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New Product Introduction Treatment – EPA Notification

"Project MEABH"

18 August 2022

Priority: Urgent

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CONTENTS

1. Introduction

ThermoFisher Scientific is planning the introduction of a new product (Project MEABH to the Cork site) for research and development. The product to be manufactured relates to the treatment of lung disease. This project is similar in scale and nature to other R&D notifications approved by the EPA i.e. small scale relative to the main products portfolio manufactured within the main production buildings. The validation campaign for Project MEABH stages 1 -4 is proposed to commence on the 26th September 2022 in the site R&D Building 9.

As with all R&D projects the priority of this notification is urgent.

This request for approval in accordance with Condition 1.4 is in keeping with the guidelines from the EPA[1] on seeking alterations which state that:

"*An activity or process at an installation solely for research, development or testing of new products and processes are excluded and may be considered and approved by OEE. New products or processes at an installation adequately controlled by the conditions of the licence may be considered and approved by OEE.*"

The product will be manufactured in 4 Stages at the Cork Facility, resulting in the manufacture of approximately 44 kg of product per batch. The process is similar to many current and previous process stages manufactured at the Cork facility. Many of the common bulk solvents are being used and standard unit operations are being employed in existing infrastructure within R&D Building 9. No changes to site management, infrastructure or control are required.

Within the existing buildings, the process uses existing modules and associated vent lines, drainage lines and abatement measures.

See Figure 1.1 for Site Layout and location of the proposed process stages. In terms of environmental operation and compliance, this process does not require a new main or minor emission point and can be readily facilitated and controlled within the existing Conditions and limits of the sites IE Licence.

[1] https://www.epa.ie/pubs/advice/licensee/Licence%20Alteration%20Guidance%20rev%20MOC%2021-06-19.pdf

