Applicant: Baxter AG
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Answers to RAC and SEAC questions – Non-confidential version

RAC Questions

Question 1: We understand that in Lessines, you intend to use the same production line as the one described in your application for authorisation, and that that same OCs and RMMs (as the one described in your application, and subsequent responses) will be applied to the manufacturing of CoVIg-19 hyperimmune? Is our understanding correct? Please confirm that the total used yearly quantity of OPnEO, the total yearly release of OPnEO and the release factor will remain the same as in your application during the requested review period in Lessines?

We confirm the committee's understanding of the planned CoVIg-19 hyperimmune production at Lessines is correct. The same OCs and RMMs as described in our application will be applied to the production of CoVIg-19 hyperimmune. The total used annual quantity of OPnEO, the total yearly release and the release factor will remain the same as in our application during the requested review period in Lessines.

Question 2: For the Vienna site, it is unclear if you intend to use the same production line as the ones described in your application for authorisation? If not, can you please clarify where CoVIg-19 hyperimmune will be manufactured (which production lines), and detail which OCs and RMMs will be applied? If yes, please confirm that the same production steps are used and only the annual volume is increased?

CoVIg-19 hyperimmune is to be manufactured in the Baxter AG pilot plant at [redacted], 1220 Vienna. The production line in the pilot plant is being adapted to the CoVIG-19 hyperimmune manufacturing requirements, thereby permitting full waste collection to be incorporated in this redesign.

A broad description of the process for the R&D pilot scale line:

WCS 2: Transfer of OPnEO to blending vessel and blending of the S/D solution
OPnEO is part of the S/D mixture (also containing [redacted]) 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 [redacted] (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: [redacted] The components are mixed for a defined period using an electric stirrer. Single-use beakers are collected as hazardous material 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 [redacted] chromatography)
S/D treatment is usually applied during the first stages of the purification processes of plasma products. The treatment uses [redacted] % (w/w) OPnEO, [redacted].

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 solution [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 in designated waste collection tanks and sent off-site for incineration.

You claim that (i) "additional annual volume of OPnEO will be required for Vienna, and is [redacted]; (ii) emissions from the line will remain zero and you also refer to the emissions from this additional volume to be zero. A 'zero-release' claim does not match indeed the description of the OCs and RMMs applied in Vienna in your application for authorisation. Please describe in more detail your claims with regards to the assumptions made in the exposure assessment of potential releases from Vienna site on how the change to the annual tonnage impacts the actual releases.

The manufacturing process for *CoVIg-19 hyperimmune* is considered for an established pilot scale production line, which is being adapted for the new product, at the Baxter AG pilot plant located at [redacted]. These adaptations include waste collection to ensure Triton X-100 contaminated material is not emitted to the communal waste systems.

The OCs and RMMs applied in Vienna as stated in our application are specific to the existing commercial-scale production lines in the [redacted] facility.

The maximum total amount of OPnEO potentially used for the Vienna product lines at [redacted] and commercial production on the pilot scale line at [redacted] is [redacted] (<10) tns with a total release of [redacted] (5.44 to 10.87) kg OPnEO per year.

[redacted].

Please also specify the volume of OPnEO increase/use per batch, if known.

The volume of OPnEO used per batch is [redacted] (0.5–1.0) kg.

Question 3: Please confirm that no manufacturing of CoVIg-19 hyperimmune is foreseen in Orth.
We confirm no manufacturing of CoVIg-19 hyperimmune is foreseen in Orth.

SEAC Question

Regarding the Analysis of Alternatives for CoVIg-19 hyperimmune, can you please briefly explain why the product was developed with 4-tert-OPnEO instead of an alternative detergent?

The rapid development of a possible medicine to meet the medical needs caused by the COVID-19 pandemic is only possible at the current pace by using a well-established platform, licensed for 15 years, with demonstrated virus inactivation and removal processes for plasma-derived medicinal products. The hyperimmune globulin manufacturing platform pools multiple plasma donations to achieve consistently high level of antibodies to the targeted treatment. Ensuring consistent, robust virus inactivation and removal from the pooled plasma is critical for product and patient safety. Introducing a change to this platform in the virus inactivation step would require full regulatory review and approval of the platform to ensure the modified step still addresses the safety needs of regulators and, ultimately, patient populations. Such a change would significantly extend clinical testing requirements, and thus delay availability of a desperately needed COVID-19 treatment option of conceptually established mechanism of action.
Takeda continues investing in R&D efforts to assess the potential alternatives [redacted] and VIENEP17020 to determine if a potential implementation would constitute a shift to less hazardous substances before initiating the required evaluation cascade described in chapter 3.3 of the AoA/SEA.