Sigma-Aldrich Ireland Ltd.

EPA Approval Request for "Bibrocathol" Project

Introduction

A new product is proposed to be introduced to the Arklow site in 2022, details are provided below.

Class of the Activity

Class 5.16: The use of a chemical or biological process for the production of basic pharmaceutical products.

Class 11.1: The recovery or disposal of waste in a facility, within the meaning of the Act of 1996, which facility is connected or associated with another activity specified in this Schedule in respect of which a license or revised license under Part IV is in force or in respect of which a license under the said part is or will be required.

Description of the Activity

The product will be produced in a combination of the production building areas and the process is similar to the existing chemical processes at Sigma Aldrich Ireland Ltd. Utilities will be the same as in the existing plant. The services required to support production are a combination of existing services. The existing services are listed below:

- Electricity
- Nitrogen
- Process water
- Air and instrument air
- Cooling water
- Chilled water
- Vacuum
- Waste air header
- Wastewater treatment plant
- Steam

There are no new services required for the production of this product.

PROCESS DESCRIPTION

Proposed Process:

Bibrocathol is an API which is used as in topical eye ointment. Bibrocathol has been manufactured and supplied by Merck, Darmstadt, MDa, for many years. For business reasons it is now planned to relocate the chemical synthesis steps to Arklow, while retaining a final milling step at MDa. MDa will also perform the final packaging, testing, product release & product distribution.

The Arklow output will be **Bibrocathol Unmilled**, which will be supplied to MDa for final processing. Individual batch sizes will be approx 50kg, while the total annual output will be in the 100 kg to 400 kg range.

Specifically, for this first production campaign, which is planned for Q1 of 2022, The project plan involves processing one batch as a pre-validation batch, followed by three batches as process validation batches.

Operational information Requirements

Contents

9.1 List of unit operations

No Change

9.2 List of abatement treatment and recovery options

Vent header is connected to the waste air thermal oxidizer system.

9.3 Emissions to the environment from unit operations

The equipment to be used is connected into the vent header.

9.4 Process Control

Instrumentation and Control:

The equipment and associated tank farm equipment are controlled by an extension of the sites Distributed Control System. Both DCS systems are validated in accordance with the requirements of FDA regulations.

9.5 Capacities and Throughput

As in the existing plant, throughput will vary depending on the products and batch sizes required by the customer. Typical vessel capacities are given below.

Item	Equipment	Material	Capacity
A16	Glass lined reactor	GL	2000 litres
PF1	Stainless Steel Filter Dryer	SS	500 litres

Note: GL= Glass Lined.
GMP All items meet GMP standard.
Explosion protection: All motors are of E Ex dII A + IIB standard.

9.6 Bund Register

No change

10.0 Raw Materials and Product.

Details are attached on the following page

Table G.1 (i) Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. Nº or Code	Material/ Substance(1)	CAS Number	Danger(2) Category	Amount Stored (tonnes)	Annual Usage (tonnes)	Nature of Use	H Statement	P Statement
cGMP intermediate	Tetrabrocathecol (TBBK) (intermediate)	488-47-1	Warning	200 kg	Initially 200kg Potential increase to approx. 400 kg in future years	Raw material for production of product for supply	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation.	P261 Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Raw material	Bismuth Oxide (Raw material)	1304-76-3	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.	200 kg	Initially 200 kg, potential increase to approx 400 kg in future years	Raw material for production of product for supply	N/A	N/A Get medical advice/ attention.
Raw material	Salicylic acid	69-72-7	Danger	200 kg	Initially 200 kg, potential increase to approx 400 kg in future years	Raw material for production of product for supply	H302 Harmful if swallowed. H318 Causes serious eye damage. H361d Suspected of damaging the unborn child.	P201 Obtain special instructions before use.P202 Do not handle until all safety precautions have been read and understood. P280 Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection. P301 + P312 IF SWALLOWED: Call a POISON CENTER/ doctor if you feel unwell. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P308 + P313 IF exposed or concerned: Get medical advice/ attention.
Intermediate	Bismuth Salicylate	14882-18-9	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.	200 kg	Initially 200 kg, potential increase to approx 400 kg in future years	Intermediate used in production	N/A	N/A Get medical advice/ attention.
Product	Bibrocathol	6915-57-7	Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.	200 kg	Initially 200 kg, potential increase to approx 400 kg in future years	Finished product	N/A	N/A Get medical advice/ attention.

