## AfA Baxter AG

**Submission number:** KA600552-65

**Communication number:** AFA-C-2114510478-49-01/F

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

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

## Answers to RAC question – Non-confidential version

Would you please provide a detailed Exposure Scenario (similar to the one available in the CSR sections 9.2, 9.3 and 9.4 for the Vienna 1, Lessines and Orth sites) which describes the (future) manufacturing of CoVIg-19 hyperimmune in the Baxter AG pilot plant at [redacted] 1220 Vienna.

# Vienna [redacted] Exposure scenario 1 for the environment

**Market sector:** Health Care/Pharmacy

**Sector of use:** SU20 – Health Services

**Article categories:** PC 0 – Detergent

**Environment contributing scenario(s):** ERC 4

**Worker/Consumer contributing scenario(s):** PROC 15, 5, 8b, 1

**Subsequent service life exposure scenario(s):** N/A

### Description of the activities and technical processes covered in the exposure scenario are subject to refining as the production process is under development for the accelerated Research & Development product:

The Vienna pilot plant is located in an industrial park situated within the city of Vienna. The site is surrounded by urban development. At the site, OPnEO is used for research and development purposes. In addition, the site is planned as a back-up commercial production line for small volumes of CoVIG-19 hyperimmune. OPnEO is used as a component in the S/D solution for virus inactivation during the manufacturing process of this medicine.

OPnEO will be applied in a similar manner as Vienna - Benatzkygasse, and Lessines, although at a much smaller scale. The maximum amount of OPnEO planned to be used at the site for commercial medicinal production is [redacted]. Releases to the environment will be avoided by collecting all waste containing OPnEO and disposing of it as hazardous waste (incineration) by a licensed contractor. This is to be ensured by engineering controls as well as administrative measures.

As the risks to the environment are the critical subjects of the present CSR, every WCS is evaluated for possible small losses of OPnEO, and RMMs are presented to avoid emissions. The occupational exposure scenario for the use of OPnEO in manufacture of plasma-derived medicinal products in Vienna, [redacted], can be broken down into the following contributing scenarios (including those with no potential for exposure, and those with potential for exposure). The whole process will be mapped in detail by standard operating procedures (SOP). The site follows GMP standards and all commercial production activities are to be conducted under GMP by trained technicians. During all steps, operators are to wear the PPE as described below, "Summary of Risk Management Measures for Vienna, [redacted]".

### WCS 1: Quality control sampling and analysis of raw materials (OPnEO)

On average five times per year samples from OPnEO arriving at the goods receiving department are taken to verify compliance with Takeda's quality criteria. All samples are taken under a safety cabinet and are delivered to the QC lab where the following tests for quality check are conducted: recording of IR spectra, HPLC chromatograms. Overall, the handling of the material takes about one hour. Unused OPnEO as well as packaging is discarded to hazardous waste. The equipment used for the sampling and testing is single-use equipment and will be discarded to hazardous waste and sent off-site for incineration.

**WCS2: Transfer of OPnEO to the blending vessel, and blending of the S/D solution**

OPnEO is part of the S/D mixture (also containing Polysorbat 80 and TNBP) which is blended according to the batch record before being applied for virus inactivation. OPnEO, stored in the original container provided by the manufacturer, is transported from the warehouse to the production area. The required amount of OPnEO ([redacted] (0.5–1.0) kg per batch) is manually poured from the container to the [redacted] single-use S/D mixing vessel. The mixture is stirred mechanically. The amount of OPnEO required is determined according to the weight of protein solution requiring viral inactivation treatment. The final target concentration of OPnEO in the protein solution is 1 % (w/w). As this protein solution volume can vary slightly, the amount of OPnEO used per batch has to be adjusted accordingly. The total transfer time of OPnEO is approximately [redacted] per batch. Once the OPnEO transfer is complete, the other ingredients of the S/D solution are added: Polysorbate 80 and Tri-n-butyl phosphate (common name: TNBP). The components are mixed for a defined period using an electric stirrer. Single-use vessels are collected as hazardous material for off-site incineration.

A single-use stirrer is being evaluated. In a worst-case scenario, the stirrer is triple rinsed and cleaned with IPA or Sporicidal wipes, with the rinse and wipes being collected for off-site incineration.

