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COMMISSION IMPLEMENTING DECISION

of 6.1.2023

granting an authorisation under Regulation (EC) No 1907/2006 of the European Parliament and of the Council to AGC Biologics A/S and AGC Biologics GmbH for certain uses of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO)

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

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THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC[1], and in particular Article 64(8) thereof,

Whereas:

(1) 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated ('4-tert-OPnEO') is listed in Annex XIV to Regulation (EC) No 1907/2006 and uses of that substance are subject to the authorisation requirement in Article 56(1), point (a), of that Regulation.

(2) On 13 June 2019, AGC Biologics A/S and AGC Biologics GmbH ('the applicants') submitted an application in accordance with Article 62 of Regulation (EC) No 1907/2006 for authorisation for two uses of 4-tert-OPnEO[2]. The uses for which authorisation was sought are as a detergent for the inactivation of viruses in the production of therapeutic proteins using mammalian cell hosts in projects where processes have been approved by authorities (where processes are Good Manufacturing Practice compliant) ('use 1') and as a detergent during purification process of recombinant biopharmaceuticals derived from microbial expression hosts in projects where processes have been approved by authorities (where processes are Good Manufacturing Practice compliant) ('use 2').

(3) On 4 January 2021, the Commission received the opinions on the application adopted by the Committee for Risk Assessment (RAC) and by the Committee for Socio-economic

[1] OJ L 369, 30.12.2006, p.1.

[2] Different names and abbreviations are used to refer to the substance, including 'Triton X-100' in the chemical safety report.

Analysis (SEAC) of the European Chemicals Agency[3] and sent to it pursuant to Article 64(5), second subparagraph, of Regulation (EC) No 1907/2006.

(4) RAC concluded in its opinions that it is not possible to determine a predicted no-effect concentration (PNEC) 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, and that therefore 4-tert-OPnEO is a substance for which it is not possible to determine a threshold for the purposes of Article 60(3), point (a), of that Regulation. As a result, Article 60(2) of Regulation (EC) No 1907/2006 does not apply to that substance and authorisations may therefore only be granted with respect to that substance under paragraph 4 of that Article.

(5) RAC noted that risk to the environment cannot be excluded for non-threshold substances, even at low exposure levels. Consequently, RAC takes the emissions of the substance as a proxy for the risk.

(6) In its opinion on use 1, RAC concluded that the risk management measures and operational conditions described in the application are appropriate and effective to limit the risk to the environment. RAC noted that the substance is handled in closed systems and, as of the sunset date, solid and liquid waste, including waste from the second wash step of the process, is collected for incineration. Negligible releases originating from subsequent cleaning and rinsing steps of the column are discharged with the wastewater. RAC therefore considered that releases to environmental compartments are prevented or minimised as far as technically and practically possible. However, taking into account the uncertainties about the representativeness of the calculated release estimates, as well as the potential increase of the use, RAC recommended a monitoring programme. Having evaluated RAC's assessment, the Commission agrees with its conclusion and recommendations.

(7) In its opinion on use 2, RAC concluded that the risk management measures and operational conditions described in the application are not appropriate to limit the risk to the environment. In particular, RAC noted that, although most of liquid waste is collected for incineration, a significant volume of wastewater contaminated with 4-tert-OPnEO, mainly originating from the cleaning of tanks and equipment during the purification process, is discharged directly to the municipal sewer system. RAC also considered that there are uncertainties about the representativeness of the calculated releases and pointed out the potential future increase in quantities of substance used, which may result in larger volumes of contaminated wastewater. Therefore, RAC recommended conditions and a monitoring programme. Having evaluated RAC's assessment, the Commission agrees with its conclusion and recommendations.