Notes:

1. In cases where a material comprises a number of distinct and available dangerous substances, please give details for each component substance.
2. c.f. Article 2(2) of SI № 77/94
3. c.f. Schedules 9 and 10 of SI No 62/2004

Table H.1 (i): WASTE - Hazardous Waste Recovery/Disposal

Waste material	EWC Code	Main source[1]	Quantity		On-site Recovery/ Disposal (Method & Location)	Off-site Recovery, reuse or recycling (Method, Location & Undertaker)	Off-site Disposal (Method, Location & Undertaker)
			Tonnes	m^3 / month			
Aqueous based Mother Liquors from the process	07 05 01	Filtration steps within the process	4 ton in 2022 Increasing to 8 tons in future years	Production scheduling dependent – some months will be zero, while one month might be the full annual quantity	Waste solvent tank	Offsite by approved contractor	Managed as per all similar existing waste streams
Organic solvent based Mother Liquors from the process	07 05 04	Filtration steps within the process	4 ton in 2022 Increasing to 8 tons in future years	Production scheduling dependent – some months will be zero, while one month might be the full annual quantity	Waste solvent tank	Offsite by approved contractor	Managed as per all similar existing waste streams
Organic solvent washings from post process equipment cleaning	07 05 04	Cleaning	1 to 2 ton in 2022 2 to 4 tons in future years	Production scheduling dependent – some months will be zero, while one month might be the full annual quantity	Waste solvent tank	Offsite by approved contractor	Managed as per all similar existing waste streams

1 All organic solvent waste will be disposed of off site for recovery or incineration

11. Emissions to Atmosphere

11.1 Process emissions

11.2 Vent listing

11.3 Abatement and Treatment and Recovery Systems

11.4 Emissions to the Environment from Unit Operations

11.5 Emissions monitoring

11.1 Process Emissions

Process emissions will be combined into the main header system and directed to a dual scrubber system and then directed to the Waste Air Treatment Plant (Thermal Oxidiser).

11.2 Vent Listing

Vent No.	Building	Description	Major	Minor	Potential	Connected to Header
A1-7	Thermal Oxidiser vent	Thermal Oxidiser	✓	-	-	Combination of all vents in header system

11.3 Abatement and Treatment and Recovery Systems

All relevant process vents are connected to vent header/abatement system.

11.4 Emissions to the Environment from Unit Operations

Emissions from Reaction Synthesis

During normal operation of a reaction, controlled emissions may result from the following operations

- Inerting a vessel with nitrogen
- Chemical reaction
- Charging liquids to a vessel
- Applying vacuum
- Applying heat
- Transferring contents from one vessel to another
- Filling bulk tanks

The following procedures are applied to control the emissions

- Condensers are cooled using Cooling Water

Emissions during a Malfunction

- Bursting disc rupture
- Failure of the cooling medium to condenser's
- Failure of cooling medium to reactor.
- Emissions during a vent failure.
- Any potential new malfunctions shall be identified as part of the HAZOP.

11.5 Emissions Monitoring

As all process vents are connected to the dual scrubber system emission monitoring from the proposed new product shall take place at A1-7 (Thermal Oxidiser stack). Any samples shall be taken and analysed as per routine method.

12 Emissions to Surface Water

There are no emissions to surface water as a result of this process.

13 Emissions to Sewer

There are no emissions to sewer as a result of this process.

