Siemens Healthcare Diagnostics Products GmbH – Response to Questions

Submission number: XP602524-19

Communication number: AFA-C-2114485120-58-01/F

<table>
<tr><th colspan="3">Reduction of risk of alternatives</th></tr>
<tr><td>1</td><td>As all tonnage of used OPnEO for the Uses 1 through 5 is claimed confidential, please provide meaningful non-confidential intervals, that could be reported FOR EVERY USE. For instance: 0-1kg, 1-10 kg, 10-100 kg, 100-1000 kg</td><td>Please see Table below and the figures are also now included in the public version of the CSR, uploaded with this submission
<table>
<tr><th>Use #</th><th>Use title</th><th>tonnage</th></tr>
<tr><td>1</td><td>Industrial use - Use of OPE in isolation of protein from recombinant cell cultures for the production of IVD-kits (protein cell extraction)</td><td>1-10 kg/a</td></tr>
<tr><td>2</td><td>Formulation - Use of OPE in formulation of IVD kit reagents</td><td>1-10 kg/a</td></tr>
<tr><td>3</td><td>Formulation - Use of OPE in formulation of IVD wash solutions</td><td>100 – 1000 kg/a</td></tr>
<tr><td>4</td><td>Widespread use by professional workers - Use of IVD kit reagents on diagnostic analyser systems</td><td>100 – 1000 kg/a</td></tr>
<tr><td>5</td><td>Widespread use by professional workers - Use of IVD wash solutions on diagnostic analyser systems</td><td>1000 – 10,000 kg/a</td></tr>
</table></td></tr>
<tr><td>2</td><td>In the CSR you state that additional RMMs to minimise OPE emissions will be implemented for Use 1 by the Sunset day (implementation of system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration).
Please specify what kind of system will be implemented and how the efficiency of the implemented system will be proven and ensured?
Please provide a clear timeline when implementations of this additional system will start and</td><td>During protein purification regarding Use 1 the solution containing OPE with the target protein is applied to an affinity chromatography column where the target protein binds to the solid phase whereas the OPE-containing solution passes the column completely.

Currently the used OPE-containing solution which has passed the column is collected in a wastewater container or in the wastewater drain together with other wastewaters from cleaning and other OPE-free processes.

After implementation of the additional risk management measure, the separation of the OPE-containing solution in a dedicated waste container will be implemented into the current chromatography system by using a dedicated single-use container which must be labelled accordingly. The container will be classified as hazardous waste and sent for incineration (see Appendix 3 of the AoA-SEA document for Uses #1-3).

The efficient implementation of this new risk management measurement will be ensured by an update of the standard operating procedure for this process step according to local process change procedures in compliance to ISO 13485.
The update of the process procedure has been initiated in September 2019 and its finalization is planned by March 2020.</td></tr>
</table>

	clearly state when this system is planned to be in operation?	
3	Please clearly justify the appropriateness of the release factor of 0.5% for water for Uses 2 & 3. Please describe the methodology that is used to determine the release factor that represents the current situation in the facility.	The default emission factor for formulations (ERC 2) is 2%. This factor was replaced by 0.5% based on the following considerations: During formulation of buffers and reagents pure or concentrated OPE is transferred into laboratory containers like measuring cylinders and then into the mixing vessel or direct into the vessels. OPE adhering to related surfaces is carefully rinsed with water and transferred to the buffer solution in order to avoid losses and ensure exact concentration. The vessels used have a conic shape with a drain in the centre in order to minimize dead volume. The concentration of OPE in the reagents and buffers after mixing is approximately [redacted]%. The vessels are emptied through a drain at the bottom of the vessel so the dead volume of the mixture not entering the filling line is kept as low as possible. For example, in a 200 l vessel a loss of 0.5% due to dead volume of the vessel and adhering buffer would be not more than 1 litre. In a 1000 l vessel the loss would be not more than 5 l. Thus, an emission factor of 0.5% for formulation processes at Marburg is considered a reasonable worst case.
4	In the CSR you state that additional RMMs to minimise OPE emissions will be implemented for Use 2 by the Sunset day (Implementation of disposable bulk containers, classify empty containers as hazardous waste and send for incineration). Please provide a clear timeline on when implementations of this additional RMMs will start and clearly state when those RMMs are planned to be in use and how the efficiency of implemented RMMs will be proven and ensured? Please specify from which sources residual emissions will still take place for USE 2?	The efficient implementation of single use containers within the affected process steps will be ensured by an update of the standard operating procedures according to local process change procedures in compliance to ISO 13485. The change impact assessment has been initiated already and implementation is planned to be finalized by end of September 2020. Residual emissions after implementation of the risk management measure will be limited to emptied laboratory scale vessels which are used for weighing (graduated cylinders).
5	Please clarify what kind of filters were considered while in Alternative scenario 4 for the	This was presented only as a theoretical scenario on the assumption that such a filter system did exist; to the best of our knowledge, there is no filter system available that is specifically designed to deal with OPEs and which has proven to be capable of coping effectively with the type of wastewater generated under this Use. Therefore, due to the testing and

	implementation of additional RMMs for USE 3 („All wastewater passes through a filter, which captures the majority of the OPE and the filters are then sent for incineration“, AoA p. 209)? Please indicate if activated carbon filters were considered as such filters could be used for OPE removal?	potential design requirements and associated investment when work is underway to reformulate the products and eliminate OPE completely, we did not consider this to be the most feasible as opposed to capturing and incinerating OPE-containing wastewater in this case.
6	Cleaning and maintenance: a. Please provide information on procedures in place for cleaning accidental spills. b. Please elaborate on procedures used during the maintenance of equipment (frequent and/ or infrequent maintenance).	a) There are local operating procedures as to the handling of Triton X-100/X-405 in the event of an accidental spillage which cover the following elements: - Clear and close the affected area, inform supervisors - Wear appropriate PPE in regard to the product which has run out/spilled - Prevent entry into soil and waterways The specific instructions for disposal are described in the further operating procedure "Leak emergency bin" ensuring that potentially contaminated material is sent for incineration. b) Maintenance of the entire equipment is scheduled by the provider once per year.
7	Please explain the discrepancy in tonnage of used OPnEO for USEs 1 to 3 provided in Figures 1, 2 & 3 (Confidential CSR p. 6, 8 & 9) and Table 1 (Confidential CSR p. 10) as well as in the flowcharts presented in AoA.	The tonnage in the flow charts refer to use volume in 2017, while Table 1 reports use volume estimations for 2021. The year 2017 is stated in the header of the flow charts, except for Figure 1 of the CSR (omitted in error).
8	Please provide: a. Excel spreadsheets for release calculations presented in Tables 2, 3 & 4 (CSR for USEs 1 to 3 p. 13). Please clearly state amounts of OPnEO used as departure points for calculating maximum local releases of OP from various processes. b. Excel spreadsheets for release calculations presented in	See 'Release Use#' worksheets for each use in the uploaded Excel file ‘Confidential – XP602524-19 Additional Tables’ See separate document uploaded with this submission ‘Documentation of EUSES Modelling – Confidential’

	Tables 1, 2 & 3 (CSR for USEs 4 & 5 p. 8, 10-11). Please clearly state amounts of OPnEO used as departure points for calculating maximum local releases of OP from various processes. c. Documentation EUSES modelling outcome (printouts of in/outputs) for all Uses.	
9	Please provide PEClocals as non-confidential information for all USEs 1 through 5. Note: providing PEClocal information does not divulge specific info. about the tonnage of OPnEO as this value cannot be back-calculated.	A public version of the CSR disclosing the related figures is uploaded along with this submission.
10	On CSR p. 7, you state that „A small proportion of the applied OPnEO (assumption: < 0.1%) adheres to disposable materials like one-time pipettes, gloves, wipes, which are collected as solid laboratory waste (WSC 7; PROC 21) for incineration“. However, in the AoA p. 57 you state that “Solid waste from the site (POTENTIALLY including gloves, pipettes, etc.) is incinerated”. Thus please clearly specify exactly what kind of solid wastes that can be potentially contaminated with OPE are collected for incineration in Siemens Marburg facility (Uses 1 to 3).	All solid materials potentially in contact with OPEs (gloves, wipes, pipettes, pipette tips) are collected as solid waste. Solid waste from Marburg is sent for incineration due to local waste treatment procedures as described in the AoASEA document pg. 57.
11	Please revise the titles of tables 10 & 11 in the CSR for USEs 1 to 3.	Our apologies, the titles were incorrect and have now been revised. Correct titles are supplied in a new public and confidential version of the CSR.

	Please clarify if those tables relate to Use 1 or Use 2.	
12	OPnEO analysis in wastewater: Can you provide detailed contextual information on the measurements carried out? Has the applicant adopted a regular procedure for OPnEO analysis in wastewater (i.e. periodical measurements, etc)?	Wastewater samples were collected at the point of discharge from the building where the bulk manufacturing activities take place and where the wash buffers are formulated. We therefore considered this to be the 'worst case' discharge point and he one where sampling would be most likely to detect OPE in the wastewater to the wastewater network on site. This network then feeds into the on-site Wastewater Treatment Plant. Samples were scheduled so that they were collected directly during the manufacturing activity so that the volume of OPE would be at its highest possible value. No periodic measurement programme was subsequently put in place beyond the analysis undertaken (which was carried out over a 2 month period) as no OPE was detected, this was the expectation as the LOD for the method was 0.01% and as any OPE entering the drain would only be from minimal residues of dilute solutions left on equipment used and then washed we expect any OPE present would be at a concentration much lower than this.
Questions from RAC part USES 4&5		
13	For USEs 4 & 5: Please explain if attempts to determine the extent in which your customers do collect and dispose of (as hazardous waste) the used IVD kits, the solutions that were possibly contaminated with OPnEO or any other materials that could have been in contact with OPnEO, etc. have been made (for example by means of a questionnaire). If such attempts to find out, if and how much downstream users (i.e. your customers) do to minimise releases, were not made, please explain reasons for not doing so.	Siemens Healthineers have made significant efforts to engage with many of its customers in the EEA. It is worth pointing out that the number of analysers potentially impacted by REACH Authorisation for OPEs is in the [redacted] and accordingly the number of potentially affected customers is significant. Appendix 1 (Section 9) to the Use 4-5 AoA-SEA document presents the consultations undertaken by Siemens Healthineers. Section 9.2 presents the transcripts of interviews with three large customers and Sections 9.3-9.4 present the findings of a much wider survey. Section 9.3, page 191 notes: *"An invitation to participate in the survey was sent via mail (using national postal systems and email) from Siemens Marburg to approximately [redacted] (range: 1,000-10,000) relevant EU companies on their customer database. The invitation provided a two-week window for responding. However, this was finally extended by another three weeks to allow for further response. The survey was launched in Week 3 of March 2019, to ensure the most up to date feedback possible from customers."* The text on the same page continues: "*The survey contained 21 questions, including 6 which were related purely to demographic information (i.e. type of IVD facility, location (country and city/town), contact name, etc.), the number and model of Siemens Healthineers analysers and number of non-Siemens Healthineers analysers used. Particular attention was paid to [redacted] (range: 1-10) Siemens Healthineers analyser models of concern as these currently use the highest volume of OPEs. Questions also covered the handling processes of analyser wastewater, wastewater volume, costs associated with waste management, alternative processes for wastewater*

management, and customer perspectives on the tangible effects that separating analyser wastewater would have. Careful attention was paid to different models of Siemens Healthineers analysers, due to variation in OPE concentration in the products used on each type of analyser." (Note text highlighted here in red font).