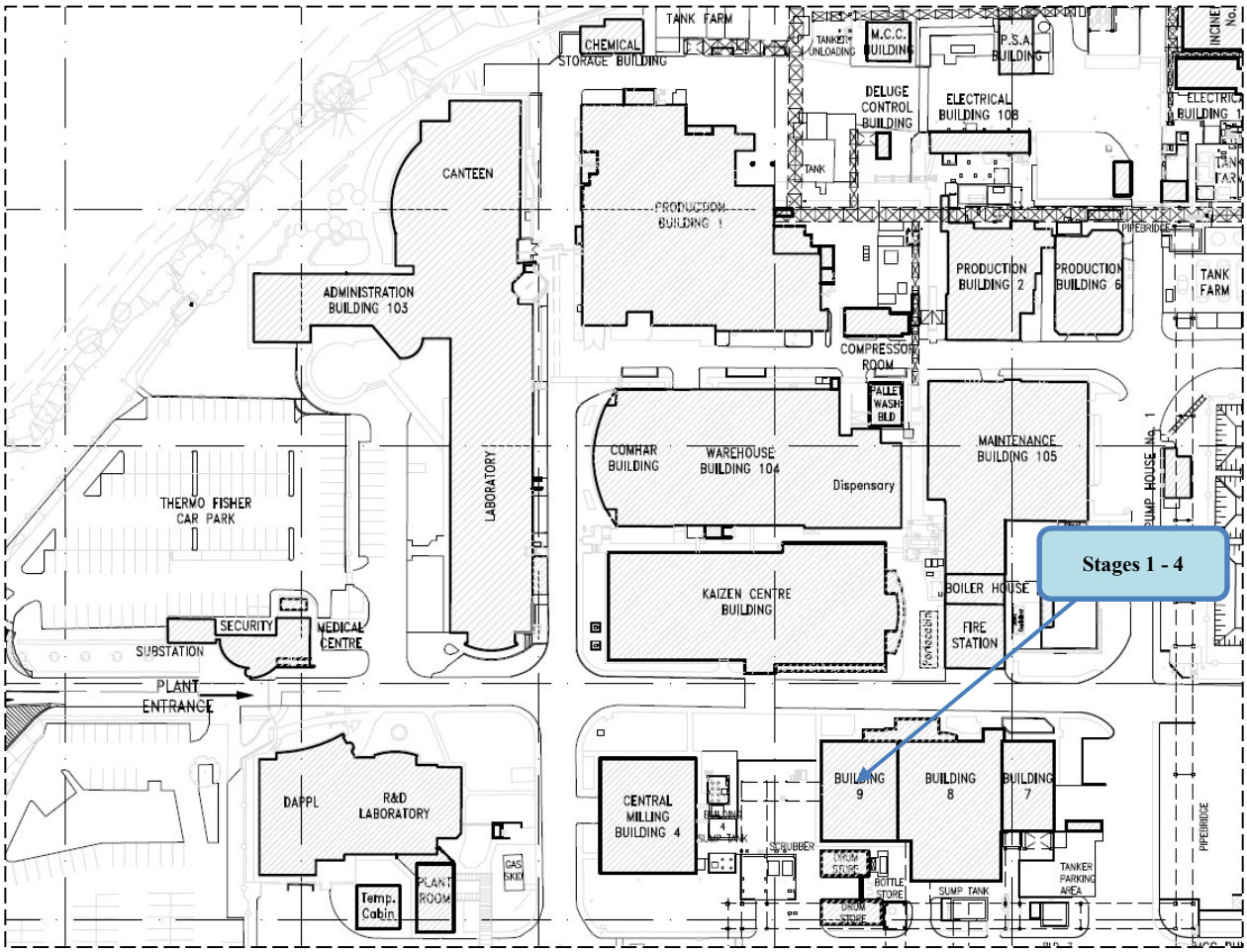

Figure 1.1 Site Layout and Location of Proposed Process for Project MEABH

2. Process Description

As outlined above, there is no change to the range of processes to be carried out in Building 9. The proposed product will be generated in 4 stages with each stage comprising a number of unit operations.

The following main unit operations will occur in the proposed process stages:

- Charging of solvent and reagents
- Mixing in standard vessels
- Chemical reaction
- Distillation
- Separation

- Drying in filter dryer
- Milling
- Storage of final product in product warehouse

Raw materials outlined in Table 2.1 will be subjected to various physical and chemical changes in order to produce the required chemical in the correct form. As a result, solid, liquid and gaseous emissions are generated. These emissions are subjected to physical and chemical treatment to remove any environmentally sensitive substances in accordance with IE Licence Reg. No. P0004-06 prior to discharge from the facility.

No changes to the existing abatement, treatment or recovery systems are required.

The associated environmental emissions for Project MEABH are outlined in Figure 2.1.

TFS have reviewed the sites raw materials database and no new H phrases arise from the new raw materials on site. All new wastes to the incinerator are assessed in terms of compatibility with current waste streams as per standard operating procedure ENVP-063 Bulk Waste Characterisation and Storage Compatibility.

In addition, the incinerator burner management system and other critical safety interlocks are monitored and controlled by a Hima-Sella Programmable Logic Controller (PLC-19-004). PLC-19-004 is a dedicated Safety System associated with the incinerators. This will shut down the incinerator in the event of a safety parameter exceedance.

