Department for Environment Food & Rural Affairs

**Authorisation Decision**
**by Rebecca Pow MP**
**Parliamentary Under Secretary of State**
**On behalf of the Secretary of State for Environment, Food and Rural Affairs**
**Decision date: 30 June 2023**

## Application Ref: 0189-01

## UK REACH authorisation No.:

| Authorisation number | Authorisation holder | Authorised use |
|---|---|---|
| UKREACH/23/01/0 | Lonza Biologics Plc. | Use of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated for virus inactivation via solvent/detergent treatment in the manufacture of recombinant medicinal active pharmaceutical ingredients from mammalian cell cultures |

## Preliminary matters

- 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO) is listed in Annex XIV to EUR 2006/1907 concerning the registration, evaluation, authorisation and restriction of chemicals ('UK REACH')[1]. As such, 4-tert-OPnEO is subject to the authorisation requirement referred to in Article 56(1) of that Regulation.
- 4-tert-OPnEO was included in Annex XIV to Regulation (EC) No 1907/2006[2] ('EU REACH') because there is scientific evidence of probable serious effects to the environment from its endocrine-disrupting properties when it degrades.
- The sunset date for 4-tert-OPnEO for this use was 4 January 2021.
- The application is made by: Lonza Biologics Plc. of 228 Bath Road, Slough, Berkshire, SL1 4DX ('the Applicant').

[1] References to EUR 2006/1907, referred to in this decision as UK REACH, are to the retained version of Regulation (EC) No 1907/2006, as amended. The retained version of that Regulation is available online at https://www.legislation.gov.uk/eur/2006/1907/contents.
[2] References to Regulation (EC) No 1907/2006, referred to in this decision as EU REACH, are to that Regulation as it has effect in EU law.

- On 28 June 2019, Lonza Biologics Plc. and Lonza Biologics Porriño, SL. (the 'EU REACH Applicants') made an application for authorisation ('the Original Application') to the European Chemicals Agency (ECHA) for the use of 4-tert-OPnEO for virus inactivation via solvent/detergent treatment in the manufacture of recombinant medicinal active pharmaceutical ingredients (APIs) from mammalian cell cultures.
- The technical function of 4-tert-OPnEO in the use is in virus inactivation. It is not present in the final products.
- The Original Application related to the use of 4-tert-OPnEO in respect of two sites: one in Porriño, Spain, and one in Slough, United Kingdom ('the Slough site').
- On 14 September 2020, ECHA sent the Consolidated Opinion of the Committee for Risk Assessment (RAC) and the Committee for Socio-Economic Analysis (SEAC) ('the RAC Opinion' and 'the SEAC Opinion' respectively) to the European Commission.
- On 23 June 2021, the Applicant notified the Secretary of State of the Original Application in accordance with Article 127G of UK REACH.
- Following correspondence between the appropriate authorities[3] and the Applicant, the Applicant wrote to Defra on 18 January 2022 indicating its desire to amend its risk management measures ('RMMs') in the Original Application.
- On 21 March 2022, Defra wrote to the Applicant stating that if it wished to amend its RMMs then a formal request to do so should be submitted by 18 April 2022. Defra agreed to extend this deadline to 22 July 2022 following a request from the Applicant.
- On 21 July 2022, the Applicant submitted a formal request to amend its RMMs in the Original Application.
- On 18 August 2022, the appropriate authorities requested the UK REACH Agency (the Health and Safety Executive, thereafter 'the Agency') to assess the Applicant's formal request.
- On 9 December 2022, the Agency sent its assessment to the appropriate authorities.
- In reaching this decision I have considered the likely emissions to the environment and the likely socio-economic benefits in respect of the Applicant's site in Great Britain.

[3] As defined under UK REACH, the appropriate authorities are: the Secretary of State, in relation to England; the Scottish Ministers, in relation to Scotland; and the Welsh Ministers, in relation to Wales.

