Department for Environment Food & Rural Affairs

Authorisation Decision

by Jo Churchill MP
Parliamentary Under Secretary of State
On behalf of the Secretary of State for Environment, Food and Rural Affairs
Decision date: 16 December 2021

Application Ref: 0157-01

UK REACH authorisation No.:

Authorisation number	Authorisation holder	Authorised use
UKREACH/21/05/0	FUJIFILM Diosynth Biotechnologies UK Limited	Use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated as a detergent in the purification process of G-CSF (Granulocyte Colony Stimulating Factor) inclusion bodies

Preliminary Matters

- 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) is listed in Annex 14 to EUR 2006/1907 concerning the registration, evaluation, authorisation and restriction of chemicals (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] because there is scientific evidence of probable serious effects to the environment from its endocrine-disrupting properties when it degrades.
- The application is made by: FUJIFILM Diosynth Biotechnologies UK Limited of Belasis Avenue, Billingham, TS23 1LH ('the Applicant').

[1] References to "EUR 2006/1907" 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" are to that Regulation as it has effect in EU law.

- On 21 March 2019, the Applicant and Merck Biodevelopment SAS ('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 as a detergent in the purification process of G-CSF (Granulocyte Colony Stimulating Factor) inclusion bodies.

- G-CSF is used as an intermediate in the production of the biosimilar drug PEG-Filgrastim. PEG-Filgrastim is the final product which results from granting an authorisation for this use. PEG-Filgrastim is an active pharmaceutical drug that is used to prevent the occurrence or reduce the duration of febrile neutropenia in cancer patients receiving immunosuppressive chemotherapy.
- The Original Application related to the use of 4-tert-OPnEO in respect of two sites: one already operating in Martillac, France (the 'Merck site') and a further planned site in Billingham, Great Britain (the 'Fujifilm site'), which is not yet operational.
- The Merck site is producing G-CSF and the Fujifilm site will produce G-CSF as contract manufacturers for the company Fresenius Kabi.
- Neither G-CSF nor PEG-Filgrastim contains 4-tert-OPnEO, since the substance is only used as a purifier, so there is no potential for emissions from the final products.
- On 17 June 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 28 June 2021, the Applicant notified the Secretary of State of the Original Application in accordance with Article 127G of EUR 2006/1907.
- In reaching this decision I have considered the likely emissions to the environment and the likely socio-economic benefits in respect of the Fujifilm site in Great Britain.

Decision

1. This Decision is addressed to the Applicant.
2. An authorisation is granted in accordance with Article 60(4) of EUR 2006/1907 for the following use of 4-tert-OPnEO:

   a. as a detergent in the purification process of G-CSF inclusion bodies.
3. The review period referred to in Article 60(9)(e) of EUR 2006/1907 is set at 9 years. The authorisation will cease to be valid on 4 January 2030 unless the authorisation holder has submitted a review report in accordance with article 61(1) by 4 July 2028.

4. The authorisation is subject to the following condition (as well as the requirement in Article 60(10) of EUR 2006/1907 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 EUR 2006/1907[3]

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[4]) in the wastewater prior to release to the local sewage treatment plant (STP) at the Fujifilm site.

    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 3 months of the use first taking place.

    c. If any measurements show a significant change in the concentrations of either substance (e.g. 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 EUR 2006/1907.

    d. When taking measurements, the authorisation holder must use an analytical method capable of adequately characterising 4-tert-OPnEO and 4-tert-OP at an appropriately low level of detection, 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 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 EUR 2006/1907.

    f. The authorisation holder must also carry out a mass balance analysis to determine the effectiveness of the RMMs and OCs at the Fujifilm site. The methodology and results of the calculations carried out for the purposes of this analysis, any assumptions made, and the corresponding

[3] This is a reference to the chemical safety report dated 19 March 2019 submitted by Merck Biodevelopment SAS and Fujifilm Diosynth Biotechnologies Ltd. on 21 March 2019 as part of the Original Application. The risk management measures and operational conditions are described in sections 9 (EXPOSURE ASSESSMENT (and related risk characterisation)) and 10 (RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE).

[4] 4-tert-OP is formed when 4-tert-OPnEO degrades in the environment.

environmental release values must be recorded. This mass balance analysis must be carried out within 3 months of the use first taking place.

g. The authorisation holder must make the information referred to in subparagraphs (e) and (f) available to the UK REACH Agency (the Health and Safety Executive) 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(g) relating to the monitoring programme and mass balance analysis.

