Applicant: Baxter AG

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Answers to RAC questions – Non-confidential version

Question 1.: For each site, please provide non confidential ranges for OPnEO quantities used per batch, per product line and frequency of use in days per year as well as information on emissions per product line/process. This question refers to the confidential information in tables 19, 21, 22, 23, 24, 25, 27, 29, 30 and in the tables located at the beginning of sections 9.2.1.1, 9.3.1.1 and 9.4.1.1.

Confidential values are blacked out and relating public ranges are presented in brackets.

Table: 19: Maximum amount of OPnEO potentially used for the product lines in Vienna.

	Immunate	**Tisseel**	**Thrombin**
Amount of OPnEO used per year	[redacted] (212–2120 kg)	[redacted] (56–560 kg)	[redacted] (54–540 kg)
Amount of OPnEO per batch	[redacted] (1–10 kg) [redacted] (≤ 300 batches per year)	[redacted] (1–5 kg) [redacted] (≤ 200 batches per year)	[redacted] (1–5 kg) [redacted] (≤ 200 batches per year)

Table 21: Residual emission of OPnEO from process waste by product washes during the manufacturing process in Vienna. The process waste is partially collected and sent off-site for incineration[1]. Emissions from one batch were measured and are extrapolated to the emissions per year. *[Comment: Values have been corrected for typing errors. Incorrect values from the CSR are shown as struck out.]*

Product	**Emissions of OPnEO [g/a]**	**Corresponding amount of wastewater sent to incineration [t/a]**
Immunate [redacted]	[redacted] (120–1200)	893
Tisseel [redacted]	[redacted] (52–520)	234
Thrombin [redacted]	[redacted] (28–280)	85
Total	[redacted] (370–3700)	**1212**

[1] 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.

Table 22: Measured concentrations of OPnEO in water from vessel CIP.

Water for injection (WFI)-rinse	Concentration OPnEO [g/L]	Flush volume [L]	OPnEO [g]
First partial quantity	[redacted] (0.01–0.1)	70	[redacted] (0.7–7)
Second partial quantity	[redacted] (0.0003–0.003)	70	[redacted] (0.03–0.3)
Third partial quantity	[redacted] (0.0002–0.002)	70	[redacted] (0.02–0.2)
Total		210	[redacted] (0.7–7)
OPnEO concentration in the product:			[redacted] (1–11 g/kg)
Residual quantity of product solution:			**0.66 L**

Table 23: Residual emission of OPnEO from CIP cleaning.

Product	Emissions of OPnEO [g/a]
Immunate	[redacted] (550–5500)
Tisseel	[redacted] (200–2000)
Thrombin	[redacted] (200–2000)
Total	[redacted] (900–9000)

Table 24: OPnEO emissions from cleaning of small vessels – Vienna.

	OPnEO emissions (rounded values)
	[ng]
Per batch Immunate	[redacted] (0.4–4.0)
Per batch Tisseel	[redacted] (0.4–4.0)
Per batch Thrombin	[redacted] (0.4–4.0)
Per year	[redacted] (200–2000)

Table 25: Local releases to the environment (Vienna). ***[Comment: Values have been corrected for typing errors. Incorrect values from the CSR are shown as struck out.]***

Release route	Release factor (per day)	Release (per annum)	Release estimation justification, method and details
Water	Release factor before on-site RMM: 100 % Release factor after on-site RMM: ~~0.39~~ 0.34 % Local release rate: [redacted] 4-t-OP/day (0.0055 to 0.011 kg 4-t-OP/day)	[redacted] (5.44 to 10.87) kg OPnEO equalling [redacted] (1.8 to 3.6) kg 4-t-OP	Parts of the process effluent are disposed of as hazardous waste. Residual amounts of OPnEO could nevertheless enter wastewater directed to the local STP via unintended small losses. Until analytical verification data are available these small losses are calculated based on worst case assumptions (see calculations above): Process waste by product washes: [redacted] (0.198–1.98) kg OPnEO/a Manual cleaning: [redacted] (0.2–2.0) µg OPnEO/a CIP (not collected): [redacted] (0.89–8.9) kg OPnEO/a Total [redacted] (5.44 to 10.87) kg OPnEO/a corresponding to ~~0.39~~ 0.34 % of the applied tonnage. Therefore, an efficiency of ~~99.61~~ 99.66 % is considered for the efficiency of the implemented RMMs.
Air	Release factor before on-site RMM: 0 % Release factor after on-site RMM: 0 % Local release rate: 0 kg/day	0	Release factor (Emission to air, site-specific, following the TGD, 2003) In a simplistic and conservative approach, the amount of OPnEO emitted via exhaust air/general ventilation can be estimated according to the release factors given in the TGD (2003), Appendix I, Table A3.1 (industrial use): The equipment used is dedicated equipment (category 1b); OPnEO has an estimated vapour pressure[2] of 1.41×10^{-7} mm Hg at 25 °C, corresponding to 1.88×10^{-5} Pa at 25 °C. The resulting release factor to air for the use in the pharmaceutical industry is 0. This assumption is supported by the Annex XV dossier on OPnEO, chapter 3.1.1.2.1, where evaporation is assessed as negligible (BAuA, 2012).
Soil	Release factor after on-site RMM: 0 %	0	All solvent waste is disposed of as hazardous waste. Release to soil does not occur.

