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Answers to RAC questions – Public version

Potential minimisation of releases:

Question 1: In Vienna site, you indicate (both in the CSR table 1, and the replies to the first RAC questions 1 and 7) that the production of the 3 medicines are performed on 'different equipment', and that on some equipment (for 2 of the medicines), the first column washes are collected for incineration. What would prevent you from collecting the first column washes from the equipment producing Tisseel? Please explain what additional measures you would need to implement to, as well as an estimation of the costs that would be incurred? If you could collect the first column washes, what would be the emissions reduction?

Answer 1: Following the viral inactivation step, the S/D solution including impurities is separated from the drug product (WCS4, p. 45 in the CSR). Separation within Tisseel production **does not** include column washes as this product is not purified by [redacted]. Separation of Tisseel (unlike Thrombin and Immunate) is achieved via [redacted] a centrifuge. The target protein is [redacted] after centrifugation the [redacted] OPnEO is collected for incineration. The target protein is [redacted] a second time. The [redacted] is again collected for incineration. By these steps the majority of OPnEO is separated from the target protein (see also Table 1). This process is different to the [redacted] steps of Thrombin and Immunate. By this duplicate [redacted] procedure, the OPnEO amount in the product is reduced by 99.897 %.

Table 1: Overview of the collected process waste and containing amounts of OPnEO per batch.

Tisseel separation step	**Measured amount of OPnEO [mg/L]**	**Supernatant volume [L]**	**Destination of waste**
[redacted]	[redacted]	540	Incineration
[redacted]	[redacted]	1050	Incineration
[redacted]	[redacted]	500	Municipal STP
[redacted]	[redacted]	440	Municipal STP

Collecting the process waste from the [redacted] reduces emissions to [redacted] OPnEO per year. This is achieved by sending 234 t of aqueous process waste to incineration.

Collecting the [redacted] step would further reduce the OPnEO emissions to [redacted] per year, resulting in an additional 73 tonnes of aqueous waste to incineration, corresponding to [redacted] EUR costs and 4 additional truck loads per year.

Collecting both [redacted] steps would reduce the OPnEO emissions to 0 g per year, resulting in an additional 183 tonnes of aqueous waste to be incinerated corresponding to [redacted] EUR costs and 10 additional truck loads per year.

The line modifications required to collect the additional washing discharge as well as the costs were not assessed due to time limitations. A modification of the collection tank is not possible because of physical limitations at the site. For either scenario (collecting the [redacted] and/or the [redacted] step) the effort and energy consumption is considered disproportionate in relation to the achieved reduction of OPnEO emissions.

Question 2: RAC takes note of the quantity of OPnEO that you claim to emit per year on the Vienna site during the CIP activities (0.89 to 8.9 kg/year). What would prevent you from reducing this emission? For example, by collecting the first washwater/CIP flush? Please explain what additional measures you would need to implement to, as well as an estimation of the costs that would be incurred? What would be the emissions reduction?

The cleaning-in-place (CIP) procedure is a validated, multi-step, computer-controlled cleaning cycle. This is performed on all fixed equipment on the manufacturing line. Given the construction of the manufacturing line, and specific to the production process for the medicine being manufactured, a defined section of the manufacturing line is cleaned by CIP once the production process has freed up the equipment. As such, each manufacturing process has multiple CIP cycles of differing durations as dictated by the volume of equipment included in the defined section. Modifying the validated process to divert a partial CIP flush to the OPnEO collection tank is not technically feasible. This would require line modifications at multiple points to divert partial flushes of the CIP cycle to the collection tank. The equipment used to divert the flushes would have to be digitally enabled in order to be controlled by the computerized cleaning cycle. Given the nature of the GMP processes and validated status of the CIP procedure, these modifications would require health authority (HA) approval across multiple markets where the product is registered before they could be used for commercially manufactured product. Obtaining approvals by Health Authorities for such a change is considered high-risk as it diverges from state-of-the-art validated processes.

Emissions could be reduced further by implementing a pre-flush step in the manufacturing process using a neutral solution (eg: reverse osmosis (RO) water). This modification would not affect the validated CIP process, however significant modifications to the production lines would be required to implement the necessary changes so this pre-flush could be diverted to the OPnEO collection tank and, similar to the CIP cycle description, multiple pre-flush steps would need to be implemented. Additionally, a tank would be required for storing the pre-flush solution, however neither the volume of this tank nor the physical capacity of the site to house such a tank has been assessed.

This option has not been evaluated in detail. A change of this nature would have a negative impact on the site's ability to supply medicines; introducing an additional process step to the cleaning cycles will extend the duration from one production run to the next, thereby reducing the overall volume of medicines the site is able to produce. Considering the life-saving nature

of the medicines being manufactured at the sites, implementing a change which reduces the site's ability to supply patients with these products excluded this from further evaluation.