**WCS 3: Transfer of S/D solution into reaction vessel**

The buffer prepared in the single-use vessel (see WCS 2) is then transferred into a [redacted] single-use mixing tank. There the protein solution is added.

The amount of buffer added is based on the master batch record calculation. The single-use vessels and unused solution are collected separately for off-site to incineration.

**WCS 4: Virus inactivation (including separation of OPnEO from protein via column chromatography)**

S/D treatment is usually applied during the first stages of the purification processes for plasma products. The treatment uses 1.0 % (w/w) OPnEO, 0.3 % (w/w) polysorbate 80, and 0.3 % (w/w) tri-(n-butyl) phosphate (TNBP).

Once the S/D solution has been added to the protein solution in the viral inactivation tank, the process of virus inactivation takes place. Incubation takes approximately [redacted] hour at room temperature. The virus inactivation tank remains sealed during the process. Once the virus inactivation step is complete, OPnEO is removed from the protein solution during the subsequent [redacted] step. The product solution (containing the target protein and the S/D solution) is loaded onto the [redacted] As the protein [redacted]. Residual amounts of OPnEO [redacted] are flushed out of the system with a buffer at the beginning of washing step #1. The first [redacted] of washing #1 still contain significant amounts of OPnEO. During the subsequent washing steps, the OPnEO concentration in the wash buffer effluent rapidly approaches non-detectable ranges (plug flow conditions).

The process waste (containing OPnEO) – the load effluent and the washes of the loaded [redacted] – is collected as hazardous waste in sealable containers and sent off-site for incineration. Process waste volumes per batch are estimated at, or below, [redacted] L.

Virus inactivation and cleaning in place are fully automated and do not involve any manual intervention.

**WCS 5: Cleaning**

The pilot-scale production line at [redacted] is planned to be used for clinical trial and commercial production of *CoVIg-19 hyperimmune* applying OPnEO. The manufacturing devices will be equipped with a clean-in-place system. All waste from the production and cleaning processes will be collected for incineration. Vessels will be single use and collected for incineration. Automated and administrative controls are being established to ensure that any liquid waste containing OPnEO is directed to hazardous waste (incineration).

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 exempt 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.

**ECS 1: Environmental emissions from the S/D treatment process**

All solid and liquid waste containing OPnEO is to be collected from the pilot-scale commercial production line and sent off-site for incineration.

Items which are used only once (e.g. mobile vessels, single-use mixing tank, beakers, pipettes) are collected as hazardous waste for off-site incineration. Overall, the disposal and collection system, as well as the instructions and SOPs for workers aim for zero losses to the environment.

**Spill and leakage management**

The site's emergency response plan includes procedures and associated training for accidental spills, 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. The site 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.

## Vienna– [redacted] Environmental contributing scenario 1: Use as detergent for virus inactivation

**Conditions of use Vienna, [redacted]**

| **Amount used, frequency and duration of use (or from service life)** |
|---|
| • Daily use at site (Vienna [redacted]): [redacted] OPnEO/day on [redacted] days per year |
| • Annual use at a site: < 1 [redacted] 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;<br>Equipment cleaning:<br>• Stirrer is rinsed three times and treated with IPA or Sporisidal wipes, with all rinsate and wipes collected as hazardous waste.<br>• Only single-use equipment is used, which is disposed of as hazardous waste.<br>• 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[1].<br>• Any equipment contaminated with OpnEO is directly incinerated (single-use equipment)<br>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 $m^3/d$<br>• 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 $m^3/d$. |

**Environmental RMMs in Vienna, [redacted]**

| Compartment | RMM | Stated Effectiveness |
|---|---|---|
| Air | No emission to air – not relevant | N/A |
| Water | All waste containing OpnEO is collected and sent to incineration[1].<br>Any equipment contaminated with OpnEO is incinerated (single-use equipment). | 100 % |
| Soil | No emission to soil – not relevant | N/A |

**Releases**

All OpnEO contaminated waste, both solid and liquid, is collected and incinerated by a licensed contractor. Accordingly, neither emission to water nor to soil is expected. Emission to air is expected to be negligible in view of the extremely low vapour pressure of octylphenol-ethoxylates

