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: 11 November 2022

Application Ref: AFA002-01

UK REACH authorisation No:

Authorisation number	Authorisation holder	Authorised use
UKREACH/22/04/0	MeiraGTx UK II Limited	Use of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated as a manufacturing aid in the production of gene therapies.

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 14 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 MeiraGTx UK II Limited of 34-38 Provost Street, London, N1 7NG ('the Applicant').
- On 19 January 2021, the Applicant submitted an application for authorisation ('the Application') to the Health and Safety Executive ('the Agency') for the use of 4-tert-OPnEO as a manufacturing aid in the production of gene therapies.

[1] This is a reference to the retained version of Regulation (EC) No 1907/2006, which is available online at https://www.legislation.gov.uk/eur/2006/1907/contents

- On 18 March 2022, the Agency sent its opinion ('the Agency Opinion') to the Secretary of State for Environment, Food and Rural Affairs, and Scottish and Welsh Ministers.

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 as set out in the table above titled 'UK REACH authorisation No.':

   Use of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated as a manufacturing aid in the production of gene therapies.

3. The review period referred to in Article 60(9)(e) of EUR 2006/1907 is set at 12 years. The authorisation will cease to be valid on 11 November 2034 unless the authorisation holder submits a review report in accordance with Article 61(1) by 11 May 2033.

4. The authorisation is subject to the following conditions (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 and operational conditions described in the chemical safety report referred to in Article 62(4)(d) of EUR 2006/1907[2].

   b. Within four months of the date of this authorisation, the authorisation holder must complete an assessment of whether any additional measures could be implemented to further reduce the level of emissions of 4-tert-OPnEO in contaminated liquid waste.

   c. The assessment must allow the authorisation holder to identify any necessary further measures to ensure compliance with Article 60(10) of EUR 2006/1907.

   d. Within six months of the date of this authorisation, the authorisation holder must prepare a report on their findings including any planned measures or measures already taken to ensure compliance with Article 60(10) of EUR 2006/1907. Those measures must be implemented as soon as practically possible.

   e. The report must be made available to the Agency on request.

[2] This is a reference to the chemical safety report dated 18 January 2021 submitted by MeiraGTx on 19 April 2021 as part of the Application. The risk management measures and operational conditions are described in sections 9 (exposure assessment) and 10 (risk characterisation related to combined exposure).

5. In the event that a review report is submitted in accordance with Article 61(1) of EUR 2006/1907 it should include:

   a. The report referred to in paragraph 4(d).

   b. A list of any measures referred to in the report that have been implemented.

   c. An assessment of the impact of those measures on reducing the level of emissions of 4-tert-OPnEO in contaminated liquid waste.

6. This authorisation is not subject to any monitoring arrangements.

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 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 Agency Opinion.

Reasons

9. In the Application, the Applicant did not derive predicted no-effect concentrations ('PNECs'). Therefore, the Agency concluded that for the purposes of the assessment of this application it was not possible to determine PNECs for the endocrine disrupting properties of 4-tert-OPnEO for the environment.

10. In accordance with Article 60(3)(a) of EUR 2006/1907, this means that Article 60(2) of that Regulation does not apply. 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 Agency Opinion concluded that the Applicant has not 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, the Agency noted that the majority of the

4-tert-OPnEO used in the process is collected for off-site incineration as hazardous waste.

13. A small proportion of contaminated liquid waste is discharged to the sewer and could enter the aquatic environment via the local sewage treatment plant. 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.

14. In its opinion, the Agency compared the surface water predicted environment concentrations provided by the Applicant for 4-tert-OP[3] with the environmental quality standards proposed for ethinylestradiol, another endocrine disruptor. On the basis of this comparison, the Agency concluded with high certainty that the environmental exposure resulting from this authorisation would not cause adverse impacts on aquatic species through endocrine disruption. 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.

