Applicant: Swords Laboratories

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Subject: Request for additional information-Public Version

Applicant response to questions from RAC and SEAC:

General question

1. ***Could you please provide a version of the confidential version of the application, where the text that has been claimed as confidential is marked up or highlighted in some way, but still readable? This will help the Rapporteurs avoid mentioning confidential data when drafting the opinion, while still assessing all of the information provided.***

   Response:

   The Applicant has provided marked up versions of the confidential AoA, SEA, CSR and OCs and RMMs uploaded as confidential attachments.

Questions from the Committee for Risk Assessment

1. ***Why is an excess solution of 4-tert-OPnEO per batch prepared, if only parts of the solution are required for the virus inactivation step? What are the monitored parameters that dose more or less of the prepared solution? In section 9.1.1.1. Conditions of use is written: "The remaining unused, residual quantity is collected and sent for incineration, [redacted] kg per batch."***

   Response:

   An excess solution of 4-tert-OPnEO is required to ensure that there is always enough 4-tert-OPnEO available for the batch. If manufacturing run out of 4-tert-OPnEO, it would result in a very significant manufacturing delay and potentially batch losses in some instances.

   Furthermore, an excess solution of 4-tert-OPnEO must be prepared as 4-tert-OPnEO will be formulated in a disposable vessel Single Use Mixer (SUM) and not all the solution will be retrieved from the disposable bag liner in the SUM. In addition, excess material is required to offset losses due to material hold-up in process pipework.

   The volume of 4-tert-OPnEO added to the virus inactivation vessel is controlled and monitored using a sophisticated Delta V control system (i.e. manufacturing process automation system) based on the weight of the residual amount of 4-tert-OPnEO left in the 4-tert-OPnEO storage bag.

Note: any unused residual 4-tert-OPnEO solution including disposable bag(s) / liners will be collected and segregated for incineration off-site at a licensed waste disposal facility.

2. ***In CSR it is mentioned that 1.1-3.4% ([redacted]) on wastewater is sent to the WWTP containing limited quantities or residues of 4-tert-OPnEO. In the light of the above question to eliminate all environmental exposure if to improve quantity management per batch, could the 1.1-3.4% ([redacted]) of wastewater be incinerated although it is mentioned that it is considered not efficient or optimal?***

   Response: See response to RAC Question 7 below which also addresses this question with respect to further removing / eliminating 4-tert-OPnEO residues to prevent them being discharged to the WWTP.

   For clarification, the 1.1-3.4% ([redacted]) figure does not refer to the volume of wastewater, but rather to 1.1-3.4% ([redacted]) of the quantity of 4-tert-OPnEO used in the process for viral inactivation. This will be present at very dilute/trace concentrations (if any) in the wastewater. The 1.1-3.4% ([redacted]) figure is also a conservative estimate, as the Applicant believes the proposed waste capture system will remove in excess of 97.1-99.4% ([redacted]) of the 4-tert-OPnEO used in the process for viral inactivation as described in the response to RAC Question 7 below.

3. ***Is the solution preparation (e.g. for viral inactivation) step a fully automated process or is it a manual activity?***

   Response:

   The formulation of the 4-tert-OPnEO is carried out in a highly controlled and classified GMP area within the manufacturing building. The facility is designed and operated to contain any accidental spills/releases of materials as outlined in the CSR. The stock solution of 4-tert-OPnEO is added manually to the SUM receiving vessel. The solution is formulated and mixed using an automated agitator in the SUM. The formulation activities such as agitation speed and timing of the formulation are recorded in the Delta V manufacturing control system (i.e. manufacturing process automation system). At the end of the formulation, the contents of the SUM are transferred using a peristaltic pump to a new disposable bag for storage prior to use.

4. ***Please provide detailed information on the planned monitoring plans to be implemented (e.g. the points of measurements) referred to on p85 of the CSR.***

   The efficacy of the 4-tert-OPnEO process waste capture system will be verified during commissioning of the new system. This will include sampling and analysis of 4-tert-OPnEO residues in the process wastewater by an accredited laboratory. This laboratory has successfully validated analytical methods for a number of monomers/analogues of 4-tert-OPnEO which are hydrolysed to the common moiety 4-(1,1,3,3-tetramethylbutyl)phenol, with the analysed concentration reported as 4-(1,1,3,3-tetramethylbutyl)phenol equivalents with a limit of detection of [redacted]

During commissioning, it is proposed to take samples of wastewater streams from process vessels that contained / have been in contact with 4-tert-OPnEO following drain-down and first wash of the equipment. [redacted]

[redacted]

Analysis of these samples for 4-tert-OPnEO residues will be used to verify the efficacy of the system in capturing in excess of 96.6-98.9% ([redacted]) of 4-tert-OPnEO used for viral inactivation, following the capture of the 4-tert-OPnEO process solution and first wash of the equipment.