## Decision

1. This Decision is addressed to the Applicant.

2. An authorisation is granted in accordance with Article 60(4) of UK REACH for the following use of 4-tert-OPnEO:

    a. for virus inactivation via solvent/detergent treatment in the manufacture of recombinant medicinal APIs from mammalian cell cultures.

3. The review period referred to in Article 60(9)(e) of UK REACH is set at twelve years from the sunset date. The authorisation will cease to be valid on 4 January 2033 unless the authorisation holder has submitted a review report in accordance with Article 61(1) by 4 July 2031.

4. The authorisation is subject to the following condition (as well as the requirement in Article 60(10) of UK REACH to ensure exposure is reduced to as low a level as is technically and practically possible):

    a. The authorisation holder must adhere to the risk management measures ('RMMs') and operational conditions ('OCs') described in the chemical safety report referred to in Article 62(4)(d) of UK REACH[4], in conjunction with the amended RMMs in the authorisation holder's formal request to the Agency on 21 July 2022.

5. The following monitoring arrangements must be applied:

    a. The authorisation holder must measure the concentration of 4-tert-OPnEO and 4-tert-octylphenol (4-tert-OP[5]) in the wastewater at the Slough site, prior to release to the local sewage treatment plant.

    b. These measurements must be taken at least once every three months for each substance, with no more than three months between measurements while the authorised use takes place. The first measurements for each substance must be taken within three months of the use first taking place.

    c. If any measurements show a significant change in the concentrations of either substance (for example, due to changes or operational fluctuations in the process) compared to previous measurements, the authorisation holder must take additional measurements. Those additional measurements must be taken frequently enough to allow the authorisation holder to understand the reasons for the change and identify any necessary further steps to ensure compliance with Article 60(10) of UK REACH.

    d. When taking measurements, the authorisation holder must use an analytical method capable of adequately characterising 4-tert-OPnEO and

[4] This is a reference to the chemical safety report dated 20 June 2019 submitted by Lonza Biologics Plc. on 28 June 2019 as part of the Original Application. The risk management measures, and operational conditions are described in sections 9 (Exposure Assessment) and 10 (Risk Characterisation Related to Combined Exposure).
[5] 4-tert-OP is formed when 4-tert-OPnEO degrades in the environment.

4-tert-OP at an appropriately low level of quantification, by reference to the level of anticipated emissions.

e. The authorisation holder must record details of the sampling point, the analytical method(s) chosen, the reasons for choosing those analytical method(s), the concentrations detected and the corresponding mean environmental release values, as well as the contextual information associated with all measurements and any necessary further steps identified in accordance with subparagraph (c) to ensure compliance with Article 60(10) of UK REACH.

f. The authorisation holder must make the information referred to in subparagraph (e) available to the Agency on request.

6. In the event that a review report is submitted in accordance with Article 61(1) it should include:

a. The information referred to in paragraph 5(e) relating to the monitoring activities.

## Background

7. This decision is made under Article 60(4) of UK REACH and having obtained the consent of Scottish and Welsh Ministers.

8. In making this decision, I have taken into account:

a. The Original Application.

b. The elements referred to in Article 60(4)(a) to (d) of UK REACH, and the aspects referred to in Article 60(5).

c. The RAC Opinion and the SEAC Opinion.

d. That the Original Application was for two sites: the Porriño site in Spain, and the Slough site. The Original Application contained details on the likely benefits of authorisation for Great Britain.

e. Additional information in the Applicant's formal request to amend its RMMs. This contained details which confirmed expected emissions of 4-tert-OPnEO at the Slough site.

f. The Agency's assessment of the Applicant's formal request to amend its RMMs. This provided a view on:

(a) whether the Applicant's amended RMMs are appropriate and effective in limiting the risk to the environment;

(b) how the amended RMMs affect the conclusions made in respect of the Original Application by SEAC, and an updated cost-effectiveness ratio; and

(c) the credibility of the justification provided by the Applicant for why the amended RMMs are compatible with its obligations under Article 60(10) to reduce exposure to as low a level as is technically and practically possible.