(8) SEAC concluded in its opinions on use 1 and use 2 that it has no substantial reservations on the quantitative and the qualitative elements of the applicants' assessment of the socio-economic benefits and the risk to the environment associated with the continued use of the substance. Taking into account SEAC's assessment, the lack of scientific knowledge

[3] https://echa.europa.eu/documents/10162/e488678e-2887-d7d0-13ff-3ecdd08cdf49
https://echa.europa.eu/documents/10162/242ce4b9-4c8d-c3b4-b655-0dd2e4199f6f

at present to quantify or monetise the risk to the environment associated with the use of the substance, the estimated emissions for both uses of a few kilograms of the substance per year and the estimated benefits due to avoided profit losses and avoided job losses at minimum in the order of tens of millions of euros over the entire review period, the estimated cost of avoiding the remaining releases of the substance in the order of hundreds of millions of euros per kilogram for use 1 and hundreds of thousands of euros per kilogram for use 2, the qualitatively assessed additional socio-economic benefits of the continued use of the substance due to the high likelihood for future availability of, among others, treatments for haemophilia and a rare genetic disorder, the Commission concludes that the applicants have demonstrated that the socio-economic benefits of the continued use of the substance outweigh the risk to human health and the environment arising from that use.

(9) A suitable alternative should be safer, available, and technically and economically feasible. Where suitable alternatives are available in the Union, but not technically or economically feasible for the applicant or its downstream users, an authorisation may be granted if the applicant for authorisation submits a substitution plan. An alternative that provides the functionality and level of technical performance necessary for the use applied for should be considered to be technically feasible.

(10) In its opinions on uses 1 and 2, SEAC concluded that there were no suitable alternative substances or technologies available by the sunset date for the applicants. Having evaluated SEAC's assessment and all relevant information available, the Commission acknowledges that the applicants need to repeat partly or completely the clinical trials undertaken so far to test whether the identified alternatives allow achieving the inactivation of viruses in the production of therapeutic proteins or the solubilisation of hydrophobic impurities in the microbial process and to obtain regulatory approvals, and that, under favourable conditions, this would require two to five years. The Commission therefore considers that it cannot be deemed that the identified alternatives allow the functionality needed for the use applied for. Therefore, the Commission agrees with SEAC's conclusion and considers that the applicants have discharged their burden of proof in demonstrating the absence of suitable alternatives both in the Union and for the applicants.

(11) Therefore, having regard to the conditions laid down in Article 60(4) of Regulation (EC) No 1907/2006, it is appropriate to authorise the use of 4-tert-OPnEO described in the application, provided that the risk management measures and operational conditions described in the chemical safety report as well as the conditions set out in this Decision are fully applied.

(12) The Commission has based its assessment on all relevant scientific evidence currently available, as assessed by RAC and SEAC, and, after having carried out a detailed examination, based its conclusions on a sufficient amount of material and reliable information allowing it to conclude. Nevertheless, additional scientific evidence would allow the Commission to perform its assessment on a more robust or broad evidentiary base in the future. Hence, it is appropriate to request that additional emission information be submitted.

(13) SEAC recommended in its opinions that the review period referred to in Article 60(9), point (e), of Regulation (EC) No 1907/2006 should be set at 12 years for both uses. The Commission agrees with that recommendation, taking into account the relevant elements from SEAC's assessments, and, in particular, the lack of suitable alternatives within a shorter timeline, the long investment cycles, as well as the regulatory approvals needed and quality requirements for medicinal products.

(14) The language used to describe the risk management measures and operational conditions in the application for authorisation may be different from the official language of the Member State where the use takes place. Therefore, in order to facilitate supervision and enforcement of compliance with the authorisation, it is appropriate to require the authorisation holders to submit, upon request, a brief summary of those risk management measures and operational conditions to the competent authority of that Member State in an official language of that Member State.

(15) This Decision does not affect the obligation of the authorisation holders to ensure that a use of a substance does not adversely affect human health or the environment, having regard to the principle set out in Article 1(3) of Regulation (EC) No 1907/2006. Furthermore, this Decision does not affect the obligation of the authorisation holders under Article 60(10) of that Regulation to ensure that the exposure is reduced to as low a level as is technically and practically possible or the obligation of the employer to eliminate or reduce to a minimum risks to the health and safety of workers at work involving hazardous chemical agents in accordance with Article 5(2) of Council Directive 98/24/EC[4]. This Decision does not affect the application of Union law in the area of health and safety at work, in particular Council Directives 89/391/EEC[5], 92/85/EEC[6], 94/33/EC[7] and 98/24/EC, or any national binding occupational limit values which may be stricter than the applicable limit values under Union law.