Figure 1: Simple Process Flow Diagram (PFD) of flow-path and capture of 4-tert-OPnEO used for Viral Inactivation in Chromatography Column

[redacted]

5. ***In section 9.0.1 in the CSR it is mentioned that currently the manufacturing process for abatacept is being transferred from US to Cruiserath facility where production will begin in Q3 2020. If comparable please argue based on the information on practices from the US site the effectiveness of the OCs and RMMs of the processes regarding releases to different environmental compartments.***

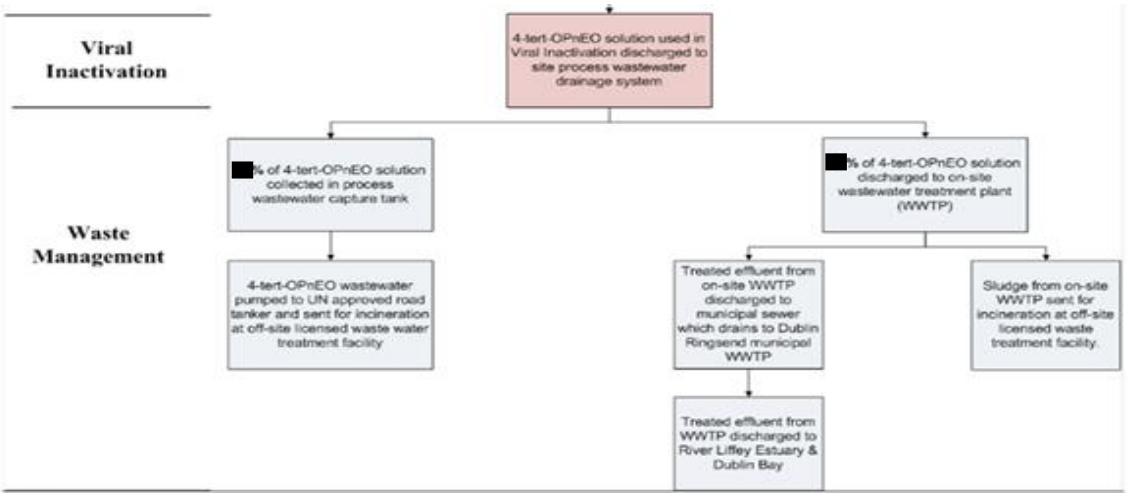
   Response:

   While the overall manufacturing process between the US and Cruiserath facilities is comparable, differences in environmental restrictions governing the two facilities result in different Operational Control (OC) and Risk Management Measure (RMM) strategies and designs. The US facility does have a capture system for a different material (process buffer) in the process wastewater but only provides partial capture of this material. In addition, 4-tert-OPnEO is introduced at a different locations in the process in the US facility. The design of the Cruiserath facility and process allows more efficient and more complete capture of 4-tert-OPnEO than is practicable (or necessary) for the buffer targeted by the US-based process.

6. ***The sludge from the on-site treatment plant is dewatered and sent for incineration (p73 and p79)/landfill (p86). It is stated that the STP sludge is applied on agricultural soil. The estimated exposure concentrations are high. Please clarify the sludge treatment processes. It is not entirely clear at what steps the sludge is incinerated and landfilled. Why could it not be possible to incinerate all sludge?***

   Response:

   Sludge treatment processes
   For clarification on the sludge treatment processes; the new process waste segregation has been upgraded to capture 96.6-98.9% ([redacted]) (minimum) of 4-tert-OPnEO from the process that will be sent for incineration at an off-site licenced waste treatment facility. The remaining 1.1-3.4% ([redacted]) (maximum) of 4-tert-OPnEO present after initial CIP of the equipment, enters the Applicant's on-site Waste Water Treatment Plant (WWTP). Within the on-site WWTP, the wastewater undergoes treatment including activated sludge secondary treatment. The sludge from the Applicant's on-site WWTP is collected for incineration off-site and the remaining treated waste water is then sent to a municipal WWTP at Ringsend, Dublin for further treatment and release. Sludge produced at the municipal WWTP is not incinerated as the municipal plant spreads all of the treated sludge onto agricultural land. The reference to landfilling on p86 of the CSR is incorrect as no landfilling of treated sludge is conducted from the municipal or site WWTPs. Please see figure below (taken from the relevant Chemical Safety Report, Section 9.1, page 73) for more clarification.