Section 9.4.1 and in particular pages 195-196 provide relevant information collected through this survey.

Processes for managing analyser wastewater

Table Error *outlines respondent processes for managing analyser wastewater. As shown the majority of processes include the disposal of water via directly connecting the analyser to the drain. Of responses to this question, [redacted]% ([redacted] (range: 10-100) indicated that [redacted]% of their water was disposed in this way). Those indicating [redacted]% disposed by collection in a sump and disposed of as waste stated an average of [redacted]% of their output. Less frequently, waste water was collected in a sump and manually emptied down the drain ([redacted]%) with an average of [redacted]% of their output. A total of [redacted] (range: 10-100) 'others' were provided. These processes are summarised as collection in containers ([redacted]) (range: 1-10), ([redacted]%), manually treated with chemicals and emptied down the drain, disposal by a waste carrier ([redacted]) (range: 1-10), ([redacted]%), and N/A ([redacted]) (range: 10-100), ([redacted]%).*

Table Error! No text of specified style in document.**-1: Current handling of wastewater from Siemens Healthineers analysers – All responses**

Responses	Collected in a sump and manually emptied down the drain	Connected directly to the drain	Collected in a sump and disposed of as waste	Other	Total
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of responses with [redacted]% of their waste disposed via this method	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of responses with [redacted]% of their waste disposed via this method	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Respondents were also asked to estimate the volume of wastewater their analysers generate annually. This question yielded low quality results ([redacted]) (range: 10-200) with [redacted] (range: 10-100) ([redacted]%) unknowns. However, of those that provided an amount, an average of [redacted]% indicated [redacted] (1,000-10,000) per annum, the average being [redacted] (range: 1,000-10,000).

[redacted]

Figure Error! No text of specified style in document.**–1: Survey question responses: "*Does your facility have access to a central waste collection system?*" – All responses**

[redacted]

Figure Error! No text of specified style in document.**–2: Survey question responses: "*Do you collect and send wastewater to a Wastewater Treatment Plant (WWTP) or Incinerator?*" – All responses**

Figure Error! *indicates a strong tendency for respondents' facilities not to have access to central waste collection systems. Nor are they currently implementing special disposal of analyser wastewater via WTP or Incinerator (**Figure Error!**). Of those that do collect and send wastewater for disposal WWTP was the more common (WWTP: [redacted], (range: 10-100) Incinerator: [redacted] (range: 1-10). This suggests that for the majority of participants, alternative measures of disposal are not currently set up and it can be anticipated, as discussed in Appendix 3 (Section 11), that the associated costs for implementing this could be significant.*

Section 9.4.1, page 196 explains the information collected through the survey on the impacts from the theoretical implementation of additional wastewater management options.

Impacts of additional Risk Management Measures

Participants were also asked to estimate the costs associated with their current wastewater management processes as well as the costs associated with separating wastewater. Responses to these requests were low. E.g. regarding the former: [redacted] (range: 10-100) responses total, [redacted] (range: 10-100) of which were 'unknown').

Nevertheless, analysis of the qualitative responses indicates that respondents generally felt negative about the potential costs associated with these changes. [redacted] (range: 1-100) comments were dissected into [redacted] (range: 100-1,000) iterations of [redacted] general topics of concern, [redacted] (range: 1-10) of 'already implemented' and [redacted] (range: 1-10) of 'unknown'. For example:

- *[redacted]% of respondents indicated that such changes would be accompanied by increased cost;*
- *[redacted]% noted the need for structural changes (including of changes to buildings, pipework and engineering);*
- *[redacted]% indicated that there would be reliance upon external disposal contractors;*
- *[redacted]% indicated the need for increased storage; and*
- *[redacted]% also stated there would be a need to alter work routines.*

The rest of Section 9.4 presents country-specific analyses for France, Germany, Greece, Spain & Italy and the UK. In the context of additional wastewater management options, we would also draw attention to Appendix 3 (Section 11) which presents a very thorough analysis of the cost-efficiency of additional risk management options.

14	As in the CSR for Uses 4 & 5 you are implying that no RMMs are applied and all OPEs are released into environment, please clarify your statement in the AoA/ SEA (p. 5 of confidential version): "This AoA-SEA document demonstrates that the current practices of the downstream users of OPEs with regard to the treatment of their OPE-containing wastewater are in accordance with existing EU and national legislation". Please elaborate what kind of treatment of wastewater is performed at the downstream user sites. Please elaborate on ways you obtained such information.	The basis of the statement you are referring to was an analysis of the existing EU framework legislation on waste water and waste that was seen as relevant for these types of fractions. Details on this legislation are shown in Appendix 3 (p. 233). Furthermore, some examples of the national legislation in Germany and the UK, were analysed, to see if these legal acts might lead to additional treatment requirements. Other countries like Poland and The Netherlands were also screened but no indication could be found that additional measures were required – in the end focus was given to these two member states as applicants originate from these two countries and have a sound understanding of the relevant legislation as they have to realise it in their own installations. The analysis was performed as a desk research. Also, a search for additional information was performed, but an overall description on the way such laboratory waters have to be treated are scarce. Several papers deal with the question radio-opaque substances and active substances from medicine, which are emitted via toilet wastewater, but papers (basically only one publication that has explicitly that focus (see Appendix 3 footnote 14) and deals with laboratory wastewater. This paper in its latest version starts a discussion on the need to collect wastewater fractions as an option but confirms that disposal via the drain is the current established and legal practice. It is also worth to mention, that the established disposal practice was also a subject issued in the DU consultation (Appendix 1 p.184 ff.). The [redacted]) confirmed the "down the drain" practice that leads to a treatment limited to the established treatment for household wastewater. Also, the data from the DU survey ([redacted] contacted DU) indicate that only very few collect the wastewater for waste treatment (8% see table **Table 9-2: Current handling of wastewater from Siemens Healthineers analysers – All responses**, p. 195). It should be noted that in some exceptional cases this might be necessary for the reason that other hazardous substances are involved in higher concentrations.
15	On the page 7 of the CSR for USEs 4 & 5, you state that "It is assumed that any disposable materials like gloves, lab coats, pipettes, one-time pipes, which may be contaminated with OPnEO, is disposed of as solid waste for incineration". Please substantiate your assumption that all these materials are disposed as	This statement is an expert judgement based on experiences of the experts who prepared this application. The presence of potentially infectious material and chemicals often leads to a situation where solid waste has to be classified as hazardous according to the EU-wide existing framework legislation and the respective national legislation. Even in cases where this is not the case, the current practice would only in exceptional cases allow disposal on landfills. See Article 5 (3) of Directive 1999/31/EC in its consolidated version (last change Directive (EU) 2018/850 as of June 2018): […] "*3.Member States shall take measures in order that the following wastes are not accepted in a landfill:* *(a) liquid waste;*

	hazardous waste and are not just simply discarded as regular waste and landfilled (for example, was information gathered about the practices of your customers, etc?.).	*(b) waste which, in the conditions of landfill, is explosive, corrosive, oxidising, highly flammable or flammable, as defined in Annex III to Directive 91/689/EEC;* *(c) hospital and other clinical wastes arising from medical or veterinary establishments, which are infectious as defined (property H9 in Annex III) by Directive 91/689/EEC and waste falling within category 14 (Annex I.A) of that Directive;* *(d) whole used tyres from two years from the date laid down in Article 18(1), excluding tyres used as engineering material, and shredded used tyres five years from the date laid down in Article 18(1) (excluding in both instances bicycle tyres and tyres with an outside diameter above 1 400 mm);* *(e) any other type of waste which does not fulfil the acceptance criteria determined in accordance with Annex II;* *▼M4* *(f) waste that has been separately collected for preparing for re-use and recycling pursuant to Article 11(1) of Directive 2008/98/EC and Article 22 of that Directive, with the exception of waste resulting from subsequent treatment operations of the separately collected waste for which landfilling delivers the best environmental outcome in accordance with Article 4 of that Directive.* *3a. Member States shall endeavour to ensure that as of 2030, all waste suitable for recycling or other recovery, in particular in municipal waste, shall not be accepted in a landfill with the exception of waste for which landfilling delivers the best environmental outcome in accordance with Article 4 of Directive 2008/98/EC.* *Member States shall include information on the measures taken pursuant to this paragraph in the waste management plans referred to in Article 28 of Directive 2008/98/EC, or in other strategic documents covering the entire territory of the Member State concerned." […]* The relevant spots are (c) and (e). For (e) Annex II further specifies that a high organic content of a waste might lead to an exclusion of a waste for landfilling. In Germany the TOC (total organic content) of a waste that is allowed on a landfill is limited to 6 % (w/w). The high plastic content of the waste alone would therefore not allow that a waste is landfilled. Given the latest discussion under the circular economy debate the trend to avoid landfilling will further increase (see https://ec.europa.eu/commission/sites/beta-political/files/report_implementation_circular_economy_action_plan.pdf) A aim of maximum 10% of waste to be landfilled by 2035 is formulated. Since waste from hospital will, due to its composition, most likely neve qualify for recycling activities, incineration will continuously be the method of choice for this waste stream, in our assumption