[2] EpiSuite estimation for 4-tert-OP2EO, Smiles code CC(C)(C)CC(C)(C)C1=CC=C(OCCOCCO)C=C1

Table 27: Amount of OPnEO used for the product lines in Lessines.

	Line [redacted]	**Line [redacted]**	**Laboratory**
Amount of OPnEO used per year	[redacted] 10000–20000 kg	[redacted] 10000–40000 kg	[redacted] 10–20 kg
Amount of OPnEO per batch	[redacted] 1–40 kg [redacted] ≤ 500 batches per year	[redacted] 1–80 kg [redacted] ≤ 500 batches per year	[redacted] 0.03–0.3 kg [redacted] ≤ 100 batches per year

Table 29: OPnEO emissions from cleaning of small vessels – Lessines. RMM: collect first rinse and dispose of as hazardous waste. *[Comment: Values have been corrected for typing errors. Incorrect values from the CSR are shown as struck out. All values assume 450 batches per year.]*

	Emission of OPnEO	**Emission of OPnEO in 4-t-OP equivalents**
	[ng/a]	
[redacted]	[redacted] (1.3×10^7–1.3×10^8)	[redacted] (4.3×10^6–4.3×10^7)
[redacted]	[redacted] (5.4×10^4–5.4×10^5)	[redacted] (1.8×10^4–1.8×10^5)
Laboratory	[redacted] (2.0×10^8–2.0×10^9)	[redacted] (6.6×10^7–6.6×10^8)
	[g/a]	
Total	[redacted] (0.21–2.10)	[redacted] (0.07–0.7)

Table 30: Local releases to the environment (Lessines)

Release route	Release factor	Release per annum	Release estimation justification, method and details
Water	Release factor before on-site RMM: 100 % Release factor after on-site RMM: 0.042 % Local release rate: [redacted] (0.01 to 0.021) kg 4-t-OP/day	[redacted] (10.00 to 20.8) kg OPnEO/a (equalling [redacted] (3.3 to 6.9) kg 4-t-OP)	The process effluent is disposed of as hazardous waste. Residual amounts of OPnEO could nevertheless enter wastewater directed to the local STP via unintended small losses. Until analytical data are available these small losses are calculated based on worst case assumptions (see calculations above): Process waste by product washes: [redacted] (0.26–2.60) kg OPnEO/a Manual cleaning: [redacted] (2.1×10^{-4}–2.1×10^{-3}) kg OPnEO/a CIP: [redacted] (1.82–18.2) kg OPnEO/a Total: [redacted] (2.08 to 20.8) kg OPnEO/a to an efficiency of 99.96 % is considered for the efficiency of the implemented RMMs.
Air	Release factor before on-site RMM: 0 % Release factor after on-site RMM: 0 % Local release rate: 0 kg/day	0	Release factor (Emission to air, site-specific, following the TGD, 2003) In a simplistic and conservative approach, the amount of OPnEO emitted via exhaust air/general ventilation can be estimated according to the release factors given in the TGD (2003), Appendix I, Table A3.1 (industrial use): The equipment used is dedicated equipment (category 1b); OPnEO has an estimated vapour pressure[3] of 1.41×10^{-7} mm Hg at 25 °C, corresponding to 1.88×10^{-5} Pa at 25 °C. The resulting release factor to air for the use in the pharmaceutical industry is 0. This assumption is supported by the Annex XV dossier on OPnEO, chapter 3.1.1.2.1, where evaporation is assessed as negligible (BAuA, 2012).
Soil	Release factor after on-site RMM: 0 %	0	All solvent waste is disposed of as hazardous waste. Release to soil does not occur.