Exposure concentrations

The estimated exposure concentrations calculations are based upon very conservative worst-case scenarios. This is due to various reasons outlined below;

- As per the guidance given by RAC-43 Risk-related considerations for 4-tert-OPnEO[1], the Applicant assumed that all 4-tert-OPnEO will degrade to 4-tert-OP within the WWTPs, without any removal.

- The distribution to the different compartments of outflow of the WWTP (water, air, sludge) were determined on the basis of the 4-tert-OP properties, instead of 4-tert-OPnEO, calculated by the SimpleTreat model integrated in EUSES (within Chesar 3.4). This approach has a greater share of the substance in sludge and agricultural soil (52.2% towards sludge, 42.9% water, 4.9% air, release degraded 0%). The current approach tends to overestimate releases of 4-tert-OPnEO to agricultural soil via application of sludge from WWTPs and underestimate the releases to surface water and sediment.

- The estimated exposure concentration calculation is based upon a very worst-case assuming all of the 1.1-3.4% ([redacted]) of 4-tert-OPnEO enters Ringsend WWTP, not taking into account of the treatment of wastewater and incineration of sludge produced within the Applicant's on-site WWTP. All sludge generated from the Applicant's onsite WWTP is collected and incinerated and any 4-tert-OPnEO bound to sludge would be removed from the wastewater stream prior to release to the municipal WWTP in Ringsend. This is not taken into account within the exposure concentration calculations as the Applicant assumed a very worst-case scenario. If one was to take this into account the 1.1-3.4% ([redacted]) of 4-tert-OPnEO would be subject to two WWTPs with the onsite WWTP incinerating 52.2% of releases through sludge (standard modelled biological STP), which would indicate that the actual exposure concentration calculation would be less than the presented exposure calculations.

As described above, the exposure concentration calculations presented within the Chemical Safety Report (especially agricultural soil) are seen are very worst case for the Applicant's emissions.

[1] https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

RAC question about further minimisation of emissions:

7. ***RAC takes note that you claim to emit [redacted] kg/yr kg of OPE/NPE per year, and that you have already provided information about the impacts of implementing an additional risk-management measure. Would you have concerns if RAC would recommend an additional condition (different to the risk-management measure you already analysed) to reduce or eliminate to zero your emissions? If yes, what in your view would prevent you from implementing this condition? Please explain what additional measures you would need to implement i) to capture the substance and ii) to dispose it as waste for adequate treatment that minimises releases to environmental compartments as far as technically and practically possible. Please also provide an estimation of the costs incurred.***

The Applicant would have a concern if RAC recommended an additional condition (to those RMMs already proposed by the Applicant) to reduce or eliminate to zero emissions, as described below:

As stated in the Chemical Safety Report (CSR), the Applicant committed to doing all that is reasonably practicable to prevent/minimise any release of 4-tert-OPnEO to the environment and will capture in excess of 96.6-98.9% ([redacted]) of 4-tert-OPnEO used for viral inactivation. This is a conservative estimate and will be verified during the commissioning of the new waste capture system. Only residual / trace amounts (1.1-3.4% (<[redacted])) of 4-tert-OPnEO will not be captured, and these will be discharged to the waste water treatment plant.

The primary flow-path and capture of 4-tert-OPnEO used in the process for viral inactivation is outlined in Figure 1 above. The new waste capture process outlined on Figure 1 will collect in excess of 96.6-98.9% ([redacted]) of 4-tert-OPnEO used for viral inactivation because:

- Following use in viral inactivation, the 4-tert-OPnEO solution will pass through the chromatography column and be collected in the captured process waste buffer tank. The column will then undergo a wash with multiple column volumes of wash solution to remove any residual amounts of 4-tert-OPnEO, which will also be collected in the captured process waste buffer tank. These two steps will capture the vast majority of 4-tert-OPnEO used in the process.
- All vessels and lines upstream of the chromatography column that have been in contact with 4-tert-OPnEO will be drained down to the captured process waste buffer tank and the vessels and lines will then undergo a first CIP rinse wash which will also be collected in the captured process waste buffer tank. The CIP route durations and flowrates will ensure the flush volumes are a minimum three times the line volume and will capture any significant surface residues of 4-tert-OPnEO in the upstream equipment.
- By draining down and washing/rinsing all process equipment that contained / was in contact with 4-tert-OPnEO, and collecting this material in the captured process waste buffer tank, the vast majority of 4-tert-OPnEO will be collected for incineration off-site, and only residual / trace amounts (1.1-3.4% (<[redacted])) of 4-tert-OPnEO (if any) will remain on the surfaces of the equipment.