Figure 2.1 Project MEABH Associated Environmental Emissions

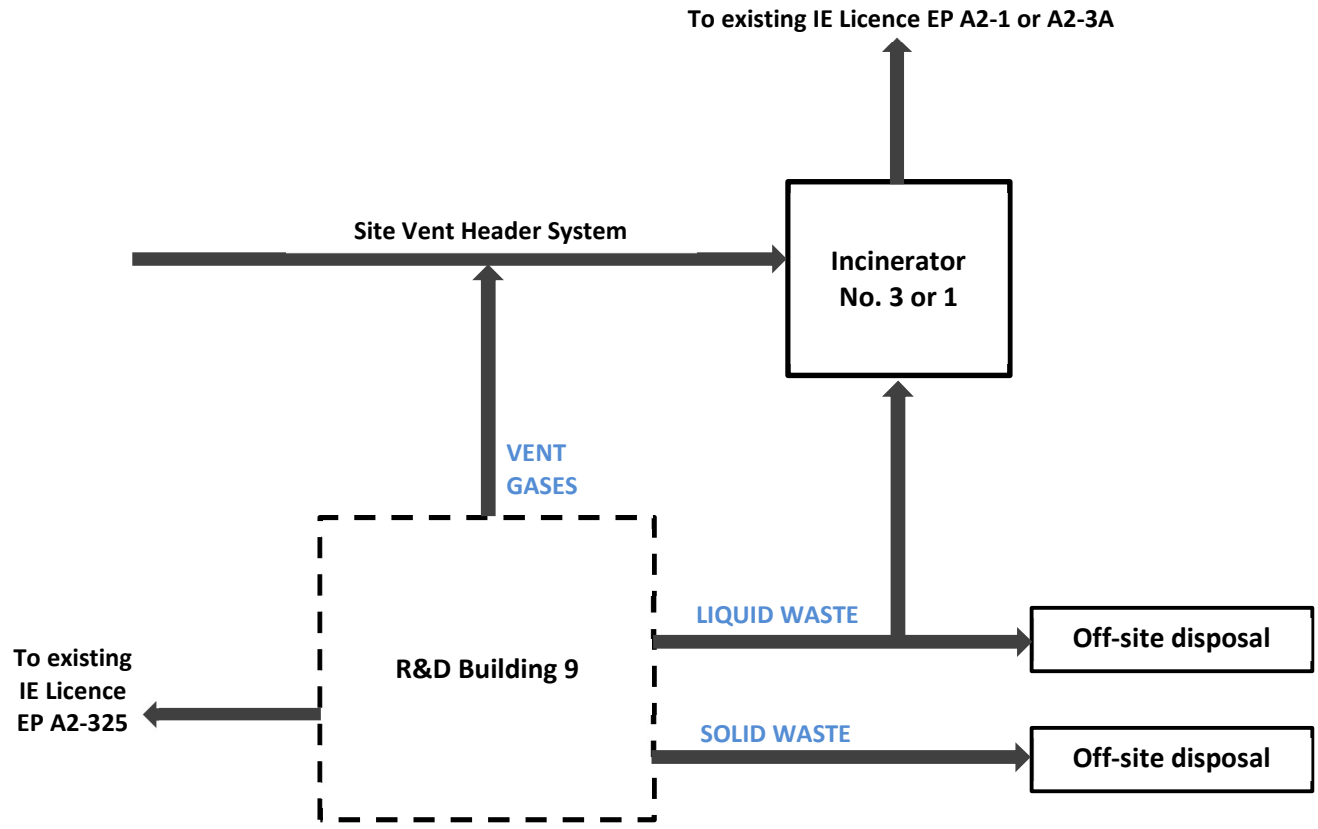

Table 2.1 Raw Materials Associated with Project MEABH

Raw Material	New or Existing to Site	SDS Hazard Phrases (Further details in attachment for new chemicals)
Stage 1		
N-methyl pyrazole	New	H226, H315, H319
Dioxaborolane	New	H226, H315, H319, H335
n-Hexyl lithium in hexane	Existing	EUH014, H225, H250, H260, H304, H314, H315, H318, H336, H361f, H373
THF	Existing	H225, H302, H319, H351, H335/H336
Glacial acetic acid	Existing	H226, H314

Raw Material	New or Existing to Site	SDS Hazard Phrases (Further details in attachment for new chemicals)
Acetonitrile	Existing	H225, H302, H312, H319, H332
Sodium Hydroxide (NaOH)	Existing	H290, H314
Stage 2		
Meabh Stage 1	New	H302, H315, H319, H335
Iodo Acid	New	n/a
Palladium-118Cl2(dtbpf)	New	H315, H319, H335
Triethylamine	Existing	H225, H302, H312, H314, H332, H335
Acetonitrile	Existing	H225, H302, H312, H319, H332
N-acetyl-L-cysteine (N.A.N.H.)	Existing	H319
Sulfuric acid	Existing	H290, H314, H315, H318, H319
Stage 3		
Meabh Stage 2	New	Not classified
1,1'-Carbonyldimidazole (CDI)	New	H302, H314, H360D
Sulfone amine	New	n/a
Acetonitrile	Existing	H225, H302, H312, H319, H332
Stage 4		
MPH966 (Meabh Stage 3)	New	Not classified
para-toluenesulfonic acid	New	H314, H318
Acetonitrile	Existing	H225, H302, H312, H319, H332
MPH-966 (API)	New	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

3. Emissions

3.1 Emissions to Atmosphere

There are no new main or minor emission points to atmosphere. As outlined above, the process will use existing modules and associated vent lines and abatement measures. As illustrated in Figure 2.1, all organic vapours from the process will be vented to the onsite abatement system incinerator IN1931 or incinerator IN1951 (Licensed emission points A2-1 and A2-3A) via each buildings vent header system.