14 Emissions to Ground

There will be no emissions to ground as a result of this process.

15 Noise

There will be no additional noise sources added as part of this process.

16 Waste Management

Although a new product is being produced, the type of wastes generated will not vary from the waste currently being produced now. There will therefore be no new requirements for the handling, storage, and disposal of waste. There should not therefore, be any significant adverse environmental impact resulting from the disposal of waste from this project. As the proposed new process will be run in existing equipment and replaces existing production while it is running, there will not be an increase in the amount of overall waste being produced.

17 Environmental Considerations

Where appropriate, Sigma-Aldrich Ireland Ltd. has sought to use the most cost-effective methods of reducing its environmental impact.

The following waste minimization technologies as outlined in the relevant Guidance Note for the Chemical Sector will be used.

a) Technologies for load minimization

I **Optimisation of Condenser Efficiency**
Checks will be carried out before each vacuum distillation on major items of equipment to ensure air leakage is kept to a minimum.

II. **Inventory Control**
Where possible, only the amount of chemical used in the process will be ordered.
There are regular stock checks done on raw materials inventory
There is a computerised inventory listing

Quantities of raw materials used are specified on batch sheets to avoid overuse of materials.

III. Separation of Cooling Water, Storm Water and Process Effluent
Storm water is kept separate to effluent and cooling water is cooled in cooling towers and recirculated for reuse.

b) Technologies for Containment of Emissions

I. Reactor operation is via computerised system to reduce the risk of Operator error.
II. Vent collection from all major items of equipment into the centralised scrubber system prior to further treatment.
III. Bunding of all stored materials with separate bunding for incompatibles
IV. A Sprinkler System on Bulk tank storage

c) Technologies for Recovery and Recycle

I. Waste solvent sent off site is recycled where possible and reused as fuel where possible.

II. Re-use in another industry

III. Solvents, steel paper, glass, pallets, are reused/recycled in other industries.

d) Technologies for Treating Air Emissions

I. Selective chemical reaction scrubbers are used e. g. caustic scrubbing for acid removal.

e) Technologies for Treating Water Emissions

I.	Primary treatment:	pH correction/ neutralization
II.	Secondary treatment:	Biological degradation of effluent
III.	Tertiary treatment:	Settleability of final effluent

f) Technologies for Treatment and Disposal of Wastes

I. **Incineration:** Toxic and dangerous waste which is unsuitable for recovery shall be sent offsite for reuse as fuel or will be incinerated.

18 Accidental Emissions

All tanks are bunded so that in the event of a spill arising all material shall be contained. All bunds shall be constructed in accordance with the agency's guidelines on bund construction as detailed in the Agency's guidance note for the Annual Environmental Report.

All control equipment is maintained and calibrated in accordance with manufacturer's instructions and inspected and tested regularly as part of the sites Preventative Maintenance Programme.

The onsite emergency plan shall be reviewed to take into account any new emergency situations arising on site. The firewater retention tank shall enable any contaminated effluent to be diverted to the firewater retention tank. The effluent can be analysed prior to feeding into the wastewater treatment plant at a pre-controlled rate.

Any contaminated surface water from this area will be detected by an online TOC meter. If levels greater then 100 ppm TOC are detected the diversion valve will divert this contaminated water to the firewater retention tank. The effluent can be analysed prior to feeding into the wastewater treatment plant at a pre-controlled rate.

Accidental air emissions shall go to the combined vent header system. Any abnormal/elevated emissions shall be detected by the online FID detector.

19 Training

Operator training for the new product manufacture will be carried out on-site and will be fully documented

20 Cessation of Activity

The site's Residual Management Programme (Closure, Restoration and Aftercare Management plan) will not be affected as a result of this new process.

21 Site Management and Control

A copy of the following is available:

- Sigma Aldrich Ireland Ltd. Environmental, Health and Safety Policy.
- Organisational charts.
- ISO14001 Overview Manual