- Sampling and analysis of the wastewater streams during commissioning of the new waste capture system as indicated on Figure 1 will verify the efficacy of the system.

The Applicant believes it would not be reasonably practicable to implement additional risk management measures (RMMs) to achieve zero emissions of 4-tert-OPnEO, and this would present a number of practical and financial difficulties including:

- To capture the additional wash streams (subsequent rinses, alkali wash and final rinse of process equipment) would require the capture of significant additional volumes of wastewater (>20m^3) containing only residual/trace amounts (if any) of 4-tert-OPnEO.
- This would require the design and installation of larger waste capture tank(s) to accommodate the increased volumes. The design of the waste capture system has been completed, the equipment has been purchased/is in process of being purchased and is due for installation in Q1 2020. Therefore, process redesign would be required at this stage, purchase contracts would have to be cancelled, the schedule would be delayed, and there would be additional costs associated with cancellation of existing purchase contracts, process redesign and the purchase of larger waste capture tank(s). While it is difficult to determine accurately the additional costs at this stage without a design and tendering process, an order of magnitude cost of an additional 25% on the existing capital investment of €4 million is estimated.
- Process redesign at this stage would result in a potential delay in the proposed schedule for commencement of manufacturing of abatacept at Cruiserath which could impact supply to patients.
- The facility has limited space to accommodate the current volume of the proposed captured process waste buffer tank (internal) and does not currently have sufficient space to accommodate a larger tank, which would require a facility extension, and the associated costs and impact to schedule.
- There would be additional costs in transporting and incinerating the additional wastewater. As stated in the CSR, the estimated cost to transport and incinerate the wastewater containing only residual/trace (if any) quantities of 4-tert-OPnEO would equate to approximately €1,500-10,000 (€ [redacted]) per kilogram of 4-tert-OPnEO, which is considered excessive. This is also a conservative estimate (cost per kilo) as it assumes the wastewater contains 1.1-3.4% ([redacted]) of the 4-tert-OPnEO used in the viral inactivation process. Use of the captured process waste collection tank (external) for the additional wastewater volumes without increasing the capacity of the tank would require significantly more frequent road tanker collections, which would have also have additional collection costs and operational/logistical implications for BMS.
- Incineration of this additional wastewater (i.e. water with only trace residues of hazardous material) is not efficient or optimal from an environmental perspective and represents an additional environmental impact. The Applicant considers the adverse energy and environmental impacts regarding the collection of the additional waste to be significant if compared to the benefits of eliminating the residual 1.1-3.4% ([redacted]) 4-tert-OPnEO. The increase of greenhouse gases (GHG) that would result from the offsite transport and the incineration of the additional wastewater collected must be considered. The low calorific status of the resulting collected waste (primarily water) will also most likely result in a need for increased fuel (fossil fuels) consumption for the incinerator under consideration
- As part of the front-end design of the proposed waste capture system, the Applicant requested an engineering consultancy to identify and assess potential alternative on-

site waste treatment systems for 4-tert-OPnEO, however they were unable to identify any proven cost-effective waste treatment systems to completely remove 4-tert-OPnEO from the process wastewater."

- In addition, the Applicant presents the following RMMs that are in either in place or are proposed in the future. These were not taken into consideration in the Applicants assessment due to the inability to quantify their effectiveness

  - Incineration of sludge produced at the Applicant's on site WWTP Any 4-tert-OPnEO that binds to the sludge will be incinerated (as explained in response to Question 6). It can be assumed that this process will reduce emissions.

  - UV treatment occurs at the receiving Municipal WWTP (Ringsend) in 'bathing season' (months of May to December)2. This cannot be quantified by the Applicant however, it can be assumed that this UV treatment will reduce emissions.

  - The receiving Municipal Ringsend WWTP is currently upgrading its treatment process[3] to include aerobic granular sludge (AGS) treatment; to be expected to be completed in 2020. This new technology has been reported to achieve higher rates of removal of endocrine disruptors.[4] [5] [6] This cannot be quantified by the Applicant however, it also can be assumed that this additional AGS treatment (to be completed in 2010) will reduce emissions

Therefore, considering the above and the supporting information included in the CSR, the Applicant would have a concern if RAC recommended an additional condition (to those RMMs already proposed by the Applicant) to reduce or eliminate to zero emissions. There would be significant cost and practical implications for the Applicant to achieve this, and the Applicant believes it is currently doing all that is reasonably practicable to prevent/minimise any release of 4-tert-OPnEO to the environment.