		In conclusion it cannot fully be excluded that some hospital waste is landfilled, but with a high likelihood, based on the existing legislation, it seems to be the method of choice. Therefore, the assumption was made that the waste is mostly incinerated.
16	As the safety data sheet for the Triton-X contains a clear warning in „SECTION 6. Accidental release measures“ that the product should not enter the drains, please provide information on measures that were taken (if any) to additionally inform the downstream users on proper disposal of materials that could have been in contact with OPnEO, specifically giving emphasis to wash water releases to municipal drain systems. Also, given that clear warning in “SECTION 6. Accidental release measures“ please clarify why it wasn’t envisaged for the wash water to be collected from the analysers.	Annex II of REACH states on section 6: “*This section of the safety data sheet shall recommend the appropriate response to spills, leaks, or releases, to prevent or minimise the adverse effects on persons, property and the environment. It shall distinguish between responses to large and small spills, in cases where the spill volume has a significant impact on the hazard. If the procedures for containment and recovery indicate that different practices are required, these shall be indicated in the safety data sheet*.” In the case of the safety data sheet it is assumed that the recommendation refers to the pure substance as supplied, which is one litre of pure Triton. The same safety data sheet indicates a toxicity level of > 1 mg/l and no PBT properties. So on that basis it seems reasonable that for smaller amounts << mg/l (highest concentration in released waters – compare CSR Use 4+5 table 9 for Use 4 p.16 highest calculated PEC 0.0030 µg/L and Table 11 p. 19 highest PEC 0.19 µg/L both freshwater) these do not automatically require the same accidental release measures. In general, the disposal information given in safety data sheets supplied to Siemens customers is that waste water should be disposed of in accordance with the national legal requirements. We would like to emphasise that to the best of our knowledge wastewater from analyser systems at customer sites are directed to Wastewater Treatment Works (WWTW) and the analyses provided in the CSR documents which assume that there is a release to the environment after processing in the WWTW has taken place, has had to be made on the basis that it is not possible to prove otherwise. Even if we were to directly measure output from any WWTW after processing, it would not be possible to confirm whether any presence of OPE is relevant to our own input as it could have come from a multitude of upstream sources.
17	RAC takes note that you claim to emit (x kg of OPE/NPE per year, depending on the use). Would you have concerns if RAC would recommend an additional condition to reduce or eliminate to zero these emissions?	An analysis of the cost and proportionality of additional measures to reduce or eliminate releases of OPEs has been included in both AoA-SEA documents. In both cases, the documents include an Appendix 3 (Section 11) which presents this analysis in detail. <u>Applied for Uses #1-3</u>

	If yes, what in your view would prevent you [or your DUs] from implementing this condition? Please explain what additional measures you [or your DUs] 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.	Appendix 3 presents a range of theoretical options for reduction/elimination of OPE releases (Section 11.2) and Tables 11-1, 11-2 and 11-3 present: • Key technical parameters; • Key cost parameters; • Anticipated reduction in OPE emissions; • Benefits; and • Risks/Drawbacks for each additional risk management measure for each of the Applied for Uses. Section 11.3 goes on to shortlist the most likely option for each Applied for Use, discuss the proportionality of each measure and Table 11-4 (page 212) and express this as a ratio of implementation costs [€] per kg of OPE release avoided. The document notes, "*This table suggests that following costs for implementing the shortlisted RMMs for each of the Applied for Uses:* • *Use #1: ca. €[redacted] (range: €1,000-10,000) per kg 4-tert-OP release prevented;* • *Use #2: ca. €[redacted] (range: €1-10 million) per kg 4-tert-OP release prevented; and* • *Use #3: ca. €[redacted] (range: €1-10 million) per kg 4-tert-OP release prevented.* *It can be seen that only for Use #1 the envisaged cost for additional RMMs can be deemed proportionate. For this Applied for Use, Siemens Marburg has formally decided to implement the shortlisted RMMs which will reduce emissions by an estimated 95% and implementation is to be completed before the Sunset Date*." <u>Applied for Uses #4 -5 – Downstream Uses</u> Similarly, for Applied for Uses #4-5, Section 11.2 of the respective AoA-SEA document discusses current legislation and practices in the IVD sector and Section 11.3 describes the challenges faced by downstream users of Siemens Healthineers' IVD kits in segregating OPE-containing wastewater for further treatment/disposal. This section further estimates the volumes of wastewater that IVD product users would have to handle and dispose and presents examples of relevant analyser platforms that would be impacted. Table 11-2 (page 239) shows an example calculation of wastewater volumes to be incinerated and associated costs for a 'hot spot' customer (NB. the CSR presents the case of two 'hot spot' [redacted] customers using one of the highest volumes of IVD products and thus OPE volumes). Subsequently, pages 241-245 offer extensive commentary on the challenges of implementing segregation of

		wastewater collection and treatment and estimates of the associated costs (NB. cost estimates re discussed on pages 243-244).
Questions related to Analysis of Alternatives		
1	Please give the classification of the alternatives per use so as to allow RAC to conclude on the reduction of risks in the substitution activities. Please use the following table format: USE Title CAsr nr Classification Safer alternative (y/n)	Please see 'Table A – Alternatives' in the document 'Confidential – XP602524-19 Additional Tables' uploaded with this submission
2	On page 10 in the description of product types a reference is made to three product types that are impacted, the subsequent text of the paragraph only speaks about 2 product types (IVD kits and raw material) is this a typo or is the third product type missing?	It is correct that 3 product types are affected in use #1 ([redacted]). Two of these product types ([redacted]) are both IVD kit reagents. They are separated in two product types as one of them is a final IVD product ([redacted]) and the other ([redacted]) is an intermediate product. They have to be processed in two different Process Change Projects.
3	The structure of the AoA is difficult to work through, please provide in a table format a clear overview per use of products, alternatives and status and stage of substitution as well review period requested.	Please see the uploaded Excel file 'Confidential – XP602524-19 Additional Tables' The 'Table C - REACH Response Plan' worksheet provides information on assay formulations/products per use, status and stage of substitution projects (in many cases a number of assay formulations/products are grouped into 1 project), alternatives, and the review periods requested. The 'Table B – Tested Alternatives' worksheet provides information on the Siemens Healthineers-manufactured (non-OEM) assay formulations/products from the above REACH Response Plan which are currently undergoing or have completed Design Change (or Product Development Project) work, and the list of alternatives which have been tested with each of these, with information on the success of each alternative in each testing stage and the status.
4	The table (assume figure?) 4-5 (of e.g. use 4) could be expanded with the number of products involved, and greater detail and explanation on the time lines for each use.	Please see 'Table C - REACH Response Plan' worksheet in the uploaded Excel file 'Confidential – XP602524-19 Additional Tables' To give an overall explanation of the timelines for each use – <u>Use#4 – IVD Reagent Formulation</u>

		As well as knowledge of the typical periods required for Design Change and product development and each stage involved, the timelines which have been planned and set out in the REACH Response Plan per project are based on a number of factors outlined below. ➢ A key factor is the number of formulations affected, and also the number of products that each formulation represents (i.e. one formulation may be used in more than one product, and therefore represents more documentation and registration work). Typically, it can be seen that where projects involve more than 1 formulation, a longer timeline for the project is anticipated. ➢ Also, the type of technology/diagnostic field involved and a degree of empirical knowledge are factors, e.g. immunoassay technology may be more sensitive to a change of formulation than clinical chemistry technology, or it may be known, based on experience, that a one particular formulation is more sensitive to change than another. ➢ Another aspect is resource, i.e. there may be more technical resource available specialising in certain product types, or even the availability of project work from design work conducted previously which may assist with the project. <u>Use#5 – IVD Wash Solution Reformulation</u> Some An additional key factor in respect to IVD Wash Solutions are in regard to is the number of IVD Reagents the IVD Wash Solution is used with (i.e. used on the same analyser), as any change in IVD Wash Solution must be tested against all IVD Kit Reagents used on that same analyser. Another factor is in regard to whether any of the IVD Reagents on the relevant analyser also contain OPE and are subject to reformulation work, in which case it would not make sense to start reformulation work on the IVD Wash Solution until completion of the Verification Stage of the Design Change Projects related to the OPE-containing IVD Reagents. Please note however that the REACH Response Plan is exactly this, a plan, and while we will endeavour to execute to plan, and earlier where possible, it will inevitably be subject to change.
5	From the long list of shortlisted alternatives in table 4-1 on page 87, please indicate which alternatives have been tested, and what the outcomes of the tests are, where do the alternatives work and where do they still fall short?	Please see 'Table B - Tested Alternatives' worksheet in the uploaded Excel file 'Confidential – XP602524-19 Additional Tables', which lists the formulations/assays that are at an advanced stage of Feasibility Testing, with a list of each alternative tested and whether they 'passed' or 'failed' each stage of the testing so far conducted. All of the listed substances marked with "yes" in column three of Table 4-1 in the dossier have been tested in a number of Siemens Healthineers products. Examples for successful testing with a summary of the substitution process specific for the products are listed on the pages below Table 4-1. For the Marburg products the projects to substitute the OPEs were just started. Therefore, it is too early to provide information about working alternatives and materials that fall short.
6a	For what specific reason has substitution taken place at the	Investigation work has already started for the Marburg products.

