Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

use of 1,2 dichloroethane (1,2-DCE) as a solvent in the manufacturing of the active pharmaceutical ingredient for epirubicin

ECHA/RAC/SEAC: AFA-O-0000006651-75-01/D

Consolidated version

Date: 24 October 2017

Consolidated version of the

Opinion of the Committee for Risk Assessment
and
Opinion of the Committee for Socio-economic Analysis

on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to an application for authorisation for:

Chemical name(s): 1,2-dichloroethane
EC No.: 203-458-1
CAS No.: 107-06-2

for the following use:

The use of 1,2 dichloroethane (1,2-DCE) as a solvent in the manufacturing of the active pharmaceutical ingredient for epirubicin

Intrinsic property referred to in Annex XIV:

Article 57(a) of the REACH Regulation

Applicant:

OLON Spa

Reference number:

11-2120132296-60-0001

Rapporteur, appointed by the RAC: **Elena CHIURTU**
Co-rapporteur, appointed by the RAC: **Lina DUNAUSKIENĖ**

Rapporteur, appointed by the SEAC: **Richard LUIT**
Co-rapporteur, appointed by the SEAC: **Lars DRAKE**

This document compiles the opinions adopted by RAC and SEAC.

PROCESS FOR ADOPTION OF THE OPINIONS

On **17/05/2016 OLON Spa** submitted an application for authorisation including information as stipulated in Articles 62(4) and 62(5) of the REACH Regulation. On **26/10/2016** ECHA received the required fee in accordance with Fee Regulation (EC) No 340/2008. The broad information on uses of the application was made publicly available at https://echa.europa.eu/applications-for-authorisation-previous-consultations on **09/11/2016**. Interested parties were invited to submit comments and contributions by **09/01/2017**.

No comments were received from interested parties during the public consultation in accordance with Article 64(2).

The draft opinions of RAC and SEAC take into account the responses of the applicant to the requests that the SEAC made according to Article 64(3) on additional information on possible alternative substances or technologies.

Due to the need to ensure the efficient use of resources, and in order to synchronise the public consultation with the plenary meetings of the Committees the time limit set in Article 64(1) for the sending of the draft opinions to the applicant has been extended until September 2017.

The draft opinions of RAC and SEAC were sent to the applicant on **03/10/2017**.

On **24/10/2017** the applicant informed ECHA that they did not wish to comment on the opinions. The draft opinions of RAC and SEAC were therefore considered as final on **24/10/2017**.

ADOPTION OF THE OPINION OF RAC

The draft opinion of RAC

The draft opinion of RAC, which assesses the risk to human health arising from the use of the substance – including the appropriateness and effectiveness of the risk management measures as described in the application and, if relevant, an assessment of the risks arising from possible alternatives – was reached in accordance with Article 64(4)(a) of the REACH Regulation on **18/09/2017**.

The draft opinion of RAC was agreed by consensus.

The opinion of RAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of RAC was adopted as final on **24/10/2017**.

ADOPTION OF THE OPINION OF SEAC

The draft opinion of SEAC

The draft opinion of SEAC, which assesses the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as described in the application was reached in accordance with Article 64(4)(b) of the REACH Regulation on **16/03/2017**.

The draft opinion of SEAC was agreed by consensus.

The opinion of SEAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of SEAC was adopted as final on **24/10/2017**.

THE OPINION OF RAC

The application included the necessary information specified in Article 62 of the REACH Regulation that is relevant to the Committee's remit.

RAC has formulated its opinion on: the risks arising from the use applied for, the appropriateness and effectiveness of the risk management measures described, the assessment of the risks related to the alternatives as documented in the application, the information submitted by interested third parties, as well as other available information.

RAC confirmed that it is not possible to determine a DNEL for the carcinogenic properties of the substance in accordance with Annex I of the REACH Regulation.

RAC confirmed that there appear not to be any suitable alternatives that further reduce the risk.

RAC confirmed that the operational conditions and risk management measures described in the application limit the risk, provided that they are adhered to as described in the application.

THE OPINION OF SEAC

The application included the necessary information specified in Article 62 of the REACH Regulation that is relevant to the Committee's remit.

SEAC has formulated its opinion on the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as documented in the application, the information submitted by interested third parties, as well as other available information.

SEAC took note of RAC's confirmation that it is not possible to determine a DNEL for the carcinogenic properties of the substance in accordance with Annex I of the REACH Regulation.

SEAC confirmed that there appear not to be suitable alternatives in terms of their technical and economic feasibility for the applicant.

SEAC considered that the applicant's assessment of: (a) the potential socioeconomic benefits of the use, (b) the potential adverse effects to human health of the use and (c) the comparison of the two is based on acceptable methodology for socio-economic analysis. Therefore, SEAC did not raise any reservations that would change the validity of the applicant's conclusion that overall benefits of the use outweigh the risk to human health, whilst taking account of any uncertainties in the assessment.

SUGGESTED CONDITIONS AND MONITORING ARRANGEMENTS

None

REVIEW

Taking into account the information provided in the analysis of alternatives prepared by the applicant the duration of the review period for the use is recommended to be **twelve (12) years**.

JUSTIFICATIONS

The justifications for the opinion are as follows:

1. The substance was included in Annex XIV due to the following property / properties:

- ☒ Carcinogenic (Article 57(a))
- ☐ Mutagenic (Article 57(b))
- ☐ Toxic to reproduction (Article 57(c))
- ☐ Persistent, bioaccumulative and toxic (Article 57(d))
- ☐ Very persistent and very bioaccumulative (Article 57(e))
- ☐ Other properties in accordance with Article 57(f):

2. Is the substance a threshold substance?

- ☐ YES
- ☒ NO

Justification:

1,2-Dichloroethane (EDC) has a harmonised classification as Carc. 1B with H350 according to Classification, Labelling and Packaging Regulation, (EC) 1272/2008.

Based on studies which show its genotoxic potential, the Risk Assessment Committee (RAC) has concluded that EDC should be considered as a non-threshold carcinogen with respect to risk characterisation (reference to the studies examined are included in the RAC document 'RAC/33/2015/09 Rev.1 Final').

3. Hazard assessment. Are appropriate reference values used?

Justification:

RAC has established a reference dose-response relationship for the carcinogenic effect following exposure to EDC (RAC/33/2015/09 Rev. 1 Final). Based on experimental animal data (cited in the RAC document), a potentially increased risk of cancer occurring due to the genotoxicity of the substance was noted.

In the absence of epidemiological studies on occupational exposure to EDC that would be useful in identifying any quantitative risk for humans, the dose-response estimations are based on the most relevant, robust study in experimental animals (development of mammary tumours in rats). A linear relationship between the exposure to EDC and the cancer risk was assumed.

The following cancer risk estimates were calculated by RAC and used by the applicant:

Table 1: **Dose-response relationship for carcinogenicity of 1,2-dichloroethane established by RAC (RAC/33/2015/09 Rev. 1 Final)**

Route of exposure	Population	Cancer risk for 1 unit [a]
Inhalation	Workers	6.0×10^{-7} per µg/m^3
	General population	3.45×10^{-6} per µg/m^3
Dermal (for 50% dermal absorption)	Workers	2.1×10^{-6} per µg/kg bw/day
	General population	6×10^{-6} per µg/kg bw/day
Oral	General population	1.2×10^{-5} per µg/kg bw/day

[a] risk calculation refers to 40 years of exposure for workers and lifetime exposure for general population

In the socio-economic analysis (SEA) the remaining human health risks are evaluated based on the dose-response relationship adopted by RAC.

Are all appropriate and relevant endpoints addressed in the application?

The endpoint identified in the Annex XIV entry is addressed in the application. Cancer risk was estimated using the dose-response curves developed by RAC for all relevant routes of exposure and exposed populations.

4. Exposure assessment. To what extent is the exposure from the use described?

Description:

OLON S.p.A is a downstream user of EDC. The application concerns the use of EDC in the manufacture of Epirubicin. Manufacturing takes place at one site, in Rodano (Milan) Italy.

EDC is used as a solvent in the manufacture of Epirubicin, an active pharmaceutical ingredient (API) used for the production of a medicinal product for cancer therapy (in particular breast cancer) marketed worldwide. Epirubicin is considered to be among the most active agents for the treatment of various malignancies as first or second-line treatment.

Manufacturing of Epirubicin is a batch process (77 batches in 2015, which is planned to increase to 140 from 2018 on), consisting of several steps. EDC is used as a solvent for the crystallization of one of the intermediates (Epi 3).

EDC has three functions in the manufacturing of the epirubicin API: (1) It helps remove residual solvents, including the reaction solvent; (2) It facilitates the precipitation of the intermediate by reducing its solubility; and (3) It helps to purify one of the epirubicin intermediates.

The applicant estimated that the total amount of EDC used for epirubicin API manufacturing of 5.5 tonnes in 2015 will in the upcoming years increase to approximately 10 tonnes per year. It should be noted that there is no solvent recovery at the site. After the process is completed, the used EDC mainly ends up in waste (95%, treated by a certified waste handler), with the rest being emitted to the environment (this part of the process is further described below).

No EDC is present in the final product.

Exposure scenario

The applicant describes one exposure scenario, concerning an industrial use at a single site, involving potential exposure of workers and humans via environment.

According to the applicant, the exposure scenario includes all relevant processes and tasks associated with the use of EDC that could result in either environmental releases or worker exposure. The exposure scenario comprises four Worker Contributing Scenarios (WCSs) and one Environmental Contributing Scenario (ECS).

Table 2: Contributing Scenarios presented in the Use

Contributing scenario	ERC / PROC	Name of the scenario
ES1	*The use of 1,2 dichloroethane (1,2-DCE) as a solvent in the manufacturing of the active pharmaceutical ingredient for epirubicin.*	
ECS 1	ERC4	Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
WCS 1	PROC 1	Storage of EDC
WCS 2	PROC 8b	Unloading of EDC and transfer to storage tank
WCS 3	PROC 3	Use of EDC in the manufacturing of Epirubicin
WCS 4	PROC 8b	Transfer of EDC containing waste to tank truck

A. Worker exposure

The tasks performed are described in sufficient detail by the applicant. They are summarised in Table 3.