[3] EpiSuite estimation for 4-tert-OP2EO, Smiles code CC(C)(C)CC(C)(C)C1=CC=C(OCCOCCO)C=C1

Table from the beginning of chapter 9.2.1.1 of the CSR:

Conditions of use Vienna *[Comment: Final emission value has been corrected for typing errors. Incorrect values from the CSR are shown as struck out.]*

Amount used, frequency and duration of use (or from service life)
• Daily use at site (Vienna): [redacted] (≤ 0.010) tonnes OPnEO/day on [redacted] (≤ 365) days per year *Corresponding to* [redacted] (≤ 0.005) *tonnes 4-t-OP per day*
• Annual use at a site: [redacted] (< 10) tonnes OPnEO/year *Corresponding to* [redacted] *(< 10) tonnes 4-t-OP per year*
• Percentage of EU tonnage used at regional scale: = 100 %
Technical and organisational conditions and measures
• Exhaust air treatment: heating, ventilation and air conditioning (HVAC) system established according to GMP demands from the European Union; • RMM: Separation of process effluents and column washes containing measurable amounts of OPnEO as hazardous waste (sent off-site to incineration[4]) *Emission sources:* *• Process waste from uncollected product washes* *• CIP* *• Manual cleaning: directions are given in associated SOPs that any OPnEO contaminated waste must be managed as hazardous waste, which is collected and sent off-site for incineration; all reusable vessels are triple-rinsed (with all rinses being collected to hazardous waste) before cleaning in washing machines.* *• Contaminated small equipment (i.e., pipettes) – disposed of as hazardous waste (→ incineration)* *In total: Emissions of* [redacted] *(5.44 to 10.9) kg OPnEO/a are discharged to the municipal STP of Vienna.*
Conditions and measures related to sewage treatment plant
• Municipal STP: Site specific [Effectiveness Water: 0 %] *As elaborated in chapter 4.1.2. and 9.1.2.1., OPnEO (4-t-OPnEO) is assumed to be ultimately degraded to 4-t-OP (4-t-OP equivalent approach). The conversion factor for degradation from OPnEO to 4-t-OP is 0.33. The physicochemical parameters applied for STP distribution are those for 4-t-OP (see Table 11).*

[4] 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.

Discharge rate of municipal STP Vienna: 420,000 m³/d *The receiving STP is EBS Wien (https://www.ebswien.at/en/wastewater/wastewater/figures/) which is fed with municipal wastewater. The current capacity is officially given as 3,000,000 population values (PV), that can be expanded to up to 4,000,000 PV. The PV results from the number of residents (NR) plus population equivalents (PE). The NR in 2018 is given as 1,900,000 (exact figure:1,898,000, see https://de.statista.com/statistik/daten/studie/317867/umfrage/prognose-zur-bevoelkerungsentwicklung-in-wien/). Thus, the PE is calculated to 2,100,000.* *Taking into account the default value of 200 L wastewater per population equivalent, the discharge rate is calculated to be 420,000 m³/d.*
• Application of the STP sludge on agricultural soil: No *The sludge from the Vienna STP is dewatered and incinerated on-site (https://www.ebswien.at/hauptklaeranlage/hauptklaeranlage/zahlen/)*
Conditions and measures related to treatment of waste (including article waste)
• Once the S/D solution is mixed and dosed to the viral inactivation vessel, the OPnEO -containing mixture is processed in a closed system. All waste containing OPnEO is collected and sent to incineration. • Any equipment contaminated with OPnEO is either directly incinerated (single-use equipment) or waste from manual cleaning is collected for incineration. • As OPnEO is not volatile and there is no generation of aerosols, emission to the air can be excluded.
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 7.534E+07 m³/d The mean low water flow rate of the river Danube at the gauge Korneuburg (closest gauge upstream) is reported as 872 m³/s in official statistics (http://www.noel.gv.at/wasserstand/static/stations/207241P/station.html), corresponding to 75 340 800 m³/d.

Table from the beginning of chapter 9.3.1.1 of the CSR:

Conditions of use Lessines

Amount used, frequency and duration of use (or from service life)
• Daily use at site Lessines: [redacted] (< 1) tonne OPnEO/day on [redacted] (< 365) days per year *Equalling* [redacted] *(< 0.1) tonnes 4-t-OP per day*
• Annual use at a site: [redacted] (< 100) tonnes OPnEO/year *Equalling* [redacted] (< 50) *tonnes 4-t-OP per year*
• Percentage of EU tonnage used at regional scale: = 100 %