(16) This Decision does not affect any obligation to comply with emission limit values or other requirements set in accordance with Directive 2008/50/EC of the European Parliament and of the Council[8] or Directive 2010/75/EU of the European Parliament and of the Council[9], nor any obligation to comply with emission limit values set to achieve compliance with the environmental quality standards established by Member States in

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4 Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 131, 5.5.1998, p. 11).

5 Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (OJ L 183, 29.6.1989, p. 1).

6 Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 348, 28.11.1992, p. 1).

7 Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work (OJ L 216, 20.8.1994, p. 12).

8 Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe (OJ L 152, 11.6.2008, p. 1).

9 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (OJ L 334, 17.12.2010, p. 17).

accordance with Directive 2000/60/EC of the European Parliament and of the Council[10] or the environmental quality standards established in Directive 2008/105/EC of the European Parliament and of the Council[11]. Compliance with the provisions of this Decision does not necessarily imply compliance with emission limit values or environmental quality standards under any other provisions of Union law, which may include further or more onerous requirements.

(17) The measures provided for in this Decision are in accordance with the opinion of the Committee established by Article 133 of Regulation (EC) No 1907/2006,

HAS ADOPTED THIS DECISION

Article 1

An authorisation is hereby granted in accordance with Article 60(4) of Regulation (EC) No 1907/2006 to the following persons for the following uses of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO):

Authorisation number	Authorisation holder	Authorised use
REACH/22/45/0	AGC Biologics A/S	As a detergent for the inactivation of viruses in the production of therapeutic proteins using mammalian cell hosts in projects where processes have been approved by authorities (where processes are Good Manufacturing Practice compliant)
REACH/22/45/1	AGC Biologics GmbH	
REACH/22/45/2	AGC Biologics A/S	As a detergent during the purification process of recombinant biopharmaceuticals derived from microbial expression hosts in projects where processes have been approved by authorities (where processes are Good Manufacturing Practice compliant)
REACH/22/45/3	AGC Biologics GmbH	

The authorisation is granted subject to the risk management measures and operational conditions described in the chemical safety report[12], as well as to the conditions set out in Article 2 of this Decision.

[10] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1).

[11] Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council (OJ L 348, 24.12.2008, p. 84).

[12] https://ec.europa.eu/docsroom/documents/44420
https://ec.europa.eu/docsroom/documents/44421

Article 2

1. The authorisation bearing numbers REACH/22/45/2 and REACH/22/45/3 shall be subject to the conditions set out in paragraphs 2 to 7.

2. The authorisation holders shall ensure that all liquid waste is subject to adequate treatment. The treatment shall minimise releases to environmental compartments as far as technically and practically possible.

3. After having implemented the measures laid down in paragraph 2, the authorisation holders shall perform a new mass balance analysis in order to confirm the effectiveness of those measures.

4. The authorisation holders shall carry out a monitoring programme of 4-tert-OPnEO and its principal degradation products in the wastewater prior to its release to the municipal sewage treatment plant. The monitoring programme shall:

   (a) be carried out once the production lines become operational or the new risk management measures are implemented, and provide for an initial sampling frequency which is sufficient to demonstrate daily fluctuations;

   (b) once the sampling frequency is established, be carried out at least four times per year while the plant is in operation. The frequency of the measurements shall be such as to capture variability in the concentrations of 4-tert-OPnEO and its principal degradation products in the wastewater due to changes or operational fluctuations in the process;

   (c) be based on an analytical method capable of adequately characterising 4-tert-OPnEO and its principal degradation products in wastewater at appropriately low limit of quantification;

   (d) be recorded so as to include details of the sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.

