

**PROJECT NAME** EU CTF Facility

**PROJECT NUMBER** A20DB037

**SUBJECT** IPPC License Requirements

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ITEM	DESCRIPTION	ACTION	
		BY	DATE
<b>1.0</b>	<b>Basis for Project Note</b>		
1.1	This project note has been generated to assess the requirement for the new European Cell Therapy Facility (CTF) to have an Integrated Pollution Prevention Control (IPPC) license.	Note	
1.2	The basis for this assessment is the Industrial Emissions Directive (IED), 2010/75/EU.	Note	
<b>2.0</b>	<b>CTF Overview</b>		
2.1	The European CTF will be a Biotech manufacturing facility for the production of Autologous Cell Therapy biopharmaceutical products.	Note	
2.2	The manufacturing process is of the Personalised Medicine scale and involves processing the Apheresate taken from an individual patient to produce medicine for that patient.	Note	
2.3	Each manufacturing batch size relates to an individual patient and is therefore small scale (manufacturing operations carried out in bench top equipment). The EU CTF will be a commercial facility with multiple patient batches being processed in parallel.	Note	
2.4	The manufacturing process is a biological based manufacturing process. There will be a certain quantity of chemicals and solvents used at the facility, but these will be associated with the laboratory operations.	Note	
2.5	The manufacturing operations will not produce any Volatile Organic Carbon (VOC) gaseous emissions. A low level of VOC emissions will be created in the laboratories which will be discharged to atmosphere via	Note	

	the fumehood exhausts but, based on the ambient operating conditions and the very high dilution air volumes, these emissions will be well below threshold limits. A calculated assessment of these emission values will be submitted as part of the main environmental permit application.		
2.6	<p>The manufacturing process will produce a level of aqueous biowaste but none of this will be discharged to the environment:</p> <ul style="list-style-type: none"> <li>• The aqueous biowaste that is generated by the process will be &lt;5L per unit operation and will be collected in single-use bags in a closed manner.</li> <li>• Each bag of biowaste will be securely sealed within the manufacturing suites before being transported to a Biowaste collection area within the facility.</li> <li>• The biowaste will then be either: <ul style="list-style-type: none"> <li>○ Securely packaged in a clearly labelled Biohazardous Waste container and then removed from site by a specialist contractor for offsite decontamination and disposal</li> <li>○ Or; decontaminated onsite via heat decontamination in an autoclave and then removed for offsite disposal as inert waste by a suitable waste handling contractor</li> </ul> </li> </ul>	Note	
2.7	<p>The facility will generate other non-biological aqueous waste. The non-biological aqueous waste is not generated by the specific manufacturing operations but some of this waste will be generated by manufacturing related activities:</p> <ul style="list-style-type: none"> <li>• Waste media and buffer solution: <ul style="list-style-type: none"> <li>○ Certain media and buffer solutions will be made up in a Single-Use Mixer (SUM) and then aliquoted into individual batch quantities</li> <li>○ The heel of each SUM batch will be drained to waste</li> </ul> </li> <li>• Cleaning of the manufacturing suites: <ul style="list-style-type: none"> <li>○ The manufacturing suites will be cleaned using dilute detergent solutions (made-up using purified water)</li> <li>○ The cleaning solutions will be drained to waste following clean down of each suite</li> </ul> </li> </ul>	Note	
2.8	<p>Non-biological aqueous waste will also be generated by other non-production related sources:</p> <ul style="list-style-type: none"> <li>• Laboratory sinks</li> <li>• Waste-water generated by the site utility systems</li> </ul>	Note	