Table 3: Summary of worker contributing scenarios

Contributing scenario	Brief description
WCS 1 Storage of EDC (PROC 1)	EDC is delivered in closed 200 L drums. The drums are stored in a warehouse for flammable liquids. EDC is also stored in an on-site underground storage tank. The volume of the tank is 3,000 L. It contains on average 1,000 L of EDC. Potential exposure sources: *Inhalation:* no handling of EDC. *Dermal:* no handling of EDC/no contact with contaminated surfaces.
WCS 2 Unloading of EDC and transfer to storage tank	EDC is transferred from the drums via fixed piping to an underground storage tank. The transfer is done via a dedicated installation that includes a large glovebox as secondary containment for the drum, when it is unloaded. The vapour space of the glovebox is connected to the site vapour collection system. After transfer of the EDC from the drum into the underground storage tank, the

(PROC 8b)	drum remains in the glovebox and is left open for 24 hours. During this time, any EDC present on the surface of the dip pipe evaporates. The vapours evacuated from the glovebox are collected by the site vapour collection system. The next day, while the drum is still in the glovebox, the drum is closed with the original stopper. The closed drums are then removed from the glove box and are temporarily stored in a dedicated storage area on site. The number of workers that are trained for this activity is 2 (not involved in WCS 3 and 4). Potential exposure sources: *Inhalation:* fugitive emissions during the transfer of EDC. *Dermal:* accidental contamination due to the possible contact with contaminated surfaces.
WCS 3 Use of EDC in the manufacturing of Epirubicin (PROC 3)	EDC is added to the Epi 3 mother liquor via fixed and dedicated piping. All further transfers of EDC and its mixtures in this WCS occur also via fixed, dedicated piping. The mixing is done in a closed reactor. The resulting mixture is partially evaporated to concentrate the Epi3 mixture. The vapours of EDC and the other solvent are condensed directly by the reactor condenser and transferred to the liquid waste storage. Any residual vapour is evacuated to the site's vapour collection system. The concentrated Epi3 mixture is cooled and crystallized from the solution and the content of the reactor is transferred via fixed piping to the closed filter-dryer in the glovebox. In the filter-dryer, the precipitate is filtered off and the obtained crystalline solid is washed, first with EDC, delivered via dedicated pipeline, then with another solvent. The EDC and the other solvent filtrates are transferred to the liquid waste storage. The solid is dried under vacuum in the closed filter-dryer equipment located inside the glovebox. Any vapours are evacuated from the glovebox to the site's vapour collection system. After rinsing and drying, a crystalline solid intermediate (Epi3) is obtained. At this point, the filter-dryer is opened (still within the glovebox) to collect the solid Epi 3 and the material is manually transferred into the primary package (glass bottle). Subsequently, the glovebox is cleaned with solvent (not EDC) and the bottle's exterior is washed. The bottle is then moved to the prechamber of the glovebox where it is put into a clean polythene bag. The bottle is taken out of the prechamber of the glovebox and inserted in the second clean bag. In total, 16 workers perform tasks in the manufacturing hall where the crystallization of Epi3 is performed (not involved in WCS 2 and 4). The workers are employed in a 3-shift regime. The Epi3 crystallization operation takes ca. 24 hours in total, i.e. 3 subsequent 8h shifts. In each shift team, 1 - 2 workers (5 out of total 16 workers) are trained to perform tasks that involve EDC ("near-field" tasks, i.e. manipulations which involve installations containing EDC), however only one worker per shift is performing such tasks. The other 11 workers are not trained for activities involving installations containing EDC and thus do not perform tasks in close proximity to the installations containing EDC ("far-field" tasks). Potential exposure sources: *Inhalation:* fugitive emissions during the manufacturing process. *Dermal:* accidental contamination.
WCS 4	(1) The EDC that is evaporated during the crystallization step and the filtrate obtained during filtration of the crystallized intermediate Epi3 is transferred via

Transfer of EDC containing waste to tank truck (PROC 8b)	dedicated piping to the liquid waste storage neutralisation reactor. In this reactor, liquid organic waste streams from different processes in Olon's Rodano site are collected, and where necessary, neutralized. The neutralisation reactor is vented to the vapour collection system. From the neutralisation reactor, the waste stream is further transferred via fixed piping to liquid waste storage tanks located outdoors (outside the production area). In these tanks, the condensates obtained from the site's vapour collection system (connected to storage tank, glove boxes, etc.) are also collected. The liquid waste is sent off site by tank trucks (600 tonnes/year or about 30 times per year) to a specialized waste treatment plant. The truck loading installation is a closed system equipped with a vapour return system. The number of workers that are trained for this activity is 2 (not involved in WCS 2 and 3). (2) Sampling of the liquid waste from the liquid waste storage tank is included in this WCS. The sample is taken at a dedicated point equipped with a sampling valve. The sample is collected into a bottle, which is stoppered directly after sampling. The concentration of EDC in the waste is less than 1%. The sampling is performed by 1 worker, occurs 3 times per year and takes less than 3 minutes. The number of workers that are trained for this activity is 2. Potential exposure sources: *Inhalation:* 1) fugitive emissions during the transfer. 2) potential exposure during the sampling process *Dermal:* 1) no direct handling of waste/no contact with contaminated surfaces 2) potential exposure during the sampling process

Following RAC's request, the applicant clarified that no sampling for quality control of the product is performed while EDC is present in the product. The quality control is performed only on the end product. No maintenance or repair activities are performed on the installation while EDC is present.

RMMs applied

The RMMs that are taken into consideration in exposure assessment for each WCS, with their effectiveness as described by the applicant, are summarised in Table 4. Technical and organisational RMMs are implemented in the plant and PPE is used. Their general description is included in the submitted CSR (Chemical Safety Report).

- Protection for inhalation route

According to the applicant the installations used for the manufacturing of Epirubicin are characterized by a high level of containment, which is inherent to the manufacturing of active pharmaceutical ingredients (API). The manufacturing occurs in closed installations (reactor, filter-dryer gloveboxes) equipped with local exhaust ventilation. All transfers of EDC and EDC-containing products occurs via dedicated and fixed piping. All local exhaust ventilation installations, and the vent of the storage tank, are connected to the site's vapour collection system. The building in which the installations are located have a general mechanical ventilation system that ensures 7 air changes per hour.

Respiratory protection (RPE) – full face mask with ABEK2P3 filter (effectiveness 95%) - is used when samples of the liquid waste are taken from the liquid waste storage tank.

- Dermal protection

According to the applicant almost all equipment and processes involving EDC operate as closed systems.

Chemical resistant gloves (Neoprene gloves of type EN374 Cat. III in the glovebox + additional disposable ANSELL BARRIER gloves with breakthrough time >480 min) are used in most of the cases. The glove box gloves are inspected before each use and replaced where necessary in accordance with the available specific procedure on glove box maintenance.

Chemical resistant gloves (PVA, EN 374, breakthrough time >480 min) are used when samples of the liquid waste are taken from the outdoor liquid waste storage tank.

At RAC's request for additional information, the applicant specified that the PPE management is site specific, not specific per installation of use. The need to use PPE is established on the basis of a task-risk analysis done jointly by the Safety manager and the Product manager. Periodic training is provided on the proper use of PPE. Operators are responsible for the proper use of PPE. Supervisors monitor the proper use of these PPE.

Regular safety audits to check the compliance with site safety rules including the use of PPE are undertaken.

- Additional PPE

Protective clothing is used by workers. A general procedure is in place which manages the use of the protective clothing.

- Further technical and organisational RMMs

According to the applicant, EDC is stored in closed drums in a dedicated marked area and in a vented underground storage tank, to which EDC is transferred via a dedicated installation equipped with a glove box.

In terms of organisational measures, the applicant stated that a strict safety policy is implemented on site, based on continual improvement of the procedures, covering training, provision of information on the risks and the importance of wearing the PPE, while working continually to reduce the exposure time to EDC to a minimum. Procedures, manuals and other relevant documents are managed through an ISO 9001 compliant document management system. The applicant has internal documented procedures for specific training of personnel in chemical handling, health and safety issues, use of personal protective equipment, risk assessment. All trainings are recorded. Specific procedures are in place to ensure that exposure to EDC is reduced and minimised, for instance procedure to verify containment of equipment prior to its use and procedure for cleaning the equipment prior to its opening.

In their answers to RAC's questions the applicant specified, that a preventive maintenance plan is in place for the waste storage tank, the waste storage level indicator, the glove box, the scrubber, and the ventilator (including motor). There is a semi-annual inspection for

parts relating to air emissions (ventilator, scrubber pumps, piping visual integrity, etc.). The process parts (including pumps and piping), glove-box and equipment are annually checked. The gloveboxes are equipped with a warning light which indicates if the proper pressure (below room pressure) level is attained inside. The room ventilation is connected to the independent ventilation system and each ventilator is equipped with an alarm. Correct pressure levels are further checked before each operation.

After each reaction step, the equipment is emptied and rinsed, in order to prepare it for the next batch. The rinsing fluid is sent to the waste tank via dedicated piping. The reactor is closed during the rinsing and all solvent transfers occur via dedicated pipes.

For inspection or maintenance, when the installation needs to be opened, a specific procedure is in place in order to assure that equipment is free of hazardous substances prior to opening. The installation is (additionally) rinsed and/or flushed before opening. The rinsing and/or flushing are done while the installation is closed. The rinsing fluid, as in the after-use rinsing, is sent to the waste tank via dedicated piping. The air used for flushing is led to the vapour abatement system. The applicant noted that this rinsing/flushing procedure is performed in addition to the standard rinsing step which is performed after every batch.

Olon's environmental management system is compliant with the ISO 14001 standard.

Current and planned improvements are presented in the CSR, such as the replacement of the single seal pumps by membrane pumps and a new installation for the thermal oxidizer (replacing the current carbon filter).

Table 4: Operational Conditions and Risk Management Measures described by the applicant*

Contributing ES	Brief Description	RMMs
WCS 1 Storage of EDC (PROC 1)	*Number of workers: -.* *Concentration of substance: 100 %* *Place of use: indoors* *Exposure frequency (F) and duration (D):* *D: -* *F: continuous*	-Technical: Substance fully contained during transport and unloading. Drums are stored in closed building on watertight floor, at marked dedicated storage location. After transfer (WCS 2), storage in closed underground tank. Underground storage tank is in secondary containment. LEV: vapour space of tank is connected to site vapour collection system (scrubbers and an active carbon adsorber unit). -Organisational: General housekeeping practices in place; training manuals for operation; safety training; site emergency procedure in place. -PPE: protective clothing.
WCS 2 Unloading of EDC and transfer to storage tank (PROC 8b)	*Number of workers: 2.* *Concentration of substance: 100 %* *Place of use: outdoors*	-Technical: Closed system. Glovebox with incorporated LEV used for transfer of EDC from the drums to underground storage tanks; Closed pump used for the transfer. Transfer is done via fixed and dedicated piping. Empty drums are closed and