5. The authorisation holders shall use the information gathered in the analysis and measurements referred to in paragraphs 3 and 4 and related contextual information to regularly review, at least annually, the appropriateness and effectiveness of the risk management measures and operational conditions and, if needed, to introduce measures to further reduce emissions of 4-tert-OPnEO to a level as low as technically and practically possible.

6. The authorisation holders shall conduct a feasibility study in view of implementing a treatment other than incineration of the foreseen increased volumes of residual wastewater containing 4-tert-OPnEO, for the first time by … [*OP: insert date – 12 months as of the date of adoption of this Decision*] and afterwards when new information becomes available. The authorisation holders shall take actions depending on the outcome of the feasibility study and shall document such actions.

7. The authorisation holders shall document and keep the information obtained in accordance with paragraphs 2 to 6 and submit it, upon request, to the competent authority of the Member State where the authorised use takes place.

Article 3

1. The review period shall expire on 4 January 2033.

2. The authorisation shall cease to be valid on 4 January 2033 with respect to an authorised use if the review report for that use has not been submitted in accordance with Article 61(1) of Regulation (EC) No 1907/2006 by 4 July 2031.

Article 4

1. As regards the authorisation bearing numbers REACH/22/45/0 and REACH/22/45/1, the monitoring arrangements set out in paragraphs 2 to 6 shall apply.

2. The authorisation holders shall carry out a monitoring programme of 4-tert-OPnEO and its principal degradation products in the wastewater prior to its release to the municipal sewage treatment plant. The monitoring programme shall:

   (a) be carried out at least four times per year while the plant is in operation. The frequency of the measurements shall be such as to capture variability in the concentrations of 4-tert-OPnEO and its principal degradation products in the wastewater due to changes or operational fluctuations in the process;

   (b) be based on an analytical method capable of adequately characterising the substance and its principal degradation products in wastewater at appropriately low limit of quantification;

   (c) be recorded so as to include details of the sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.

3. The authorisation holders shall use the information gathered in the measurements referred to in paragraph 2 and related contextual information to regularly review, at least annually, the appropriateness and effectiveness of the risk management measures and operational conditions and, if needed, to introduce measures to further reduce emissions of 4-tert-OPnEO to a level as low as technically and practically possible.

4. The authorisation holders shall carry out a mass balance analysis after the implementation of the risk management measures and operational conditions as well as after an increase in the use of the substance, and document it.

5. The authorisation holders shall conduct a feasibility study in view of implementing a treatment other than incineration of the foreseen increased volumes of residual wastewater containing 4-tert-OPnEO, for the first time by … [*OP: insert date – 12 months as of the date of adoption of this Decision*] and afterwards when new information becomes available. The authorisation holders shall take actions depending on the outcome of the feasibility study and shall document such actions.

6. The authorisation holders shall document and keep the information obtained in accordance with paragraphs 2 to 5 and shall submit it, upon request, to the competent authority of the Member State where the authorised use takes place.

Article 5

Where an authorisation holder submits a review report, it shall include:

1. as regards authorisation bearing numbers REACH/22/45/0 and REACH/22/45/1, the information referred to in Article 4(6);

2. as regards authorisation bearing numbers REACH/22/45/2 and REACH/22/45/3, the information referred to in Article 2(7).

Article 6

Upon request, the authorisation holders shall submit a brief summary of the applicable risk management measures and operational conditions described in the chemical safety report to the competent authority of the Member State where the authorised use takes place in an official language of that Member State.

Article 7

This Decision is addressed to:

1. AGC Biologics A/S, Vandtårnsvej 83 B, 2860 Søborg, Denmark;

2. AGC Biologics GmbH, Czernyring 22, 69115 Heidelberg, Germany.

Done at Brussels, 6.1.2023

For the Commission
Thierry BRETON
Member of the Commission

CERTIFIED COPY
For the Secretary-General

Martine DEPREZ
Director
Decision-making & Collegiality
EUROPEAN COMMISSION