Background

7. This decision is made under Article 64(8) of EUR 2006/1907.

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 EUR 2006/1907, 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 existing Merck site and the planned Fujifilm site. The Fujifilm site was described as analogous to the Merck site by the EU REACH Applicants, referring to construction, the manufacturing process, the RMMs and OCs including waste treatment via incineration, as well as expected emissions of 4-tert-OPnEO.

e. Additional information provided by the Applicant to the Secretary of State, indicating the likely quantified benefits for the Fujifilm site, and stating that emissions containing 4-tert-OPnEO at that site will be zero.

Reasons

9. In the Original Application, the EU REACH Applicants derived predicted no-effect concentrations (PNECs). The RAC Opinion concluded that the EU REACH Applicants have not demonstrated a threshold level for the endocrine disrupting properties for the environment of 4-tert-OPnEO. 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 Regulation (EC) No 1907/2006.

10. In accordance with Article 60(3)(a) of EUR 2006/1907, 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 1. 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 EUR 2006/1907 if it is shown that the socio-economic benefits outweigh the risks 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.

Risks to the environment

12. The RAC Opinion concluded that in respect of the Merck site, the EU REACH Applicants demonstrated that releases to environmental compartments (air, water and soil) have been prevented or minimised as far as technically and practically possible. In reaching this conclusion, RAC noted that all solid waste and the majority of 4-tert-OPnEO in liquid waste is collected for incineration.

13. The only liquid waste at the Merck site containing residual 4-tert-OPnEO that is not incinerated ('contaminated waste'), results from the surfaces of the processing equipment after draining and rinsing during the cleaning procedures. RAC accepted the EU REACH Applicants' modelled worst-case estimate of emissions at the Merck site, which would result in very low yearly emissions of 4-tert-OPnEO to the environment.

14. As OCs and RMMs are expected to be analogous for both sites, RAC concluded for both sites that whilst risks to the environment cannot be excluded for non-threshold substances even at low exposure levels, the likelihood of adverse effects is negligible (i.e. nearing zero). RAC based this conclusion on the EU REACH Applicants' description of the Merck site, namely the RMMs and OCs, the total amount of 4-tert-OPnEO used per year, the mainly closed system production process and incineration of solid and liquid wastes.

15. In relation to the Fujifilm site, RAC concluded that the OCs and RMMs are expected to be appropriate and effective in limiting the risk, provided that they are implemented as stated in the application and then adhered to. In response to my request for additional information on the analogous nature of the two sites, the Applicant further clarified that once operational, the Fujifilm site will take additional measures to segregate, collect and incinerate all waste containing 4-tert-OPnEO, resulting in zero emissions of contaminated waste to the environment. Therefore, I consider the above conclusions in relation to the negligible likelihood of adverse effects, relevant to Great Britain.

16. 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 these risks cannot be excluded even at low levels. However, I conclude that the risk is low because the emissions arising from the rinse water containing 4-tert-OPnEO at the Fujifilm site are likely to be very low. Having evaluated RAC's assessment, I conclude that releases to environmental compartments at the Fujifilm site will be prevented or minimised as far as technically and practically possible. In reaching this

conclusion, I also note the Applicant's responses to my request for additional information which stated that there will be zero emissions of contaminated waste at the Fujifilm site.

17. RAC concluded that the RMMs and OCs at the Fujifilm site are expected to be appropriate and effective in limiting the risk, provided that they are adhered to. Therefore, RAC did not propose any additional conditions. Based on the described RMMs and OCs at both sites, RAC concluded that the EU REACH Applicants have demonstrated that releases to environmental compartments have been or will be prevented or minimised as far as technically and practically possible. RAC also concluded that the exposure estimates provided for both sites are appropriate. Therefore, RAC did not propose any monitoring arrangements but did recommend, in the event a review report was submitted, a monitoring programme for the Fujifilm site to confirm the estimated releases.

18. Having evaluated RAC's assessment and the RMMs and OCs described in the Original Application, 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 Original Application and RAC Opinion, that already take place at the Merck site, will take place at the Fujifilm site in Great Britain.