Technical and organisational conditions and measures
• Exhaust air treatment: heating, ventilation and air conditioning (HVAC) system established according to GMP demands from the European Union; • RMM: Separation of process effluents and column washes and CIP washes expected to contain measurable amounts of OPnEO as hazardous waste (sent off-site to incineration[5]) Emission sources: • Process waste – the first [redacted] column washes are collected for incineration • CIP – The first CIP flush from two pre-formulation vessels is collected, as these vessels contain S/D stock solutions with a concentration of OPnEO of [redacted](w/w); • Manual cleaning; directions are given in the according SOP that any waste must be disposed of as hazardous waste which is collected for incineration; cleaning steps will be verified analytically; vessels are triple rinsed before a manual wash; the rinse is collected for off-site incineration • Contaminated small equipment (i.e. pipettes) – disposed of as hazardous waste. Hazardous waste is incinerated
Conditions and measures related to sewage treatment plant
• Biological on-site STP: Site specific [Effectiveness Water: 0 %] *As elaborated in chapter 4.1.2. and 9.1.2.1, OPnEO (4-t-OPnEO) is assumed to ultimately degrade to 4-t-OP (4-t-OP equivalent approach). The conversion factor for degradation from OPnEO to 4-t-OP is 0.33. The physicochemical parameters applied for STP distribution are the ones for 4-t-OP (see* Table 11*).*
• Discharge rate of STP: ≥ 1000 m³/d *The annual capacity of the on-site STP of Takeda Lessines is specified as 370 000 m³/a, corresponding to approximately 1000 m³/d (rounded)*
• Application of the STP sludge on agricultural soil: No *The sludge from the Lessines STP is dewatered and incinerated.*
Conditions and measures related to treatment of waste (including article waste)
• Once the S/D solution is mixed and dosed to the viral inactivation vessel, the OPnEO containing mixture is processed in a closed system, aimed at prevention of product contamination and minimisation of emissions to the environment. All waste containing OPnEO is collected and sent to incineration. • Any equipment contaminated with OPnEO is either directly incinerated (single-use equipment) or waste from manual cleaning is collected for incineration (rinse water). • As OPnEO is not volatile and there is no generation of aerosols emission to the air can be excluded.

[5] 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.

Other conditions affecting environmental exposure
• Receiving surface water flow rate: ca 864 000 m^3/d *The mean low water flow rate of the river Dender nearby Lessines is reported as 10 m^3/s in official statistics (https://nl.wikipedia.org/wiki/Dender), corresponding to 864 000 m^3/d.*

Table from the beginning of chapter 9.4.1.1 of the CSR:

Conditions of use Orth

Amount used, frequency and duration of use (or from service life)
• Daily use at site: Orth: [redacted] (≤ 0.002) tonnes OPnEO/day on [redacted] (≤ 365) days per year
• Annual use at a site: [redacted] (< 1) tonnes OPnEO/year
• Percentage of EU tonnage used at regional scale: = 100 %
Technical and organisational conditions and measures
• Exhaust air treatment: heating, ventilation and air conditioning (HVAC) system established according to GMP demands from the European Union; Equipment cleaning: • Only single-use equipment is used, which is disposed of as hazardous waste
• No emission to a sewage treatment plant
Conditions and measures related to treatment of waste (including article waste)
• Once the S/D solution is mixed and dosed to the viral inactivation vessel the OPnEO containing mixture is processed in a closed system, aimed at prevention of product contamination and minimisation of emissions to the environment. All waste containing OPnEO is collected and sent to incineration[6]. • Any equipment contaminated with OPnEO is directly incinerated (single-use equipment) • As OPnEO is not volatile and there is no generation of aerosols, emission to the air can be excluded.
Other conditions affecting environmental exposure
• Receiving surface water flow rate: ≥ 7.534E+07 m^3/d The mean low water flow rate of the river Danube at the gauge Korneuburg (closest gauge upstream) is reported as 872 m^3/s in official statistics (http://www.noel.gv.at/wasserstand/static/stations/207241P/station.html), corresponding to 75 340 800 m^3/d.

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

Question 2.: For each site, please provide a non-confidential range for the OPnEO concentration in the formulations (concentrations indicated on page 44, 55, and 66).

The concentrations were recently published (https://doi.org/10.1002/eng2.12078, December 2019) and are no longer claimed confidential by Baxter. The redacted passages are presented below:

p. 44 (Vienna): The final OPnEO concentration is 1 % (w/w) of the S/D solution in the viral inactivation tank (WCS 4).

The treatment uses 1 % (w/w) OPnEO, 0.3 % (w/w) polysorbate 80, and 0.3 % (w/w) tri-(n-butyl) phosphate (TNBP) for [redacted].

p. 54 (Lessines): The final target concentration of OPnEO in the protein solution is 1 % (w/w).

p. 55 (Lessines): Plasma products: S/D treatment is usually applied during the first stages of the purification processes of plasma products. The treatment uses 1 % (w/w) OPnEO, 0.3 % (w/w) polysorbate 80, and 0.3 % (w/w) tri-(n-butyl) phosphate (TNBP) for [redacted].

p. 66 (Orth): The final OPnEO concentration is approximately 1 % (w/w).

Question 3: WCS2-PROC 5 (in ES1, ES2 and ES3), and WCS3-PROC8b (in ES1) describe manual tasks, and in particular manual pouring from one (heavy) container to another. How do you prevent splashes and spills during the transfers and handling of the liquids?

