AfA Baxter AG

Submission number: KA600552-65

Communication number: AFA-C-2114498661-37-01/F

Substance: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated

Use name: *Use of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (as a detergent) for virus inactivation via S/D (Solvent/Detergent) treatment in recombinant and plasma-derived medicinal products*

Answers to SEAC questions – Public version

AoA related questions

Q 7 - Please provide an update on the state of the research on potential alternatives. In particular, are there any updates on the information summarised in tables 30, 31 and 33 of the AoA/SEA document? Have any additional alternatives been shortlisted?

Takeda continues investing in R&D efforts to assess the potential alternatives [redacted] and VIENEP17020[redacted] will not be investigated further due to the substance's poor water solubility properties causing insurmountable process limitations under the required conditions such as temperature, concentrations, additives, etc.

In the current evaluation phase of [redacted] and VIENEP17020, tests according to OECD guidelines [redacted] are being conducted to compare the eco-toxicity of the compounds and their degradation products with OPnEO and 4-tert octyl phenol. Analyzing the degradation pathways and identifying the degradation products and their actual concentration in the corresponding bio-degradation mix is essential as this will determine if a potential implementation would constitute a shift to less hazardous substances. Only once the eco-toxicological profile of the substances is studied, the subsequently required evaluation cascade described in chapter 3.3 of the AoA/SEA can be initiated. Otherwise, time and money would be lost if the substances show the same eco-toxicological concerns as OPnEO (regrettable substitution) at a later stage. As such, the information as summarized in tables 30 and 31 remains unchanged.

Takeda has reviewed the published applications for authorisation to compare the alternatives for virus inactivation in the solvent/detergent process currently under assessment by other companies. To date, no publicly available alternate has been cited which has the potential to be included in the shortlisted alternatives. Throughout, Takeda remains in frequent contact with chemical providers to gain early insights on any alternatives these companies are developing as a potential replacement of OPnEO in solvent/detergent treatment for virus inactivation.

Q 8 - Will your substitution program seek specific detergents for each of the medicinal products produced by your companies, or do you aim to find a detergent that would be applicable for all the products?

It is highly desirable to find one single alternative detergent for replacing OPnEO in all production processes of the corresponding medicinal products manufactured by Takeda. The overall timeline for substitution of OPnEO in all medicinal products in scope of the AfA (estimated with at least [redacted] years) would be much longer if different alternative detergents were to be implemented. This is because synergies and knowledge derived from investigating one alternative cannot be used between production processes. This accounts especially for the initial testing phase (Identification of alternatives – R&D on candidate alternate) described in chapter 3.3.1 of the AoA/SEA. In other words, if Takeda would consider different potential alternatives for each production process, the full development and approval process described in chapter 3.3 of the AoA/SEA would need to be performed.

Additionally, having only one alternative detergent offers multiple advantages regarding the following points:

- Patient safety: known efficacy of the detergent to inactive lipid enveloped viruses (viral safety);
- Production process: mode of removal of the detergent is known (e.g. [redacted]);
- Handling: only one reagent needs to be analyzed (quality control) and kept in stock (especially important when special storage conditions (e.g. low temperature) are required for the potential alternative detergent);
- Economic: buying bigger quantities of one single detergent is cheaper.

Q 9 - Regarding the key functionalities, you define as a requirement a virus inactivation capacity of more than 4 log10 reduction in 1 hour, comparable to OPnEO. What is exactly required by the health authorities' guidelines? If it's different to the above, what is the justification for the requirement (particularly the timing of 1 hour)?

Per health authorities' guidelines, the incorporation of two distinct *effective* virus clearance steps into the manufacturing process of biologically-derived medicinal products is required (EMA/CHMP/BWP/706271/2010[1]), where *effective* is defined as "log reductions in the order of 4 logs or more" (CPMP/BWP/268/95[2]). The guidelines describe the incorporation and validation of virus clearance procedures in the manufacture of human blood plasma derivatives. The validation of virus clearance procedures also applies to drug compounds manufactured through biotechnological approaches (i.e. recombinant medicinal products), which could be affected by viral contamination during the cell culture processing.