Venting from any dust handling activities such as solids charging, solids dig out, filters, dryers and from milling will be double HEPA filtered and routed to existing IE Licenced emission point A2-325 (Building 9).

3.1.1 Parameters from the Process

Parameters expected to arise in the emissions to air from the new process before it reaches the onsite abatement system (incinerator IN1931/ incinerator IN1951 (Licensed emission points A2-1/A2-3A)) are outlined in Table 3.1 along with the associated IE Licence ELVs.

Table 3.1 Parameters from the proposed new process to incinerator IN1931/ incinerator IN1951

Gaseous Waste pre abatement	Chemical Formula	Combustion Products	ELV in Licence Daily Average (mg/m³)
Stage 1			
Traces of solvents: THF, Hexane, acetonitrile, isopropyl alcohol	C_4H_8O C_6H_{14} C_2H_3N C_3H_8O	CO, CO_2, H_2O, NO_X	CO: 50 NO_X: 200
Stage 2			
Traces of solvents: acetonitrile, sulfuric acid, triethylamine	C_2H_3N H_2SO_4 $C_6H_{15}N$	CO, CO_2, H_2O, SO_2, NO_X	CO: 50 SO_2: 50 NO_X: 200

Gaseous Waste pre abatement	Chemical Formula	Combustion Products	ELV in Licence Daily Average (mg/m³)
Stage 3			
Traces of solvents: acetonitrile	C_2H_3N	CO, CO_2, H_2O, NO_X	CO: 50 NO_X: 200
Stage 4			
Traces of solvents: acetonitrile	C_2H_3N	CO, CO_2, H_2O, NO_X	CO: 50 NO_X: 200

It is assumed the maximum concentrations are above the relevant BAT threshold values and appropriate abatement in the form of incineration is being employed. As this is a batch process, gaseous emissions from this process to the vent header system and incineration are not continuous.

In both incinerators on site (A2-1 and A2-3A) waste liquids and vent gases are incinerated at a temperature of 1150°C, in 5% excess oxygen and a two second residence time to ensure complete destruction of all organic components to CO_2 and H_2O. In addition, NO_X and SO_2 would be anticipated from N and S containing wastes. No other combustion products are expected from the burning of liquid wastes and vent gases from the proposed process.

The following ELVs and continuous monitoring are in place within the IE Licence for both incinerators to address combustion products from all wastes incinerated.

Parameter	Units	Half Hour Average		Daily Average	10-minute average
Carbon monoxide (CO) Note 1	mg/m³	100		50	150
		Column A	Column B		
Total dust	mg/m³	30	10	10	-
Volatile organic compounds expressed as total organic carbon	mg/m³	20	10	10	-
Hydrogen chloride (HCl)	mg/m³	60	10	10	-
Hydrogen fluoride (HF)	mg/m³	4	2	1	-
Hydrogen bromide (HBr)	mg/m³	5	3	2	-
Sulphur dioxide (SO_2)	mg/m³	200	50	50	-
Oxides of Nitrogen (NO and NO_2 expressed as NO_2)	mg/m³	400	200	200	-

Parameter	Sampling Period	Emission Limit Value
Cadmium (as Cd) + thallium (as Tl), and their compounds Note 2	30minute – 8-hour sample	Total 0.05 mg/m³
Mercury (as Hg) and its compounds Note 2	30minute – 8-hour sample	0.05 mg/m³
Antimony (as Sb), arsenic (as As), lead (as Pb), chromium (as Cr), cobalt (as Co), copper (as Cu), manganese (as Mn), nickel (as Ni), and vanadium (as V) and their compounds Note 2	30minute – 8-hour sample	Total 0.5 mg/m³
Dioxins/furans (TEQ) Note 3	6 – 8-hour sample	0.1 ng/m³

No ELV including the flow ELV is likely to be exceeded during the manufacture of the new product. For context, Incinerator No. 3 was designed to burn up to 10,000 MT of hazardous waste per year and Incinerator No. 1 7,000 MT within the limits of our IE Licence. In 2021, a total of 4,710 MT of hazardous waste in total was burned on site. Therefore, there is significant spare capacity in terms of compliant incineration on site.