	Process temperature: ambient *Annual amount: ~ 10 tonnes / year.* *<u>Exposure frequency (F) and duration (D):</u>* *D: 15 min* *F: 41 × per year*	disposed as hazardous waste. -Organisational: General housekeeping practices in place; training manuals for operation; safety training; site emergency procedure in place. -PPE: Neoprene gloves of type EN374 Cat. III in the glovebox + additional ANSELL BARRIER gloves breakthrough time >480 min. (effectiveness 95%); protective clothing.
WCS 3 Use of EDC in the manufacturing of Epirubicin (PROC 3)	*Number of workers: 16 (5 out of 16 trained to perform tasks with EDC).* *Concentration of substance: 100 %* *Place of use: indoors* *Process temperature: depending on process step: 0 – 55 °C;* *Annual amount: ~10 tonnes / year.* *<u>Exposure frequency (F) and duration (D):</u>* *D: ~ 8 hours* *F: 140 × per year (far-field)** *84 × per year (near-field)*** ** Frequency of far-field exposure: as 140 batches of Epi3 are crystallized per year, a farfield worker can be exposed to EDC 140 times per year* *** Frequency for near field exposure: as 140 batches of Epi3 are crystallized per year, and completion of each batch takes 3 subsequent shifts, each of the five workers trained for work with EDC performs near field activities 3×140/5 = 84 times per year.*	-Technical: General ventilation (7ACH). Closed reactor with LEV (effectiveness 90%) over installation; separation of the reactor from the rest of the area with additional transparent shield (installed in early 2016); closed filter-dryer in glovebox. LEV and glovebox integrated in vapour abatement system. All transfers of EDC and EDC containing mixtures via dedicated fixed piping. Transfer of liquid waste EDC to neutralisation reactor under gravity (no pump used). Neutralisation of waste in closed dedicated reactor. Transfer of liquid waste from neutralisation tank to liquid waste storage via fixed and dedicated piping (as of August 2016 membrane pumps are used). Removal of the EDC-free EPI 3 from glovebox in double packaging via airlock. -Organisational: General housekeeping practices in place; training manuals for operation; safety training; site emergency procedure in place. -PPE: Neoprene gloves of type EN374 Cat. III in the glovebox + additional ANSELL BARRIER gloves breakthrough time >480 min. (effectiveness 95%); protective clothing.
WCS 4 Transfer of EDC containing waste to	*Number of workers: 2.* *Concentration of substance: < 1 %*	-Technical: (1) Transfer to waste truck via dedicated installation. Vapour phase of truck and liquid waste storage are

tank truck (PROC 8b)	*Place of use: outdoors* *Process temperature: ambient* *Annual amount: ~10 tonnes / year.* *<u>Exposure frequency (F) and duration (D):</u>* *D: ~ (1) 1 hour* *(2) 3 min* *F: (1) 30 × per year* *(2) 3 × year*	connected (vapour collection system); (2) dedicated position equipped with a sampling valve. -Organisational: General housekeeping practices in place; training manuals for operation; safety training; site emergency procedure in place. -PPE: (1) Polyvinyl alcohol gloves, breakthrough time >480 min. (effectiveness 95%); standard work clothing . (2) PPE: gloves (PVA, EN 374 Cat. III, breakthrough time >480 min effectiveness – 95%), and a full face mask with ABEK2P3 filter (APF = 20); protective clothing.

* The projected frequency is mentioned in the table (i.e. the higher frequency planned for the years 2018-2023)

Exposure estimation methodology:

A qualitative and a quantitative exposure assessment was carried out for dermal and inhalation exposure for workers.

<u>Inhalation exposure:</u>

For inhalation exposure assessment, the applicant used a combination of air monitoring data (3 short-duration personal sampling measurements for WCS 2 and 18 long-duration personal sampling measurements for WCS 3) and modelling data with the Advanced REACH Tool (version 1.5, 90th percentile value used, for WCS 4). The air monitoring was undertaken by the applicant in February and March 2016. It should be also noted that after the request from RAC, the applicant provided detailed information regarding the input parameters, methodology and results for all the modelling. RAC considered that the chosen models and parameters are appropriate for exposure estimation.

The applicant considers that the potential inhalation exposure for WCS 1 “Storage of EDC” is virtually non-existent as during the storage EDC is in closed drums or in an underground closed storage tank checked for its integrity annually.

For the activities covered by WCS 2 “Unloading of EDC and transfer to storage tank”, 3 short-term personal measurements were available. Personal air monitoring was carried out in 2016; exposures were measured on 3 separate days during the total duration of the activity (15 min) specified in WCS 2. It should be noted that all measured concentrations obtained during the samplings were below the detection limit of the method used and resulted in calculated 8 h TWA exposures of 9.7 µg/m^3, 10.3 µg/m^3 and 10.3 µg/m^3 (assuming concentration = LOD). For sensitivity analysis, due to limited number of personal measurements at RAC’s request, the applicant provided a modelled exposure value of 27 µg/m^3 using ART 1.5. The applicant decided that the average inhalation exposure estimate (**10.1 µg/m^3**) from personal sampling is sufficiently conservative and more representative of the actual exposure conditions (taking into account the available RMMs) for this WCS

than more generic estimates derived using ART 1.5. RAC accepts that the personal monitoring data which was obtained while the workers were performing their usual tasks as sufficiently representative of the actual exposure situation. Therefore RAC decided to use the personal monitoring data and the 8h TWA exposure estimate of 10.1 µg/m^3 for further risk assessment.

For the activities covered by WCS 3 "Use of EDC in the manufacturing of Epirubicin", 18 long-term (8 h) personal measurements were available, 9 for near-field activities and 9 for far field activities, performed over all 3 shifts. Personal air monitoring was carried out in 2016 and exposures were measured on 3 separate working days. It should be noted that all measured concentrations obtained during the samplings were also below the detection limit of the method used and resulted in calculated 8h TWA exposure of 52 µg/m^3 (assuming concentration = LOD) used by the applicant and RAC for further risk assessment.

As no personal or static measurement were available for WCS 4, "Transfer of EDC containing waste to tank truck", modelled data using the ART 1.5 90th percentile value of **130 µg/m^3** was used for the risk characterisation. This value was considered as a worst case by the applicant, as the reduction factor for the vapour collection system of 80%, used in modelling, was considered to be a conservative value, due to the fully closed system used for EDC-containing waste transfer. RAC points out that workplace measurement data was not available for this WCS. Personal and/or stationary measurements are preferred for exposure estimation and the absence of any measurement data introduces uncertainties in the assessment.

At RAC's request for clarification on the transfer methods, the applicant explained that the only task not performed via fixed pipes or via glovebox is sampling of the liquid waste from the waste storage tank located outdoors, outside the production area, by 1 trained worker, 3 times per year and for less than 3 minutes. An ART 1.5 90th percentile value of **3.3 µg/m^3** (8h daily average) was provided for comparison - it is 40 times lower than the value used for risk characterisation for the respective WCS (WCS4). It should be noted that this value is not corrected for PPE use, although the PPE is worn (PVA gloves and full face mask with ABEK2P3 filter) during this specific task.

In summary, regarding overall inhalation exposure, RAC considers that the combination of short-term and long-term personal measurements and modelling using ART 1.5 comprises a sufficient dataset for the risk assessment and characterisation. For WCS 1 qualitative assessment was used, as there is no potential exposure for workers during storage. For WCS 2 short term personal measured data were used. Long-term personal sampling measurements of near-field and far-field exposure were used in WCS 3. Modelling data were used for WCS 4 due to the absence of personal or static measurements.

Dermal exposure:

According to the applicant, the dermal exposure to EDC in the Epirubicin plant is deemed negligible due to the use of vented gloveboxes and additional inner gloves used by the workers, preventing the direct contact with liquid EDC. Nevertheless, in the CSR the applicant provided modelled dermal exposure estimates using an EPA permeability equation. Two modes of exposure were taken into account: i) direct contact of EDC with the skin due to splashing or manipulation of contaminated objects; ii) and absorption of airborne concentration of volatiles through the skin, using the permeability and the skin surface area exposed.

The applicant claimed that direct EDC dermal exposure is possible only due to permeation of airborne EDC through the skin for WCS 3 "Use of EDC in the manufacturing of Epirubicin" (1.5×10^{-2} µg/kg bw/day) and WCS 4 "Transfer of EDC containing waste to tank truck" (4.7×10^{-3} µg/kg bw/day). During storage (WCS 1) EDC is in closed drums or in a closed tank and during WCS 2 the connection and disconnection of the pump to the drum takes place inside a glovebox were direct contact of the operator with EDC as well as exposure by diffusion of airborne EDC through the skin is prevented.

In response to RAC's request for sensitivity analysis and in reaction to the RAC's remark that the neoprene gloves incorporated into the glove box are not the most suitable for the work with EDC (also the applicant itself reported in the CSR that the breakthrough time for chlorinated solvents is limited for this material), the applicant provided dermal exposure estimates obtained with ECETOC TRA for WCS 2, 3 and 4. The modelled values using ECETOC TRA were 69 µg/kg bw/day, 34 µg/kg bw/da, and 14 µg/kg bw/day for WCS 2, 3 and 4 respectively. It should be noted the modelled values are higher than the estimated values presented in the CSR. The applicant considered that the modelled values using ECETOC TRA cannot be used for risk characterisation, as they are not taking into account the glovebox gloves and the local exhaust ventilation. The applicant noted that for WCS 3, the process temperature used as input parameter for modelling is 55ºC (the highest value during this activity), however the glovebox tasks are at ambient temperature. After evaluation of the arguments presented by the applicant and information made available, RAC agrees with the applicant's conclusions that the modelled estimates obtained using ECETOC TRA might be overestimating actual exposures for WCS 2, 3 and 4, due to the OCs and RMMs in place, not fully considered in modelling. Therefore, for risk characterisation and health impact assessment RAC decided to use the dermal exposure estimates provided by the applicant in the CSR.