The health authorities' expectations and requirements are that virus clearance steps provide in addition to *effective* virus clearance (i.e. > 4 log10 reduction) also a high safety margin. This means that even if effective virus inactivation would be obtained in the virus clearance study (part of alternative testing, see chapter 3.3.1 of AoA/SEA) after e.g. 30 minutes, a prolonged solvent/detergent (S/D) treatment time for the actual production process of the medicinal product will be implemented. This is required to simply provide the production process with additional virus safety margins ensuring that absolutely no active viruses make their way into the final medicinal product.

When using the [redacted] S/D treatment [redacted] and OPnEO) the treatment time typically applied in industry is [redacted] Please note that the S/D treatment condition of [redacted] incubation time has been included in the all market authorisations of the medicinal products in scope of this application for authorisation.

Q 10 - Similarly, you mention that the depletion factor using the alternative should be equivalent to the one using OPnEO. Please explain what that depletion factor is.

As described on page 37 in chapter 3.2.3 of the AoA/SEA, OPnEO is used as detergent in the S/D treatment during the manufacture of biologic medicinal products. After the S/D treatment to inactivate lipid enveloped viruses has been performed in the protein solution, the S/D-mixture has to be removed from the target protein. The removal is carried out by a [redacted] step and, in principle, all subsequent purification steps contribute to the reduction of the S/D-reagents in the target protein raw material. [redacted] Any alternative substances must be easily removable from the process, i.e. the target protein, after the S/D treatment because the resulting drug substance must be free of the S/D-reagents used to ensure patient safety.

The depletion of the alternative detergent from the process by the individual purification steps following the S/D treatment must also be monitored. This requires the availability of an analytical

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plasma-derived-medicinal-products_en.pdf

[2] https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-virus-safety-evaluation-biotechnological-investigational-medicinal-products_en.pdf

[redacted]

testing method and adequate test sample preparation. The depletion factor after each purification step must be identical to OPnEO, meaning that if e.g. the first purification step by chromatography reduces approximately 99 % (w/w) of the S/D reagents in the target protein raw material, the potential alternative must also be reduced by approximately 99 % (w/w) after the first purification step.

A pre-requisite for this is that the potential alternative does not bind to the target protein [redacted]. If the potential alternative has different depletion factors compared to OPnEO for the respective purification steps, significant changes to the manufacturing process would entail. These changes could potentially influence the efficacy and tolerability of the medicinal product and thus the performance of clinical studies is required. The time required for clinical studies is not considered in overall timeline for substitution described in chapter 3.3 of the AoA/SEA.

Q 11 - Regarding the development and approval process, point 3.3.7 ("Supply with alternative"): you have estimated this step to take 36 months. Please explain why this process is expected to take this long. What are the estimates based on? Could the process be done in parallel to some of the steps in your timeline? The same question applies to point 3.3.8 ("Material qualification").

The timeline for the "Supply with alternative" applies to a scenario where the supply is for a customized solution, i.e. Takeda issues this in contract. This scenario is applicable for both shortlisted alternatives for which further R&D is performed, [redacted] and VIENEP17020. If a readily available substance from a third party turns out to be a suitable alternative with availability in the appropriate grade and scale, the timeline may be reduced. However, as stated under Q 1, Takeda has not identified additional potential alternatives to be shortlisted. Therefore, it is impossible to assess whether a reduction of the presented timeline will be possible in the future.

For the "supply with alternative" timeline, 36 months are estimated based on Takeda's experience with sourcing compounds for manufacturing medicines and the unknown requirements for manufacturing either of the current potential alternatives at the scale required by Takeda to substitute OPnEO across the affected portfolio.

The currently considered alternatives, [redacted] and VIENEP17020, are not available at Good Manufacturing Practice (GMP) grade. Therefore, the process design for consistently manufacturing either of these alternatives at this grade would have to be established first. In parallel, if feasible, the process design will establish a scalable manufacturing method, i.e. the manufacturing processes of the alternative compound for quantities between 100 g and 10 kg should not differ in requirements (e.g. process conditions such as temperature, concentrations of reactants and/or potential catalysts, purification steps, etc.) other than equipment dimensions to the manufacturing of the alternative substance in quantities exceeding multiple tons. The scalability of the manufacturing process will be tried in a small-scale manufacturing model, producing material from 100 g to 10 kg first to confirm this is viable. This effort is expected to take 12 months.