	level of the general concern but not yet at the Marburg site.	In the first step products under development after 2013 were designed or re-designed to prevent OPE use, and thus work to identify alternatives where normally OPE would have been used. Examples are given in the AoA/SEA Uses#1-3 document on page 95. The next step was to rework the existing products and procedures described in Marburg AoASEA Uses#1-3 document. Design Changes for Use #1 relevant products are initiated and process changes started. The next step is to rework the products listed under Uses #2 and #3. Initial experiments to test alternatives started at Marburg site in 2019. As examples, products [redacted] were tested already with several alternative detergents like Tergitol TMN 10 and Tergitol 15S9. As described in the dossier changing the design of an IVD product is a lengthy process which must follow specific sequential steps. Firstly, the testing of the new detergent for standard parameters, this includes testing of standards and controls, calibration curves, reproducibility, precision, accuracy, etc. It is important to note that Marburg products are only a small part of the Siemens Healthineers global portfolio and OPE phase out programme known internally as the 'REACH Response Plan', with the rationale for prioritisation of products described in summarised in Sections 1.2 & 1.7, also Section 4.1.1 p.81 of the Marburg Uses #1,2,3 AoA-SEA document, and in further overall detail in Section 6.3 of the Customer Uses 4,5 AoA-SEA document.
6b	Please elaborate on the 'one size fits all ' statement (e.g. use 4 page 84 of AoA/SEA)	The statement means that an alternative detergent working for one application may not work for others. To clarify, it is not a "one size fits all" statement, it is "not one size fits all" statement. When re-designing an IVD Formulation with an alternative substance to OPE, it must be demonstrated through extensive testing that the alternative substance can a) perform the exact same function that OPE performed; b) not cause any inadvertent reaction with other chemical, biological or even physical components within that formulation The testing needs to be undertaken individually per each IVD assay formulation affected. It has already been shown through the testing and re-design activities carried out (each of these projects and their status are described on p.88 - 95 of the Uses 4&5 AoA-SEA document) that there will be no "one size fits all" alternative, i.e. while Surfactant X may prove itself an acceptable alternative in IVD Formulation A, it may cause an adverse effect in IVD Formulation B, and thus Surfactant Y will be used. Given that [redacted] of IVD formulations need to be re-designed in total, it is highly likely that this will result in a list of alternative surfactants being used overall to replace OPE. That exact list is not known until the testing activities for each IVD Formulation has been completed.
7	Describe why the products at Marburg site have not yet been substituted, and why in other sites this has taken place	See answer for Question 6a
8	Explain further what it means: adequate substitute for functionality will often lead to poorer performance on other key	We appreciate we should have phrased this more clearly in the application, there is no specific "trade off" as such, the scenario we were referring to here is in the regard to the technical description described earlier in this section of the AoASEA text, i.e. that an alternative substance may have the same functionalities as OPE and thus perform those functions adequately in the product, however it may perform another inadvertent and unwanted functionality which itself then throws

	functionality, explain the trade-off that are being made (e.g. more of the washing products, lower efficiency, etc) and substantiate this with test examples. Explain how this is applicable throughout the entire product range.	the biochemical reaction out of balance, or only be able to match one of the functions that OPE performs and is inadequate for another. As a result, the test does not give the right result. OPEs are not used throughout the entire SHS product range, only the products referred to in the application. In regard to the entire product range of OPE-containing products the scenario referred to above is part of the technical challenge for every single affected IVD Reagent. This could also apply to the IVD Wash Solution because, as described in the response to Question 11 (Use 4,5 specifically) any residues left of the wash solution on any parts of the analyser system where a test is performed has the potential to affect the biochemical reaction that is afterwards performed on that system.
9	In the AoA for all 5 uses (p.10-11 conf. AoA-SEA for Uses 1, 2, 3 & p. 14-15 conf. AoA-SEA) a reference is made to: 'case of Siemens Marburg a period typically of 5-12 years applies to the re-design of each formulation. The re-design of a product that does not contain itself OPE can be red-designed in a shorter timeframe, the applicant assumes a typical timeframe of 3 years'. Please justify this 8 and 3 years time period, including description of testing steps that need to performed, relevant uncertainties and references to regulatory approvals that are needed.	The AoA-SEA documents state that "*the re-design process leading to full substitution of OPE in one formulation and the commercialisation of all products associated with that one formulation can typically take 8 years; in the IVD sector, it is widely accepted that whilst the duration varies per product, a range of 5-12 years is realistic*" (see, for example, page 14 of the Use 4-5 AoA-SEA document). This estimate originates from a review undertaken by MedTech Europe (member of which is Siemens Healthineers) among its members. This timeframe is therefore considered 'standard' in the industry and we anticipate that other REACH Authorisation applicants are referring to this range in the same context. From a Siemens Healthineers-specific perspective, the types of substitution projects that the overall Substitution Plan (The so called "REACH Response Plan") involves are given in Section 6.3.1 of both AoA-SEA documents. Those sections explain the concepts of **Design Change Process (DCP)**, **Product Development Process (PDP)** and **Process Change** (the latter is only relevant to Use #1). Figure 6-1 (reproduced below for convenience) shows the typical duration of a DCP and PDP project. The figure shows a typical duration of 8 years and this is where the estimate of the duration of a single substitution project will be 8 years.  ***Figure** Error! No text of specified style in document.–3: **Overview of the duration of different types of substitution projects***

The different steps in each project type are shown in the figure. Furthermore, each step is described in Table 6-6 (page 163) which is reproduced below.

Table** Error! No text of specified style in document.**-2: Terms used in the description of activities encompassed in Siemens Healthineers' REACH Response Plan

Terms	***Description***
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

As far as the length of a Process Change Project is concerned, in Siemens Healthineers' experience such a project would indeed take ca. 3 years as noted in the AoA-SEA documents and on the assumption that there are no re-registration requirements. On the other hand, Process Change Projects are of relevance to Use #1 only and it can be seen in Figure 6-2 (copy below) that [redacted].

Figure** Error! No text of specified style in document.**–4: OPE Substitution Programme for Siemens Marburg's Applied for Uses #1, #2 and #3 - Overview

The apparent discrepancy between the typical duration of a Process Change Project of 3 years and the duration of Project #1 is that it involves more than one Process Change Projects running in parallel, also the work includes a number of other changes not related to the use of Triton™ X-100.

10	Please explain why substitution cannot be achieved within a shorter timeframe (normal review period), explain this carefully with simulations, calculations, etc.	As described in Section 4 of the AoASEA for Uses 4&5 the primary reasons for requesting a long review period are the high volume of products affected and the time and resources it takes to change the design of an IVD product. • Testing must be done on a 'per formulation' basis. While the substitution strategy described later aims to group similar or high priority products in the same project, there are no short-cuts in terms of feasibility testing. Each design must be subject to its own set of feasibility testing often with a different set of OPE alternatives; • The successful alternative cannot be known upfront. While technical feasibility criteria can be used as a guide, alternatives are primarily selected on an empirical basis and it is only through 'trial and error' testing with each identified alternative on a 'per formulation' basis that a successful alternative can be identified in the case of each IVD formulation design; and • The impacted range of products which use OPE is significant - within the Siemens Marburg portfolio [redacted] formulations use OPE (and [redacted]) and within the wider Siemens Healthineers portfolio [redacted]
Use 4,5 specifically		
11	Could you explain in further detail why after a product that contains OPE is used on an analyser machine the same machine must be cleaned using another product that also contain OPE.	Firstly, it is important to note - IVD Reagents and IVD Wash Solutions do not directly 'work together' on an analyser system as such, *however* the Wash Solution must be proven not to interfere with the biochemical reaction which happens as part of the test involving the reagent. To explain this further - The IVD Reagent and IVD Wash Solution do not meet on the analyser system and perform a reaction together. They are two separate products used on the same analyser system and have two separate functions. The IVD reagent is a key part of the biochemical reaction required to perform the test and analyse for the disease or condition. The function of the wash solution is to wash the system parts between every test to ensure there is no 'carry over' (i.e. molecules from one reagent and patient sample contaminate the next). An IVD Wash Solution must be proven not to cause any interference with the test result, e.g. if any molecules from the IVD Wash Solution were left as a residue in the reaction cup between tests, then it is perfectly possible that those molecules could interfere with the next test, so it must be proven over and over that those particular molecules do not cause that issue with any IVD reagent used on that analyser system. It is also important to note, while most of our analyser systems use IVD reagent formulations which contain OPEs, only some of those systems also use an IVD wash solution that contains OPEs. Therefore it is not essential that a system using OPEs in its reagents must also have OPE in the wash solution designed for that system, it is simply that it has proven to be the most effective combination in the scenarios where it is used in both reagents and washes. The reason why some systems use OPEs in IVD reagent formulations and also in the IVD wash solution goes back to the initial design of those formulations for the analyser system. The simple reason is because these solutions were proven at that initial stage (decades ago when OPEs had not been highlighted as an environmental concern) to work well together. It is

		certainly the case that when the initial solutions were designed, other surfactants would have been tried but were not successful. OPE proved itself in these cases to ensure a repeatable biochemical reaction without causing an adverse result, while also proved itself to be the most effective tested surfactant that would also wash the machine between tests.
12	Can one analyser handle multiple types of IVD kits, or does one type of kit fit only one type (make, type) of analyser? Can multiple wash solutions be used in the same analyser?	See response to Question 14 below. The same applies to an IVD Wash Solution (see also response to Q11 above) - each IVD Wash Solution used on an analyser is specifically designed for the analyser it is used on and has been tested with all the IVD Reagents used on that analyser to ensure it cleans the parts effectively without causing any interference with the biochemical reaction performed as part of each test.
13	What is a lifetime of an analyser, please clarify when most of them will be replaced? How many of the analyser currently on the market still use OPE and how many are using alternatives.	The information requested is presented in a dedicated table; this is Table 3-21, page 56-57 of the Use 4-5 AoA-SEA document. This table shows for each impacted analyser model the following information: • Number of analysers in the EEA • Average age of analysers in the EEA • Typical lifetime of analysers • Whether this mode is (a) Currently in use, (b) Currently on sale, (c) On sale in Jan 2021 A further two tables, Table 4-4 and Table 4-5, pages 112-113 explain our assumptions in scoping, quantifying and monetising impacts from a potential replacement of analysers. The first table is focused on the existing (2017) stock of analysers while the latter focuses on 'new' analysers projected to be sold in the years 2018-2020. It should be appreciated that the existing stock comprises a wide variety of analysers in terms of ages; some were sold in 2016 some others were sold in the mid-2000s and have been used for longer than their originally anticipated lifetime. To address this uncertainty, we have taken forward the average age of the stock of each analyser model (based on sales data held by Siemens Healthineers), add 3 years (to account for the period 2018-2020) and compared this to the expected/typical lifetime of that model to establish how many years of lifetime are left post-2020. For the 'new' analysers sold in the period 2018-2020, essentially the same approach has been followed, however, as there are projections of sales per year, we have used those projected sales numbers to generate the average lifetime of each analyser model and the compare it to its typical lifetime. This approach is described in Section 4.3.1, pages 109-110: *The approach taken to quantifying the costs for each Applied for Use is based on the following:* • *For existing stock, the average estimated age of the analysers is increased by 3 years (to see what their average age will be at the end of 2020) and is compared to the typical lifetime of each analyser platform to see what*