## Reasons

9. In the Original Application, the Applicant did not attempt to derive predicted no-effect concentrations (PNECs). The Applicant therefore treated 4-tert-OPnEO as a substance for which it is not possible to determine a threshold for the purposes of Article 60(3)(a) of EU REACH. Therefore, the RAC Opinion concluded that for the purposes of the assessment of this application it was not possible to determine PNECs for the endocrine disrupting properties for the environment of 4-tert-OPnEO in accordance with Section 6.4 of Annex I to EU REACH.

10. In accordance with Article 60(3)(a) of UK REACH, this means that Article 60(2) of that Regulation does not apply to this application. Article 60(2) does not apply to substances for which it is not possible to determine a threshold in accordance with Section 6.4 of Annex I. Therefore, an authorisation may only be granted on the basis of Article 60(4) of that Regulation.

11. An authorisation may only be granted under Article 60(4) of UK REACH if it is shown that the socio-economic benefits outweigh the risk to human health or the environment and there are no suitable alternative substances or technologies. A suitable alternative should be safer, available, and technically and economically feasible.

### Risk to the environment

12. The RAC Opinion concluded that the Applicant demonstrated that releases to environmental compartments (air, water and soil) have been prevented or minimised as far as technically and practically possible, provided the Applicant's planned RMMs were implemented and adhered to. In reaching this conclusion, RAC noted that all three washes of the chromatography column would be collected and transported for incineration (the 'Original RMMs').

13. RAC accepted the Applicant's modelled estimate of emissions at the Slough site, which would result in up to 100kg of yearly emissions of 4-tert-OPnEO to the environment. This was based on a worst-case assumption of small losses from collection and incineration.

14. In September 2021, the Applicant indicated its desire to amend its initial proposal to collect the second and third column washes for incineration. In the Applicant's formal request to amend its RMMs, the Applicant made a request to only collect the first column wash for incineration because:

    a. there are low amounts of 4-tert-OPnEO in the second and third column washes;

b. the costs of storing and transporting large volumes of liquid waste can be reduced; and

c. CO2 emissions resulting from the incineration of liquid waste can be halved.

15. The Applicant's intention to release the wastewater from the second and third column washes to sewer (the 'Amended RMMs'), rather than to collect them for appropriate treatment (the Original RMMs), represents a significant change in RMMs compared with the Original Application.

16. In the Applicant's formal request to amend its RMMs, the Applicant provided measured data of the releases arising from its Amended RMMs, using a new and more accurate analytical method. These measurements allowed the Agency to conclude that, as a result of implementing the Amended RMMs, emissions of 4-tert-OPnEO from the Slough site would be significantly smaller than estimated in the Original Application. These releases enter the environment as contaminated liquid waste *via* the sewer. They are received at the Slough sewage treatment plant (STP), which discharges to a tributary of the River Thames.

17. In its assessment, the Agency concluded with regard to paragraph 8.f.(a) that the Amended RMMs would be appropriate and effective at limiting environmental risk. In reaching this conclusion, the Agency compared the surface water predicted environment concentrations provided by the Applicant for 4-tert-OP with the environmental quality standards proposed for ethinylestradiol, another endocrine disruptor. On the basis of this comparison, the Agency concluded that the residual emissions from the Slough site would not result in discernible environmental impacts on wildlife in the receiving surface waters. Having evaluated the Agency's assessment, I agree with its conclusion that the use applied for will have no adverse environmental impacts in relation to endocrine disruption.