Once the manufacturing method for consistently achieving the same material quality and grade has been established, performing the tests necessary to register the compound under REACH for commercial use has to be conducted and the registration dossier has to be prepared and submitted to ECHA.

In a best-case scenario, all required tests for a substance registration according to REACH Annex VIII (10-100 t/a) will take approximately 18 months to be performed. Taking into consideration, that laboratories need to be found and that potential re-runs could be required, a timeline of 24 months is estimated for the registration of the substance.

Overlapping with the chemical registration, Takeda plans to initiate and finalize agreements with detergent manufacturers to establish and initiate manufacturing. This effort is assumed to take 12 months, including transfer of manufacturing know-how, equipment assessment, installation and validation, and contract negotiations for the supply agreement. This duration will include all requirements for routinely supplying the substance in desired quantities and to the necessary quality standards required at the Takeda sites.

"Material qualification" is in fact performed in parallel to point 3.3.9 ("Process Performance Qualification") and thus the respective content of this phase does not impact the overall substitution timeline. Please refer to Figure 3 on page 49 of the AoA/SEA.

Q 12 - Regarding the previous question, please explain why these steps are performed only at this point, and not earlier, before investing so much time in pilot scales studies, non-clinical studies, etc.

It needs to be highlighted that the manufacturing processes of recombinant and plasma-derived medicinal products are highly sophisticated and sensible processes where each unforeseen event could have tremendous impacts on patient safety. Therefore, the R&D process described in chapter 3.3 needs to be carried out with extraordinary care and for each step potential risks impacting the medicinal product need to be excluded. Therefore, artificial acceleration of the R&D timeline by performing R&D steps in parallel is clearly unintentionally and has more potential to prolongate R&D timelines. To put it into a technical perspective, the steps are performed in the sequence as preceding steps, as described in chapter 3.3 of the AoA/SEA, first need to be confirmed with a positive outcome.

In addition, the development of a potential alternative is a cost and capacity intensive task supporting the approach of only initiating subsequent R&D steps if the alternative under evaluation has demonstrated effectiveness in the preceding step.

Q 13 - Please explain why the stability studies cannot be run in parallel with other steps in your timeline? And in particular why they can only start after the Performance Qualification, and cannot be performed on batches that would have been produced for non-clinical studies? In case the stability studies could start earlier, would that impact the regulatory approval timelines?

Currently, it is completely unknown how a potential alternative to OPnEO will perform in a production environment. The substitution scenario described in chapter 3.3 of the AoA/SEA has been designed to ensure resources, restricted laboratory & facility capacities and investments in the tests are allocated once the previous task has demonstrated an effective outcome. As mentioned under Q 12, patient safety is paramount. It is a prerequisite for many submissions of core documents to health authorities, that the stability of the material gathered in performance qualification runs is proven. Therefore, these two steps have to be performed consecutively. Stability studies for material derived from pre-clinical batch productions are only indicative but cannot be a replacement for stability studies performed on material derived from performance qualification runs. If there is confidence in stability studies performing positively whilst performance qualification is ongoing, these may run in parallel with a stability start off-set to the start of the performance qualification. Determining the level of off-set, and therefore the improvement on overall approval times, cannot be determined at this stage.

Q 14 - Please provide more details regarding step 3.3.12 ("Regulatory approval"). What is the estimate of 60 months based on? Is it based on particular territories that you sell to? Which?

The estimate for the regulatory approval period lasting 60 months is based on the cumulative standard health authority approval times from all markets where a product is registered and sold. After confirmation of the stability of the material produced from Process Performance Qualification runs, the first core document submissions including all data required for the post approval change of the manufacturing process of the medicinal product would likely occur in the US, European and Japanese markets. The required data comprises all information gathered through the steps described in chapter 3.3 of the AoA/SEA. The evidence of health authority approvals from these markets are, in the majority of cases, prerequisites for submitting the same change request in markets spanning non-EU Europe, Canada, Asia, Latin America and Africa. Additionally, the submission of the change request to markets in these territories requires adaptations of the core documentation to meet the market specific requirements, including any updates to the documentation resulting from the health authority assessments in the first markets (EU, US and Japan). These updates can only be made once the health authorities reviewing these submissions have completed their assessment and any requested change to the manufacturing process for the medicinal product has been confirmed as feasible. The documentation has to be updated prior to submitting the change to subsequent health authorities as the majority do not permit updated documents to be submitted whilst the assessment of the change is ongoing.