Table 5: Exposure estimates - inhalation and dermal routes used for further risk assessment (values in bold used by applicant and by RAC)

Contributing scenario	**Route of exposure and Method of assessment**	**Exposure values**	**Exposure estimation corrected for PPE per worker**	**Frequency and duration adjustment factor ***	**Exposure estimation corrected for PPE, frequency and duration per worker**
WCS 1 Storage of EDC (PROC 1)	Inhalation [qualitative]	No exposure	N/A		**No exposure**
	Dermal [qualitative]	No exposure	N/A		**No exposure**
WCS 2 Unloading of EDC and transfer to	Inhalation [3 pers. ST (short-term) measured,	<10.1 µg/m³	N/A	0.17[a]	**<1.72 µg/m³**

storage tank (PROC 8b)	8h TWA]				
	Dermal [qualitative]	No exposure	N/A		**No exposure**
WCS 3 Use of EDC in the manufacturing of Epirubicin (PROC 3)	<u>*a) Near Field Workers (NFW)*</u> Inhalation [9 pers. LT (long-term) measured near-field, 9 pers. LT measured far-field, 8h TWA]	<52 µg/m^3 (near-field) <52 µg/m^3 (far-field)	N/A	0.35 [84 days/y near-field][a] 0.23 [56 days/y far-field][a]	**<18.2 µg/m^3 (near-field)** **<12.1 µg/m^3 (far-field)**
	Dermal [EPA equation]	1.5 × 10^{-2} µg/kg bw/d	N/A	0.58 [140 days/y far-field][b]	**8.75 × 10^{-3} µg/kg bw/d**
	<u>*b) Far Field Workers (FFW)*</u> Inhalation [9 pers. LT measured far-field, 8h TWA]	<52 µg/m^3 (far-field)	N/A	0.58 [140 days/y far-field][a]	**<30.3 µg/m^3 (far-field)**
	Dermal [EPA equation]	1.5 × 10^{-2} µg/kg bw/d	N/A	0.58 [140 days/y far-field][b]	**8.75 × 10^{-3} µg/kg bw/d**
WCS 4 Transfer of EDC containing waste to tank truck (PROC 8b)	Inhalation [modelled ART 1.5, 90th perc., 8h TWA]	130 µg/m^3	N/A	0.125 [30 days/y][a]	**16.3 µg/m^3**
	Dermal [EPA equation]	4.7 × 10^{-3} µg/kg bw/d	N/A	0.125 [30 days/y][b]	**5.88 × 10^{-4} µg/kg bw/d**

* The projected frequency was used instead of the frequency in 2015

[a] for inhalation exposure the frequency correction factor is calculated as 41/240=0.17 for WCS 2, 84/240=0.35 (NFW performing near-field tasks (NF)), 56/240=0.23 (NFW performing far field tasks (FF)) and 140/240=0.58 (FFW performing far field tasks) for WCS 3, and 30/240=0.125 for WCS 4,

[b] for dermal exposure the frequency correction factor is calculated as 41/240=0.17 for WCS 2, 140/240=0.58 (NFW performing near field and far field tasks) and 140/240=0.58 (FFW performing far field tasks) for WCS 3, and 30/240=0.125 for WCS 4.

Combined exposure:

According to the applicant, all workers involved in the manufacturing of epirubicin are performing only one of the relevant activities described in WCSs. In case the duration of an activity as described in the contributing scenario covers only part of a shift, the worker combines this activity with another task not involving exposure to EDC. As there are no workers performing activities described in more than one contributing scenario - combined exposure assessment was not considered to be necessary.

Biomonitoring:

According to the applicant, even though some data exists, biomonitoring is not considered appropriate or useful for exposure to EDC. There are two biomarkers for human biomonitoring: EDC in blood (outdated and invasive method which is usually avoided) and the metabolite TDGA in urine (a non-specific biomarker, with no biological limit value related to EDC exposure, so interpretation of the results is not possible). RAC considered the applicant's explanation as appropriate and did not request additional information.

Uncertainties related to the exposure assessment:

RAC notes that the inhalation exposure assessment is based on workplace air measurement data and on modelling with ART 1.5.

RAC notes that the available monitoring data set for WCS 2 is small - originate from a single year, and that only modelled data exist for WCS 4. Even though personal and/ or stationary measurements are preferred for exposure estimation and absence of any measurement data introduces uncertainties in the assessment due to the low frequency of the tasks and low concentration of EDC in waste the modelling results can be acceptable.

RAC notes that modelled dermal exposure values as presented by the applicant using an US EPA permeability equation may be underestimated, as the modelled exposure values with ECOTOC TRA are higher. However, RAC also notes the limitations of ECETOC TRA in dermal exposure modelling and high level of protection offered by the technical measures in place, complemented by PPE used to minimise exposure.

The applicant has reported a planned increase in the frequency of use (number of batches per year) it the coming years, from 77 to 140 batches per year. As the volume used per batch will remain the same, RAC concludes that the estimated exposures cover also the projected situation in the years 2018-2023. It is noted that the planned frequency has been taken into account by the applicant in the calculation of exposure and excess risks (section 6).

Taking into account the assessment performed, RAC considers that the uncertainties detailed above are of low significance for the purpose of exposure and risk assessment.

Conclusion on worker exposure assessment

RAC considers that:

- the description of exposure situations, including the risk management measures and operational conditions, allows drawing conclusions related to exposure assessment;

- the methodology used to assess exposure through inhalation and skin is suitable for risk characterisation;

- the information provided related to exposure resulting from the use applied for is considered to be sufficient to use in the risk characterisation.

- Nevertheless, RAC considers that the applicant would be well advised to base the exposure assessment to be potentially presented in any review report on a more extensive data set (from more than one year or batch).

B. Environmental releases / Indirect exposure to humans via the environment

RMMs applied

The processes are taking place in a closed system, with a dedicated underground EDC storage system. All EDC pipes are above ground, all transfers are made via dedicated pipes.

Most of the EDC used in the process ends up in waste (95.02%). No solvent recovery takes place at the site.

All vapour spaces of vessels and gloveboxes are connected to an abatement system consisting of a water scrubber, a three step cryogenic condensation (100% EDC removed) and an active carbon adsorber. The active carbon filter system was replaced by a thermal oxidizer at the end of 2016.

In order to further limit fugitive emissions, single seal liquid waste pumps have already been replaced by closed membrane pumps.

All process water from the cleaning of the equipment and from the scrubber is collected in a wastewater collection system connected to the on-site wastewater treatment plant (WWTP) (capacity of 150 m^3/h, 93% of EDC removed) and then to the municipal WWTP. The on-site WWTP consists of a wastewater collection network, a collection tank, pre-treatment of neutralization and primary sedimentation, equalizer, a biological reactor and a final decanter. Any water evacuated from the secondary underground concrete basin is analysed for EDC detection. In the same time, the integrity of the primary storage tank is annually checked.

The WWTP sludge is evacuated once every week and is analysed every six months for EDC. It is not considered as hazardous waste by the applicant, however it is disposed in a landfill provided with geo-membranes and waterproofing system, according to the requirements of the Italian legislation.

EDC evaporated during the crystallization and the filtrate is transferred to the liquid waste neutralization reactor on-site. The waste stream is then transferred to the liquid waste storage tank, together with the collected vapours (from storage tank, gloveboxes, etc.). Liquid waste is sent to a specialized off-site waste treatment plant (about 30 times per year).

Releases and exposure estimation methodology:

Releases to air: The applicant used measurements for the estimation of atmospheric releases and of releases from the wastewater treatment plant. The calculation of specific release factors used as input data for EUSES 2.1.2 modelling is based on measured releases in 2016 and on the amounts of consumed EDC during 2015.

Releases to water: Measured releases of EDC in wastewater effluent from the WWTP performed in 2015 were used by the applicant.

Inhalation exposure estimation: The applicant used EUSES to assess the local indirect inhalation exposure at 100 m distance from the emission source and assumed as a worst

case scenario that the same exposure occurs in the whole area within 1 km around the source of emission.

Oral exposure estimation was based on EUSES modelling.

Estimation of releases

The applicant considered that "Use of non-reactive processing aid at industrial site (no inclusion into or onto article) (ERC 4)" is the most appropriate Environmental Release Category for the use.

Indirect exposure of 'humans (general population) via the environment' through both inhalation and oral routes of exposure were assessed.

Guided (emissions from production system and from on-site WWTP) and fugitive emissions (unassigned emissions) to air were identified by the applicant. In response to RAC's request for clarification detailed contextual information about sampling and analytical measurements of releases to the different environmental compartments (air and water) were provided.

Air emission measurements at the exit of the abatement system were performed in 2016 (1 hour duration, four data points), by an accredited laboratory[1] and according to the applicant all measured values were below the detection limit of 0.0388 mg/m^3.

Regarding the emissions from on-site WWTP, based on EUSES modelling, the EDC distribution was considered to be 88% to air, 7% to water, 5% to sludge, from a volume of 211 kg of incoming EDC determined based on the measured concentrations in waste water.

Unassigned emissions are all considered fugitive emissions and their extrapolation is based on the number of batches in 2016.

Current and predicted mass balances were provided by the applicant. The mass balance calculations were based on data from 2015 (77 batches of Epi 3 were made in 2015, 71.36 kg EDC per batch is consumed). The applicant explained that for the future, 140 batches of Epi 3 per year are projected, which will result in total yearly consumption of 9,990 kg of EDC.

The releases of EDC in wastewater to and from the on-site WWTP are based on the measurements in 2015[2].

[1] EDC air concentrations measured according to UNI CEN/TS 13649:2015 method, LoD of 0.0388 mg/m^3.

[2] EDC wastewater concentrations measured according to EPA 5030C 2003& EPA 8260 methods.

Table 6: Local releases to the environment

Release	Release rate	Release per year	Release estimation method and details
Water	Final release factor: 0.27% Local release rate: 0.193 kg/day	26.85 kg/year	Measured release. 140 emission days/year
Air	Final release factor: 4.71% Local release rate: 3.361 kg/day	470.38 kg/year	Measured release. 140 emission days/year
Soil	Final release factor: 0%	0	No releases to soil. Sludge of the on-site WWTP goes to landfill (no hazardous waste).

The exposure to man via the environment at regional scale and the related risk were only provided for combined uses 1 and 2.

Table 7: Regional releases to the environment

Release	Release per year	Release estimation method and details
Water	27.46 kg/year	Measured release. 140 emission days/year
Air	478.9 kg/year	Measured release. 140 emission days/year
Soil	0 kg/year	No releases to soil. Sludge of the on-site WWTP goes to landfill (no hazardous waste).

Estimation of exposure via the environment:

Indirectly exposed workers

For indirectly exposed workers, the estimated by EUSES EDC concentration at 100 m from the emission source (0.359 µg/m^3) was used for risk characterisation.

No dermal exposure is expected for indirectly exposed workers.

Table 8: Summary of exposure to indirectly exposed workers

Exposed Workers	Exposure value (µg/m^3)
Indirectly exposed workers – Inhalation	0.359 [100 m from the emission source]

General population

In order to estimate the exposure of the general population at the local and the regional scale for the inhalation and oral routes of exposure, an assessment based on the EUSES model was used by the applicant, who provided also the respective input parameters.

The exposure estimates are based on release factors calculated from measured data (see Tables 6, 7).

The results are reported in Tables 9 and 10.

It is noted that exposure due to the contaminated food and drinking water was only assessed for the general population, but not for the indirectly exposed workers, as it was assumed that food/drinking water consumed by workers is not locally sourced.

The estimated values of exposures of the general population via the inhalation and oral route were used to estimate the risks to the general population at local and regional scale.

Table 9: Summary of indirect exposure to humans via the environment

Parameter	**Local**
PEC in air (µg/m^3)*	3.59×10^{-1}
PEC in surface water (µg/l)	5.2×10^{-3}
Daily dose via oral route (µg/kg bw/d)	3.22×10^{-3}

** the value was assumed to be constant for a radius of 1 km around the emission source, as a worst case, i.e. additional air dilution was not accounted for*

Table 10: Summary of indirect exposure to humans via the environment

Parameter	**Regional**
PEC in air (µg/m^3)*	1.33×10^{-4}
PEC in surface water (µg/l)	6.66×10^{-5}
Daily dose via oral route (µg/kg bw/d)	1.44×10^{-6}

Uncertainties related to assessment of exposure to humans (indirectly exposed workers and general population) via the environment:

RAC notes that the releases to soil are assumed to be zero although sludge from the on-site WWTP is landfilled. The applicants mentioned that no EDC could be detected in this sludge (no details about the analysis method - sampling every 6 months), and added that the specific landfill is designed to handle disposal of hazardous waste.