ES1 (Vienna)

- **WCS2-PROC5:** Manual pouring for WCS2 refers to pouring from the manufacturer's [redacted] bottle into a glass beaker. From the glass beaker substance is poured into [redacted] (Tisseel and Thrombin) or [redacted] (Immunate) blending container. The manufacturer's container and the glass beaker are small enough to be easily manipulated by one person. Splashes and spills are avoided by minimizing transport distances and using open-top blending containers.

  In accordance with the site procedures, if a spill of less than 10 litres were to occur, it would be cleaned up by area staff using sorbent materials stored in the immediate area. In the event of a spill of greater than 10 litres or a spill of any amount that reaches a floor drain (i.e., sewage drain), the internal spill response team (Fire Brigade) is activated and the wastewater discharge is stopped until the OPnEO contamination is contained. All spill debris is collected as hazardous waste and shipped offsite for incineration.

- **WCS3-PROC8b:**
  - Tisseel and Thrombin: From the [redacted] blending container, the SD solution is poured manually into the viral inactivation tank. The blending container is small enough to be easily manipulated by one person.
  - Immunate: From the [redacted] blending container, the SD solution is pumped into the viral inactivation tank (as shown in Figure 5 in Section 9.2.1.2 Releases) using a peristaltic pump and tubing. Used tubing is collected as hazardous waste and sent offsite for incineration.

  Splashes and spills are avoided by using large opening receiving tanks and strict adherence to standard operating procedures. Any significant spills would result in a product quality deviation and associated formal reporting.

In accordance with the site's written emergency response plan, if a spill of less than 10 litres were to occur, it would be cleaned up by area staff using sorbent materials stored in the immediate area. In the event of a spill greater than 10 litres or a spill of any amount that reaches a floor drain (i.e., sewage drain) or are otherwise beyond the capabilities of area employees to contain or clean up, the internal spill response team (Fire Brigade) is activated and the wastewater discharge is stopped until the OPnEO contamination is contained. All spill debris is collected as hazardous waste and shipped offsite for incineration.

ES 2 (Lessines)

- **WCS2-PROC5:** [redacted]: For these products, OPnEO is weighed in a [redacted] stainless steel container, and then poured into the process tank ([redacted] mixing tank). [redacted]: OPnEO is weighed in a [redacted] stainless steel container and poured into a [redacted]. [redacted]: OPnEO is weighed in a [redacted] stainless steel container, then poured into a fixed process tank [redacted].
- PDTS: OPnEO is weighed and blended in smaller containers ([redacted], respectively) that are easily manipulated by one person

Splashes and spills are avoided by using large opening receiving containers/tanks and strict adherence to standard operating procedures, which require 2-person lift for [redacted] weighing containers as shown below. Any significant spills would result in a product quality deviation and associated formal reporting.

[redacted]

In accordance with the site's written procedure [redacted], small spills would be cleaned up by area staff using sorbent materials stored in the immediate area. The site also maintains a spill response team, which is activated for spills that threaten the environment, the sewage drain or are otherwise beyond the capabilities of area employees to contain or clean up. All spill debris is collected as hazardous waste and shipped offsite for incineration.

ES3 (Orth)

- WCS2-PROC5: Only small single-use containers are currently used or anticipated for preparing and transferring OPnEO solutions. Splashes and spills are avoided by using large opening receiving containers/vessels and strict adherence to standard operating procedures. Any significant spills would result in a product quality deviation and associated formal reporting.

In accordance with the site's written procedures, small spills would be cleaned up by area staff using sorbent materials stored in the immediate area. The site also maintains a spill response team, which is activated for spills that threaten the environment, the sewage drain or are otherwise beyond the capabilities of area employees to contain or clean up. All spill debris is collected as hazardous waste and shipped offsite for incineration.

Question 4: Please describe the spill and leakage management in place at each site (ES1, ES2, ES3) for all process steps?

The use of internal storage and secondary containment minimize the potential for OPnEO spills and leaks to wastewater or the environment during the storage of raw material and OPnEO contaminated waste. Raw material is stored within the respective warehouses and typically on spill pallets or within appropriate containment totes. All OPnEO waste segregation tanks are either double-walled or within secondary containment with at least 100 % capacity of the tank volume and equipped with a liquid sensor.

Each of the affected sites also have incidental spill procedures and associated training, so that employees are qualified to address smaller spills. In the event of an incidental spill or leak, operators wearing suitable protective clothing would contain/clean-up the spill with absorbent material (spill kits) available in the immediate area and place any contaminated debris into sealed bags for disposal and offsite incineration. Each of the affected sites also maintains a trained spill response team or fire brigade to address larger chemical spills or spills that are otherwise beyond the capabilities of the area employees to address. Employees are trained to notify the spill response team (typically through Security) in the event of a larger or uncontrolled spill.

Question 5: On page 42 of the CSR, you indicate: 'A potential for exposure is only given if the different openings (manhole, bung hole, etc.) are open; the addition of OPnEO to the S/D solution and the subsequent addition of the S/D solution to the process is a manual task with exposure potential through the open vessels.' Describe the situations where the openings may be left unclosed and for how long?