		remaining life would be forfeited if the analysers were prematurely replaced. For new analysers (sold in 2018-2020), based on projected sales in each of these three years, the average age of the analysers at the end of 2020 is calculated and then compared to the typical lifetime of each analyser platform. This approach means that several analyser types can be omitted from the calculations as they were launched several years ago, their average age is old and thus it is assumed that these analysers would be due for replacement by 2021 anyway and therefore the associated replacement cost cannot be considered an impact relevant to the "Non-use" Scenario; All the analysers presented in the tables referred to above use OPE-containing IVD kits and/or wash solutions. If the last part of the rapporteurs'' question above refers to all (incl. non-Siemens) analysers on the market, Siemens Healthineers is in no position to give estimates or speculate as to how many competitor analysers aimed at testing the same conditions/diseases use OPE-containing IVD products. Section 4.3.3, page 115 notes: *"In terms of competitor platforms, there are analysers available which offer similar diagnostic tests (with some exceptions), however it is unknown whether these are OPE-free. If a customer chose to move to a different platform, presumably the requirement for the analyser to be OPE-free would be a specification of the tendering process and customers would be able to ascertain that this was the case before proceeding."*
14	In your AoA/SEA on page 13 you make reference to that in the majority of cases third party kits can't be used, would that imply that some do, what hinders or stops others from doing so? Would those that can use it already be re-certified?	As explained on pages 106-108 of the AoASEA, some – but not all – Siemens analysers also accept third-party reagents. Those that do not ("closed systems") can only be operated using Siemens reagents. Other instruments will also accept third-party reagents. However, in order to be able to use a reagent on a specific instrument a number of requirements have to be met. 1. The methodology of reagent and instrument must match. An ELISA test, for example, cannot be run on a nephelometric instrument. 2. The reagent containers must physically fit into the instrument. 3. The reagent must be validated on the instrument. For IVDs, reagents and instruments are not separate, interchangeable entities. Regulatory clearance is given for the system comprised of instrument, reagent, calibrators, controls and consumables, i.e. all that is needed in order to obtain the test result. This includes a number of parameters (e.g. pipetting volumes, incubation time, wavelength of the light) detailing how the instrument performs the test. These parameters influence the test result and thus the patient management decision by the physician. Therefore, in order to use a third-party reagent, it must be ensured that the results obtained are valid. This requires substantial testing and documentation. This would be under the responsibility of the third-party reagent manufacturer or the customer.
15	How costly would the replacement of analysers be, in your AoA/SEA you state on page 13 that the	Table 4-4 on page 112-113 presents the average cost per Siemens analyser model. In the absence of pricing information on competitor analysers (NB. this information would never become available to Siemens Healthineers), we have assumed that the cost of a replacement analyser would be the same as the price of the Siemens analyser that is being replaced. Section 4.3.3., page 110 explains this approach:

<table>
<tr><td></td><td>analysers are not affected by REACH Authorisation.</td><td>“Since the third-party analysers exists in the same market as Siemens Healthineers’ analysers, it is reasonable to assume that the prices of the third-party analysers are similar in price to that of Siemens Healthineers ones. A typical price for a Siemens analyser is between [redacted] (range: €10,000-100,000). The analyser prices are also assumed to grow with the same pace as the inflation, which mean that the real prices are assumed to be constant throughout the review period”
The comment made on the text on page 13 is probably a misunderstanding. Section 2.2.1, page 13 states:
“If theoretically such OPE-free third-party IVD kit reagents could be found on the market, validation efforts required to adapt a third-party reagent to an existing analyser would be significant. In many cases DUs would in the medium to long-term switch analyser together with the reagent (and so having an IVD compliant solution at hand for all testing) or if available, add additional analysers that perform the OPE-free reagent testing. The replacement of the analyser would be a costly and, in many cases, premature solution, provided the new analyser is not affected by REACH Authorisation requirements.”

The text only aims to emphasise that all this replacement process and associated procedures and costs would arise under the key assumption that the new (i.e. replacement, third party) analyser will not be affected by the presence of OPEs on the Authorisation List, i.e. would not use OPE-containing OPE products.</td></tr>
<tr><td>16</td><td>The total market for analysers is difficult to grasp from the analysis you present in the AoA/SEA, statements like on p.87 ' ... this project ultimately identified the use of more then xxx products , representing over >xxx years unique formulations of IVD kits and IVD wash-solutions". At the same time in different places of AoA/SEA (ex. p. 1 & 9 conf. AoA/SEA) you provide different numbers for IVD products and IVD formulations. In order to clarify the discrepancies, please provide SEAC with exact numbers per each use. Does bigger number of products than the number of formulations imply that the same formulations are used in the products with different brand names?</td><td>The relevant summary is provided in Table 2-1 and Table 2-2, page-9-10 of the Use 4-5 AoA-SEA document. These are replicated below for convenience.

<table>
<tr><th colspan="3">Table Error! No text of specified style in document.-3: Overview of relevant IVD products within the scope of Applied for Uses #4 and #5</th></tr>
<tr><th>Product group</th><th>Number of IVD products</th><th>Number of IVD formulations</th></tr>
<tr><td>Number used by DUs in Use #4</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>…of which made in Marburg</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Number used by DUs in Use #5</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>…of which made in Marburg</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total number of relevance to Uses #4 and #5</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

Table *Error! No text of specified style in document.*–**4: Overview of relevant IVD products within the scope of Applied for Uses #4 and #5 with indication of reformulation plans under the Siemens Healthineers REACH Response Plan**

Applied for Use	Origin	Total No. products	Group
Use #4	*Siemens Marburg Use #2*	[redacted]	[redacted]
	Siemens Healthineers USA or OEMs	[redacted]	[redacted]
Use #5	*Siemens Marburg Use #3*	[redacted]	[redacted]

	Siemens Healthineers USA or OEMs	[redacted]	[redacted]

For comparison, the equivalent table from the Use 1-2-3 AoA-SEA document is Table 2-2, page 8.

Table** Error! No text of specified style in document.**–5: OPE containing products of relevance to this AfA (Uses #1, #2 and #3)

Applied for Use	***Total No. of products***	***Products***		
		Group	***Number of products***	
			Currently manufactured	***Planned to be reformulated (i.e. not end-of-life)***
Use #1	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
Use #2	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]
		The observation on the difference between number of products and formulations is essentially correct. A certain formulation may be used in more than one IVD product that detect different conditions/diseases (NB. these different IVD products will indeed have different names, but these are not 'brand' names). Reformulation/substitution will primarily focus on the number of formulations rather than products, although the presence of different components in two products based on a single formulation could have some bearing on the feasibility or not of any given potential alternative.
17	Please clarify whether the wash solutions needs to contain OPE in the same way as IVD kits? Where can other third party wash solutions be used?	It must be understood that all platforms have three main parts which are designed to work together to accurately perform a specific menu of tests when combined with patient samples. These are: • Analyser System (i.e. the machine the tests are performed on) • IVD Kits (a component of which is the IVD Reagent and basically performs the biochemical reaction) • IVD Wash Solution (which washes the analyser between tests) All protocols performed on an analyser rely on the IVD-kit and the application of an analyser-specific wash solution. There are in fact some analysers (also Siemens products) that have wash solutions without OPE, but it is not possible to apply this solution on an analyser that does include OPE, because test results will be influenced. Therefore, such a substitution would require testing with each IVD-kit that is performed on this analyser and all test parameters need to be verified again. This is irrespective of whether OPE is used in the IVD-kit itself or not. In principle, a

		DU could adapt the analyser but they would no longer receive comparable test results because each test is calibrated for the platform system (including all three parts listed above). So it could be concluded that the dependency on the technical level might be less for a wash solution than for the IVD-kit, as the core test principle is not affected. However, the entire test is optimised for all three parts (also the liquid handling on the analyser needs to follow a strict protocol to ensure reproducible test results) so not one of these parts can just be changed without affecting the test performance. As a result of this dependency, one part of the substitution strategy proposed is to start substitution of an IVD Wash Solution containing OPE only when all IVD-kits that run on an analyser system are OPE free. This is to avoid the change of test parameters at the same time and directly develop a wash solution that then works for the future. In the meantime, DUs are able to perform the full range of testing with the existing system and to keep up patient diagnostics. The role of the wash solutions and the differences to IVD-kit reagents are described in chapter 3.1.2 Introduction to IVD kits reagents and IVD wash solutions and chapter (p. 19 ff) and in particular 3.1.4 Use #5: Use of IVD wash solutions (p. 26). Further information is also given in 4.1.1 Research and development of the AoA-SEA document on use 4+5 (p.76 ff)
18	How does the concept of the IVD wash kit work? Is there one universal wash solution for all analysers?	Wash solutions ensure proper accuracy in test results due to samples and reagents coming in contact with common instrument hardware - typically fluidic tubing, reaction cuvettes, sample probes and/or reagent probes. Not all systems need OPE containing wash solutions, e.g. some use NaOH, others, like [redacted] use disposable sample tips. An universal wash solution is not currently available, and may not be possible for the reasons explained in the response for Question 17. Even if it was possible, all the steps of re-designing an IVD product must be stepped through to prove the efficacy of any new IVD Wash Solution.
Siemens use 1, 2, 3 Non-use scenario		
1	The NUS relocation implies that also in the long-term customers would not move back to Siemens Marburg products and analysers, after relocation and regulatory approval of production is completed. This implies that competitors´ capacities at least over the mid-term are sufficient to close the market gap, and IVD products and wash solutions have comparable quality, and the performance of OPE-independent	The reality is that Siemens Healthineers is in no position to assess whether competitors use OPE, to what extent they can or will substitute, which models rely on OPEs, which conditions/diseases are detected/measured by competitor analysers or whether competitors have spare capacity. The market is opaque, particularly given that Siemens Healthineers markets a significant range of OPE-dependent products. The assumption that customers would switch to alternative analysers/OPE supplied by competitors is thus probably over-optimistic, particularly as some competitors are also known to face OPE-related challenges. However, it has been taken forward for two key reasons: • It allows some quantification (and monetisation) of potential downstream impacts in the event of non-Authorisation, with the understanding that the actual impacts may be significant more severe; • The severity of impacts that would actually arise if competitors were not able to close the market gap would, to put it simply, unthinkable. The public health and political implications of healthcare providers in the EEA becoming unable to