Monitoring Arrangements

19. In the RAC Opinion, RAC noted that no measurements have been conducted to date at either site. RAC concluded that the lack of confirmation of the effectiveness of the RMMs and OCs on the Merck site as unfortunate. However, RAC accepted the conclusions made in the Original Application related to the effluent segregation and mass balance at the Merck site.

20. RAC considered that the release estimates for the Merck site are appropriate and effective in limiting risk to the environment. However, to address the uncertainty about the representativeness of the release estimates, RAC recommended a quarterly monitoring programme at the Fujifilm site, once this site is operational. RAC recommended the results of this monitoring should be included in any subsequent review report.

21. The Applicant has since confirmed to me that the Fujifilm site will be operational from 2022. Therefore, I conclude the monitoring programme recommended by RAC for the review report, should instead be included as a monitoring arrangement. This will confirm the predicted effectiveness of the RMMs and OCs and the release estimates prior to the submission of any review report.

22. Noting RAC's conclusion on the unfortunate lack of measures to confirm the effectiveness of the RMMs and OCs at either site, I conclude that the Applicant should also conduct a mass balance analysis at the Fujifilm site to further confirm the predicted effectiveness of the planned RMMs and OCs at that site.

23. I also conclude that the authorisation holder should make the information collected from the monitoring programme and mass balance analysis available to the UK REACH Agency on request. This information should also be provided to the UK REACH Agency in the event of a review report being submitted.

Socio-economic analysis

24. The SEAC Opinion concluded that SEAC has no substantial reservations on the quantitative and qualitative elements of the EU REACH Applicants' assessment of the socio-economic benefits and the risk to the environment associated with the continued use of 4-tert-OPnEO. However, only quantified benefits for Fresenius Kabi and avoided job losses at the Merck site were quantified in the Original Application. No quantified benefits were provided for the Fujifilm site in the Original Application. SEAC concluded that not quantifying job losses for the Fujifilm site, could represent an underestimate of the overall social costs of unemployment as a result of non-authorisation.

25. SEAC had no reservations on the EU REACH Applicants' assessment of the qualitatively assessed additional socio-economic benefits. These included:

    a. avoided profit losses for both the Merck site and Fujifilm site;

    b. avoided social costs of future employment that would be denied for the employees at the Fujifilm site; and

    c. avoided health impacts on patients through increased prices and disrupted availability.

26. In response to my request for further information on the likely benefits to Great Britain, the Applicant provided estimated quantified benefits for the Fujifilm site. These included contractual agreements for the period 2021-2023, as well as for 2023 onwards with a total benefit value of tens of millions of pounds sterling. The Applicant described that the majority of this total accounted for employment associated with the Fujifilm site. As the Fujifilm site is not yet operational, employment benefits reflect future benefits that would be denied if the authorisation was not granted.

27. The Applicant also gave a quantified estimate of the number of healthcare patients for the United Kingdom who would likely benefit from the product produced at the Fujifilm site.

28. I have considered the Applicant's quantified costs including those to future employment that would be denied, as well as the associated impacts on patient health, in making a decision on this application.

Conclusion on whether the benefits outweigh the risks

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

a. The likely benefits such as avoided profit losses and losses of planned jobs in Great Britain.

b. The likely avoided negative health impacts on some patients in Great Britain.

c. The likelihood of zero emissions in Great Britain.

Alternatives

30. The SEAC Opinion concluded that there are no available alternative substances or technologies with the same function and a similar level of performance that are safer and technically and economically feasible for the EU REACH Applicants by the sunset date. SEAC agreed with the EU REACH Applicants that given the necessary steps to determine a suitable alternative and achieve substitution, and the time required to do so, there is no feasible or suitable alternative available before the sunset date.

31. Having evaluated SEAC's assessment, I agree with that conclusion 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 assessment of the technical feasibility of alternative substances already on the market and I consider this to be applicable to Great Britain.

Review period

32. The SEAC Opinion recommended the review period referred to in Article 60(9)(e) of Regulation (EC) No 1907/2006 should be set at 9 years. I agree with that recommendation. In reaching this conclusion, I have considered SEAC's Opinion that the substitution timelines proposed by the EU REACH Applicants are appropriate to achieving complete substitution. I consider that SEAC's assessment is applicable to Great Britain.

Conclusion

33. 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.

34. The Scottish Ministers and the Welsh Ministers have given their consent to this decision in accordance with Articles 4A and 64(8) of EUR 2006/1907.

Jo Churchill MP

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