EUROPEAN
COMMISSION

Brussels, 11.4.2022
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**COMMISSION IMPLEMENTING DECISION**

**of 11.4.2022**

**granting an authorisation under Regulation (EC) No 1907/2006 of the European Parliament and of the Council to Hospira Zagreb d.o.o., a Pfizer company 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 18 June 2019, Hospira Zagreb d.o.o., a Pfizer company ('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 as a surfactant in the manufacture of one biopharmaceutical protein, a biosimilar product, used to prevent infection and neutropenic fevers.

(3) On 29 September 2020, 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), second 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 (‘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.

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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/10162/1e013ca0-e3d0-9bd0-f5b6-d781b7b11c7c

(5) RAC noted that the 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) RAC concluded that the risk management measures and operational conditions described in the chemical safety report are appropriate and effective to limit the risk to the environment. In particular, RAC noted that only a residual amount of 4-tert-OPnEO, in the order of grams per year, is released into wastewater and that the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible. Having evaluated RAC's assessment, the Commission agrees with that conclusion.

(7) SEAC concluded that it has no substantial reservations on the quantitative and the qualitative elements of the applicant's assessment of the socio-economic benefits and the risk to the environment associated with the continued use of the substance. Taking into account that conclusion, 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 remaining emissions of few grams 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, and the qualitatively assessed additional socio-economic benefits of the continued use due to the availability of the medicinal product used to increase the quality of life of patients undergoing cancer chemotherapy, 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 and 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. Certain potential alternatives may provide this functionality but at some loss to performance or in a manner that involves technical compromises that would impair the functionality. In such cases, unless justified by particular circumstances, the Commission should not consider a potential alternative to be technically feasible for the applicant where the applicant has demonstrated that it or its downstream users are not able to accommodate such losses to performance or technical compromises by applying an additional effort which is reasonable taking into account the circumstances of the case.

(9) In its opinion, SEAC concluded that there are no available alternative substances or technologies by the sunset date for the applicant. The Commission, having evaluated SEAC's assessment and all relevant information available, acknowledges that, for the time being, more testing at commercial scale is still required to establish whether the identified alternative allows achieving the necessary functional performance during the production process of the biopharmaceutical protein used for the preparation of the final biosimilar drug product, in terms of the removal of biological contaminants, namely residual E. coli host cell proteins and host cell DNA, and that the regulatory approvals from the relevant medicines authorities still need to be obtained. Thus, the Commission considers that it cannot be deemed that the identified alternative allows

the functional performance needed for the use applied for. 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 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 a sufficient amount of material and reliable information allowing it to conclude.

(12) SEAC recommended in its opinion that the review period referred to in Article 60(9), point (e), of Regulation (EC) No 1907/2006 be set at 12 years. The Commission agrees with that recommendation, taking into account the relevant elements from RAC's and SEAC's assessments, and, in particular, the emissions and the socio-economic benefits, the lack of suitable alternatives within a shorter timeline, as well as the time required for the regulatory approvals and the quality requirements 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 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.

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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).

(15) This Decision does not affect any obligation to comply with any emission limit values 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/22/23/0 | As a surfactant in the manufacture of one biopharmaceutical protein, a biosimilar product, used to prevent infection and neutropenic fevers |

The authorisation is granted subject to the risk management measures and operational conditions described in the chemical safety report[12].

*Article 2*

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

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

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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/43210

*Article 3*

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 4*

This Decision is addressed to Hospira Zagreb d.o.o., a Pfizer company, Prudnicka cesta 60, 10291 Prigorje Brdovecko, Croatia.

Done at Brussels, 11.4.2022

*For the Commission*
*Thierry BRETON*
*Member of the Commission*

CERTIFIED COPY
For the Secretary-General

Martine DEPREZ
Director
Decision-making & Collegiality
EUROPEAN COMMISSION