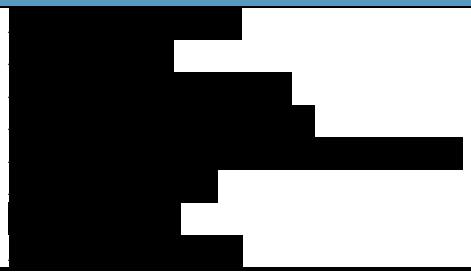
	IVD kits covers the similar range of diagnostics. However, it is stated in the application regarding analysers that "it is not known if […] any competitor analysers diagnose the identical set of diseases as the Siemens Healthineers ones"(p. 111). It is also not clear whether competitors´ IVD kits have a comparable performance.	diagnose and treat a wide range of diseases (including life-threatening or terminal ones) would be unprecedented, but also very difficult to scope. Therefore, please consider the approach taken as a very optimistic one rather than as confirmation that the IVD market would cope well if Siemens Healthineers abruptly withdrew their products for several years or permanently. Section 5.1.6, pages 126-127 of the Use 1-2-3 AoA-SEA document (but also Section 4.3.3 of the Use 4-5 AoA-SEA document), outlines the process of replacing an analyser. For convenience, this is replicated here: "A typical customer in a large hospital reference lab may be running up to [redacted] (range: 10-100) analysers from a particular platform, or potentially a range of analysers from different platforms. Faced with the situation whereby they can no longer utilise some or all of their existing analysers because the tests they need to run contain OPEs, these are the steps they would need to follow to purchase new analyser systems: 1. Define their testing needs: this would require a full review of all the tests they are required to perform across the range of analysers currently in use, looking at numbers and types of tests, throughput, turnaround times, performance requirements, reference ranges, available staff numbers, etc. 2. Analyse capacity: this could potentially be compared to 'building a new house', plans and schematics are normally drawn up of the laboratory areas to calculate how much space is available. Analysers, and especially groups of analysers, can take up quite a lot of space, as well as the adjacent space required for peripheral services for sample prep, hand-washing, waste management, etc. 3. Put the contract out to tender: IVD companies (suppliers of analysers) are invited to tender. The laboratory's requirements are reviewed, analysers within each supplier's range are identified and confirmed as to whether they meet the customer's needs from a testing and capacity perspective. This can involve several rounds of site visits and exchanges of information to ensure all needs are fully known and understood. 4. Discuss contract details: contractual arrangements are discussed, for example the ongoing purchase of IVD products for specific analysers (i.e. IVD kit reagents and IVD wash solutions), pricing, contractual terms and periods, ongoing sales and service arrangements, etc. 5. Delivery and installation: once a contract has been agreed, delivery and installation of the analyser systems take place. This can sometimes involve civil work to cater for any changes in layout or analyser size, to ensure a power supply, access to water and potentially to accommodate waste or drainage arrangements. In addition, a period of validation based on the customers' Quality Management System would be required after installation and before the start of routine testing. For larger installations this can take 8 weeks or more. 6. Training: training on the safe and effective operation of the new analyser systems is arranged and takes place, normally provided by the supplier IVD company. 7. Adaptation to local procedures: local procedures in the laboratory are updated and training on any changes are documented.

		8. Follow-up communication: communications are arranged by the customer to their healthcare provider network to ensure any changes, for example reference ranges or turnaround times, are fully understood and incorporated into any of their local procedures or required documentation. The above tendering process through to completion normally takes longer than 12 months, often up to 2 years in the case of larger laboratories." This is clearly a very complex process. Even at the IVD product (not the analyser level), switching to an alternative IVD product is not straightforward due to the validation process involved. Section 4.3.3, page 114 notes: "Validation costs: as mentioned above, there will be a transition period when switching from one platform to another. The new analyser would need to be tested, tests results will need to be verified and, in some cases, new benchmark values (values against which tests results are measured) would have to be established. This process usually takes 12+ months, but may be possible to carry out in 10-12 months under significant time pressure. To carry out the validation, both staff and IVD kits and accessories will be needed to carry out the tests. The number of person hours needed during 10-12 months period is difficult to estimate due to the variation in time needed per test and the level of automation. Each analyser offers a range of assays that can be tested; some or all of them could be of interest to any one customer and for each of the assays of interest additional kits would need to be purchased for the needs of validation tests. The material cost of validation is not quantified here as it is deemed to be only marginal, compared to the cost of replacing the analysers themselves." Overall, a switch to a new analyser and set of IVD products would require significant investment in time, resources and funds. Page 109 also notes "Siemens Healthineers' analysers typically have a lifetime of [redacted] years with the majority having a lifetime of [redacted] years". It is reasonable to assume that that competitor analysers have similarly long lifetimes. Purchasing new analysers (and many customers would have to invest in several analysers) would be a significant investment which would not be abandoned if and when Siemens Healthineers returned to the market. As Section 4.3.2, page 111, concludes: "Ultimately, if Siemens Marburg initiated the relocation of its manufacturing activities, it would engage in a lengthy process which would keep its IVD products off the market for a period of time too long for the customers to persevere. Customers would move to alternative means of delivering their diagnostic services (certainly hospitals could not afford to wait until Siemens Healthineers sorted out its manufacturing relocation issues). Once such operation changes and investments would be made, those customers would not return to Siemens Healthineers' analysers and IVD products. In other words, absence from the market for up to 30 months would mean that the market would be lost".
2	Can you characterize the performance of competitors´ IVD-kits in such a way that it is plausible that customers would shift to alternative analysers and to alternative suppliers of IVD-kits permanently.	The reason behind the assumption that customers would move to alternative analysers and products are explained above. Essentially it is not a matter of performance and Siemens Healthineers cannot offer an informed opinion on the relative performance of competitors' IVD products. Generally speaking, performance is indeed one of the criteria used by healthcare and lab testing service providers when selecting analysers and the kits that come along with them. For example, looking at the input made by consultees presented in Section 9, criteria used in selecting new analysers include:

		Page 184: [redacted] Page 186: [redacted]. Page 189: [redacted] Other criteria may also be important on a case by case basis, e.g. compatibility with existing stock of analysers or ability of an analyser to meet the specific needs of the lab (i.e. an analyser that combines tests for Conditions, X, Y and Z which the lab is interested in). However, irrespective of relative performance, two IVD kits measuring the same parameter may have different benchmark ranges, require the development of new protocols, extra training of staff, and therefore will not be directly interchangeable. The assumption that customers would move to alternative IVD kits has been made to allow for some quantification of impacts under a best-case Non-use Scenario, rather than to suggest por imply that competitors' IVD products are performing equally 'well' as Siemens Healthineers' ones.
3	Can you provide information e.g. on development of market shares, production volumes of the applicants´ competitors which make it plausible that competitors´ capacities may be adapted in adequate time to cover increased market demand?	This is not an analysis that we have conducted at this point, it is typical manufacturing practice to assess volumes, trends of our own internal capacity, usually with a 5-10 year outlook. We know from market reports the general market share and in our view it could be assumed that any competitor would look to adapt and absorb if there was the opportunity to increase market share, for example due to the addition on Annex XIV of OPE. However it would be very difficult to conduct a focused analysis on competitor capacities specifically in regard to this substance as we don't know the exact capacities of competitors, e.g. manufacturing environments, people employed, functional distribution etc, and we also do not know which specific competitor products are impacted by the addition on Annex XIV of OPE.
Economic impacts Use 1,2,3,4,5		
1	Can you provide, annual figures and ranges for figures for profit losses of Siemens Marburg, Siemens Llanberis, Siemens Healthineers, and for the social costs (for each of the use, please).	Please find the requested information in Table E – Annualised Costs of the worksheet in the uploaded Excel file 'Confidential – XP602524-19 Additional Tables'. As the AoA-SEA documents explains, profits under the Applied for Use Scenarios (and therefore losses under the Non-use Scenarios) will vary on a year-on-year basis as the market develops. The table thus uses the cumulative discounted costs to back-calculate annualised estimates of costs/impacts.
2	P. 44, Table 3-20: Can you describe the set of IVD kits which are dependent from the wash solution	The wash solution can influence all IVD kits run on an automated system irrespective of whether the IVD kits contain OPEs or not. Please find in Table D of the uploaded Excel file 'Confidential – XP602524-19 Additional Tables' for the list of reagents which are dependent on the wash solution. It is important to highlight that the wash solution is extremely important in

<table>
<tr><td></td><td>(use 3). We suppose this set encompasses IVD kits of use 2&4 and others.</td><td>ensuring consistent test result generation on an automated analyser system. As well as running in sequence, often several IVD kits are run in parallel on an automated system. During this process the pipettors will use the same needles for pipetting the different kit reagent (including a wash step in between). It could be that reagents from one IVD kit will interfere with substances of another IVD kit and therefore influence the results of the second test if the washing step in-between is not adequate.</td></tr>
<tr><td>3</td><td>Table 4-6: Can be please clarify whether the profit losses for use 1 comprise the lost sales of the raw TSI protein extract to Siemens Llanberis, third-parties, and from lost sales of IVD kits produced with this protein extract by Siemens Marburg?</td><td>The profit losses shown in Table 4-6 reflect profits from sales of IVD kits that depend on Use #1 extracts to customers (third parties). As the footnote in Table 4-6 notes, “profits from sales of [redacted] IVD kits are allocated to Siemens Llanberis and thus are not included here to avoid double-counting”.