RAC notes that the applicant did not provide separate estimate for the exposure of the general population at regional scale and only provided a combined estimate for both Uses 1 and 2. Thus it could be noted that the regional exposure for a single use is to some extent overestimated.

RAC acknowledges that the assessment of indirect exposure to humans via the environment using default assumptions in the EUSES model is likely to overestimate exposure, particularly at the local scale, leading to an overestimation of risk (and number of statistical cancer cases). However, RAC notes that the applicant based their assessment of inhalation exposure at the local scale on measured data, rather than modelled exposure concentrations. This refinement will reduce the potential for exposure to be overestimated for the inhalation route at the local scale, but does not address all sources of uncertainty in the model.

RAC considers that the exposure assessment provided by the applicant in the CSR and complemented by the responses to RAC's requests, is robust and remaining uncertainties are minor.

Conclusion on indirect exposure to workers and general population via the environment

RAC considers that

- EDC is used as a solvent in a closed system, with no subsequent exposure by professionals or consumers;

- the description provided, including the risk management measures and operational conditions, allows to draw conclusions related to exposure situations;

- the methodology used to derive the indirect exposure of workers and the general population is suitable for further risk characterisation.

5. If considered a threshold substance, has adequate control been demonstrated?

☐ YES

☐ NO

☒ NOT RELEVANT, NON THRESHOLD SUBSTANCE

Justification:

RAC has concluded that 1,2-dichloroethane should be considered as a non-threshold carcinogen with respect to risk characterisation.

6. If adequate control is not demonstrated, are the operational conditions and risk management measures described in the application appropriate and effective in limiting the risk?

☒ YES

☐ NO

Justification:

Evaluation of RMMs

The RMMs implemented by the applicant are presented in Section 4 (Table 4). In summary, they mainly include the following:

- The manufacturing occurs in closed installations (reactor, filter-dryer, gloveboxes) that are equipped with local exhaust ventilation.
- All transfers of 1,2-EDC and 1,2-EDC-containing products occur via dedicated and fixed piping.
- Storage of 1,2-EDC is in closed drums and in a vented underground storage tank, to which the 1,2-EDC is transferred via a dedicated installation equipped with a glove box.
- The building in which the installations are located has a general ventilation system that ensures 7 air changes per hour.
- All local exhaust ventilation installations, and the vent of the storage tank, are connected to the site vapour collection system.
- All vapour spaces are connected to an abatement system consisting of a scrubber, a cryogenic condensation unit and an active carbon absorber (thermal oxidizer as of December 2016).
- All waste is treated as hazardous chemical waste by a certified waste handler.
- All waste water is sent to an on-site WWTP, which removes 93% of the EDC from the water. The effluent of the on-site WWTP is sent after treatment via pipeline to a municipal WWTP.
- Direct exposure of soil is avoided by means of hard, watertight flooring and a concrete basin for the secondary containment of the underground storage tank.

The applicant stated in the CSR that a number of improvements, such as replacement of single seal liquid waste pumps by closed pumps (membrane or equivalent) and a replacement of the previously used active carbon adsorber with thermal oxidizer, were scheduled for the end of 2016. In his answers to RAC questions the applicant informed that replacement of single seal pumps with membrane pumps has been already completed in 2016 (these liquid waste pumps are located inside the building where is Epi3 manufactured thus the emissions from these pumps are relevant for WCS 3). The applicant also informed that the construction of the new thermal oxidizer has been completed and the start-up of the new installation has been initiated at the end of 2016 (the old installation is kept on standby).

RAC concludes that predominantly closed systems are used to minimise the potential of exposure to workers. For those activities where the applicant has identified potential for exposure, a high level of occupational health and safety is implemented.

RMMs implemented to control exposure of workers and emissions to environment are considered to be appropriate in limiting the associated risks.

Risk characterisation

Workers

As mentioned above, the applicant has estimated cancer risks according to the RAC reference dose response relationship for EDC carcinogenicity, based on assumed exposure time of 8 h/day, 5 days/week, 48 weeks/year for 40 years.

Based on data from the personal sampling exposure measurements and modelled data corrected for PPE, frequency (projected for the years 2018-2023) and duration, the excess cancer risk was estimated for the activities that can lead to exposure to EDC.

Table 11: Excess risk estimates for 40 years exposure for workers

Contributing scenario		Inhalation route		Dermal route		Combined route
		Corrected exposure estimates (µg/m³)*	Excess cancer risk	Corrected exposure estimates (µg/kg bw/d)*	Excess cancer risk	Excess cancer risk
WCS 1 Storage of EDC (PROC 1)		0	0	0	0	0
WCS 2 Unloading of EDC and transfer to storage tank (PROC 8b)		1.72	1.03×10^{-6}	0	0	1.03×10^{-6}
WCS 3 Use of EDC in the manufacturing of Epirubicin (PROC 3)	*a) Near Field Workers (NFW)*	18.2 (NF) 12.1 (FF)	$1,82 \times 10^{-5}$ **	8.75×10^{-3}	$1,84 \times 10^{-8}$	$1,82 \times 10^{-5}$
	b) Far Field Workers (FFW)	30.3	$1,82 \times 10^{-5}$	8.75×10^{-3}	$1,84 \times 10^{-8}$	$1,82 \times 10^{-5}$
WCS 4 Transfer of EDC containing waste to tank truck (PROC 8b)		16.3	9.75×10^{-6}	5.88×10^{-4}	$1,23 \times 10^{-9}$	9.75×10^{-6}

** Values corrected for PPE, frequency and duration.*

*** ECR for NFW is calculated by adding ECR = 1.09×10^{-5} (NF) and ECR = 7.28×10^{-6} (FF)*

The maximum excess cancer risk to an individual worker is **1.82×10^{-5},** for specific tasks during the WCS 3 "Use of EDC in the manufacturing of Epirubicin".

According to the applicant, all workers involved in the manufacturing of epirubicin are performing only one of the relevant activities described in WCSs. Therefore - combined exposure assessment was not needed.

Indirect exposure via the environment

Similarly, the risk characterisation for human via the environment is based on ECHA's dose-response relationship for EDC carcinogenicity.

Indirectly exposed workers via atmospheric releases

For indirectly exposed workers, the estimated EDC concentration at 100 m from the emission source (0.359 µg/m^3) was used for risk characterisation, which resulted in an excess cancer risk of **2.15×10^{-7}** for an individual worker over 40 year period of exposure.

Indirect exposure to general population via the environment

For indirectly exposure to humans via the environment at local and regional level, the EUSES estimated exposure values were used to calculate the excess cancer risks.

The results are presented in Tables 12 and 13.

Table 12 Exposure to humans via the environment – local scale (75 years)

Protection target	**Exposure estimate**	**Excess cancer risk (individual)**
Human via Environment – Inhalation (µg/m^3)	3.59×10^{-1}	1.24×10^{-6}
Human via Environment – Oral (µg/kg bw/day)	3.22×10^{-3}	3.87×10^{-8}
Human via Environment - Combined		1.28×10^{-6}

Table 13 Exposure to humans via the environment - regional scale

Protection target	**Exposure estimate**	**Excess cancer risk (individual)**
Human via Environment – Inhalation (µg/m^3)	1.33×10^{-4}	4.59×10^{-10}
Human via Environment – Oral (µg/kg bw/day)	1.44×10^{-6}	1.73×10^{-11}
Human via Environment - Combined		4.76×10^{-10}

Uncertainties related to RMM

RAC has not identified any particular uncertainty regarding the appropriateness and effectiveness of OCs and RMMs.

The only task not performed in closed system – sampling of waste – is infrequent, related to low (<1%) EDC concentrations and is of short duration.

Conclusion

RAC considers that the estimates of excess cancer risk for workers and for indirect exposure of humans (workers and general population) via the environment account for all relevant

routes of exposure and are sufficient to allow a health impact assessment. However, RAC notes that the risks related to the regional scale of exposure to the general population might be overestimated as the applicant did not estimate regional cancer risks separately for uses 1 and 2.

Taking into consideration the information provided, **RAC concludes that the risk management measures and operational conditions described in the application are appropriate and effective in limiting the risk to workers and the general population**.

7. Justification of the suitability and availability of alternatives

7.1 To what extent is the technical and economic feasibility of alternatives described and compared with the Annex XIV substance?

Description:

Summary of the analysis of alternatives undertaken by the applicant

The applicant Olon SpA applies for authorization to use 1,2-dichloroehane (EDC) as a solvent in the manufacturing of the active pharmaceutical ingredient (API) epirubicin. The API is sold to a single client company that manufactures a medicinal product which is a drug used in chemotherapy for a number of malignancies. The client is one of the leading global suppliers of the epirubicin-based medicinal product using Olon as its sole source of the API.

In the search for alternatives, the applicant has taken an integrated strategic approach, looking at all possible business options as alternatives to applying for authorization for continued use of EDC in the epirubicin manufacture under REACH after the sunset date. In this integrated approach the applicant closely collaborated with the client. The applicant together with the client has undertaken research to identify possible alternative substances, technologies and managerial / organisational responses which could enable the cease of EDC use for this purpose in the EEA. Table 1 lists the alternative options identified.

Table 14: Long-list of alternatives identified by the applicant (copy from the Analysis of Alternatives and Socio-Economic Analysis submitted by the applicant).

N°	Name	Type	Brief description
1	Alternative solvent	Substance	Replacing 1,2-DCE as a crystallization/precipitation solvent with a “drop-in” alternative. No change in the synthesis route.
2	Alternative synthesis route	Technology	The use of 1,2-DCE is linked to the route developed by Olon from the publication by Arcamone *et al.* This alternative covers routes with no use of 1,2-DCE.
3	Alternative API	Technology	Manufacturing of a different API with the same therapeutic coverage but with no use of 1,2- DCE during the synthesis.

4	Relocation of manufacturing	Managerial	Relocation of the manufacturing of epirubicin outside of the EEA.
5	Shutdown of manufacturing	Managerial	Decommissioning and no further manufacturing after the sunset date.

For each of the alternatives listed in Table 1, the applicant presents the research and development they performed, the technical and economic feasibility, the availability and an overall conclusion. The main findings are summarized below.