Ensuring globally harmonized change assessment and eventual approval by health authorities permits a more seamless implementation of the change and eventual supply of medicines to all

markets. National change approvals of diverging data would impede the supply of product to the detriment of patients globally, as additional or differing product release steps would have to be performed for these markets, thereby reducing the overall capacity of the company in releasing medicines from the impacted sites.

As stated in the application for authorization, Takeda can currently not state if a potential alternative in the S/D treatment step for virus inactivation will be directly interchangeable with OPnEO. Changes to the production process or technical equipment cannot be excluded, nor can it be stated that any change will be reversible in the production process to permit the production of product using the alternate substance and then to revert to the current OPnEO-based process. A change must therefore be considered uni-directional. As the sites manufacture products for global markets, the change will require approval from all destination market Health Authorities before this can be implemented on the production line. In other words, it is not possible to switch between OPnEO-free and OPnEO-based production processes for a product going to different markets.

Q 15 - Alternative 2 is one that has been developed and synthesized by yourselves. Is it possible for you to manufacture the substance by yourselves? If not, why not? If yes, how does that affect the development and approval process timelines?

Takeda is specialized in the manufacture of advanced biopharmaceutical products and the respective manufacturing processes are completely different compared to those used for the manufacture of small synthetic molecules (e.g. detergents). The manufacture of small synthetic molecules requires different equipment, facilities and expertise to that established in Takeda's facilities.

Under the assumption that one of the two shortlisted alternatives, [redacted] and VIENEP17020 (Alternative 2), would be the future OPnEO replacing substance, inhouse manufacturing at Takeda would not constitute a shorter overall substitution timeline. This is because the applicant would need to establish the required production facility including equipment and knowledge to synthesize one of the potential alternatives on large scale and under the conditions needed for pharmaceutical use.

Using a contracted manufacturer with the required environment (facility, equipment and knowledge) in place improves time towards substitution. The prerequisite for such a scenario is an alternative identified as a suitable for the replacement for OPnEO.

Q 16 - Please consider the paper published by the commission regarding the criteria for longer review periods (CA/101/2017), and provide argumentation based on your specific case.

According to the commission paper, "longer review periods than 12 years could be appropriate if all relevant information referred to in REACH Article 60(8) justifies it. According to the RAC and SEAC document on criteria for the duration of the review period, review periods longer than 12 years could be considered in *exceptional cases*".

In order to consider a review period longer than 12 years, in addition to the criteria for a 12-year review period established in the document *setting the review period when RAC and SEAC give opinions on an application for authorisation*, two additional conditions should jointly be met.

The justifications that the applicant clearly meets the criteria for a 12-year review are described in detail on p.21 and p.22 as well as on p.159 and p.160 of the AoA/SEA document.

In addition, the applicant has evaluated the criteria set by the commission for potentially granting longer review periods than 12 years. The criteria set in the CARACAL paper (CA/101/2017) are stated below including the corresponding evaluation of the applicant.

As evaluated by the RAC, the risk assessment for the use concerned should not contain any deficiencies or significant uncertainties related to the exposure to […] the emissions to the environment that would have led the RAC to recommend additional conditions for the authorisation. […] For applications for non-threshold substances, the applied risk management measures and operational conditions should be appropriate and effective in limiting the risks […]. For substances for which the risk cannot be quantified, a review period longer than 12 years should normally not be considered, due to the uncertainties relating to the assessment of the risk.

Currently, no agreement is available on committee level on how to monetize the risk of OPnEO emissions to the environment. However, Takeda tried to the best of its knowledge during the AfA

preparation in 2018/2019 to provide a monetized value for environmental impacts based on a benchmark study[4] investigating the costs of emissions of PBT substances. The calculations are described in detail in chapter 3.6 of AoA/SEA. The applicant is aware that this calculation method can only have supporting character[5] and therefore qualitative descriptions of environmental impacts were included in the SEA when possible.