[2] http://www.epa.ie/licences/lic_eDMS/090151b2801ee419.pdf
[3] https://www.water.ie/projects-plans/ringsend/proposed-solution/
[4] https://www.ncbi.nlm.nih.gov/pubmed/30586813
[5] https://www-sciencedirect-com.ucd.idm.oclc.org/science/article/pii/S1001074208600261
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5511329/

Questions from the Committee for Socio-Economic Analysis

SEAC questions about the Analysis of Alternatives:

1. ***Can you explain the reasons why the use of a patented substance/alternative would be difficult for you? Concretely, what would be the consequences, particularly regarding costs?***

   Response

   Optimally, the Applicant should first consider selecting an unencumbered alternative in an effort to avoid patent litigation. If the Applicant must use an encumbered (patent listed) alternative detergent, then it should review the validity of the patent for infringements and consider taking a license as an alternative to litigation. Patent litigation is a costly endeavour and drain on the company's resources, such as people, time and money. If an encumbered detergent is required to be utilised, the Applicant will need to initiate the review of existing patents for possible infringements.

2. ***Regarding the treatment under low pH, would the addition of another step of filtration or centrifugation to remove the additional aggregate created not be possible? What would be the effect on the yield and cost?***

   Response:

   The addition of another filtration step would not be effective as aggregate can form various sizes and configurations. To use filtration, would mean that a very small pore filter would have to be used which may not capture all particles (due to different configurations) and would result in very significant losses of product which would render the process economically non-viable. Furthermore, the removal of such large amounts of protein would present other challenges and have a knock-on impact on product quality of the protein.

3. ***Same question as the previous question: what about for thermal inactivation?***

   Response:

   Non-chemical viral inactivation alternatives namely thermal inactivation were evaluated for suitability with abatacept as discussed in Section 4.1.1 of the AoA. Studies conducted by the Applicant concluded that these methods are not feasible substitutes for viral inactivation in the purification process for abatacept due to the intolerable impact of thermal inactivation on the biochemical and biophysical properties of the molecule.

4. ***Why were the shortlisted alternatives tested at lower temperatures specified at the top of page 25, compared to the specification of OPnEO?***

   Response:

   Lower temperatures are considered worst-case for viral inactivation for all of the Applicants drug manufacturing processes.

5. ***Could you update us on the progress of the feasibility studies on Polysorbate 80?***

   Response:

   [redacted]

6. ***Are you also testing mixtures of the detergents identified as potential alternatives? i.e. No1 + No2?***

   Response:

   No, the Applicant is not evaluating mixtures.

7. ***Could you provide more information on the planned timeframe for substitution, from which derive the required review period? For instance, SEAC question the need for 2 years to verify the supply sustainability of a potential alternative. Can you elaborate on the reasons why it would take such a long time?***

   Response:

   As described in the AoA section 4.2.1.3, the estimated timeframe for complete substitution and phase out is based on the Applicants experience with the introduction of new processes into its manufacturing network of a biopharmaceutical product. The substitution plan-derived timeline accounts for the following phases:

   Feasibility studies (2 years)
   Initial and full-scale technical feasibility studies are conducted largely by a Contract Research Organisation (CRO). Studies must be planned, agreed, budgeted, scheduled before laboratory work can commence. In addition, samples of both the test agent and the Applicants BDS must be manufactured to the required quality and transported to the testing laboratory. Studies with the CRO are scheduled based on the CRO availability to author protocols, execute, and complete a final report. Scheduling alone may take [redacted] Two years is anticipated.

Supplier/Material Sustainability Qualification (2 years):
Once a potential substitute is selected, the supplier must complete manufacturing process validation and three lot qualifications according to the Applicants quality system standards. This requires establishing a material stability program and three months material stability prior to use in the Applicants operations. The general timeline for this activity is [redacted] based on supplier manufacturing facility scheduling and availability. The Applicant will further need to perform internal qualification work and validation that requires at a minimum [redacted] for Quality Agreement completion and internal three lot release testing. This time also accounts for the revision of existing GMP documentation and practices for the new materials management, operational use, and process validation. Supply agreements to ensure the material may be procured sustainability from the supplier or a supplier's distributor by the Applicant are also evaluated during this time. If a distributor is required, the Applicant requires quality review and approval of the selected distributor. Both Quality and Supplier Agreements require legal review by both the Applicant and the supplier. The process of legal review takes [redacted] at a minimum for document review and approval.

