result in a reduction in overall risk to the environment through the elimination of the endocrine disrupting properties.

6 . OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES FOR USE 1

6.1 Conclusions on Suitability

The Applicant has completed initial laboratories studies to assess the impact of known alternative viral inactivation techniques on the abatacept molecule and has concluded that UV, heat treatment and low pH inactivation methods are not compatible with the abatacept molecule. This was demonstrated by observed and unacceptable levels of aggregation and reduction in bioactivity of the molecules in laboratory studies. Therefore, these methods cannot be considered as suitable alternatives to 4-tert-OPnEO in viral inactivation for the abatacept BDS. The Applicant therefore focused efforts on finding a potential alternative surfactant for use in chemical viral inactivation.

Eleven potential alternative surfactants were identified through literature review. In order to verify technical feasibility, the Applicant contracted a specialist CRO to conduct viral inactivation trials on ten of the eleven shortlisted surfactants. Initial viral inactivation studies demonstrated that seven of the identified potential alternatives demonstrated ability to inactivate the model virus [redacted] in a laboratory setting. Two alternatives failed to demonstrate acceptable viral inactivation capability and the remaining potential alternative studies had not commenced.

Potential alternatives under approved patents were not considered for further assessment owing to potential IP constraints. The Applicant has planned further viral inactivation studies with the CRO of the top three ranked potential alternatives ([redacted]), using an expanded viral panel and the abatacept molecule. In parallel, the Applicant will conduct in-house laboratory studies on process stream clearance. These studies are planned to start before the Sunset Date and estimated to take two years to complete. A further potential Alternative, No. 4 is currently planned for initial feasibility assessment with the CRO and will also be progressed to full scale studies should viral inactivation studies prove acceptable.

A final conclusion on the suitability of the shortlisted alternatives in the viral inactivation process cannot be made until further viral inactivation studies have concluded and the Applicant has confirmed that the abatacept molecule integrity is not impacted by the change in detergent. Therefore, the Applicant concludes that there are no suitable alternatives for the substitution of 4-tert-OPnEO from the abatacept purification process before the Sunset Date.

6.2 Conclusions on Availability

In assessing the availability of the shortlisted potential alternatives, one potential alternative ([redacted]) was ruled out as the manufacturer could not guarantee future supply. The four shortlisted potential alternatives that will progress to the next phase of assessment are not currently listed in approved patent applications seeking alternatives to the use of 4-tert-OPnEO in viral inactivation processes. Three of the four alternatives have been listed in previous patent applications and as such the Applicant will assess any possible constraints from patent applications associated with future use of these potential alternatives. In addition, the Applicant will conduct a complete quality and sustainability assessment to ensure sustainable commercial pharmaceutical grade supply with consistent quality and stability as well as a supply chain that meets the requirements of the Applicant's quality systems. It is therefore concluded that none of the assessed potential alternatives are available for substitution before the Sunset Date.

6.3 Overall conclusions

The Applicant concludes that there are no suitable, available or technically feasible alternatives for the substitution of 4-tert-OPnEO from the viral inactivation step in the production of abatacept before the Sunset Date. In order to find a suitable alternative, the Applicant will progress with planned viral inactivation studies of the three top ranked potential alternatives and complete initial feasibility on a fourth potential alternative. If the expanded viral inactivation studies with the four alternatives prove unsuccessful, the Applicant will return to the other shortlisted alternatives and prioritise further assessment based on next ranked candidates.

Should a suitable alternative be confirmed through the above studies the substitution and phase-out program will then be initiated and dependent on the following activities.

Supply sustainability: An assessment that aims to confirm that production of the selected alternative is commercially sustainable, routinely meeting Applicant material quality specifications as well as supply demands. This will also include an assessment of REACH registration requirement. None of the potential alternatives are currently produced to meet the quality system requirements of a biopharmaceutical company. This activity is estimated at two years. One year to confirm commercial supply and one year to validate the alternative within the Applicant's process.

Technology transfer & process validation: As the Applicant will start commercial production of abatacept in late 2020, it would not be possible to make any substitutions within this timeframe**.** If a successful alternative is identified, a second validation campaign would have to be executed at commercial scale to validate the new process with the alternative. Technology transfer and process validation is estimated to take three to five years from the identification of an available alternative.

Regulatory filing and approval: Changes in the viral inactivation step will require the filing and approval or new market authorisations from each country where Orencia is marketed within**.** Since the potential alternative shortlist have not been filed by the Applicant previously there is a degree of uncertainty as to how the regulatory authorities may view novel viral inactivation methods. Owing to this uncertainty the Applicant is estimating the possibility of a minimum of one year to complete the new filing submission. Regulatory approval for process changes vary depending on the markets, some markets can take three years for approval.

Clinical trials: The possibility of repeat clinical trials for the introduction of a new or novel detergent into the viral inactivation step would add three years to the substitution program, if it is not possible to perform trials in parallel with the above-mentioned activities.

Substitution activities are estimated to cost in the region of € h.i million to complete. The Applicant considers the estimated substitution to be economically viable over the course of the requested 12-year review period. However capital investment into plant adaptation will only be made when a technically feasible alternative has been identified and is confirmed as having sustainable supply of pharmaceutical grade quality.

The Applicant has identified some of the shortlisted surfactants on the basis of no or low risk to the environment. Moving to any one of the four shortlisted potential alternatives would result in a reduction in overall risk to the environment owing to the removal of the endocrine disrupting properties.

The Applicant's request for a review period of 12 years will allow for the complete assessment of potential alternatives while maintaining the supply of Orenica to patients. Within the review period

the Applicant has committed to an extensive R&D program to find a suitable alternative that is commercially available while minimising the risk to the environment through the implementation of a waste containment system for 4-tert-OPnEO in the abatacept process at its Cruiserath site.

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