18. In its assessment, the Agency concluded with regard to paragraph 8.f.(c) that the Applicant's justification for why the amended RMMs are compatible with its obligations under Article 60(10) is economically sound and credible. The Agency concluded it would be inappropriate to require the Applicant to carry out the Original RMMs due to the very high financial and environmental costs of storing, transporting and incinerating significant amounts of water containing only a very small amount of 4-tert-OPnEO. 4-tert-OPnEO presents a risk to aquatic life when it degrades in water. When degraded, it can adversely affect the endocrine systems of aquatic organisms. I note that this risk cannot be excluded even at low levels. However, I conclude that the risk is low because the emissions of 4-tert-OPnEO arising from the Amended RMMs at the Slough site are likely to be low.

19. Having evaluated the Agency's assessment, I conclude that releases to environmental compartments at the Slough site have been reduced to as low a level as is technically and practically possible.

20. RAC concluded that the Applicant's RMMs and OCs are expected to be appropriate and effective in limiting the risk, provided that they are implemented and adhered to. Therefore, RAC did not propose any additional conditions. In its assessment of the Amended RMMs, the Agency concluded that the Applicant's Amended RMMs demonstrate that releases have been minimised as far as technically and practically possible.

21. Having evaluated the Agency's assessment and the RMMs and OCs described in the Applicant's request to amend its RMMs, I agree that no additional conditions are required. In reaching this conclusion, I note that all of the RMMs and OCs referred to in the Agency's assessment take place at the Slough site in Great Britain.

**Monitoring arrangements**

22. In the Original Opinion, RAC recommended that the Applicant should monitor, at least quarterly, 4-tert-OPnEO and its principal degradation products in the wastewater prior to release to the local municipal sewage treatment plant. RAC explained that this monitoring programme would be used to review the effectiveness of the Original RMMs and to introduce measures to further reduce the emissions, as well as to provide information on the trends in releases over the authorisation period. RAC recommended the results of this monitoring should be made available to enforcement authorities on request and included in any review report.

23. In the Applicant's request to amend its RMMs, the Applicant had adopted a new and more accurate analytical method to measure (rather than estimate) releases of 4-tert-OPnEO, and the results of these measurements were provided to the Agency. These confirmed a reduction of emissions greater than that predicted in the Original Application. Additionally, the Applicant has outlined in its formal request that it is already carrying out monitoring, similar to those recommended by RAC in the Original Opinion.

24. In the Applicant's request to amend its RMMs, the Applicant did not specify precisely how often or for how long it will carry out monitoring. Therefore, I agree with RAC's recommendations on monitoring to ensure the Applicant provides information on the trends in releases over the recommended 12-year review period. In setting the monitoring arrangements in paragraph 22 as a condition for authorisation, and by stipulating the timing of those monitoring activities, this will ensure a more robust and reliable approach to ensuring emissions are minimised over the whole review period.

25. I also conclude that the authorisation holder should make the information collected from monitoring available to the Agency on request. This information should also be provided to the Agency in the event of a review report being submitted.

**Socio-economic analysis**

26. The SEAC Opinion concluded that SEAC has no substantial reservations on the quantitative and qualitative elements of the Applicants' assessment of the benefits and the risk to the environment associated with the continued use of 4-tert-OPnEO. Avoided profit losses for the Slough site represent all the quantified benefits and are greater than ten million euros[6].

27. Qualitative benefits consist of:

    a. avoided external environmental costs from transport emissions associated with relocating outside of Great Britain.

    b. avoided possible impact on orphan drugs[7] and patients being treated with novel products under clinical trials.

28. The Applicant provided additional quantified benefits which include avoided relocation and closure costs, avoided job losses, avoided transport costs, and avoided impacts on consumers due to inferior quality, higher prices, and reduced quantity of products. However, in its Opinion, SEAC concluded the other economic impacts are highly uncertain. Therefore, SEAC did not included them in its estimate of the monetised benefits.