15. The Agency concluded that the operational conditions (OCs) and risk management measures (RMMs) described in the application are potentially appropriate and effective in limiting the risk. The Agency did not feel able to conclude with certainty that they were appropriate and effective because of the discharge of contaminated liquid waste to the sewer. The Agency considered that the Applicant had not demonstrated that this discharge could not be further reduced.

16. Therefore, the Agency recommended a condition requiring the Applicant to identify and implement any measures that could further reduce these emissions. Having evaluated the Agency's assessment, I agree with its conclusion, and that the recommended condition will ensure that the requirements of Article 60(10) are demonstrably achieved.

Socio-economic analysis

17. The Agency considered that the Applicant's socio-economic analysis was proportionate in its scope and depth, and the evidence and information included in the application sufficient for the Agency to reach a definitive conclusion on the benefits of the use applied for.

18. In its opinion, the Agency concluded that the Applicant has demonstrated that the socioeconomic benefits of granting the authorisation are over one hundred million pounds per kg of emissions of 4-tert-OPnEO. In reaching its conclusion, the Agency assessed the following quantified estimated benefits:

    a. avoided profit losses;

    b. avoided relocation or closure cost of the Applicant's London facility;

[3] 4-tert-OP is formed when 4-tert-OPnEO degrades in the environment.

c. avoided additional cost for transportation, quality testing etc.;

d. avoided loss of profit to the Applicant's suppliers; and

e. avoided social cost of unemployment.

The Agency concluded that these quantified benefits would total tens of millions of pounds per year.

19. The Applicant also attempted to quantify the additional health benefits of patients receiving the Applicant's treatments. The Agency disregarded the Applicant's quantified additional health benefits and instead expressed the benefits as the expected number of patients that would be treated. The Agency concluded that, based on the number of patients who would be negatively affected in the non-use scenario, these non-quantified benefits are significant.

20. Having evaluated the Agency's assessment, I agree with its conclusions on the quantified and non-quantified benefits.

Conclusion on whether the benefits outweigh the risks

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

a. the likely significant quantified benefits, in particular avoided profit losses;

b. the likely significant non-quantified benefits in respect of healthcare; and

c. the likely low level of emissions and low risk of adverse environmental impacts.

Alternatives

22. The Agency concluded in its Opinion that currently 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 Applicant by the sunset date. The Agency agreed with the Applicant that the alternatives tested by the Applicant either failed to meet the cell lysing efficiency criteria or were not sufficiently available at the required GMP (good manufacturing practice) grade.

23. Having evaluated the Agency's assessment, I agree with that conclusion and consider that the Applicant has discharged their burden of proof in demonstrating the absence of suitable alternatives. In reaching this conclusion, I have considered the Agency's assessment of the technical and economic feasibility of alternative substances already on the market.

Review period

24. In its Opinion, the Agency recommended the review period referred to in Article 60(9)(e) of EUR 2006/1907 should be set at 12 years. In reaching its conclusion, the Agency noted:

a. the clear socio-economic benefits of the use;

b. the limited environmental risks which the Agency considers would not result in discernible adverse environmental impacts at population level;

c. the time needed for the Applicant to recoup their investment in alternatives;

d. that there are currently no technically and economically feasible alternatives available; and

e. the time required to identify and implement alternatives, given:

   i. the difficulty in identifying suitable patients and performing additional clinical studies given the low prevalence of the relevant ocular diseases;

   ii. the need for bridging studies to be carried out on the patient response data from the clinical studies; and

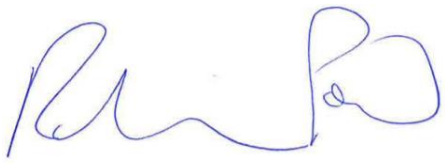
   iii. the requirements for regulatory approval under legislation relating to the use of medicines.

25. I agree with the Agency's conclusions on these points and its recommendations.

Conclusion

26. 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.

27. 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.



Rebecca Pow MP

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