Technical feasibility

Alternative 1: use of an alternative solvent

The manufacturing of epirubicin occurs in a closed batch process. EDC is needed as a solvent for the crystallization of one of the intermediate substance Epi3 (the exact substance name was claimed as confidential by the applicant) which is formed in one of a series of reaction steps in API manufacture. EDC is removed from the reaction mixture at transfer to the next step. EDC waste is collected in a tank and transported to a waste treatment facility.

EDC has three main functions in this process:

- Eliminate impurities from the recovered Epi3
- Support the separation of the solvent of the mother liquid from Epi3
- Allow the crystallization of Epi3

The procedure for the precipitation and crystallization of Epi3 originates from a 1980 US patent by Suarato ea. Olon adapted the patented process by eliminating the use of diethyl ether, chloroform and acetone, which are all hazardous substances (i.e. physical hazards). EDC was used as a replacement solvent, as it requires lower volumes and was then considered to be of lesser concern. By using EDC, an additional crystallization step was introduced. The applicant states not to be aware of any further substitute solvents which are being used by other API manufacturers and which could be used as a drop-in solvent for this process. In the authorization documentation the applicant has listed 26 solvents selected from 53 classical solvents taken from a solvent guide published in 2016 (Prat *et al*.). Some of the short-listed solvents were discarded based on human health or physical hazards (e.g flammability), their potential to react and their boiling point. The applicant has put no further effort in analysing the potential of these 26 solvents to replace EDC. For this, according to the applicant, a development plan would have to be set up together with the client to check all key functional requirements of the solvent and the API. These 12 key functional requirements, EDC performance and an assessed impact of deviations from the requirements, are listed in the application. The functional requirements are the following: solubility of epirubicin, miscibility with methanol, product quality, boiling point, solubility power, chemical compatibility, toxicity, flammability/explosion hazard, purity, composition of the API, formation of hazardous side products and build-up of electrostatic charge.

Based on the above, the applicant concludes that currently no other solvent can be

considered technically feasible. This conclusion is drawn based on the following findings:

- the fact that the past research by Olon for the replacement of diethyl ether and chloroform did not deliver any other suitable solvent in addition to EDC;
- Olon has no knowledge of any other substitute solvents used by other API manufacturers;
- the solvents listed in literature have no description as being used as a substitute for EDC.

Alternative 2: alternative synthesis route

The applicant did not perform any research and development in order to find alternative synthesis routes for manufacturing the epirubicin API besides the work that was initially performed when the current process was implemented. A literature review was performed finding four possible routes:

- synthesis starting from daunorubicin (this route is the origin of the process currently used by the applicant);
- synthesis starting from hydroxyanthraquinone;
- synthesis starting from 1,3-dihydrodaunorubicin;
- synthesis by direct fermentation.

The applicant states that the first route would be technically feasible, however the applicant has already moved away from this process in order to reduce the use of hazardous substances (mainly chloroform). Based on studies and patents, the applicant concludes that the three remaining routes are technically infeasible, and impossible to implement without further technical development. Difficulties relate to impurities formed, affecting the level of purity and product quality, and the use of substances included in the candidate list for authorisation under REACH (other than EDC) in the process (risk related). Some routes (3rd and 4th option) are still patent protected and currently not available to the applicant.

Alternative 3: use of an alternative API

The epirubicin API belongs to the group of anthracyclines, a group of medicines having the same therapeutic application in the treatment of malignant cancers. The alternative should be at least as effective as epirubicin to treat the same types of cancers without additional side effects. Olon already manufactures another anthracycline API (doxorubicin) at another site in Italy, without use of SVHCs. However, the applicant has provided a number of arguments claiming why an increase in production and marketing of doxorubicin is not a technically feasible alternative. First, they state that they do not currently have sufficient spare doxorubicin production capacity to compensate for the loss of epirubicin manufacturing. More importantly, doxorubicin is not used in the treatment of the same range/types of cancers as epirubicin. Furthermore, even if there is an overlap (i.e. both products could be used in the treatment of the same type of cancer), doxorubicin may not be a suitable alternative due to different side effects and differing patient characteristics (e.g. health state).

Development of other APIs covering the same therapeutic range is regarded by the applicant beyond the scope of their technical and financial means.

Alternative 4: relocation of API manufacturing outside of the EEA

The applicant argues that the relocation of the API manufacture outside the EEA is complex and requires substantial expertise, which they do not have. In addition, Olon has no

manufacturing locations outside the EEA. Nevertheless, the physical relocation (construction project) is considered technically feasible. The applicant's client would consider relocation a major change requiring requalification of the API and market approval of the resulting medicinal product. Until requalification of the API is finished, it is considered uncertain if the API made at the new location would be acceptable for the production of the medicinal product. Hence, there are time constraints because of the need for re-qualification and re-approval and uncertainties related to the re-qualification of the API and the overall technical feasibility of alternative 4.

Alternative 5: closure of the epirubicin manufacture and business

The applicant concludes closure to be a technically feasible option as there are no barriers preventing them from going along this route.

Economic feasibility

Alternative 1: use of an alternative solvent

For the phase-in of any alternative drop-in solvent the applicant identifies four phases (a research plan with breakdown of anticipated costs and the timeframe needed is included in the AoA/SEA):

- identification of alternative solvent and proof of concept;
- development of an industrial process;
- qualification of the API produced with the alternative solvent;
- filing for market approval of the medicinal product produced with the API.

The applicant further provided a generic summary of the costs of re-designing the epirubicin manufacturing process including steps to be taken by the client such as the qualification of the API and worldwide product market approval of the medicinal product. The total anticipated costs add up to less than €25m (exact figure claimed confidential) and the total timeframe needed is estimated at 12.5 years. The time needed for RandD, changes to the manufacturing process by Olon and API manufacturing for medicinal product testing adds up to 6.5 years. The qualification steps and market approval by the client take an estimated 10 years. As some steps would be run in parallel, the total estimated time needed is 12.5 years.

Hence, it would take 12.5 years and up to €25m before the client would be able to start selling the newly qualified medicinal product in all 100 markets. The applicant states the estimated cost of switching to an alternative solvent as a 'fixed cost', which means that if it was to be economically feasible, any such alternative would need to result in a reduction of costs or an increase in product price which would at least compensate for this amount. They state that further reduction of manufacturing costs are unlikely as the original process, applied over the years, has already been optimized. Further, they state that significant increases in price of the product are also unlikely in a competitive market with relatively comparable product quality. The applicant concludes that this places an additional constraint on the identification of suitable alternatives. Even if a technically feasible alternative could be identified, it would be unlikely ever to be economically feasible and hence suitable. This removes the commercial rationale to search for a technically feasible alternative. The applicant states: '*In reality, given the significant costs associated with developing a substitute and then gaining approval for it and the associated medicinal product, and the intervening loss of profits, it will never be economically feasible for Olon to substitute away from the use of 1,2-DCE in the manufacture of epirubicin*'. From the above it can be

deducted that the applicant is not currently investing further into research and development on alternative solvents. In reply to a question by SEAC the applicant confirmed that, based on economic feasibility considerations, the collaborative search for alternative solvents and processes would be limited to literature reviews, consultations and monitoring of new developments rather than targeted RandD efforts.

In assessing the economic feasibility of phasing in an alternative solvent, the applicant assumes that during the 12.5 years transition period, they would no longer make any epirubicin API, resulting in a loss of profit of less than €200m (exact figure claimed confidential) Net Present Value (NPV). Other costs are technical costs of switching to the alternative solvent (e.g. changes in equipment) and worker redundancy costs (60 workers at the Rodano plant in 2018). These costs add up to a total of less than €10m NPV (exact figure claimed confidential). During the transition period it is assumed that Olon will gain profits because of sales of their newly qualified API to the client due to a gradual regaining of market share by the client. The profits by Olon are estimated at less than €50m NPV (exact figure claimed confidential). Costs to the client are not included in this assessment. Therefore, the applicant considers the alternative not economically feasible.

Alternative 2: alternative synthesis route

The economic feasibility assessment of changing the manufacturing process is the same as for alternative 1, hence with similar costs and timelines associated with a theoretical implementation. The applicant considers the alternative not economically feasible.

Alternative 3: use of an alternative API

This option is assessed as not economically feasible. The scenario is assessed where Olon replaces current epirubicin API manufacture with doxorubicin API manufacture. Capacity is limited and hence, capital investment would be needed and because of the similarities of the two APIs, this would be possible at reduced costs. Qualification of the additional doxorubicin API produced from the converted epirubicin line would be needed but presumably without a need for full re-qualification and re-approval by authorities.

The main driver for economic feasibility is the response of clinicians as a result of the client's epirubicin medicinal product not being available on the market. As the generic epirubicin product in the majority of markets is available from competing suppliers, the applicant expects that the demand would switch almost completely to these competing versions. As a result there would not be an increased demand for doxorubicin, although there could be a temporary increase in demand as competing epirubicin suppliers would not be able to scale up their supply immediately. Furthermore, the differences in the therapeutic application will also limit the potential of significant increase of demand for doxorubicin. Because of the competing epirubicin products available on the markets, the applicant considers alternative 3 not a sustainable solution. Costs are estimated to be less than €220m (exact figure claimed confidential) and consist of lost profits (epirubicin sales), redundancy costs for 60 workers at Rodano and shut-down (decommissioning) costs. Costs for expanding the doxorubicin line were not included.

A possible switch to other APIs covering the same therapeutic range is not assessed as these are regarded by the applicant beyond the scope of their technical and financial means.

Alternative 4: relocation of API manufacturing outside of the EEA

This alternative is considered not economically feasible as the associated costs are estimated to add up to a total of less than €250m NPV (exact figure claimed confidential). The main cost drivers are: costs of the actual relocation, lost profits and redundancy of

Rodano workers. The alternative is not available at present as Olon does not have any site outside the EEA. The total time needed for a relocation is estimated as 12 years (finding and procuring a site, construction, qualification and approval of API).

Alternative 5: closure of the epirubicin manufacture and business

After the sunset date Olon would no longer make the epirubicin API resulting in an overall net loss in profit of less than €200m NPV (exact figure claimed confidential). Redundancy and decommissioning costs included would add up to a total cost of this alternative of less than €220m NPV (exact figure claimed confidential) relative to the applied for use scenario. The applicant concludes this option available to them but not economically feasible.

Conclusion

SEAC notes that the applicant approached the analyses of alternatives in an integrated way combining it with the SEA. The applicant assessed 5 relevant alternatives as business options allowing a comparison of these options for the SEA in order to define the appropriate non-use scenario. The analysis is considered sufficiently structured and complete, assessing suitability of business alternatives against the applied for use scenario. Technical feasibility, economic feasibility, risk reduction and availability are assessed for each alternative in a systematic way. SEAC finds the analysis to be credible, but because of the grouped and integrated approach primarily focussing on economic infeasibility, SEAC cannot judge the completeness of the technical feasibility assessment of specific solvents and synthesis route alternatives.