This table follows from Table 3-11 (page 41) which refers to “profits from sales of IVD kits relevant to Use #1” and <u>excludes</u> [redacted]-related sales.</td></tr>
<tr><td>4</td><td>On p. 50 weighting factors are used to attribute the profits due to the sales of analysers in EEA to the three different uses. Can you roughly describe how these factors were calculated, please?</td><td>Table 3-23 has demonstrated the overlaps between Applied for Uses in terms of relevant analysers (see for instance [redacted] analysers being relevant to both Use #1 and Use #3). In the EEA in 2017 there were a total of [redacted] relevant analysers but if the analyser numbers per Applied for Use shown in the table below are summed up ([redacted]) a larger total number is obtained.

<table>
<tr><td colspan="4">Table Error! No text of specified style in document.-6: Relevant analyser models per Applied for Use</td></tr>
<tr><td rowspan="2">Applied for Use</td><td rowspan="2">Requested review period (years)</td><td rowspan="2">Relevant analyser models</td><td colspan="2">Number of existing (2017 stock) analysers in use by customers</td></tr>
<tr><td>EEA</td><td>Non-EEA</td></tr>
<tr><td>Use #1</td><td>9</td><td>  </td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

		Use #2 | *12* | [redacted]
		Use #3 | *12* | [redacted]

When looking into the profits that Siemens Healthineers is projected to make from 2021 onwards, we need to reflect these overlaps in order to allocate portions of the total profit to each of the Applied for Uses. Table 3-24 (see copy of it below) has shown that Use #1 is associated with a number of analysers that is larger than the other two uses combined and Use #3 is associated with the lower number of analysers sold. We therefore made the following assumptions:

- We ignored any differences in profit margins between analyser models – if we had not done this, the analysis would become unduly complex. Instead, we focused on the numbers of analysers per Applied for Use;
- Use #1 accounts for the largest number of analysers hence the highest relative proportion of profit, followed by Use #2 and finally Use #3 accounts for the lowest number of analysers/share of profit;
- The three profit shares for each Applied for Use need to add up to more than a 100% to reflect the overlaps discussed above; and
- Finally, taking into account the relevant analyser sales in Table 3-24 ([redacted]) we came up with assumed profit shares, i.e. [redacted]

Clearly, these percentages are not robust and have only been used to split the overall profit figure of €[redacted] (range: €10-100 million) in three parts. Other combinations of percentages might well be used. This is acknowledged on page 50: "*Again, these are rough estimates which take into account of the overlaps and cannot be aggregated. The correct overall profit figure is €[redacted], as shown above*."

5	Figures for Sales of EEA-made analysers for uses 1-3 (p. 50) and figures for sales of relevant analysers (p. 47ff) are shown. Does the later one include EEA- and Non-EEA manufactured analysers?	We assume that this question refers to Table 3-24 (page 47-48) and Table 3-26 (page 51) of the Use 1-2-3 AoA-SEA document. These are reproduced below, for convenience. Your interpretation is correct. The former table shows all analysers sold by Siemens Healthineers which are relevant to Uses #1, #2 and #3, while the latter table focus on a sub-set, those analysers which are manufactured in the EEA (NB. this is done to scope impacts within the EEA).

Table** Error! No text of specified style in document.**-7: Number of affected analysers envisaged to be sold in the future per Applied for Use

EEA-sales for the year…	*Use #1*	*Use #2*	*Use #3*

	Can you clarify the difference, please?				

2018	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]
Post-2022	[redacted]	[redacted]	[redacted]
EEA total over the review period	[redacted]	[redacted]	[redacted]
Non-EEA sales for the year…	***Use #1***	***Use #2***	***Use #3***
2018	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]
Post-2022	[redacted]	[redacted]	[redacted]
Non-EEA total over the review period	[redacted]	[redacted]	[redacted]
Grand total over the review period	[redacted]	[redacted]	[redacted]

Table** Error! No text of specified style in document.**-8: Number of affected EEA-made analysers envisaged to be sold in the future– Analysers relevant to Uses #1, #2 and #3

Year	***Total EEA-made analysers sold to EEA customers***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***Use #1***	***Use #2***	***Use #3***
2018	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-2022	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Year	*Total EEA-made analysers sold to non-EEA customers*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Use #1*	*Use #2*	*Use #3*	
		2018	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2020	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2021	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2022	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		Post-2022	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
6	On p. 66 and 67 two tables 3-26 are shown. Which one is the correct one?	There is only one Table 3-26 (pages 61-62 of the Use 4-5 AoA-SEA document) which (perhaps confusing, our apologies for that) is split into two parts. The part shown on page 61 shows data relevant to **EEA-made analysers sold to <u>EEA customers</u>**, while the part shown on page 62 shows data for **EEA-made analysers sold to <u>non-EEA customers</u>**.										
7	On page 120 it is stated that "This profit could be in jeopardy if the sale of 12+1 relevant IVD kits are impacted. The exact extent of impacts cannot be estimated so the profit figure shown above [(Tab 3.4)] should be assumed to be the maximum benefit achieved through the continued use of OPE in Marburg under Applied for Use #1." Can you explain, please.	The text indicates that profits made by Siemens Healthineers from sales of analysers which are relevant to Applied for Use #1 would be impacted if the relevant IVD kits were unavailable. The total profit from EEA sales of the relevant analysers is estimated at €[redacted] (range: €10-100 million - see explanation of assumptions made to reach this estimate). Profit from sales to non-EEA customers are ignored, but it might well be impacted. The fact that a range of IVD kits would become unavailable does not automatically mean that the relevant analysers would not be sold. In fact, some customers may have no interest in those specific IVD kits; they may be interested in running different tests. As such, a loss of €[redacted] in profit would be the maximum loss under the "Non-use" Scenario or, put differently, the maximum benefit from the continued use of OPEs in the context of this Authorisation.										
Social impacts												
8	The employment effects are estimated separately for uses 1, 2, 3, and then aggregated by summing up. There seems to be some overestimation possible in case workers are involved in production steps of use 1, 2 and 3	The number of associated job losses in Marburg for the three Applied for Uses is [redacted] (range: 1-10%) of total employment in Marburg. Although it is possible that some of these workers may be suitable for being allocated to operations relevant more than one of the Applied for Uses, the number of job losses estimated is certain an **underestimate**. We can demonstrate this with a simple example: if IVD kits X, Y Z became unavailable, sales of analysers A, B and C would be impacted. However, analysers A, B and C use a much wider range of IVD kits made in Marburg which do not rely on or contain OPEs; their sales would consequently be impacted, demand for them would decline and this could lead to additional indirect job losses in Marburg.										

<table>
<tr><td></td><td>simultaneously. Can you clarify this, please?</td><td>If we further considered the reputational damage for Siemens Healthineers from its inability, under the Non-use Scenario, to supply a wide range of IVD products to [redacted], it would be very reasonable to assume that the [redacted] jobs lost estimated above is too modest a number.</td></tr>
<tr><td>9</td><td>For monetization of social impacts of unemployment the SEAC approach was followed, and for calculation the average salary for Germany was used. Could you please provide information on the average salary of Siemens Marburg staff (pre-tax worker compensation) employed in the production of IVD kits compared to the German average salary. Can you also characterize their competence level and skills in comparison to workforce of the Marburg region, and whether their expected duration of unemployment is comparable to the German average.</td><td>The average salary of Siemens Marburg staff is estimated at [redacted] (range: €10,000-100,000)[1], i.e. [redacted] average salary in Germany of €45,252 which has been used in the calculation of social impacts. The estimated average salary of Siemens Marburg staff was calculated according to local policies and includes holiday and bonus allowances. We cannot make any valid statement in respect to the difference of the duration of unemployment Marburg areas vs. Germany. Therefore, we refer to the German average as highlighted in the AoA-SEA document.

If we change the salary for Siemens Marburg workers to [redacted] but retain the salaries of [redacted] 3rd party works in Germany at €45,252, the social costs can be recalculated as shown in the extended Table 5-10 (originally on page 152) shown below.
<table>
<tr><th colspan="4">Table Error! No text of specified style in document.–9: Estimation of social benefits from the continued use of Triton™ X-100/Triton™ X-405 in Marburg</th></tr>
<tr><th>Use #1</th><th>Number of jobs lost</th><th>Social costs
Original estimate</th><th>Social costs
Updated estimate</th></tr>
<tr><td>Siemens Marburg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Siemens Llanberis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Suppliers and customers</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3rd party contractors - Marburg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3rd party contractors - Llanberis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total avoided jobs lost</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>Use #2</th><th>Number of jobs lost</th><th>Social costs
Original estimate</th><th>Social costs
Updated estimate</th></tr>
<tr><td>Siemens Marburg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Siemens Llanberis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Suppliers and customers</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3rd party contractors - Marburg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3rd party contractors - Llanberis</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total avoided jobs lost</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th>Use #3</th><th>Number of jobs lost</th><th>Social costs</th><th>Social costs</th></tr>
</table></td></tr>
</table>

[1] This is an average for **all** Siemens Marburg employees, excluding senior management.

