EUROPEAN
COMMISSION

Brussels, 15.6.2023
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COMMISSION IMPLEMENTING DECISION

of 15.6.2023

granting an authorisation under Regulation (EC) No 1907/2006 of the European Parliament and of the Council to LFB Biomedicaments for a use 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 20 May 2019, LFB Biomedicaments ('the applicant') submitted an application in accordance with Article 62 of Regulation (EC) No 1907/2006 for authorisation for a use of 4-tert-OPnEO[2]. The use for which authorisation was sought is use of 4-tert-OPnEO as virus inactivation into the manufacture process of plasma-derived immunoglobulins.

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

(4) RAC concluded in its opinion that it is not possible to determine a predicted no-effect concentration 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 4-tert-

[1] OJ L 396, 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.

[3] https://echa.europa.eu/documents/10162/b7a3772e-9684-f738-3796-9f7a3f13bd02

OPnEO and an authorisation 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, such as 4-tert-OPnEO, even at low exposure levels. Consequently, RAC takes the emissions of the substance as a proxy for the risk.

(6) In its opinion, RAC concluded that the risk management measures and operational conditions described in the application are not appropriate and effective to limit the risk to the environment. RAC noted that, although all solid waste and most of the wastewater contaminated with 4-tert-OPnEO are collected and disposed of for incineration, there are still releases of contaminated wastewater to the municipal wastewater treatment plant, originating from the ultra-filtration step and from cleaning-in-place discharges into wastewater. Therefore, RAC considered that the applicant has not demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible, and recommended conditions for authorisation. Moreover, RAC also noted that the applicant plans to implement new risk management measures as regards the chromatography step and recommended to carry out monitoring programmes to confirm the effectiveness of those measures and clarify the contribution of the different steps of the process to the releases. As regards the chromatography steps, on 17 January 2023, the applicant notified the Commission that the relevant risk management measures have been successfully implemented. Having evaluated RAC's assessment, the Commission agrees with its conclusion and recommendations.

(7) In its opinion, SEAC concluded that it has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the socio-economic benefits and the risk to the environment associated with the continued use of 4-tert-OPnEO. Taking into account SEAC's assessment, the lack of scientific knowledge at present to quantify or monetise the risk to the environment associated with the use of the substance, the estimated emissions of up to 10 kilograms of the substance per year, the estimated benefits due to avoided profit losses, job losses and costs for employment protection plan at minimum in the order of hundreds of millions of euro over the review period, the estimated cost of avoiding the remaining releases of the substance in the order of millions of euro per kilogram, the qualitatively assessed additional socio-economic benefits due to avoided negative health impacts on patients related to the unavailability of the applicant's medicinal products used in immunology, intensive care and haemostasis, as well as any relevant distributional impact, the Commission concludes that the applicant has demonstrated that the socio-economic benefits of the continued use of the substance outweigh the risk to human health or the environment arising from that use.

(8) 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.

(9) In its opinion, SEAC concluded that there were no suitable alternative substances or technologies available for the applicant by the sunset date. The Commission, having evaluated SEAC's assessment and all information available, acknowledges that the applicant needs to perform further regulatory viral clearance studies and scaling-up of

pilot installations to verify whether the identified alternative provides the required virus inactivation in the manufacture of plasma-derived immunoglobulins. Thus, the Commission considers that it cannot be deemed that any of the identified alternatives provides the functionality needed for the use for which authorisation is sought. Therefore, the Commission agrees with SEAC's conclusion and considers that the applicant has discharged its burden of proof in demonstrating the absence of suitable alternatives both in the Union and for the applicant.

(10) 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.

(11) 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 the existence of 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 require the generation of additional information on emissions.

(12) In its opinion, SEAC recommended that the review period referred to in Article 60(9), point (e), of Regulation (EC) No 1907/2006 should be set at 7 years. The Commission agrees with that recommendation, taking into account the relevant elements from RAC's and SEAC's assessment and, in particular, the level of emissions, the socio-economic benefits, the lack of suitable alternatives within a shorter timeline, the applicant's ongoing research and development efforts, as well as the time necessary to perform the required testing and obtain the regulatory approvals needed for medicinal products.

(13) 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 holder 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.

(14) This Decision does not affect the obligation of the authorisation holder 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 holder 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

[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).

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.

(15) 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 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.

(16) 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 for the following use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO):

Authorisation number	Authorised use
REACH/23/19/0	Virus inactivation into the manufacture process of plasma-derived immunoglobulins

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.

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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).

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/44425

Article 2

1. The authorisation shall be subject to the conditions set out in paragraphs 2 to 7.

2. The authorisation holder shall carry out a mass balance analysis. The analysis shall be based on the outcome of the monitoring programme referred to in paragraph 4 and shall:

   (a) be carried out for the first time by 15 September 2023 and annually thereafter;

   (b) include details of the calculations carried out;

   (c) include the assumptions made, if any;

   (d) include the corresponding release values;

   (e) include the cleaning-in-place discharges.

3. Taking into account the results of the first analysis referred to in paragraph 2, the authorisation holder shall adjust the risk management measures and operational conditions at the latest by 15 March 2024 in such a way that the emissions of 4-tert-OPnEO are reduced to a level as low as technically and practically possible. If technically and practically possible, to achieve such reduction, the authorisation holder shall ensure that wastewater following the ultrafiltration and the cleaning-in-place steps is collected for adequate treatment. Release into the sewage system or to surface waters does not constitute adequate treatment.

   The authorisation holder shall document the adjustments of the risk management measures and make those documents available, upon request, to the competent authority of the Member State where the use takes place.

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

   (a) be carried out at least four times per year, during the time of operation. The initial sampling frequency shall be sufficient to account for daily fluctuations. The frequency of the measurements shall be such as to capture the variability in 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 4-tert-OPnEO and its principal degradation products in wastewater with appropriately low limit of quantification;

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

5. The authorisation holder shall use the information gathered in accordance with paragraphs 2 and 4 and related contextual information to 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 holder shall finalise by 15 June 2024 and thereafter when new information becomes available, a study to assess the feasibility to improve the quantity management of the excess solution of 4-tert-OPnEO per batch prepared at the virus inactivation step and shall act in accordance with the outcome of that study.

7. The authorisation holder shall document and keep the information obtained from the monitoring programme referred to in paragraph 4, as well as the outcome and conclusions of the review and any action taken in accordance with paragraph 5, together with the outcome and conclusions of the analysis referred to in paragraph 2 and the feasibility study and any action taken as referred to in paragraph 6. The authorisation holder shall submit that information, upon request, to the competent authority of the Member State where the authorised use takes place.

Article 3

The review period shall expire on 4 January 2028.

The authorisation shall cease to be valid on 4 January 2028 if the authorisation holder has not submitted the review report in accordance with Article 61(1) of Regulation (EC) No 1907/2006 by 4 July 2026.

Article 4

When the authorisation holder submits a review report, it shall include the information referred to in Article 2(3), second subparagraph, and (7).

Article 5

Upon request, the authorisation holder 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 6

This Decision is addressed to LFB Biomedicaments, 3 avenue des Tropiques, ZA de Courtaboeuf, 91940, Les Ulis, France.

Done at Brussels, 15.6.2023

For the Commission
Thierry BRETON
Member of the Commission

CERTIFIED COPY
For the Secretary-General

Martine DEPREZ
Director
Decision-making & Collegiality
EUROPEAN COMMISSION