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IPPC Licencing

Environmental Protection Agency,

Regional Inspectorate,

McCuskey House,

Richview,

Clonskeagh Road,

Dublin 14

11th May 2023

Licence Register No: P0125-02

Company Name: Clarochem Ireland Ltd

Introduction of New Product

Pyrantel Pamoate

Cas No.: 22204-24-6

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1. Introduction

This screening assessment had been carried out to determine how the process can be accommodated from a licensing perspective.

The new product assessment had been carried out having regard to the EPA Guidance for Licensees on Requests for Alterations to the installation/facility.

Licence alteration is not required for the Pyrantel Pamoate new process.

The conclusion is that the proposed new process does not require a change in any licence condition and therefore requires only approval by the EPA.

2. New Process Description

Pyrantel Citrate and Pyrantel Pamoate, previously produced at the Cosma facility in Italy, to be produced at the Damastown plant.

This material is the API in a well-established anthelmintic veterinary drug product which is used to treat intestinal worm infections in cats and dogs. It has been manufactured for several years at one of our sister sites in Italy. Due to increasing demand and a direct customer request to provide a second site for this product to facilitate them maintaining a supply to the key US market, the validated manufacturing process will be introduced into the Clarochem Ireland site. There are two key starting materials for this process which will be sourced externally, using suppliers previously qualified by our sister site. The process will be manufactured in the existing production plant equipment and no new emission points will be created. Three validation batches will be manufactured in Q2/Q3 2023 to facilitate the customer obtaining regulatory approval to use Clarochem as a supplier of the API. It is difficult at this point to accurately forecast commercial volumes once regulatory approval is obtained, but they are likely to be of the order of 20MT – 30MT per annum.

Pyrantel Pamoate Cas number 22204-24-06 is not classified as hazardous substance.

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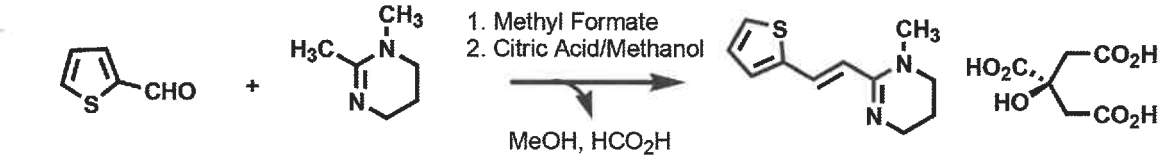
Details of Process related Raw Materials, Intermediates, Products, used or generated on the site in relation to the Manufacture of Pyrantel Pamoate

Material/ Substance[1]	**CAS Number**	**Classification of the substance or mixture**	**Nature of Use**
2-Thiophenealdehyde	98-03-3	Acute toxicity, Oral (Category 4), H302	Raw material
1,2-dimethyl-1,4,5,6-tetrahydropyrimidine	4271-96-9	Acute Tox. 4: H302; Skin Corr. 1B: H314	Raw Material
Methyl Formate	107-31-3	Flammable Class 3	Raw Material
Methanol	67-56-1	Flammable Class 3	Raw Material
Citric Acid Monohydrate	5949-29-1	Eye Irrit. 2; STOT SE 3; H319, H335	Raw Material
Sodium Pamoate	6640-22-8	Non-Hazard	Intermediate/Raw material
Acetone	67-64-1	Flammable Class 3	Raw material

2.1 Process Details



2-Thiophenaldehyde
C_5H_4OS
MW: 112.15

1,2-dimethyl-1,4,5,6-tetrahydropyrimidine
$C_6H_{12}N_2$
MW: 112.17

Pyrantel citrate
$C_{17}H_{22}N_2O_7S$
MW: 398.43

Pyrantel Pamoate Process Description

2-thiophenaldehyde and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine are mixed together at ca 36 DegC react in the presence of Methyl Formate to give Pyrantel Formate via a Knoevenagel reaction. The resultant solution is added to methanol and citric acid in a second reactor at ca. 40DegC which facilitates the formation of Pyrantel Citrate. The product crystallizes on cooling the batch to ca. 5DegC; whereupon it is centrifuged and washed with methanol.

The wet Pyrantel Citrate is then dissolved in water at ca. 80°C and this is added to another aqueous solution (ca. 75°C) of Disodium Pamoate to give Pyrantel Pamoate. The final solution

is hot filtered to a clean crystallizer whereupon the product crystallizes on cooling to ca. 50DegC. The suspension is then centrifuged and washed with ambient water until cool, and then with acetone. The wet final product is dried under vacuum at 90C for 8-12 hours.

Details of any changes to the on-site storage of raw materials and waste material:

Item	CAS Number	Annual Change to on-site storage	Physical Form
2-Thiophenealdehyde	98-03-3	+ 1,500kg	Liquid
1,2-dimethyl-1,4,5,6-tetrahydropyrimidine	4271-96-9	+ 2,000kg	Liquid
Methyl Formate	107-31-3	+ 1,200kg	Liquid
Methanol	67-56-1	No change	Liquid
Citric Acid Monohydrate	5949-29-1	+ 3,000kg	Solid
Sodium Pamoate	6640-22-8	No Change	Solid
Acetone	67-64-1	No change	Liquid

Note: The figures above represent quantities for the validation batches scheduled for manufacture in Q2/Q3 2023. Commercial manufacturing is not expected to start until 2025.