29. In its assessment, the Agency also concluded with regard to paragraph 8.f.(b) that by adopting the Amended RMMs, the Applicant will have additional cost savings which in turn would mean the avoided profit losses would be higher than if authorisation was not granted. The Agency calculated a new cost effectiveness ratio which demonstrated that the cost per kilogram of prevented emissions achieved by refusing authorisation would be greater for the Applicant under its Amended RMMs, compared to the cost-effectiveness ratio in SEAC's Original Opinion, which was based on the Original RMMs.

30. I agree with SEAC's and the Agency's conclusions on the quantified benefits and consider them to be applicable to the benefits and risk in respect of Great Britain.

## Conclusion on whether the benefits outweigh the risk

31. I consider that the Applicant has shown that the socio-economic benefits of granting authorisation outweigh the risk to the environment because of:

    a. The likely quantified benefits such as avoided profit losses in Great Britain.

    b. The likely qualitative benefits to patients in Great Britain.

[6] The Original Application was submitted to ECHA while the UK was still an EU member state and therefore provided all monetary calculations in euros. On 13 April 2023, the Bank of England exchange rate was EUR/GBP = 0.8830.

[7] Orphan drugs are drugs that have been developed for rare, often serious diseases and medical conditions, where the medicine is unlikely to generate sufficient profit to justify research and development cost.

c. The likelihood of low emissions in Great Britain.

**Alternatives**

32. The SEAC Opinion concluded that no available alternative substances or technologies with the same function and a similar level of performance that are safer and economically feasible for the EU REACH Applicant would be available by the sunset date.

33. The Applicant has identified a shortlist of potential alternatives for technical evaluation and will assess each affected process individually, so multiple alternatives may be necessary to replace 4-tert-OPnEO. In its Opinion, SEAC concluded that the Applicant's assessment and prioritisation of alternative detergents is justified. Noting the high compatibility requirements with different APIs, as well as the time needed for identification, assessment, validation and implementation of alternatives, in addition to the required regulatory approval, SEAC concluded that the Applicant had convincingly demonstrated that there were no technically and economically feasible alternatives available before the sunset date. Substitution activities are expected to continue for 12 years after the sunset date or until the end of 2033. The SEAC Opinion concluded that the activities, timelines and monitoring proposed in the Applicant's substitution plan are robust and take into consideration all regulatory requirements for APIs.

34. Having evaluated SEAC's assessment, I agree with its conclusions and consider that the Applicant has discharged its burden of proof in demonstrating the absence of suitable alternatives. In reaching this conclusion, I have considered SEAC's conclusion on the time it would take to implement a technically feasible substance. I consider SEAC's assessment to be applicable to Great Britain.

**Review period**

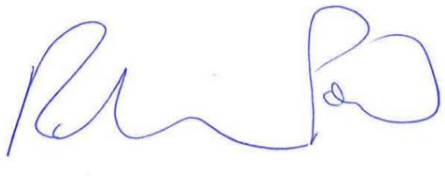
35. The SEAC Opinion recommended the review period referred to in Article 60(9)(e) of EU REACH should be set at 12 years. I agree with that recommendation and set the review period at 12 years under Article 60(9)(e) of UK REACH. In reaching this conclusion, SEAC agreed that a 12-year review period appears necessary and represents the time required for conducting research and development activities for substituting 4-tert-OPnEO in virus inactivation treatment.

36. SEAC concluded that the Applicant's substitution plan, including the activities, timelines, and monitoring, is robust and takes into consideration all regulatory requirements for APIs. I consider that SEAC's assessment is applicable to Great Britain.

## Conclusion

37. For the reasons set out above I conclude that the socio-economic benefits outweigh the risk to the environment for the use of 4-tert-OPnEO referred to in paragraph 2 and that there are no suitable alternative substances or technologies.

38. The Scottish Ministers and the Welsh Ministers have given their consent to this decision in accordance with Articles 4A and 64(8) of UK REACH.



Rebecca Pow MP

On behalf of the Secretary of State for Environment, Food and Rural Affairs