Notwithstanding the above, incinerator performance and emissions profiles will be monitored carefully during each new campaign on site.

It is not possible to estimate the pre-abatement particulate emissions concentrations for the emission point from the dust handling activities i.e. A2-325. There is no change in the dust handling activities and the same abatement measures (double HEPA filtration with >99.99% removal efficiencies) will be in place as for the particulate emission points attached to the process on site.

For existing emission point A2-325 the following monitoring programme will be put in place with 'Element Ireland' (ISO 17025 accredited) and in accordance with the requirements of EPA Air Emission Monitoring Guidance Note AG2.

Monitoring for total particulate matter (TPM), velocity and volumetric flow rate will be carried out in accordance with the following standards:

	Monitoring			
Parameter	Standard	Technical Procedure	Sampling Status	Testing Lab
Total Particulate Matter	EN 13284-1	CAT-TP-01	MCERTS	EET
Water Vapour	EN 14790	CAT-TP-05	MCERTS	EET
Velocity & Vol. Flow Rate	EN 16911-1 (MID)	CAT-TP-41	MCERTS	EET

Results will be compared against the following emission limits as specified within Schedule B.1 of the IE Licence to demonstrate that the emissions remain minor in nature:

Parameter	Emission Limit Value
Total Particulates	1 mg/m^3
Pharmaceutical dust - as active ingredient	0.15 mg/ m^3 at a mass flow >1 g/hour.

The above emission limit values apply to the following emission points as outlined in Schedule C.1.2 of the sites IE Licence:

Emission Point Reference Nos.: A2-12, A2-13, A2-14, A2-112, A2-116, A2-123, A2-124, A2-128, A2-146, A2-149, A2-150, A2-152, A2-162, A2-163, A2-166, A2-301, A2-303, A2-308, A2-316, A2-317, A2-318, A2-319, A2-320, A2-325, A2-328, A2-338, A2-339, A2-340, A2-341, A2-342, A2-343, A2-344, A2-345, A2-346, A2-347, A2-348, A2-351, A2-352, A2-353, A2-354, A2-355, A2-357 - A2-366 (inclusive).

Parameter	Monitoring Frequency	Analysis Method/Technique
Total particulates	Annually	Isokinetic/Gravimetric

3.2 Aqueous Emissions

As illustrated in Figure 2.1, aqueous waste will be routed to:

- either of the on-site incinerators IN1931/IN1951 which includes Licensed air emission points A2-1/A2-3A and internal aqueous emission point W1.
- Or offsite to an approved and permitted hazardous waste facility.

Table 3.2 provides an overview of the constituents of the aqueous waste.

Table 3.2 Liquid Waste Stream to On Site Incinerator

Waste Stream, L/Batch, Approx Composition	Chemical Formula	Combustion Products	ELV in Licence Daily Average (mg/m³)
Stage 1			
Stage 1 aqueous layer waste, 100 L. Major constituents: Water, acetic acid, THF Trace: PBP (Meabh Stage 1), IPA and boron containing species	$C_2H_4O_2$ C_4H_8O $C_{10}H_{17}BN_2O_2$ C_3H_8O	CO, H_2O, CO_2, NO_X	CO: 50 NO_X: 200
Stage 1 distillate waste, 600 L. Constituents: THF, Acetonitrile and caustic	C_4H_8O C_2H_3N NaOH	CO, H_2O, CO_2, NO_X	CO: 50 NO_X: 200
Stage 2			
Stage 2 mother liquors waste, 700 L. Major constituents: Acetonitrile, THF, water Trace: Pyrazole acid (Meabh Stage 1), 1-methyl pyrazole, palladium contained residues, inorganic iodide boron and sulphate by-products	C_4H_8O C_2H_3N $C_{18}H_{14}F_3N_3O_3$ SO_4^{2-} $C_4H_6N_2$ Pd^{2+} I^-	CO, H_2O, CO_2, NO_X, HF, SO_2	CO: 50 NO_X: 200 HF: 1 SO_2: 50
Stage 2 cake washes waste, 400 L. Major constituents: water, Acetonitrile. Trace: Meabh Stage 1, 1-methyl pyrazole, palladium contained residues, inorganic iodide, boron and sulphate by-products.	C_4H_8O $C_{18}H_{14}F_3N_3O_3$ SO_4^{2-} $C_4H_6N_2$ Pd^{2+} I^-	CO, H_2O, CO_2, NO_X, HF, SO_2	CO: 50 NO_X: 200 HF: 1 SO_2: 50