Technology (tech) Transfer and process validation (3 years)
During the tech transfer and validation phase there are many different activities that are executed ahead of process implementation at commercial scale. When scaling up the process with the suitable alterative, the new process needs to be characterised at small-scale beforehand. This characterisation work is required to develop a comprehensive understanding of the process capabilities and to derive the process parameters by which the process will operate at larger scale. These characterisation activities can take up to [redacted] years and also involve some work with an external company to build viral clearance safety data. At the same time, the consumable designs and raw materials specifications are being developed for the process to enable the procurement of such components for manufacturing scale. Once the process characterisation work is nearly complete, often pilot scale runs are executed to build additional data at a larger scale to demonstrate process consistency and also enable some characterisation studies to be done at a larger scale that wouldn't be possible at smaller scale. Once complete, a lot of time is spent documenting the process shape and control strategy. This process definition then forms the basis of design for the automation teams to build their automated control platforms. Typically, based on previous experience in the applicant's facilities, a min of [redacted] are completed to shake down the new process at manufacturing scale to identify any potential issues on scale-up. Following this activity, process validation runs are executed at scale. The number of batches required will depend on the agreed validation strategy with the various functional groups within the applicant's organisation. After the drug substance has been filled from these process validation batches, the applicant has to check the stability of the drug substance by putting the drug substance batches on stability for a defined period of time (which can take up to [redacted]) Cumulative timeframes can take up to 3 years.

Regulatory approvals: (1-2 years)
After the process validation is completed, the applicant must prepare a type II variation filing submission in the EU and a post approval submission in the US. There are also many additional filings in ROW markets. Preparation of the various filing submissions can take up to [redacted] with the applicant prioritising the EU and US submission preparations first. The filings are prepared internally within BMS using different partner groups across the organisation located in different geographical regions.

Based on recent experience with the Nivolumab filing submission experience in Cruiserath, it can take up to [redacted] to prepare a filing submission as the filing dossier is a very large documents (e.g.1,700 pages) where a lot of time is required to author, review and verify sections of the filing.

The US and EU health authorities typically take up to [redacted] to review a submission whereas ROW markets such as [redacted] In some instances, the Applicant can only submit to these markets when the US EU and other major agencies have approved their filings. Leading to cumulative timeframes of up to 2 years.

Clinical trials: (3 years)
The timelines for clinical studies are based on the applicant experience with clinical trials for a similar molecule, also a fusion protein. Based on that experience and the fact that the molecules are very similar in structure and mode of actions, it has taken several years to prove in clinical studies that the process changes do not impact the efficacy of the molecule. Typically, clinical studies are done in different clinical centres around the globe. However, certain countries require that patients from the specific country be included in the clinical study in order to get approval in that country. Three years for this phase is not unexpected.

8. ***Can you describe the substitution process you undertook for implementing an alternative to OPE in the production of [redacted]? How long did the different phases take, particularly the verification of the supply sustainability of a potential alternative?***

Response

4-tert-OPnEO is a non-product contact material utilised for [redacted] manufacturing operations. Specifically, the material is utilised in small quantities to test the viral filter after use in the process for post-filtration integrity. The Applicant's filter supplier identified a safer alternative to 4-tert-OPnEO, and substitution was initiated. The substitution of 4-tert-OPnEO from this use does not require the same rigour as is the case for the viral inactivation use. As a non-product contact use, substitution was achieved without the requirement for development, engineering or Process Performance Qualification (PPQ) batches. There is also no requirement around clinical studies and will only require a minor update to the agencies to inform them of the change. Specifically, there was no requirement for the Applicant to conduct Supply Sustainability assessment as the filter supplier had validated a supplier for the alternative. Hence substitution was achieved in a reduced timeframe.

9. ***What is your expectation regarding whether the European Medicines Agency (EMA) would require or not clinical trials before abatacept produced using an alternative could be marketed?***

Response:

Due to well-known sensitivity of abatacept, whereby even subtle process changes can have a significant impact on product quality and consequently product efficacy, it is anticipated that the EMA would require a clinical study to demonstrate that the product produced using an alternative delivers the same level of efficacy as the product that is currently produced using 4-tert-OPnEO.