**Local releases to the environment (Vienna – [redacted])**

| Release route | Release factor | Release (per annum) | Release estimation justification, method and details |
|---|---|---|---|
| Water | Initial release factor: 0 % | 0 | The OpnEO waste is completely separated from the wastewater stream by the measures described in the WCS above and disposed of as hazardous waste. |
| Air | Initial release factor: 0 %<br>Final release factor: 0 % Local | 0 | Release factor<br>(Emission to air, site-specific, following the TGD, 2003)<br>In a simplistic and conservative approach, the amount of OPnEO emitted via exhaust air/general ventilation can be estimated |

[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

| | | | |
|---|---|---|---|
| | release rate: 0 kg/day | | 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 $1.41 \times 10^{-7}$ mm Hg at 25 °C, corresponding to $1.88 \times 10^{-5}$ Pa at 25 °C. The resulting release factor to air for the use in the pharmaceutical industry is 0.<br>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. |

**Releases to waste**

**Release factor to external waste:**

100 % of OPnEO are collected as hazardous waste and sent off-site for incineration[3].

**Release factor to waste from on-site treatment:**

N/A.

**Exposure and risks for the environment and human via the environment**

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

**Exposure concentrations and risks for the environment**

| Protection target | Exposure concentration | Risk characterisation |
|---|---|---|
| Freshwater | 0 mg/L | 0 |
| Sediment (freshwater) | 0 mg/kg dw | 0 |
| Marine water | Not applicable, site-specific assessment for inland site | N.a. |
| Sediment (marine) | Not applicable, site-specific assessment for inland site | N.a. |
| Air | 0 mg/m³ | N.a. |
| Agricultural soil | 0 mg/kg dw | 0 |
| Man via environment – inhalation | Not required | N.a. |

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

[3] 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

### Conclusion on risk characterisation (minimisation of emission/exposure)

Product development is still being established, including the commercial production design on the development line, incorporating elaborate risk management measures for implementation at the Vienna pilot plant, [redacted], i.e. complete separation of the manufacturing process waste by the measures described in the worker and environmental scenarios above, so that emissions to the environment are essentially zero. Definitive proof of implementation of the risk management measures is not yet possible.

## Worker contributing scenario

In accordance with Regulation (EC) No 1907/2006, Article 62(4)(d) risks for workers need not to be considered, hence exposure calculations are not needed.

# SUMMARY OF RISK MANAGEMENT MEASURES

## Vienna – [redacted]

**Table 1: Succinct summary of the Risk Management Measures (RMMs) and Operational Conditions (OCs) for the safe handling and use of 4-(1,1,3,3- tetramethylbutyl) phenol, ethoxylated (OPnEO) in Vienna, [redacted] (Austria).**

| ECS and WCS | Task (ERC/spERC or PROC) | Annual amount per site (tonnes /year) | Technical RMMs, including: *Containment, *Ventilation (general, LEV...) *customised technical installation, etc | Organisational RMMs, including: *Duration and frequency of exposure *OSH management system *Supervision *Training, etc. | PPE (characteristics) | Other conditions | Effectiveness of wastewater and waste air treatment (for ERC) | Release factors: water, air and soil (for ERC) |
|---|---|---|---|---|---|---|---|---|
| ECS 1 | ERC 4: Use as detergent for virus inactivation and subsequent discharge | < 1 ([redacted]) | All process waste is collected and sent to off-site incineration[4] by a licensed contractor. | SOPs for handling and disposal of any OPnEO contaminated items and materials<br>Only trained personnel handle OPnEO.<br>Off-site incineration applies to:<br>- contaminated process effluents<br>- contaminated wastewater from cleaning of mechanical stirrer<br>- disposable material contaminated with OPnEO is collected as hazardous waste | N.a. | Room temperature (20 °C)<br>Automated process | N.a., strict separation from the sewerage; liquid waste is collected separately and disposed of as hazardous waste (external incineration) | Water: no release<br>Air: no release<br>Soil: no release |

[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.