3. Emissions to the atmosphere

All VOCs in the manufacturing process will come within the parameters and emission limit values set out in Schedule B of the IE Licence. No new emission points will be required. The process will result in emissions from the drying process in small quantities of VOC (already in our IPPC licence). The equipment emission is directed to our Scrubber attack system (PS-1 emission point) over short period of time.

There will be no change to the number of air emission points, as the product will be manufactured in the existing plant and equipment. The main emission point from the synthesis plant is as follows:

Emission Point	Reference	Location	Grid Reference
P1-S	Synthesis Plant	Scrubber Stack	304885E, 241219N

There are 2 scrubbers in-line. The first contains a Sodium Hydroxide solution (4-6%) and the second contains Sulphuric Acid (>3% +/- 0.5%).

The emission from Pyrantel Pamoate drying process won't have significant increase on our current emissions parameters average and will be well below IE licence limits.

Fugitive Emissions

The CCI facility has been designed to minimize potential sources of fugitive emissions arising from process areas and buildings. Fugitive emissions sources at the CCI facility are limited to vapour losses during storage and transfer of materials, stripping of VOC's and odours in wastewater treatment tanks, bursting disks, relief valves, minor leaks from connections, isolation. valve glands and cleaning operations. Measures have been taken to minimize the fugitive emissions and these are described below:

Vapour Losses during storage, filling and emptying of Bulk Solvent Tanks and Drums.

- Conservation vents are employed on bulk storage tanks, which also have a nitrogen blanket;
- Transfer hoses are blowen clear before decoupling.
- A fixed vapour recovery line reduces nuisance odour during unloading of solvents.
- Stripping of VOC's and odours in Wastewater Treatment Tanks;
- Organic solvent wastes packaged in UN approved containers for treatment off-site.
- Bursting disks and relief valve discharges: all reactor valves and bursting discs vents into a safety tank.
- Leaks from flanges, pumps, seals, and valve glands: double mechanical seals are used for critical applications. Otherwise, single mechanical seals are employed.

Existing fugitive emissions control measures will be maintained throughout the manufacture of this process.

Losses due to fugitive emissions are monitored on a campaign basis by balancing materials inputs and outputs. The solvent mass balance of outputs versus inputs for 2022 campaigns show fugitive emissions to be in the order of <3.5%. the EC Directive on "the limitation of the emissions of organic compounds due to the use of organic solvents in certain processes and

industrial installations" sets a limit of 5% for such fugitive emissions so that the figure calculated here falls well within these limits.

4. Wastewater

4.1 Emissions to Surface Water

CCI discharge storm water and surface water run-off from unbunded areas to the river Tolka and emission point SW-D1. The site emissions to surface water effectively comprise of rainwater only and incorporates roof and ground run-off including the following sources at the facility:

- Carparks/roadways.
- Concrete yard.
- Roof area.

The main potential sources of contamination are:

- The car park with the possibility of oil and petrol spillage.
- The yard area with the possibility of spillage from drums/IBCs in transit from the storage areas to the plant.
- The gas oil storage tank loading bay with the possibility of spillage during refilling operations.

The total collection area for surface water is 6,017 m2. The effective surface areas and potential sources of contamination will not change as a result of the introduction of this new product.

4.2 Emissions to the Sewer

No emissions will be sent to sewer from this process. The new process will not affect the existing emission limit value for discharge to sewer.

Cleaning of equipment is controlled by written procedures, which determine suitable agents and washing cycles. The primary cleaning substance will be a solvent such as methanol. Washes will be collected for treatment/disposal by a licenced waste disposal facility. The potential for re-use of cleaning solvents will be investigated at the commercial stage of the product.

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4.3 Mother liquor and waste from washes

The process will result in the generation of aqueous waste containing methanol mother liquor, methanol washes and acetone/water washes.

The waste streams do not require amendment of the IE Licence conditions, as the category of waste ".

All wastes generated, included those from the cleaning process, will be contained and removed off site for incineration by licenced waste disposal contractors (Indaver) under existing arrangements.

The waste stream does not require amendment of the IE Licence conditions See category of waste "Aqueous washing and mother liquid", below.

Item **- Hazardous Waste**	**EWC Code**	**Annual Change to on-site storage**	**Physical Form**
Methanol mother liquor	07 05 04*	+ 6,600kg	Liquid
Methanol washes	07 05 01*	+ 3,750kg	Liquid
Acetone/water washes	07 05 01*	+ 1,400kg	Liquid

Note: The figures above represent quantities for the validation batches scheduled for manufacture in Q2/Q3 2023. Commercial manufacturing is not expected to start until 2025.

No waste containing methanol or acetone will be discharged to sewer and therefore no changes to ELVs are required.

5. Emission to Ground

There will be no emissions to ground from the CCI facility.

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6. Noise Emissions

The product will be manufactured using existing plant and equipment. Most of the processing plant is located indoors. The plant located externally consists of a cooling tower and the associated pumps. No new plant will be added to the external area of the plant. The noise profile of the site will not change as a result of the introduction of this process.

7. Conclusion

Clarochem proposes to introduce the chemical steps of the production of a new active pharmaceutical ingredient (API), Pyrantel Pamoate.

The process does not require any additional emission points.

The off-site disposal of waste aqueous washing liquids and mother liquids containing methanol or acetone and are already covered by the existing IE Licence.

For these reasons and because the proposed alteration of the new product won't result in increase or modification of our current emissions, a Request for Approval is the most appropriate approach for agreement.

If you require any additional information, please do not hesitate to contact us.

Kind regards,

Dr. Brian Kearney

Plant Director