Question 3:For the CIP flush effluents sent to on-site STP at Lessines site, it is assumed as a worst-case scenario that the vessel walls may still be wetted with a thin layer of process liquid (p. 59 of CSR): based on the measurements it is assumed that all surfaces are covered by a 0.132 mm solution layer. In your reply to the first RAC question #13, you clarified that this assumption is based on analytical measurements presented for Vienna site, and that only the surface of the vessels connected to CIP are considered. In the CSR you also indicated that the process waste in transfer pipes is considered negligible as pipes are blown down and/or are washed after transfers for product recovery. However, on p.56 of the CSR, it is stated that the remaining amount of buffer containing OPnEO in the vessels that are discharged to the normal drain in the form of CIP flushes is calculated by "considering the surface of all vessels a<u>nd pipes coming into contact with OPnEO</u>". Can you please clarify which description is correct?

Answer 3: For calculation only the surface of vessels was considered. The above underlined statement "and pipes coming in contact with OPnEO" is a relict and was missed to be deleted.

Question 4: In your response to question 18(a) and (b) from RAC, you refer to increases in operating costs in Lessines and Vienna as a result of additional waste collection. Please provide more details regarding this. Is this estimate covering the costs of treating an additional volume of effluent? If not, what does it cover? And what would be the additional cost in EUR (rather than as a % increase)?

Answer 4: The increase in operating costs for Lessines and Vienna as provided in the responses to question 18(a) and (b) are estimated based on the additional volume of waste to be collected or incineration, including all process waste, CIP cycles and industrial washing waste. The implementation costs of modifying the process lines to divert waste to the collection tanks has been cited in the initial response.

The limited physical space at both sites precludes installing an additional collection tank to house the additional waste to be captured for off-site incineration. Given the volume of process waste emanating from the production processes, a change to capture all process waste in an effort to achieve zero emission status would require a contracted company to drain the collection tank for off-site incineration multiple times per day. Without considering cost adjustments over the period of time for this activity, the projected annual cost for incineration according to the projected process waste volume are:

Lessines: EUR [redacted]

Vienna: EUR [redacted]

Implementing a change of this nature is considered unfeasible, given the logistical impact this will have on site operations. The tank draining would need to be closely coordinated with production cycles to avoid the tank reaching capacity before it was drained, as this would halt all manufacturing. Close coordination with the waste management vendor would have to consider the variable traffic congestion throughout the day to ensure collection trucks would

be in place on time to drain the tanks. This scenario also assumes the vendor has the capacity to handle the waste volumes this scenario would produce which has not been evaluated.

Question 5: Throughout the CSR a footnote related to the off-site incineration indicates that : "However, in case a more sustainable or technically better method is available in the future that leads to at least the same level of emission reduction, the applicants will consider this as an option for its process waste management." Is it already possible to provide additional information on the future investigations in finding better methods for your sites for emission reduction?

Answer 5: Evaluation of available methods considering the site-specific needs (including physical constraints) is still ongoing and will be further pursued. So far results indicate that incineration is the most efficient removal method.

Question 6: What will be the LOD of the analytical method(s) used for the planned monitoring program? Please also specify, if possible, the different sampling points for each of the sites (Vienna, and Lessines).

Answer 6: The LOD of the method (Bendig, 2019)[1] (which is used at all Takeda locations included in this application) is 0.5 ng/L. The LOQ is 10 ng/L.

Lessines: The Lessines site incorporates an on-site activated sludge biological wastewater treatment plant prior to discharge to a tributary of the Dendre River. The site will perform wastewater monitoring both immediately upstream of the wastewater treatment plant (effluent from the site equalization tanks) to verify the removal efficiency of the upstream segregation processes and downstream of the site's wastewater treatment system to ascertain final effluent concentrations.

Vienna: The Vienna site will perform wastewater monitoring at the final effluent from the site waste neutralisation system.

These sites are currently assessing and optimizing the removal efficiencies of their respective OPnEO segregation systems. Once the sites are consistently meeting target removal rates, the monitoring frequencies will be quarterly. If more sustainable or technically better methods are available in the future that demonstrably lead to removal rates that meet or exceed our commitments, monitoring plans may be modified or discontinued.

[1]Bendig, P (2019): Study Report: Analytical Method for the Determination of 4-tert-Octylphenol and its ethoxylates in Industrial Sewage Treatment Plant Effluent. Report no. P 4873 G. EAG Laboratories GmbH. Ulm, Germany.