As stated, the virus inactivation, subsequent separation of OPnEO from the pharmaceutical product and associated equipment cleaning take place in closed systems – predominantly, to minimize human contact with, and potential contamination of, the drug product. Vessels are only opened under very controlled conditions to accommodate the transfer of the S/D solution and the discharge of associated wastes. The closed systems are closely monitored and all human interaction with the vessels is strictly controlled – again to protect the drug product. Accordingly, it would be extremely unlikely for any opening to be inadvertently left unsealed. In the very unlikely event that an opening was left unsealed, it would be detected immediately, and the transfer would be halted by trained employees wearing appropriate PPE.

Question 6.: Do we understand correctly that both in Vienna and Lessines (ES1 and ES2), during WCS1 (PROC 15-QC of raw material), only single-use equipment is in contact with OPnEO? If not, how is the non-single-use equipment cleaned? (is it covered by WCS5 in ES1 and WCS6 in ES2)?

ES 1 Vienna: WCS1-PROC15: Single-use equipment and multi-use equipment is in contact with OPnEO. Cleaning of multi-use equipment is performed according to WCS5-ECS 1, Manual cleaning procedure. This applies to small glass beakers (100 mL) and test equipment (i.e.: thermometers). There is no expected OPnEO emission from this step.

ES 2 Lessines: WCS1-PROC15: Yes, only single-use equipment is in contact with OPnEO.

Question 7: In Vienna, on page 45 of the CSR, it is indicated that there is currently no separation of liquid waste for the T. line, and that 'construction works for installing RMM ensuring separation of liquid waste from the T. production are still ongoing hence full effectiveness of emission minimisation is not yet achieved.'

a) As the production of T. and the 2 other medicines, is performed in the same facilities, on the same equipment, can you explain why the handling of the T. liquid waste is currently different than the other medicines?

Production of the three medicines occurs in the same facility, but in the production areas with different equipment tailored to the manufacturing process of the specific medicine. The reference on p.44, "the needed amount of OPnEO is weighed in a glass beaker and poured into either a [redacted] (Tisseel and Thrombin) […] blending container" is correct insofar as the vessel size is the same for both Tisseel and Thrombin, however the task occurs on different manufacturing lines.

b) Can you please provide additional details on the 'construction works for installing new RMM ensuring separation of liquid waste', and on the status of this work?

The status quo is that required modifications to the line have been completed at the time of authoring this response. The site is due to restart production Q1 2020 when analysis of waste streams can be conducted to confirm effectiveness of waste segregation measures.

Question 8.: On page 60 in the CSR, figure 13 mentions an equipment washer from where the residues are flushed down the drain. Can this be considered as an industrial washing machine?

Yes.

Question 9.: In Lessines, for product line [redacted], the fixed mixing tank is indicated as having a volume of [redacted] on page 59 of the CSR, and a volume of [redacted] on page 54. Which size is correct? On which tank size have the release estimates been calculated?

The volumes for the SD mixing tanks are almost the same ([redacted] at Line [redacted] and [redacted] at Line [redacted]). The value of [redacted] in figure 11 is wrong. For the calculation of releases for Line [redacted], the mixing tank of [redacted] volume was considered and for Line [redacted] the [redacted] tank.

Question 10.: Can you please clarify why there is no QC sampling in production (identified as WCS5-PROC15 in ES2) in the Vienna and Orth sites?

QC sampling in production occurs at both sites:

Vienna: Production samples are taken from the process after critical process steps. A production technician samples 3.5-7 mL from a batch (single-use PE pipettes) which is then delivered to the quality control (QC) Lab in PE-Falcon tubes. Quality control is exempted from authorisation and therefore only briefly described. The QC technician samples only one drop to perform HPLC analysis. The rest of the sample, including the vessel (PE-Falcon tube), is collected as hazardous waste. No emissions of OPnEO are expected from this step.

Orth: A production technician samples 3.5-7 mL from a batch (single-use equipment) which is then delivered to the quality control (QC) Lab in PE-Falcon tubes. Quality control is exempted from authorization and therefore only briefly described. The QC technician samples only one drop to perform HPLC analysis. The rest of the sample, including the vessel (PE-Falcon tube), is collected as hazardous waste. No emissions of OPnEO are expected from this step.

Question 11: Are transport containers at Orth site also single-use and sent for incineration or are they cleaned and the effluents collected for incineration?

"OPnEO is transported from the warehouse to the relevant laboratory in a sealed container." The sealed container referenced is the original OPnEO container from the manufacturer (i.e., the commercial packaging), which is opened in the manufacturing suite and added to the blending vessel. Unused OPnEO and empty OPnEO containers are collected as hazardous waste for off-site incineration.