SEAC question about the Substitution Plan:

10. ***On 7 March 2019, the General Court of the European Union annulled a Commission decision granting an authorisation for certain uses of two lead chromate pigments (Case T-837/16, Sweden v. Commission). As regards the assessment of the suitability of alternatives under Article 60(4) of REACH, it follows from the judgment that if suitable alternatives are available in general, albeit not technically or economically feasible for the applicant, and if the applicant demonstrates that the socio-economic benefits of continued use outweigh the risk to human health and the environment, an authorisation may be granted if the applicant submits a substitution plan. Please consider whether, in light of the Court's judgment, you should submit a substitution plan.***

    - ***If you wish to submit a Substitution Plan (SP), Version 3.2 (of May 2017) of the format for the Substitution Plan is available with instructions and explanations on ECHA's website under: https://echa.europa.eu/documents/10162/13637/sub_plan_template_en.pdf. Please submit a meaningful public version of the SP, together with the answers to the SEAC questions. You can also submit a confidential version of the SP as for the CSR, AoA and SEA.***

    - ***In case you do not wish to submit a substitution plan because you consider that the relevant information is already covered in your application, please indicate the sections in your AoA/SEA that cover the elements of the SP. You may consider complementing any missing information (e.g. monitoring of the implementation of the substitution plan).***

    - ***In case you do not wish to submit a substitution plan for any other reasons, please explain why.***

    Response

    The Applicant is preparing a Substitution Plan for submission.

SEAC questions about the Socio-Economic Analysis:

11. On page 18, it is described that a higher yield of abatacept per kg of 4-tert-OPnEO has been achieved due to process improvements since 2012. What improvements have been established? Could further improvements be done to reduce the amount of 4-tert-OPnEO?

Response

From 2012 to 2019 various minor continuous improvements have been implemented which combined together have increased the quantity of abatacept protein output per batch, namely modification to the chromatography step preceding the use of 4-tert-OPnEO, which increased the amount of abatacept produced per column cycle, hence reducing the product pool volume and hence the volume of 4-tert-OPnEO added to the process

In 2019/2020 BMS is introducing a major process improvement using chemically [redacted] to allow for [redacted] higher abatacept titres in the cell culture process. The purification process has been modified as well, [redacted] and moving the use of 4-tert-OPnEO to after abatacept protein harvest. The increase in the amount of abatacept product generated has allowed for a reduction in the amount of 4-tert-OPnEO used per kg of abatacept produced.

12. Under the description of NUS A1, you mention that it would take time to identify a CMO with the right equipment and then to transfer and qualify the process at the new site. What are the issues with using the CMO which was producing the drug previously?

Response

The CMO that previously produced the drug manufactured it using an older process and has never manufactured the drug using the new modified process. The newer 2019/2020 process uses different downstream purification steps, meaning the CMO current facility would have to be significantly modified to fit the 2019/2020 process for manufacturing abatacept. Due to these differences, this activity is envisaged to take a minimum of three years.

13. Only a global estimate is provided for the potential relocation costs for NUS A1B2. Can you provide more detailed information? What is the estimate based on?

Response:

The transfer, qualification and subsequent regulatory approval costs of abatacept into a new facility are estimated to cost in excess of €[redacted] million. This estimate is based on the applicant's prior experience of transfers into CMOs in the past and also the applicant's own experience of set-up costs for new products in its own facilities.

This cost includes the following elements:

- The materials and overhead costs for the development, engineering and Process Performance Qualification (PPQ) batches at large scale in the new facility (accounts for >[redacted]% of the overall cost)
- Development costs associated with any facility fit studies that would have to be executed ahead of transfer (accounts for >[redacted]% of the overall costs)
- Regulatory filing costs for the major markets (>[redacted]% of the overall cost)

14. One of the elements in the relocation costs that would be incurred under the NUS is "Regulatory filing costs for the major markets". This is a category of cost that is also present in the Applied for Use scenario, as part of the costs of substitution, with an estimate presented in section 5.1.3. Would the estimate for this element in the NUS be the same?

Response:

The regulatory filing costs refer to the cost of resubmitting the application for regulatory approval of abatacept after the modification of the manufacturing process or the transfer of the process to a different facility. In the AfUS, this cost will be incurred as a result of the substitution of 4-tert-OPnEO from an alternative and it is expected to be paid at least 8 years after the Sunset Date. In the NUS, this cost will be incurred as a result of the transfer of the manufacturing process to a new facility.

In both cases (AfUS and NUS), the costs are expected to be the same. However, the cost in the AfUS will be paid later than in the NUS. If both costs were discounted to current values, the AfUS would be lower. Using a 4% discount factor could mean that the cost would be approximately 25% higher in the NUS.