Waste Stream, L/Batch, Approx Composition	Chemical Formula	Combustion Products	ELV in Licence Daily Average (mg/m^3)
Stage 3			
Stage 3 mother liquors & wash waste, 1,100 L. Major constituents: Acetonitrile, water. Trace: MPH966 Free base, sulfone amine, imidazole, imidazole hydrochloride	C_2H_3N $H_8N_2O_4S$ $C_{28}H_{33}ClN_2O_6S_2$ $C_3H_4N_2$ $C_3H_5ClN_2$	CO, H_2O, CO_2, NO_X, SO_2, HCl	CO: 50 NO_X: 200 SO_2: 50 HCl: 10
Stage 4			
Stage 4 mother liquors & wash waste, 1,200 L. Major constituents: Acetonitrile. Trace: MPH966, p-TSA.	C_2H_3N $H_8N_2O_4S$ $C_7H_8O_3S$	CO, H_2O, CO_2, NO_X, SO_2	CO: 50 NO_X: 200 SO_2: 50

3.3 Emissions to Sewer

There are no emissions to sewer from the ThermoFisher site.

4. Solid Waste Generation and Disposal

All solid waste will be sent off site for incineration, in line with existing site procedures and IE Licence requirements.

Table 4.1 Solid Waste for off-site incineration

Solid Waste Material	Quantity (kg)	Further Treatment	Recovery / Reuse / Recycle	Final Disposal
Bags/liners etc.	2.5 drums approx. per batch	n/a	n/a	Off-site incineration

5. SDS Hazardous Data for <u>new</u> chemicals, raw materials and products to site

Item	H Phrase
n-Methyl pyrazole	**SECTION 2: Hazards identification** **2.1 Classification of the substance or mixture** **Classification according to Regulation (EC) No 1272/2008** Flammable liquids (Category 3), H226 Skin irritation (Category 2), H315 Eye irritation (Category 2), H319 For the full text of the H-Statements mentioned in this Section, see Section 16. **2.2 Label elements** **Labelling according Regulation (EC) No 1272/2008** Pictogram  Signal word: Warning Hazard statement(s) H226: Flammable liquid and vapour. H315: Causes skin irritation. H319: Causes serious eye irritation.

Item	H Phrase
Dioxoborolane	**SECTION 2: Hazards identification** **2.1 Classification of the substance or mixture** **Classification according to Regulation (EC) No 1272/2008** Flammable liquids (Category 3), H226 Skin irritation (Category 2), H315 Eye irritation (Category 2), H319 Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335 For the full text of the H-Statements mentioned in this Section, see Section 16. **2.2 Label elements** **Labelling according Regulation (EC) No 1272/2008** Pictogram  Signal word: Warning Hazard statement(s) H226: Flammable liquid and vapor. H315: Causes skin irritation. H319: Causes serious eye irritation. H335: May cause respiratory irritation.

Item	H Phrase
Meabh Stage 1	**SECTION 2: Hazards identification** **2.1. Classification of the substance or mixture** **Classification according to Regulation (EC) No. 1272/2008 [CLP]** Acute toxicity (oral), Category 4 — H302 Skin corrosion/irritation, Category 2 — H315 Serious eye damage/eye irritation, Category 2 — H319 Specific target organ toxicity – Single exposure, Category 3, Respiratory tract irritation — H335 Full text of H- and EUH-statements: see section 16

Item	H Phrase
Iodo Acid	**HAZARDS IDENTIFICATION** Most Important Hazards — Safety information please read this sheet carefully Health Effects — No specific information available regarding the toxic effects in Human beings. Physical and Chemical Hazards — NA Specific Hazards — NA

Palladium-188Cl_2

SECTION 2: Hazards identification

To the best of our knowledge, the toxicological properties of this product have not been thoroughly investigated.

2.1 Classification of the substance or mixture

Product definition : Mono-constituent substance

Classification according to Regulation (EC) No. 1272/2008 [CLP/GHS]

The product is not classified as hazardous according to Regulation (EC) 1272/2008 as amended.