Question 12.: In reference to the date provided page 48 in Table 22, what was the LOD (Limit of Detection) and the measurement method used to measure OPnEO from the diluted CIP wastewater effluents of process vessel cleaning process? (Vienna) Can you please justify why you consider the measurement from one batch representative enough to be used for a yearly release estimate?

The method used in Vienna for determination of OPnEO is based on HPLC and done according to specifications of European Pharmacopoeia current Edition, 2.2.29 (Liquid Chromatography), European Pharmacopoeia current Edition, 2.2.46 (Chromatographic Separation Techniques), USP current Edition <621> (Chromatography) as well as USP Monograph Octoxynol 9. The LOD for this method is [redacted]. Hence this value differs from the Lessines' method LOD ([redacted]). However, this is not unexpected as methods are validated for each Takeda lab separately and determined LODs are depending on the used equipment. The presented test was an interim solution to substantiate the estimation of emissions until the emissions can be measured more precisely. Whereas it is acknowledged that a single experiment may conceal unknown bias in the measurement results, repeating the trials was not possible due to time constraints when preparing the AfA. However, the observed decrease of OPnEO concentrations over the partial CIP washes is consistent and plausible hence we believe they are also sufficiently representative.

Question 13.: On page 56 of the CSR, you indicate that: 'It is assumed that all surfaces are covered by a 0.132 mm layer of product solution. This assumption is based on analytical measurements presented in chapter 9.1.2.2.' Is this the correct reference? Can you please explain further how you came to the conclusion of 0.132 mm from the analytical measurements?

The correct reference is chapter 9.2.1.2, p. 48. Please apologise this typo.

A representative [redacted] tank was investigated which has an inner surface (without lid) area of [redacted]. The remaining amount of liquid in the tank was determined to be [redacted]. Dividing the volume by the surface area results in the remaining surface layer of 0.132 mm:

$$\frac{[redacted]}{[redacted]} = 0.000132\ m = 0.132\ mm$$

The remaining amount of liquid in the tank was calculated based on the analytical measurements: The remaining mass of OPnEO in the solution was determined analytically (as presented in Table 22 of the CSR) with a sum of [redacted]. The known concentration of the buffer in the tank is [redacted]. Dividing the mass of remaining OPnEO by the known concentration reveals the remaining amount of liquid in the tank (the rounded value of 0.66 L was carried forward to assessment):

$$\frac{[redacted]}{[redacted]} = 0.6614\ L = 0.0006614\ m^3$$

Question 14.: Have there been measurements done for the Lessines site of the following emissions:

a) vessel residues after CIP washing sent to sewer? (Lessines)

b) manual washing residues sent to process sewer? (Lessines)

No analytical measurements were conducted on the mentioned residues, as the vessels and the cleaning procedure is similar to the one in Vienna which was used to predict emissions. The estimated release values will be further verified analytically.

The triple-rinse during manual cleaning is collected for incineration and only the subsequent cleaning steps are directed to the sewer (destination on-site STP).

Question 15.: If any, please describe the plans (methods and frequency) to produce analytical verification data of the following emissions for each site:

a) The diluted wastewater of product washes during the protein purification process

The diluted wastewater of product washes during the protein purification process was measured for Vienna (see Table 21 in the CSR) and Lessines (p. 58). Based on these measurements, it was decided which amount of waste has to be collected.

Details:

Table 1: Results from the measurement in Lessines. Based on these measurements the decision was taken that the effluents from the first [redacted] column volumes will be collected. 1 column volume equals ca. [redacted].

[redacted]

Table 2: Results from the measurement in Vienna. Based on these measurements the decision was taken how much waste is incinerated. For Immunate each washing step consists of [redacted]. For Tisseel washing and precipitation volume varies from [redacted] per step. For Thrombin one column volume equals ca. [redacted].

[redacted]		[redacted]		[redacted]	
Washing step	**OPnEO conc. in mg/L**	**Surplus after…**	**OPnEO conc. in mg/L**	**Column volume**	**OPnEO conc. in mg/L**
1	[redacted]	First precipitation	[redacted]	2 *	[redacted]
2	[redacted]	Second precipitation	[redacted]	10 *	[redacted]
3	[redacted]	First wash	[redacted]	18	[redacted]
4	[redacted]	Second wash	[redacted]		

[redacted]		[redacted]		[redacted]	
Washing step	**OPnEO conc. in mg/L**	**Surplus after…**	**OPnEO conc. in mg/L**	**Column volume**	**OPnEO conc. in mg/L**
5	[redacted]				
6	[redacted]				
*collected for incineration # value not measured. but predicted					

b) Manual cleaning effluents from weighing and blending vessels and from the washing machine effluents sent to sewer, and c) The buffer residues emitted with second-tier washing/rinsing solutions

The applicant has no plans to verify emission sources independently, as they are combined with all production waste prior to sewer discharge. For identifying and understanding emission sources, the process waste emissions and a representative measurement for residues in wastewater from cleaning procedures were analytically evaluated. For further evaluation the applicant is planning to measure amounts of OPnEO (including intermediate degradation products and 4-t-OP) in the final sewage. If the estimated releases are not exceeded, this confirms that modelling was precise and further evaluation of each single emission source is not needed.