Despite the missing agreed-on methodology for quantifying risks for Takeda's OPnEO emissions, Takeda clearly considers this additional criterion developed by RAC for potentially granting review periods longer than 12 years as fulfilled. All sites in scope of the AfA having had high OPnEO emissions have implemented RMMs to reduce these as far as economically feasible and reasonable. For detailed information on the measures implemented and the figures on the emission reduction levels for the respective sites please consider the CSR and responses to RAC's inquiries (reference can be found in Annex I of document).

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

Please refer to chapter 4 of the AoA/SEA where Takeda describes in detail all performed and ongoing activities related to the substitution of OPnEO in the production process of the medicinal products in scope of the AfA. Furthermore, in this chapter (chapter 4.3.) Takeda elaborates in detail that, based on the required substance functionalities (see chapter 3.2.3 of AoA/SEA), there is currently no technical feasible alternative available. In chapter 3.3 of the AoA/SEA, a detailed Development and Approval process including all phases and time estimates required to find and implement an alternative to OPnEO is presented.

Taking the findings derived from chapters 3.3 and 4 into account, Takeda considers this additional criterion developed by SEAC for potentially granting review periods longer than 12 years as fulfilled. Both chapters clearly demonstrate that a technical feasible alternative is currently not available, and that implementation cannot be performed within 12 years.

Furthermore, Takeda manufactures medicinal products which are subject to country specific marketing authorisations, i.e. approval from health authority such as EMA, FDA, etc., having tremendous impact on the overall substitution timeline. The required R&D steps and resulting data which needs to be gathered for substituting OPnEO in the manufacturing process of Takeda's medicinal products are described in chapter 3.3 of the AoA/SEA and clearly justify a review period longer than 12 years. At the end, it is the patient safety which is of highest importance and which needs to be ensured at all times. This is further in line with point d) of the commission paper (CA/101/2017).

[4] https://echa.europa.eu/documents/10162/13647/R15_11_pbt_benchmark_report_en.pdf

[5] https://echa.europa.eu/documents/10162/13637/seac_ed_approach_opneo_npneo_en.pdf/26c7779a-7228-2670-ad41-085d10ca056b

SEA-related questions

17) Please provide more information about Baxter, the company for which Takeda is acting as a CMO. Is it correct to say it is the Marketing Authorisation Holder for Tisseel, Artiss and Floseal? Is it completely independent from the applicants and Takeda? Is it based in the EEA?

In January 2016, Shire (acquired by Takeda in 2019) purchased the company Baxalta (which had been spun-off from the company Baxter in 2015). The applicant (now a Takeda company) still holds the name "Baxter" in its legal entity name only due to the previous transactions discussed above.

Baxter Healthcare International is a separate, multinational company, independent of the applicants or Takeda, which contract the applicant as a CMO. Baxter Healthcare International's national affiliates hold the market authorisations for Tisseel, Artiss and Floseal. Baxter has multiple locations around the globe and, in the European Economic Area, the company has legal entities in the following countries: Austria, Belgium, Czech Republic, Denmark, Finland, France, Poland, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain and Sweden.

18) Please provide clarification regarding the forecasted net profits for Baxter products summarised in table 40. Are these the profits accruing to Baxter? Or do they also include the profits gained from these products by the applicants through CMO activities? Please provide the information disaggregated by profits to Baxter and profits to the applicants.

Profits summarized in table 40 refer only to profits generated with sales of Tisseel, Artiss and Floseal as final products to customers, accruing therefore to Baxter. Profits related to the provision of CMO services by the applicant have not been considered in the monetisation of impacts due to its complex cost structure (see revenues amount in the first paragraph of section 3.4.1.3 in the AoA/SEA document). The profits generated with the provision of the CMO services must be considered as benefits of a granted authorisation, although they are described only qualitatively.

19) Similarly, who is expected to incur the costs described and detailed in section 5.1.3?

Costs foreseen in section 5.1.3 are foreseen to be incurred by the applicant.