See Section 11 for more detailed information on health effects and symptoms.

2.2 Label elements

Signal word : No signal word.

Hazard statements : No known significant effects or critical hazards.

Precautionary statements

Prevention : Not applicable.

Response : Not applicable.

Storage : Not applicable.

Disposal : Not applicable.

Hazardous ingredients : 1,1' - bis (di-tert-butylphosphino) ferrocene Pd dichloride

Supplemental label elements : Not applicable.

Annex XVII - Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles : Not applicable.

Special packaging requirements

Containers to be fitted with child-resistant fastenings : Not applicable.

Tactile warning of danger : Not applicable.

Item	H Phrase
Meabh Stage 2	**SECTION 2: Hazards identification** **2.1. Classification of the substance or mixture** **Classification according to Regulation (EC) No. 1272/2008 [CLP]** Not classified **Adverse physicochemical, human health and environmental effects** No additional information available **2.2. Label elements** **Labelling according to Regulation (EC) No. 1272/2008 [CLP]** No labelling applicable **2.3. Other hazards** PBT: not yet assessed vPvB: not yet assessed

Item	H Phrase
MPH966 Free base (Meabh Stage 3)	**SECTION 2: Hazards identification** **2.1. Classification of the substance or mixture** **Classification according to Regulation (EC) No. 1272/2008 [CLP]** Not classified **Adverse physicochemical, human health and environmental effects** No additional information available **2.2. Label elements** **Labelling according to Regulation (EC) No. 1272/2008 [CLP]** No labelling applicable **2.3. Other hazards** PBT: not yet assessed vPvB: not yet assessed

Item	H Phrase
Carbonyldimidazole (CDI)	Pictogram  Signal word Danger Hazard statement(s) H302 Harmful if swallowed. H314 Causes severe skin burns and eye damage. H360D May damage the unborn child. **SECTION 2: Hazards identification** **2.1 Classification of the substance or mixture** **Classification according to Regulation (EC) No 1272/2008** Acute toxicity, Oral (Category 4), H302 Skin corrosion (Sub-category 1B), H314 Serious eye damage (Category 1), H318 Reproductive toxicity (Category 1B), H360D For the full text of the H-Statements mentioned in this Section, see Section 16. **2.2 Label elements** **Labelling according Regulation (EC) No 1272/2008**
Sulfone amine	**HAZARDS IDENTIFICATION** Most Important Hazards: Safety information please read this sheet carefully Health Effects: No specific information available regarding the toxic effects in Human beings. Physical and Chemical Hazards: NA Specific Hazards: NA

Item	H Phrase
p-toulenesulphonic acid	

Section 2 - HAZARDS IDENTIFICATION

2.1 Classification of substance or mixture according to Regulation (EC) No 1272/2008 (CLP) :

Human health hazard categories and codes :	Eye Damage Skin Corrosive	Category 1; H318 Category 1C ; H314

2.2 Labeling according to Regulation (EC) No 1272/2008 (CLP) :

Hazard Pictogram :	**Signal Word : Danger**  GHS05 Corrosion
Hazard Statements :	H314: Causes severe skin burns and eye damage.
Precautionary Statements :	P280: Wear protective gloves/protective clothing/eye protection/face protection. P260: Do not breathe dust/fume/gas/mist/vapours/spray. P301+P330+P331: IF SWALLOWED: rinse mouth. Do NOT induce vomiting. P303+P361+P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower. P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310: Immediately call a POISON CENTER/doctor if you feel unwell.
2.3 Other hazards :	Not known.

Item	H Phrase
Meabh API	**SECTION 2: Hazards identification** **2.1 Classification of the substance or mixture** **Classification (REGULATION (EC) No 1272/2008)** Not a hazardous substance or mixture. **2.2 Label elements** **Labelling (REGULATION (EC) No 1272/2008)** Not a hazardous substance or mixture. **2.3 Other hazards** This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher. See Section 11. May form explosible dust-air mixture if dispersed. **2. HAZARDS IDENTIFICATION** **2.1. Classification of the substance or mixture** **EU Classification according to Regulation (EC) No 1272/2008:** Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008. **Adverse physical, human health and environmental effects:** See sections 9, 10, 11 and 12.