7.2 Are the alternatives technically and economically feasible before the sunset date?

☐ YES

☒ NO

Justification:

The applicant has assessed five alternatives and concludes as follows on their overall technical feasibility:

- no other solvent is currently technically feasible, a development plan would need to be developed together with the client if it was decided to further investigate this option;
- 3 out of 4 alternative synthesis routes are technically infeasible and cannot be implemented without further RandD; several technical and economic drawbacks were identified by the applicant.
- Increase of production of the doxorubicin API is not a technically feasible option, primarily due to imperfect therapeutic overlap with epirubicin;
- Physical relocation outside the EEA is technically feasible but there are uncertainties on the technical feasibility of the newly manufactured API;
- Closure is a technically feasible option.

Based on an assessment of expected costs the applicant assessed all five alternatives as economically infeasible.

Conclusion

SEAC concludes that none of the five alternatives presented by the applicant is an economically feasible business option for them replacing the use of 1,2-dichloroethane in the manufacture of the epirubicin API.

As a result of the integrated approach of the analysis of alternatives with the SEA, assessing alternatives as business options and primarily focussing on their overall economic feasibility, the applicant has not provided in depth analyses of specific solvents within the identified groups. The technical feasibility of alternative solvents and synthesis routes was not further investigated because these options were clearly not economically feasible. SEAC however notes that the applicant has provided information on the basis of which some of the substance and technology related alternatives could become technically feasible in the future after being further developed by the applicant in cooperation with their client. However, even if a hypothetical alternative would be identified, given the time needed for RandD, qualification of the API and of the medicinal product (estimated by the applicant at approximately 12.5 years), it is unlikely that an alternative would be technically feasible before the sunset date.

SEAC notes that the economic infeasibility of any change towards an alternative hampers the applicant's search for a technically feasible alternative. SEAC accepts this conclusion as a key finding of the analysis of alternatives.

SEAC accepts the statement by the applicant that developing other new APIs is outside their scope as they have neither the knowledge nor the financial means for such a development. SEAC notes that the relationship of Olon to their client is as a toll manufacturer for epirubicin.

SEAC concludes that there are no technically and economically feasible alternatives before the sunset date.

7.3 To what extent are the risks of alternatives described and compared with the Annex XIV substance?

Description:

The alternatives to the Use 1 of EDC can be grouped into three types:

- Alternative solvent;
- Alternative API manufacturing (synthesis) process;
- Alternative API;

Alternative 1: Use of an alternative solvent

This alternative would involve using a different solvent from EDC for the precipitation of the intermediate product, Epi3. Olon started its evaluation with 53 potential solvents and after removing the 22 solvents that ranked as either hazardous or highly hazardous was left with 25 solvents that were given further consideration:

methanol, ethanol, isopropanol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone, ethyl acetate, isopropyl acetate, n-butyl acetate, THF, MethylTHF, anisole, heptane, cyclohexane, methyl cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, formic acid, acetic acid and water as well as methylene chloride.

RAC notes that the reduction in risk to human health and the environment by using alternative solvents was not discussed by the applicant, as none of the solvents was found to be technically or economically feasible.

Alternative 2: Alternative synthesis route

This alternative would involve the re-engineering of the synthesis process for epirubicin to avoid the use of EDC.

As a result of the literature search on possible alternative synthesis routes for epirubicin, the following four options were identified by the applicant:

- Synthesis starting from daunorubicin;
- Synthesis starting from hydroxyanthraquinone;
- Synthesis starting from 13-dihydrodaunorubicin;
- Synthesis by direct fermentation.

The option to manufacture epirubicin via direct fermentation does not appear to constitute a (significant) reduction of risk as the use of sodium tetraborate is required for this synthesis. Sodium tetraborate is classified as Repr. 1B, Eye Irrit. 2.

Similarly, the option to manufacture epirubicin starting from 13-dihydrodaunorubicine does not appear to present a (significant) reduction in risk as the use of N,N-dimethylformamide is required for this synthesis. N,N-dimethylformamide is classified as Repr. 1B, Acute Tox. 4, Eye Irrit. 2, Acute Tox. 4.

Same applies for hydroxyanthraquinone, as the use of mercury is required for this synthesis. Mercury is harmonized classified as Aquatic Chronic 1, STOT RE 1, Repr. 1B, Aquatic Acute 1 and Acute Tox.

The original patent makes use of large quantities of chloroform for the manufacturing of the Epi3 intermediate. Chloroform is harmonized classified as Carc. 2, Skin Irrit. 2, Acute Tox. 4 (swallowed), Eye Irrit. 2, Repr. 2, STOT RE 1, Acute Tox. 3 (inhaled). Chloroform has a much lower boiling point (61-62°C) compared to EDC (83.6°C). Based on the higher volume required and the lower boiling point of chloroform, an increased exposure compared with the exposure of EDC can be expected.

Overall, it can be concluded that a shift to one of the discussed alternative synthesis routes would not constitute shift to a (significantly) less hazardous alternatives.

Alternative 3: Use of an alternative API

The medicinal product itself, epirubicin, is the result of an optimisation of existing similar APIs, such as doxorubicin, still the main alternative therapeutic product for epirubicin. Doxorubicin is chemically very similar to epirubicin and has the same mode of action. Both medicines provide treatment for a variety of cancers. The use of EDC is specific for the manufacture of Epi3. The applicant already manufactures doxorubicin API and no SVHCs are used in that process. The applicant has no knowledge of whether EDC or any other SVHC is used for the manufacture of any of the other alternative epirubicin APIs.

As manufacturing of doxorubicin does not involve the use of SVHCs, it is likely to result in an overall reduction in risk.

7.4 Would the available information on alternatives appear to suggest that substitution with alternatives would lead to overall reduction of risk?

☐ YES

☐ NO

☒ NOT APPLICABLE

Justification:

Considering the applicant's short-listed alternatives:

i) RAC notes that a quantitative risk assessment/comparison has not been performed by the applicant and therefore a comparison of risks cannot be concluded by RAC;

ii) RAC notes that use of an alternative API and manufacture routes not involving EDC are likely to entail lower risks than the use applied for; RAC cannot conclude without further details and assessment by the applicant.

RAC considers the extent to which the applicant has assessed the relative hazards and risks of the candidate substances as appropriate.

RAC recognises that, for the purpose of the analysis of alternatives, when the applicant can show that an alternative that could be assumed to entail lower risks is not technically or economically feasible for them, it would not be necessary to continue with further assessment of the risks of the alternative.

Therefore, RAC considers that the basic requirement of a comparative hazard assessment was fulfilled and that a detailed comparative quantitative risk assessment is not necessary.

Conclusion

RAC agrees with the applicant`s conclusion that alternative solvents among the ones short-listed in the application could result in a risk reduction for human health (workers and general population via the environment). A shift to any of the discussed alternative synthesis routes would on the contrary not constitute shift to a less hazardous alternative. Finally, synthesis of an alternative API is likely to result in an overall reduction in risk.

7.5 If alternatives are suitable (i.e. technically, economically feasible and lead to overall reduction of risk), are they available before the sunset date?

☐ YES

☐ NO

☒ NOT RELEVANT

Justification:

No suitable alternatives are identified.

8. For non-threshold substances, or if adequate control was not demonstrated, have the benefits of continued use been adequately demonstrated to exceed the risks of continued use?

☒ YES

☐ NO

☐ NOT RELEVANT, THRESHOLD SUBSTANCE

Justification:

Additional statistical cancer cases estimated by RAC

The estimated number of additional statistical cancer cases has been calculated using the excess risk value presented in section 6 and the estimation of the number of exposed people as provided by the applicant. It reflects the expected number of statistical cancer cases for an exposure over the working life of workers (40 years) and entire life for general population (lifetime exposure). For workers, the results are presented in Table 15 and Table 16.

Table 15: Estimated additional statistical cancer cases due to direct workers' exposure.

Contributing scenario		**Excess cancer risk**	**Excess cancer risk**	**Number of exposed people**	**Estimated statistical cancer cases (40 years)**	
		Inhalation	**dermal**		**inhalation**	**dermal**
WCS 1 Storage of EDC (PROC 1)		0	0	-	0	0
WCS 2 Unloading of EDC and transfer to storage tank (PROC 8b)		1.03×10^{-6}	0	2	2.05×10^{-6}	0
WCS 3 Use of EDC in the manufacturing of Epirubicin (PROC 3)	*a) Near Field Workers (NFW)*	$1,82 \times 10^{-5}$	$1,84 \times 10^{-8}$	5	9.10×10^{-5}	9.19×10^{-8}
	b) Far Field Workers (FFW)	$1,82 \times 10^{-5}$	$1,84 \times 10^{-8}$	11	2.0×10^{-4}	2.02×10^{-7}
WCS 4 Transfer of		9.75×10^{-6}	$1,23 \times 10^{-9}$	2	1.95×10^{-5}	2.47×10^{-9}

EDC containing waste to tank truck (PROC 8b)						
Total					3.13×10^{-4}	2.96×10^{-7}
Total per person					1.56×10^{-5}	1.48×10^{-8}

Table 16: Estimated additional statistical cancer cases, workers, at the Rodano site in Italy

Routes	**Excess lifetime cancer risk per person**	**Number of exposed people**	**Estimated statistical cancer cases, per year**
Inhalation	1.56×10^{-5} [40y]	20	7.82×10^{-6}
Dermal	1.48×10^{-8} [40y]	20	7.41×10^{-9}
Total*			7.83×10^{-6}

* For the 20 year period the total is 1.57×10^{-4}

Table 17: Estimated additional statistical cancer cases, general population and workers at nearby plants

Routes	**Excess lifetime lung cancer risk per person**	**Number of exposed people**	**Estimated statistical cancer cases, per year**
Inhalation, general population.	1.24×10^{-6} [75y]	300	4.95×10^{-6}
Inhalation, workers at nearby plants	2.15×10^{-7} [40y]	400	2.15×10^{-6}
Oral	3.87×10^{-8} [75y]	300	1.55×10^{-7}
Total*			7.25×10^{-6}

* For the 20 year period the total is 1.45×10^{-4}

Assessment of impact

The assessment of impact associated with this authorisation application which has been undertaken by the applicant includes a quantitative monetary assessment of the societal impacts associated with the non-use scenario, i.e. assuming authorisation is not granted, for EDC in this use.

The assessment of impacts is based on impacts occurring within the EU and which are incremental to the baseline situation, these impacts being defined in terms of a non-use scenario in which the production ceases.

The applicant has provided arguments for why the chosen non-use scenario, which assumes that the applicant closes its production of epirubicin at is site in Rodano (Milan), is the most likely one. In short, this scenario creates the least losses for the applicant. The client that is using the epirubicin is likely to lose some of its market share when the applicant can't deliver and before the client has found a new source.