20) Under the NUS, you expect a gap in production under the Non-Use Scenario. Could you provide a description (with a non-confidential summary) of the potential effect on the market (for instance, on supply and on price) of the lack of the medicinal products you produce? Do you expect competitors would have the capacity to be able to take over your market share? If so, what would be the timescale?

There will basically be 3 markets affected in case there is a lack of medicines manufactured by the applicant (own products + CMO): immunoglobulins, Haemophilia + Von Willebrand disease (vWD) treatments and fibrin sealants.

Immunoglobulins: the applicant is a very significant participant in the immunoglobulin market (in the top 3, see figure 10 in the AoA/SEA document). The supply of immunoglobulins is moreover highly dependent on the sourcing of plasma, which is very limited, and Takeda (with acquisition of Shire) has a quite a large network of plasma donation centres established over the years. Nearly every litre of raw plasma collected in the industry is used to produce IG products, (source: Marketing Research Bureau in the Worldwide Plasma Proteins Market 2018 report). Any company which wants to take over market shares from competitors, besides increasing its own capacity for medicines production, must also be able to increase its supply with plasma. The price of plasma has significantly increased in the recent years and pharmaceutical companies are often monitoring the prices paid for immunoglobulins in the different countries. Prices for immunoglobulins in the USA are significantly higher than the prices set by policies in European countries and this might trigger a supply shortage in Europe (in the short term) if a significant participant, such as the applicant, is required to leave the market.

Haemophilia + vWD: Shire (acquired by Takeda) has long been, and still is, considered the largest haemophilia therapy company in the world [redacted]. Its presence as a supplier of vWD treatments is also related to its engagement in treatments for rare diseases. Although the haemophilia/vWD markets are quite competitive, it can be a significant hurdle to switch to different

brands due to differences in the concentrates' properties (e.g. composition, level and functionality of von Willebrand factor and factor VIII).

Fibrin sealants: Baxter products manufactured by Takeda have very high market shares in EU, placing them as undisputed leaders (see "market position and competitors" description in section 3.4.1.3). Tisseel has been in the market for over 40 years and has an estimated [redacted] market share in EU. Artiss has virtually no direct competitors while Floseal is estimated to have [redacted] market share in EU. This leadership might make it difficult to adapt production capacity and take over Baxter's market shares in the short term.

In conclusion, we cannot say that competitors would not be able to take over our market share after they adapt capacities and find ways to increase their plasma supply. These efforts however may take multiple years (no information available to allow an estimation). The Immunoglobulin market is constrained globally and based on current supply evidence; no combination of competitor presence would be able to immediately assume the applicant's market share. Until supply chains are restructured/adapted, assuming this is feasible, a supply shortage both for Europe and globally would need to be considered as unavoidable.

21) We note that a great deal of information has been marked as confidential in the application. For the SEAC rapporteurs to be able to justify their conclusions in the opinion, they need to refer to certain key figures. Please provide non-confidential estimates or ranges for the following data:

a) Number of patients treated (in the EU and globally) with the medicinal products in scope of this authorisation (these can be grouped by 'family' of products)

It is important to stress that this application for authorisation aims to ensure continued global supply of the affected medicines, securing the needs of patients not only in EU but also abroad. For the sake of transparency, ranges for the number of patients in EU and non-EU countries (breakdown) are provided in Table 1**.**

Table 1: Number of patients

Product/product group	**Nr. Patients EU**	**Nr. Patients non-EU**
Kiovig + Cuvitru + HyQvia	1,000- 10,000 [redacted]	10,000 – 100,000 [redacted]
Gammagard S/D	100 – 1,000 [redacted]	1,000 – 10,000 [redacted]
Immunate	10-100 [redacted]	1,000 – 10,000 [redacted]
Tisseel	100,000–800,000 [redacted] annually	100,000–800,000 [redacted] annually
Artiss	10,000 – 16,000 [redacted] annually	10,000 – 45,000 [redacted] annually
Floseal	100,000–700,000 [redacted] annually	100,000–1,700,000 [redacted] annually

b) Economic costs under the NUS. Please provide estimates that are at least disaggregated into investment costs and opportunity costs (for the applicant and for Baxter). For lost profits, please use the methodology summarised in table 43 and also provide a nonconfidential estimate for the calculation you have done if only 1 year of lost profits is considered.