| ECS and WCS | Task (ERC/spERC or PROC) | Annual amount per site (tonnes /year) | Technical RMMs, including: *Containment, *Ventilation (general, LEV...) *customised technical installation, etc | Organisational RMMs, including: *Duration and frequency of exposure *OSH management system *Supervision *Training, etc. | PPE (characteristics) | Other conditions | Effectiveness of wastewater and waste air treatment (for ERC) | Release factors: water, air and soil (for ERC) |
|---|---|---|---|---|---|---|---|---|
| WCS1 | PROC 15: Quality control sampling and analysis of raw materials (OPnEO) | N.a. | Analysis is conducted under laminar flow hood | Representative sampling of lots received per defined cGMP requirements.<br>< 10 times per year. | Dermal protection: Nitrile gloves (EN374), specific activity training, and coveralls (covering arms and legs as part of the GMP/clean room procedure.)<br>Eye protection: Goggles or safety glasses with side shields | Place of use: Indoor<br>Operating temperature: 20.0 to 26.0 °C<br>Housekeeping: Clean room procedure/GMP<br>Skin surface potentially exposed: One hand face only (240 cm²) | N.a. | N.a. |
| WCS2 | PROC 5: Transfer of OPnEO to the blending vessel, and blending of the S/D solution | N.a. | N.a. | < 1 h/batch ([redacted]) | Dermal protection: Nitrile gloves (EN374), specific activity training, and coveralls (covering arms and legs as part of the GMP/clean room procedure.)<br>Eye protection: Goggles or safety glasses with side shields | Place of use: Indoor<br>Operating temperature: 20.0 to 26.0 °C Clean room procedure/GMP | N.a. | N.a. |
| WCS3 | PROC 8b: Transfer of S/D solution into reaction vessel | N.a. | N.a. | < 1 h/batch ([redacted]) | Dermal protection: Nitrile gloves (EN374), specific activity training, and coveralls (covering arms and legs as part of the GMP/clean room procedure.)<br>Eye protection: Goggles or safety glasses with side shields | Place of use: Indoor<br>Operating temperature: 20.0 to 26.0 °C Clean room procedure/GMP | N.a. | N.a. |

| ECS and WCS | Task (ERC/spERC or PROC) | Annual amount per site (tonnes /year) | Technical RMMs, including: *Containment, *Ventilation (general, LEV...) *customised technical installation, etc | Organisational RMMs, including: *Duration and frequency of exposure *OSH management system *Supervision *Training, etc. | PPE (characteristics) | Other conditions | Effectiveness of wastewater and waste air treatment (for ERC) | Release factors: water, air and soil (for ERC) |
|---|---|---|---|---|---|---|---|---|
| WCS4 | PROC 1: Virus inactivation (including separation of OPnEO from protein via column chromatography or centrifugation) | N.a. | General ventilation: Basic (1–3 air changes per hour) Occupational Health and Safety Management System: Advanced Local exhaust ventilation: None | Viral inactivation step: < 10 h/batch ([redacted]) Separation: < 10 h/batch ([redacted]) | Dermal protection: Nitrile gloves (EN374), specific activity training, and coveralls (covering arms and legs as part of the GMP/clean room procedure.) Eye protection: Goggles or safety glasses with side shields | Closed system. Place of use: Indoor Operating temperature: 20.0 to 26.0 °C Clean room procedure/GMP | N.a. | N.a. |
| WCS5 | PROC 1: Cleaning | N.a. | General ventilation: Basic (1–3 air changes per hour) Occupational Health and Safety Management System: Advanced Local exhaust ventilation: None | CIP step: 60 min (= 1 h/day) | Dermal protection: Nitrile gloves (EN374), specific activity training, and coveralls (covering arms and legs as part of the GMP/clean room procedure.) Eye protection: Goggles or safety glasses with side shields | Closed system. Place of use: Indoor Operating temperature: = 80.0 °C Clean room procedure/GMP | N.a. | N.a. |

**Abbreviations**: WCS = worker contributing scenario, ECS = environmental contributing scenario, ERC = environmental release category, PROC = process category, LEV = local exhaust ventilation, RPE = respiratory protective equipment, PPE = personal protective equipment, APF = assigned protection factor; CIP = cleaning in process; N.a. = not applicable