2.9	The non-biological aqueous waste will drain to a waste collection vessel with pH neutralisation capability. The neutralised waste-water will discharge to the local municipal sewer system.	Note	
2.10	Certain chemicals will be used for sanitisation of equipment and utensils prior to moving into a suite and clean down of work areas post use. These chemicals will be sprayed onto the surface of the item or area being sanitised and then wiped off following a pre-defined residence time. The main chemicals that will be used for these operations will be: <ul style="list-style-type: none"> <li>• Sporklenz</li> <li>• 70% IPA</li> </ul>	Note	
<b>3.0</b>	<b>Requirements for an IPPC License</b>		
3.1	The IED, 2010/75/EU is used as the guidance document to determine whether a manufacturing facility being constructed in Holland requires an IPPC license.	Note	
3.2	An IPPC license is required when one or more of the activities stated in Annex 1 of the IED apply, and the emissions created by the applicable activity are above the specified threshold limit.  Note: Some IPPC categories do not have a threshold.	Note	
3.3	If a facility is subject to an IPPC license then Best Available Techniques (BAT) in accordance with the applicable BAT Reference Document (BREF) need to be applied.	Note	
3.4	The section in Annex I of the IED that relates to pharmaceutical products is under Section 4: <ul style="list-style-type: none"> <li>• Section 4 - Chemical Industry: <ul style="list-style-type: none"> <li>○ For the purpose of this section, production within the meaning of the categories of activities contained in this section means the production on an industrial scale by chemical or biological processing of substances or groups of substances listed in points 4.1 to 4.6</li> </ul> </li> <li>• 4.5: Production of pharmaceutical products including intermediates</li> </ul>	Note	
3.5	It can be seen in the line item above that the description of Annex I, Section 4 does state 'by chemical or biological processing'.  However, for biological based processing to fall into the category of requiring an IPPC license, the manufacturing process will need to produce	Note	

	VOC emissions and (or) liquid waste to the level where they are subject to BAT, based on the applicable BREF.																																				
3.6	The applicable BREF for pharmaceutical manufacturing is the Organic Fine Chemicals BREF.	Note																																			
3.7	Section 2 of the Organic Fine Chemical BREF (Applied Processes and Techniques) outlines the specific process operations that are applicable to this BREF.	Note																																			
3.8	<p>The following table is taken from Section 2 of the BREF:</p> <table><tr><th>Unit processes</th><th>Unit operations</th></tr><tr><td>Acylation</td><td>Charging reactants and solvents</td></tr><tr><td>Addition</td><td>Inerting</td></tr><tr><td>Alkylation</td><td>Reaction</td></tr><tr><td>Carboxylation</td><td>Discharging</td></tr><tr><td>Carboxymethylation</td><td>Crystallisation</td></tr><tr><td>Condensation</td><td>Filtration</td></tr><tr><td>Diazotisation and modification of the diazo group</td><td>Product washing</td></tr><tr><td>Esterification</td><td>Drying</td></tr><tr><td>Halogenation</td><td>Extraction</td></tr><tr><td>Nitration</td><td>Electro dialysis</td></tr><tr><td>Oxidation</td><td>Absorption</td></tr><tr><td>Rearrangements</td><td>Phase separation</td></tr><tr><td>Reduction</td><td>Adsorption</td></tr><tr><td>Substitution</td><td>Distillation</td></tr><tr><td>Sulphitation</td><td>Milling</td></tr><tr><td>Sulphonation</td><td>Apparatus cleaning</td></tr></table> <p><b>Table 2.1: Main unit processes and unit operations used in industrial fine organic chemistry</b></p> <p>None of the Unit Processes or Unit Operations shown in Table 2.1 above are applicable to the new EU CTF.</p> <p>The manufacturing operations will be carried out in small scale single-use systems which will be securely packaged and removed from site by a suitable waste contractor for offsite disposal. Apparatus (equipment) cleaning operations, is therefore not applicable.</p>	Unit processes	Unit operations	Acylation	Charging reactants and solvents	Addition	Inerting	Alkylation	Reaction	Carboxylation	Discharging	Carboxymethylation	Crystallisation	Condensation	Filtration	Diazotisation and modification of the diazo group	Product washing	Esterification	Drying	Halogenation	Extraction	Nitration	Electro dialysis	Oxidation	Absorption	Rearrangements	Phase separation	Reduction	Adsorption	Substitution	Distillation	Sulphitation	Milling	Sulphonation	Apparatus cleaning	Note	
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4.0	<b>Summary and Conclusion</b>																																				
4.1	The new EU CTF will carry out small scale biologically based manufacturing processes for the production of biopharmaceuticals.	Note																																			
4.2	The manufacturing operations will not produce any level of VOC emissions.	Note																																			
4.3	The relatively small volumes of aqueous biological waste that will be produced by the facility will be removed from site by a suitable waste management contractor and will not be discharged to the environment.	Note																																			
4.4	The Organic Fine Chemical BREF does not apply to this facility and therefore BAT is not applicable.	Note																																			

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4.5	Annex I of the IED does not therefore apply to the EU CTF.	Note	
4.6	The new EU CTF should not therefore require an IPPC license.	Note	