See Table 2. It is important to note that the ranges shown reflect only the minimum estimation of impacts and are not an extensive calculation of all impacts that could occur (conservative approach)

Table 2: Economic costs

Costs to be incurred by	**Cost Type (in EUR million)**	Investment **lower bound**	Investment **upper bound**	Opportunity costs (lost net profits during relocation) - **lower bound: 1 year**	Opportunity costs (lost net profits during relocation) - **upper bound: 3 or 4 years at least**	**Total (in million EUR) - lower bound**	**Total (in million EUR) - upper bound**
Applicant	**Ig Product Family**	100-1,000 [redacted]	100-1,000 [redacted]	1,000-10,000 [redacted]	1,000-10,000 [redacted]	1,000-10,000 [redacted]	1,000-10,000 [redacted]
	Immunate	100-1,000 [redacted]	100-1,000 [redacted]	10-100 [redacted]	10-100 [redacted]	100-1,000 [redacted]	100-1,000 [redacted]
	Orth-related commercial activities	100-1,000 [redacted]	100-1,000 [redacted]	Not monetised	Not monetised	> 100-1,000 [redacted]	> 100-1,000 [redacted]
Baxter	**Baxter Products**	0.1-1 [redacted]	0.1-1 [redacted]	100-1,000 [redacted]	1,000-10,000 [redacted]	100-1,000 [redacted]	1,000-10,000 [redacted]
					Total (million EUR)	**>1,000-10,000** [redacted]	**>1,000-10,000** [redacted]

c) If possible, years during which foregone profits are expected to occur.

It is not possible to define with certainty for how long foregone profits are expected to occur due to the multiple uncertainties regarding ramp up and regulatory efforts. Using a very conservative approach and only for illustrative purposes to show the very minimum costs that would occur in any case, the lower bound of the foregone profits estimation was calculated for 1 year and the upper bound for 3 or 4 years (depending on the facility/products) which is the minimum time for relocation only considering engineering efforts (total time for relocation, considering ramp up and regulatory efforts, to be more than a decade).

d) Number of jobs lost under the NUS

100-1,000 [redacted] jobs only considering the Lessines and Vienna facilities

e) Social cost of unemployment due to dismissal of workers.

EUR 10-100 [redacted] million

Annex I – References to CSR and RAC's inquiries

- CSR, page 45 description of the ECS, update of ECS description for Vienna given in the answer to question 7 from RAC's 1st round of questions; and paragraph 9.2.1. Vienna– Environmental contributing scenario 1: Use as detergent for virus inactivation and subsequent discharge
- CSR, page 56 to 57 description of the ECS, and paragraph 9.3.1. Lessines – Environmental contributing scenario 1: Use as detergent for virus inactivation and subsequent discharge
- CSR, page 66 description of the ECS, and paragraph 9.4.1. Orth - Environmental contributing scenario 1: Use as detergent for virus inactivation

The final release rates and efficiency of the RMMs are summarised in Table 25, CSR (final release rates for Vienna) and Table 30 CSR (final release rates Lessines) – corrected values are reported in answers to RAC questions (1st and 2nd round). Reasons why it is technically and practically not possible to further reduce emissions are given e.g. in the answer to question 18 from RAC's 1st round of questions. An overview of the efficiency of the implemented RMMs is presented in Table 3 below.

Table 3: Overview of the efficiency of implemented risk management measures (RMM) per site.

Release route	**Release estimation**
Vienna	
Water	As far as technically and economically possible OPnEO containing waste is incinerated[6]. Efficiency of RMM = **99.66 %**
Soil	No release
Air	No release
Lessines	
Water	As far as technically and economically possible OPnEO containing waste is incinerated[7]. Efficiency of RMM = **99.96 %**
Soil	No release
Air	No release
Orth	
Water	No release Efficiency of RMM = **100 %**
Soil	No release
Air	No release

[6] However, in case a more sustainable or technically better method is available in the future that leads to at least the same level of emission reduction, the applicants will consider this as an option for its process waste management.

[7] However, in case a more sustainable or technically better method is available in the future that leads to at least the same level of emission reduction, the applicants will consider this as an option for its process waste management.