In addition to that, paying for resubmission of regulatory approval applications in the NUS could divert funding for other R&D activities of BMS. BMS could use these funds to develop more life-saving and life-improving products and safer and environmentally friendlier production processes. If significant costs have to be paid at short notice, funds for these R&D activities would be more limited and there could be delays in development and marketing of new and improved drugs, which could have a significant impact to patients that could benefit from these and for BMS's revenues and reputation.

Moreover, if transfer to a non-EU facility requires a wider reshuffling of manufacturing activities in BMS's network (as mentioned in NUS A2B2), there will be need for multiple submissions for several drug products. In that case, the regulatory filing costs would be a multiple of those in the AfUS and would increase the overall economic impacts compared to the AfU scenario. This was not calculated in the SEA, because BMS cannot determine the level of reshuffling that would be required at this time.

SEAC question on distributional impacts:

15. The current opinion template includes an overview table on distributional impacts (see below). Please complete the table below by adapting it to your circumstances (note that not all entries may be relevant for your case), as it will be helpful when addressing distributional impacts in the opinion.

Response:

Table 1 below summarises the distributional impacts of a granted authorisation to the various stakeholders and regions. The information can be found in Section 4.1 (Table 4-1 and Table 4-2) and Section 4.2 (Table 4-3) of the SEA. A discussion of the combined impacts and the distributional impacts was included in the text of these sections as well. The SEA did not present distributional impacts for geographical regions separately. The discussion was added in the table below to match the template and assist SEAC in developing their opinion.

Table 1: Distributional impacts

Affected group[1]	**Economic impact**	**Health and environmental impact**
Economic operator		
Applicant(s)	+ + + €10-100 million for process transfer and €0.62-3.1 million in lost revenue over 3 years.	n/a
Suppliers of alternatives in the EU	- (n/a?) Could not be quantified. Small impact due to low cost and quantities of 4-tert-OPnEO sold	n/a
Suppliers of alternatives outside the EU	- (n/a?) Could not be quantified. Small impact due to low cost and quantities of 4-tert-OPnEO sold	n/a
Competitors in the EU *(mostly palliative treatment – other conventional and biologic medicines have been tried before using Abatacept)*	- - Not quantifiable. BMS's treatment is second-line treatment, which means that it is used if other first line treatments have failed. Palliative treatment could benefit from sales of painkillers or other treatments, that only alleviate the pain.	n/a

Competitors outside the EU	- Not quantifiable	n/a
Customer group 1: RA, JIA and PsA patients	n/a	+ + + Life-improving drug will be available to patients who have no other option.
EU suppliers of raw materials	+ Loss of sales to Cruiserath. €5-50 million over 12 years	n/a
Public at large in the EU (identify) - *Does not include patients*	+ Investment in EU creates more job opportunities. Any improvement in patient wellbeing will have consequent positive impact on their friends and family.	- Environmental impacts from use could affect recreational activities, e.g. angling. Localised in Dublin.
Geographical scope		
Ireland	+ + + Job opportunities – investment – development of biologics industry	- - Up to 34 kg/year of 4-tert-OPnEO could be released to Dublin Bay + + + Patients suffering from RA, JIA and PsA will have access to a life-improving drug and have improved quality of life
Rest of the EU	n/a Economic activity of Applicant relevant to 4-tert-OPnEO and abatacept is localised in Ireland	+ + + Patients suffering from RA, JIA and PsA will have access to a life-improving drug and have improved quality of life
Outside the EU	n/a	+ + Continued use in the EU would prevent use of 4-tert-OPnEO in non-EU location and its release to the non-EU environment. + + + Patients suffering from RA, JIA and PsA will have access to a life-improving drug and have improved quality of life

Within the applicant's(s') business		
Employers/Owners	+ + Operating facility may see more work and investment as a result.	n/a
Exposed workers	n/a	n/a
Non-exposed workers and other employees	+ + Jobs are created and potential for expansion and more investment increases.	- Any environmental impacts would be localised to Dublin Bay, which is close to where many of BMS's employees live and may be used for recreational activities.

Notes: [1] Adapt the groups as relevant for your application. [2] Identify group or groups as relevant. These may comprise the downstream or end users of the substance or the final customers of the products.
Severity of impacts: either monetary [annualised to € million per year] or using scale high (+++ or ---), medium (++ or --), low (+ or -) or not applicable (n/a)
Adapted from Table 12 (Chapter 4.2.3.) of SEA Guidance on the preparation of SEA in the Applications for Authorisation.