The assessment of economic impacts undertaken by the applicant conforms with methodologies accepted by SEAC. The analysis of the economic burden of human health impacts is based on established procedures for the calculation of economic welfare changes as a result of human health risk reductions and is in line with methodology endorsed by SEAC.

Human health impacts of continued use

In the quantitative analysis of the costs of continued use, the applicant estimates the change in physical health impacts (disease burden) due to changes in exposures. The approach is based on linking quantitative relationships between exposure and the health impact of interest. This general methodology is widely used for the assessment of benefits related to pollutants.

RAC's dose-response relationship was used in the applicant's assessment assuming **worker exposure** of 8 hours per working day (5 days/week) over a working life of 40 years. The dose-response relationship was also used in the applicants' assessment assuming **general population exposure** (man via environment) of 24 hours per day 7 days/week over a lifetime of 75 years[3].

The quantitative health impact assessment for workers estimates the number of avoided cases of cancer as a result of the change in exposure to EDC under the non-use scenario to be of the order of 1/100,000 per year. For 'man via environment' the estimated additional avoided cancer cases due to local exposure, is also of the order of 1/100,000 per year.

Since the exposure response relationships are based on an exposure time period of 40 years for workers and life-long exposure for the general population and 40 years for workers at nearby plants ('man via environment'), the applicant treats exposures as 'separable' over time in order to derive annual cases. SEAC considers such an approach appropriate and consistent with existing practice in authorisation applications.

Concerning the estimation of economic welfare losses associated with these numbers of excess cancer cases, the applicant assesses the 'human' welfare losses associated with morbidity and mortality. The valuation of morbidity and mortality effects uses a willingness to pay (WTP) value of €4.127 million to avoid a fatal cancer case, €432,756 for a non-fatal cancer case. With a non-fatal to fatal ratio of approximately 57:43 (taken from all-age, five-year survival rates for cancer, for Italy in the years 2000–2007) the resulting cost per cancer case is €2.030 million. Medical costs, which are on a lower level of magnitude, are not included (for comparison, the applicant has provided an estimate of €13,000 average treatment cost per case). This calculation results in a total annual cost of excess cancer risk

[3] The Guidance document R15 on "Consumer exposure assessment" assumes 70 years as the average human lifetime. Calculating for 70 years would have slightly increased the total number of estimated statistical cancer cases.

of about €16 per year for workers at the Rodano site and €15 per year for local residents and workers at nearby plants. Adding up for 20 years using a 4% discount rate gives less than €387 for workers and residents exposed as 'man via environment'.

It is relevant to also consider the positive health impacts of the medicine produced. It is not possible to estimate the number of lives saved or the number of patients treated in the EU but the number of dosages has been declared by the client. The average number of dosages the last three years are 3.5 million globally, of which a large fraction is sold in the EU, i.e. on the level of a million dosages. The client has around 50 % (or more) of the market in many EU countries, for the epirubicin medicinal product, and competitors will most likely expand their market shares in case of close down of Olon's production. However, there may be a transition phase with temporary shortage of epirubicin on the EU market. The applicant states that during this time, some clinicians might switch where possible to other anthracyclines or change their treatment regimes. To the extent that this would represent a divergence from preferred clinical practice, there could be implications for patients. No quantification and justification was provided on any such implications. Hence, SEAC cannot assess the likelihood of such shortage occurring and any associated negative human health impacts that would be incurred upon the patient group as a result of the non-use scenario.

Benefits of continued use (cost of non-use scenario)

The applicant's analysis of the benefits of continued use is based on a non-use scenario in which their production is shut down. In order to choose the most probable non-use scenario the applicant has calculated the economic outcome of implementing each of the five different alternatives described in section 7.1, each corresponding to a different non-use scenario. The applicant has thus estimated the sum of profits under the applied for use scenario, the costs to implement the alternative and the profits gained by using this alternative. The net outcome in each of the scenarios is negative, i.e. the applicant would incur losses. It is, however, assessed that the shut-down scenario is among those with smaller losses. In addition, the other scenarios are based on optimistic assumptions that might not be achieved in practice. In the calculation of the costs, the activities directly related to production of epirubicin have been taken into account. The sum of profits lost is declared as less than €220 million (the actual value has been claimed confidential by the applicant), for the entire review period requested by the applicant (20 years) and using a 4% discount rate.

Social valuation of Olon's lost profits in a long or medium long period are likely to be reduced since resources that become idle as a result of a non-authorisation would be used for other things. Meaning that in the first years of the non-use scenario society is likely to incur the losses estimated by the applicant, however year after year the magnitude of these losses will diminish. It is difficult to calculate how much it is reduced over time. For that reason, it is questionable to use the same amount of yearly loss for the entire review period requested (20 years) in order to calculate the benefits of continued use.

In addition to economic impacts, the applicant also assesses the expected social impacts of the non-use scenario. The primary impact considered here is the unemployment associated with redundancies resulting from the cessation of production of epirubicin at the Rodano site and resulting redundancies for the client's workers. The applicant provided estimates of salary costs of less than €25 million per year and a total cost for those unemployed after a close down of its operations of less than €25 million. The calculations are based on the loss in economic output/value for the duration of this unemployment. The value of output lost

during this period is taken to be equal to the gross employee wage including employer labour tax contributions. The calculation is based on 21.5 months of employment for Italy and 18.5 for Belgium. This deviates somewhat from what is recommended by SEAC for this type of calculations. A correction would however not change the overall conclusion.

Conclusion

In order to compare the benefits and costs of continued use, the applicant adjusts the human health impact estimates which are presented per year of exposure, such that they cover the same period of analysis used to assess socio-economic costs. The human health impacts associated with the applicant's use of EDC are estimated at about €387 for the requested 20-year period. The sum of profits for Olon under the applied for use scenario is less than €220 million of which some are considered as benefits on a societal level. As such, the benefits of continued use of EDC as analysed by the applicant considerably exceed the risks of continued use caused by exposure of workers and man via the environment in the production process. SEAC considers any uncertainties to be minor such that they would not affect the overall conclusion.

SEAC consider the conclusion that benefits outweigh the risks of continued use to be robust.

9. Do you propose additional conditions or monitoring arrangements

☐ YES

☒ NO

Description for additional conditions and monitoring arrangements for the authorisation:

None

Description of conditions and monitoring arrangements for review reports:

Justification:

RAC considers that there is no need to recommend any additional conditions or monitoring arrangements. The information provided in the application, while containing a minor uncertainty, is sufficient to derive an opinion on the use conditions and acceptability of the OCs and RMMs, which are found to be appropriate and effective in limiting the risk.

10. Proposed review period:

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. _years)

☐ Other:

Justification:

In identifying the review period SEAC took note of the following considerations:

RAC's advice:

RAC gave no advice to SEAC on the length of the review period.

Other socio economic considerations

In identifying the proposed review period, SEAC took note of the following considerations:

- The exposure of workers and general population plus workers at nearby plants results in monetised costs of continued use in the order of €387 over the requested review period of 20 years. In comparison, the socio-economic benefits of continued use are less than €220 million (exact value claimed confidential), and this benefit/risk ratio is not likely to change in the near future;
- Based on past literature and laboratory research the applicant has not been able to identify any technically feasible alternatives for the use of EDC in the manufacture of epirubicin. A broad range of solvent families, synthesis routes and alternative APIs were assessed, but all showed technical, safety and availability shortcomings.
- In case an alternative with equivalent performance was to become available, implementing such alternative would require at least 12.5 years of development for re-designing the epirubicin manufacturing process, API qualification and product market approval of the final product by the client on 100 markets;
- Even if a technically feasible alternative would be identified, the expected net costs for changing the manufacturing process would be high. Net costs are estimated to be less than €200 million (lost profit plus investment costs minus profits made on the alternative), while the remaining risks are low.

These arguments support a long review period.

The applicant has applied for a 20 year review period. They provided some justification for this in the application, but did not set out sufficient justification for an exceptional review period. In response to questions from SEAC, they provided further arguments aimed at supporting this review period. In summary, their arguments for a 20 year review period are:

- The applicant states their use of EDC for the manufacture of a medicinal product has characteristics that are comparable with uses for the manufacture of spare parts of legacy articles, which is used by SEAC in the review period paper (SEAC/20/2013/03) as a possible exception to the 12 year review period. These characteristics are "limited remaining lifetime of the product, low remaining sales volumes, high fixed costs of approval and qualification of variations to existing products and technologies, and/or high costs associated with 'non-use'". SEAC notes that a number of these characteristics are however, not applicable to this specific medicinal product case (e.g. there is no evident limitation to the lifetime of the medicinal product the API is manufactured for (and EDC is needed for). It is also unclear why or when the future sales of the medicinal product will be considered as low as currently, and according to forecast data provided in the application, the total volume produced for 2016 – 2023 is shown to increase at the beginning and stabilise afterwards. In addition, legacy spare parts concern items which are employed in articles (e.g. cars, aeroplanes), however those articles are not anymore in production (and hence it becomes virtually impossible to test a spare part manufactured with an alternative solution inside the equipment in which it will be used). In contrast, epirubicin is used in a drug which is still in production. In conclusion the comparison with legacy spare parts is not straightforward, as such SEAC cannot take this argument in consideration when recommending the review period for this

application.

- There are “major barriers to the introduction of alternatives – in the form of qualification and national regulatory approval”. This implies that there are no expectations that any technically and economically feasible substitute to EDC will appear that could provide benefits such as cost reductions or improved treatment outcomes. Implementation of an alternative to the use of EDC in the manufacture of epirubicin would effectively represent a new drug being developed requiring time and efforts. Olon claims the medical product into which their epirubicin is incorporated is effectively a ‘fixed’ legacy drug with no possibilities to change to alternatives to EDC in the production without losing their business case. SEAC concurs with the information provided on limitations to develop alternative APIs. However, the arguments are not unique to this case and this industry sector and no specific reasoning is provided underpinning the requested 20 years review period.
- Finally, SEAC has requested the applicant to describe any negative impact that would occur if a 12 year review period was granted. The main impact identified by the applicant was the fact that the costs the company would face in providing a review report would be brought forward by several years. Still, the applicant has not explicitly linked this argument to his request for an exceptional review period. SEAC concurs with the applicant and notes that although these costs are relevant societal costs, they do not constitute sufficient argumentation for an exceptional review period case.

Based on the above considerations and on SEAC’s view on how the length of review period would be established (SEAC/20/2013/03), the applicant did not demonstrate that its use would be a particular and exceptional case for which a review period longer than 12 years would be warranted. A review period of longer than 12 years cannot be recommended by SEAC, unless criteria for such period are established. Therefore, SEAC recommends a 12 year review period for this use.

11. Did the Applicant provide comments to the draft final opinion?

☐ YES

☒ NO

11a. Action/s taken resulting from the analysis of the Applicant’s comments:

☐ YES

☐ NO

☒ NOT APPLICABLE