Question 16.: On page 56 of the CSR, it is mentioned that the current RMMs will be implemented for contaminated residues collection. Please describe the plans to produce analytical verification data of the effectiveness of the applied measures.

Quarterly measurements will be conducted to monitor release rates to the environment, and to verify that the applicant is compliant to his commitment made regarding the releases. Currently confirmatory sampling is ongoing to verify the predicted releases and to establish a sampling procedure. At mid-year 2020 quarterly measurements will start. This applies to the sites in Lessines and Vienna.

Sewage will not be monitored in Orth because the entire OPnEO related manufacturing process is completely separated from the sewer and all waste is collected for incineration. There is no connection of OPnEO containing liquids to the municipal sewer.

Question 17.: On page 50 of the CSR, it is indicated [redacted] is sent down the drain (last rinse with a washing machine). What is preventing you from eliminating the use of the washing machine? (Vienna)

We would like to reiterate the amount of [redacted] (33 to 330) nanograms per year, thus contributing 2.6×10^{-9} % to the total site emissions.

The washing machine is required to ensure that all parts are cleaned accurately for use in the next production run. A validated wash cycle is run according to the manufacturing process where the parts were used. Pharmaceutical manufacturing under GMP requires such high

hygienic standards. The washing machine ensures elimination of further contamination not related to OPnEO, since enabling higher temperatures than manual washing.

Eliminating the washing machine would require all parts to be washed manually with a high probability of retaining contaminants (not OPnEO) which would cross-contaminate the products, thereby increasing the likelihood of production batches failing to meet the release criteria as approved by global health authorities with the consequence of reducing critical medicine availability.

Question 18.: RAC takes note of the quantity of OPnEO that you claim to emit per year on the different sites. What would prevent you from reducing or eliminating this emission to zero? Please explain what additional measures you would need to implement to:

a) capture the substance (e.g. by eliminating liquid discharges down the drain)

Significant changes to the production lines would be needed to capture further waste volumes. This would result in excessive construction work at each site and for each production line.

Lessines: The holding capacity of the current waste collection tank would be exceeded twice per day, requiring the tank to be emptied by the waste management company **multiple times per day**, closely aligned with the production schedule. To avoid these logistical challenges, the collection tank would have to be replaced by a tank of larger capacity, and also the second containment would have to be significantly enlarged. There is insufficient physical space at the site for such a modification without impacting the site access to employees. Assuming no reconstruction of the collection tank, an investment of [redacted] EUR would have to be made only for the modification of piping. The potential expenses for additional waste collection would result in an increase in operating costs of [redacted].

Vienna: The current waste collection tank is located inside the facility, prohibiting an increase in the storage capacity. Therefore, changes to the collection tank are impossible. Eliminating liquid discharges would require an investment of [redacted]EUR to reconstruct piping. An increase in operating costs for routine waste collection for incineration of xxx x compared to the current state would have to be expected. To implement any changes, the site would need to cease operations in order to modify the waste lines to divert all liquid waste to the collection tanks. Any additional line modifications could be implemented during a scheduled shut-down to avoid any supply impact.

b) de-water liquid waste

De-watering liquid waste is being assessed for Lessines. A reverse osmosis system, capable of concentrating the waste by a factor of 5 and with a treatment limit of 20 m^3/day. As the site with the highest waste volume, assessing the availability of installing the system is in progress.

Vienna's limited physical capacity for a de-watering system precludes further investigating this option.

c) dispose of the remainder 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 that would be incurred.

Takeda launched a project to evaluate several treatment technologies. None of them was as effective as incineration. Therefore, it was decided to incinerate the waste fraction containing the bulk of OPnEO. Collection of further amounts of wastewater and sending it to incineration is technically and practically not possible as outlined in answer 18a).

To treat the remaining waste with a different method will require investments above those cited in 18.a) as the production lines would need to be modified so as to divert production waste to the secondary treatment system with sufficient capacity to hold, or transfer, the volume of waste subject to this treatment. This would require a physical footprint, additional to that already used for the current waste collection system, which is unavailable at the sites. Under consideration that Takeda evaluated several treatment technologies to treat the majority of OPnEO contaminated waste, and none were considered as effective as incineration, it is considered unlikely an alternate system can effectively remove the limited amount of OPnEO from the volume of waste which would be subject to such a secondary treatment.