				Original estimate	Updated estimate
		Siemens Marburg	[redacted]	[redacted]	[redacted]
		Siemens Llanberis	[redacted]	[redacted]	[redacted]
		Suppliers and customers	[redacted]	[redacted]	[redacted]
		3rd party contractors - Marburg	[redacted]	[redacted]	[redacted]
		3rd party contractors - Llanberis	[redacted]	[redacted]	[redacted]
		Total avoided jobs lost	[redacted]	[redacted]	[redacted]
		Sum of all 3 Uses	[redacted]	[redacted]	[redacted]
		Worst-case scenario	**Number of jobs lost**	**Social costs Original estimate**	**Social costs Updated estimate**
		Siemens Marburg	[redacted]	[redacted]	[redacted]
		Siemens Llanberis	[redacted]	[redacted]	[redacted]
		Suppliers and customers	[redacted]	[redacted]	[redacted]
		3rd party contractors - Marburg	[redacted]	[redacted]	[redacted]
		3rd party contractors - Llanberis	[redacted]	[redacted]	[redacted]
		Total avoided jobs lost	[redacted]	[redacted]	[redacted]
Siemens use 4 & 5 Market trend					
10	P. 51, Table 3-13: Table shows Siemens´ profits of selling IVD kits. The left column shows the profits of Marburg and other production sites, and the right column the profits of Siemens without Marburg. Thus it can be concluded that profits of Marburg are small. Can you clarify, please?	The table shows that profits from sales of Marburg-made IVD kits is relatively small when compared to sales of kits made outside the EEA by other Siemens Healthineers facilities. Still as shown in Table 3-14 on the same page, Marburg-made IVD kits represent a total profit of [redacted] (range: €10-100 million) over the requested review period. Although relatively small, this is a considerable amount of profit which is very important for Siemens Healthineers operations.			
Non-use scenario					
11	The switch to analyser platforms using OPE-free IVD kit reagents and IVD wash solutions was considered as the most likely non-use scenario. But, it seems very uncertain whether OPE-independent IVD kits and analysers	Please see our answer to Non-use Scenario Question 1 above. As we mention above, Siemens Healthineers is in no position to offer an informed view as to whether competitors use OPE, to what extent they can or will substitute, which models rely on OPEs, which conditions/diseases are detected/measured by competitor analysers or whether competitors have spare capacity. The market is opaque, particularly given that Siemens Healthineers markets a significant range of OPE-dependent products.			

	with a comparable range of test capabilities are available provided by competitors. Can you provide some more argumentation to support the plausibility of this scenario, please?	The assumption that customers would switch to alternative analysers/OPE supplied by competitors is thus probably over-optimistic, particularly as some competitors are also known to face OPE-related challenges. However, it has been taken forward for three key reasons: • To ensure that impacts under the Non-use Scenario are not overestimated (rather they are considerably underestimated); • It allows some quantification (and monetisation) of potential downstream impacts in the event of non-Authorisation, with the understanding that the actual impacts may be significant more severe; • The severity of impacts that would actually arise if competitors were not able to close the market gap would, to put it simply, unthinkable. The public health and political implications of healthcare providers in the EEA becoming unable to diagnose and treat a wide range of diseases (including life-threatening or terminal ones) would be unprecedented, but also very difficult to scope. Therefore, please consider the approach taken as a very optimistic one rather than as confirmation that the IVD market would cope well if Siemens Healthineers abruptly withdrew their products for several years or permanently.
Economic impacts		
12	To estimate sales of analysers for use 4 and 5 assumptions have to be taken. Can you provide some more foundation for these assumptions which were taken on p. 59 and 60?	We would like to acknowledge the complexities that accompany our analysis. There is a multitude of interlinked operations without the wider business which are difficult to express in simple terms and our business operations are clearly not structured around “Use 4” and “Use 5”. As a starting point, Siemens Healthineers different departments do generate projections of future sales of analysers and their IVD products. This information is available and spans a number of future years and has been the basis of our projections of sales and profits. The practical issue we had to grapple with when developing our AoA-SEA documents was to make distinctions and separate socio-economic parameters between the different Applied for Uses to allow the ECHA Committees and ultimately the European Commission and member States to develop opinions and make decisions on a per Use case. This has required certain assumptions and possibly some (over-)simplification be made and a degree of flexibility. Firstly, we had to ‘allocate’ projected sales of different types of analysers to the two Applied for Uses taking into account the types of OPE-containing IVD products they are using and the different review periods requested for each Use. We thus started this ‘split’ at the bottom of page 59: - [redacted] analysers do not need wash solutions so are irrelevant to Use #5 and thus their sales were fully ‘allocated’ to Use 4; - Sales of [redacted] analysers are allocated exclusively to Use #5 because there are only relevant to a specific wash solution covered by that Use;

- For the remaining seals of analysers, we had to distinguish between the period 2021-2032 and 2033-2040. During the former, OPEs are used in IVD products of both Use #4 and Use #5; during the latter, only Use 4 continues. As a result, for the period 2021-2032, sales of [redacted] analysers are allocated fully to both Applied for Uses (because those sales would be affected under either Non-use Scenario or Use #4 or Use#4). Conversely, for the period 2033-2040, sales of [redacted] analysers are allocated exclusively to Applied for Use #4.

These assumptions are robust as they are simply based on two key facts: which types of IVD products specific analysers types use and when sales take place (i.e. before or after 2032, when Applied for Use #5 ceases). The outcome of these assumptions when applied to our internal projections of analyser sales is provided in Table 3-23 on page 60 (reproduced below for convenience).

Table** Error! No text of specified style in document.**-10: Projected numbers of Siemens Healthineers analysers to be sold in the period 2021-2040

Customer group	***Use #4 analysers (2021-2040)***		***Use #5 analysers (2021-2032)***	
	EEA sales	***Non-EEA sales***	***EEA sales***	***Non-EEA sales***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	

The next step is to project profits from analysers sales into the future for all analyser sales and then somehow split this overall profit between Applied for Use #4 and #5. Table 3-24 on page 60 shows our profit figures for the years 2018-2040 for the different groups of relevant analysers ([redacted]).

We have then made the following assumptions for each of these analyser groups, as explained on page 60:

In order to provide estimates of the benefits of continued use of OPE per Applied for Use, we will make the following assumptions:

- [redacted] analysers: post-Sunset Date, these are only sold in the year 2021 and only use a wash solution covered by Applied for Use #5. So profits from these limited sales are allocated exclusively to Use #5;

- [redacted] analysers: these are relevant exclusive to IVD kits falling under Applied for Use #4. Therefore, profits from sales of these analysers over the years 2021-2040 are allocated exclusively to Use #4;

- [redacted]): this group includes analysers which utilise both IVD kits of Applied for Use #4 and wash solutions of Applied for Use #5. A separation is required. For simplicity, we have assumed the following:

  - Period 2021-2032: both Applied for Uses of OPEs will be active, hence we have split projected profits forms ales of these analyses in two and allocated each half to each of the Applied for Uses; and
  - Period 2033-2040: use of OPEs under Applied for Use #5 has now stopped. So any profit made from selling analysers from this group will be exclusively relevant to Applied for Use #4.

With these assumptions as our guide in splitting profits, Table 3-25 on page 60 was generated. This shows profits for each Applied for Use and over their different timeframes (2021-2040 vs. 2021-2032). This is replicated below for convenience.

Table** Error! No text of specified style in document.**-11: Projected pre-tax profit from sales of Siemens Healthineers analysers in the period 2021-2040

Customer group	***Use #4 analysers (2021-2040)***	***Use #5 analysers (2021-2032)***
EEA customers	[redacted]	[redacted]
Non-EEA customers	[redacted]	[redacted]
All customers	[redacted]	[redacted]

Social impacts of non-use scenarios		
13	The employment effects are estimated separately for uses 4, 5 and then aggregated by summing up. There seems to be some overestimation possible in case workers are involved in production steps of use 4 and 5 simultaneously. Can you clarify this, please?	Please consider our response to Question 8 on social impacts above. The combined job losses for Siemens Marburg and the European Distribution Centre are [redacted], a small fraction of overall employment at those locations. Inability of Siemens Healthineers to sell IVD products covered by Uses #4 and #5 would have devastating consequences on Siemens Healthineers globally and would certainly have very far reaching adverse impacts on Siemens Healthineers' German (and UK) operations. The assumed job losses (as presented in Table 6-1, page 151) are most certainly an **underestimate**.

14	For monetization of social impacts of unemployment the SEAC approach was followed, and for calculation the average salary for Germany was used. Could you please provide information on the average salary of Siemens Marburg staff (pre-tax worker compensation) employed in the production of IVD kits compared to the German average salary. Can you also characterize their competence level and skills in comparison to workforce of the Marburg region, and whether their expected duration of unemployment is comparable to the German average.	(see also answer to Question 9 above) The average salary of Siemens Marburg staff is estimated at [redacted] (range: €10,000-100,000), i.e. [redacted] average salary in Germany of €45,252 which has been used in the calculation of social impacts. The estimated average salary of Siemens Marburg staff was calculated according to local policies and includes holiday and bonus allowances. We cannot make any valid statement in respect to the difference of the duration of unemployment Marburg areas vs. Germany. Therefore, we refer to the German average as highlighted in the AoA-SEA document. If we change the salary for Siemens Marburg workers to [redacted] but retain the salaries of [redacted] and 3rd party works in Germany at €45,252, the social costs can be recalculated as shown in the extended Table 5-6 (originally on page 138), as shown below.

Table Error! No text of specified style in document.**–12: Estimation of social benefits from the continued use of OPE-containing IVD products by customers of Siemens Healthineers**

Use #4	**Number of jobs lost**	**Social costs Original estimate**	**Social costs Updated estimate**
Siemens Marburg	[redacted]	[redacted]	[redacted]
European Distribution Centre	[redacted]	[redacted]	[redacted]
Siemens Llanberis	[redacted]	[redacted]	[redacted]
Suppliers and customers	[redacted]	[redacted]	[redacted]
3rd party contractors - Marburg	[redacted]	[redacted]	[redacted]
3rd party contractors - Llanberis	[redacted]	[redacted]	[redacted]
Total avoided jobs lost	[redacted]	[redacted]	[redacted]
Use #5	**Number of jobs lost**	**Social costs Original estimate**	**Social costs Updated estimate**
Siemens Marburg	[redacted]	[redacted]	[redacted]
European Distribution Centre	[redacted]	[redacted]	[redacted]
Siemens Llanberis	[redacted]	[redacted]	[redacted]
Suppliers and customers	[redacted]	[redacted]	[redacted]
3rd party contractors - Marburg	[redacted]	[redacted]	[redacted]
3rd party contractors - Llanberis	[redacted]	[redacted]	[redacted]
Total avoided jobs lost	[redacted]	[redacted]	[redacted]
Sum of all 2 Uses	[redacted]	[redacted]	[redacted]
Worst case scenario	**Number of jobs lost**	**Social costs Original estimate**	**Social costs Updated estimate**
Siemens Marburg	[redacted]	[redacted]	[redacted]

		European Distribution Centre	[redacted]	[redacted]	[redacted]		
		Siemens Llanberis	[redacted]	[redacted]	[redacted]		
		Suppliers and customers	[redacted]	[redacted]	[redacted]		
		3rd party contractors - Marburg	[redacted]	[redacted]	[redacted]		
		3rd party contractors - Llanberis	[redacted]	[redacted]	[redacted]		
		Total avoided jobs lost	[redacted]	[redacted]	[redacted]		

[redacted]