Attachment-4-8-1-Operational Report

AstraZeneca UK Ltd.
Project Joyce
IE0313009-22-RP-0013, Issue: A

Customer Project Number: TH6100259
Customer Document Number: APIC-X-XX-RP-PMG-EN-0013

Issue date: 09 Feb 2024

Document Sign Off

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CURRENT ISSUE					
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Signature	**Authorised Electronically**				
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PREVIOUS ISSUES							
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1 Introduction

1.1 General

This Operational Report has been completed to support a review of Alexion and AstraZeneca's IE Licence (Application Ref. No. LA011910) to accommodate development works at their existing pharmaceutical manufacturing campus in College Business & Technology Park, Blanchardstown Road North, Blanchardstown, Dublin 15, D15R925. It fulfils the information requirements as per Section 4.8 of the Industrial Emissions (IE) Licence Review Application Form. It is presented under the main headings as per outlined below to reflect the requirements of the EPA's "*Licence Application Form Guidance: Industrial Emissions (IE), Integrated Pollution Control (IPC) and Waste (Version 2.1, June 2021)".*

Alexion Pharma International Operations Limited (hereinafter referred to as Alexion) is a subsidiary of AstraZeneca. AstraZeneca is a global, science-led biopharmaceutical business delivering innovative medicines to millions of patients worldwide. AstraZeneca is expanding its internal capability for late stage development and early commercial supply of small molecule Active Pharmaceutical Ingredient (APIs) to meet the future growing drug pipeline. As part of this expansion, AstraZeneca are constructing a new API manufacturing facility at the existing Alexion manufacturing campus in College Business and Technology Park, Blanchardstown, Co. Dublin. The new API manufacturing facility will be operated by AstraZeneca Ireland Limited and will target the high value, low volume, highly potent products within the AstraZeneca organisation's future portfolio.

The existing campus is operational 24/7 and employs approximately 983 no. personnel, across a range of manufacturing, operations, engineering, laboratory, HR, finance and related functions. The proposed API Manufacturing facility will require a total of 105 additional operational staff and contractor personnel.

This Operational Report describes the plant, methods, processes, ancillary processes, abatement, recovery and treatment systems, and operating procedures for all activities to be carried out at the existing Alexion Bulk Drug Substance (BDS) manufacturing facility and the new AstraZeneca API manufacturing facility at the campus.

1.2 Overview of Existing Biopharmaceutical Manufacturing Facility and Site Layout

Alexion's existing campus was acquired from IDA Ireland, for the purpose of establishing a pharmaceutical facility within the College Business and Technology Park (College Park), approximately 12km north-west of Dublin City Centre, adjacent to the Technological University Dublin – Blanchardstown.

The existing Biopharmaceutical (abbreviated to Biopharma) manufacturing facility was developed in two phases as follows;

Phase 1 constructed between 2014 to 2015 comprises:

- a four-storey Administration Building;
- single storey laboratory building;
- packaging / warehouse;
- utility building and spine corridor; and
- a data centre.

Phase 2 constructed between 2015 to 2019 comprises:

- a four storey Bulk Drug Substance (BDS) manufacturing building;
- two-storey Central Utilities Building (CUB);
- single storey warehouse;
- an electrical substation building and associated support buildings;

- external utilities yard; and
- wastewater pre-treatment area.

The ancillary external utilities within the utility yard consist of:

- a single storey control building;
- single storey pump house;
- single storey electrical building;
- process water and wastewater storage tanks;
- bunded water treatment chemical tanks;
- bunded diesel storage tank;
- and back-up emergency diesel generators.

Refer to *Site Layout Plan Drawing Ref. No. IE0313009-22-DR-0002* and Figure 1.1 for an overview of the site layout.

The four-storey BDS building was designed to manufacture cell culture derived drug substances. It is a multi-product facility producing mammalian cell culture based protein therapeutics with both campaign and concurrent manufacturing capabilities. These proteins are produced to the bulk or formulated state, and filled for shipping from the site.

Manufacturing of pharmaceutical products at the existing Biopharma manufacturing facility commenced in 2019. The facility is operational 24 hours a day, 7 days per week and manufactures cell culture derived drug substances – Soliris® (eculizumab); Strensiq® (asfotase alfa); Ultomiris® (ravulizumab-cwvz) and Andexxa® (andexanet alfa).

The existing facility is owned and operated by Alexion only who was granted an Industrial Emissions (IE) licence (Licence Reg. No. P1030-01) by the EPA in September 2016 for the following scheduled activity, subject to conditions, under the Environmental Protection Agency Act 1992 (as amended):

"Activity 5.16 The production of pharmaceutical products including intermediates"

In April, 2024 the IE Licence (Reg. No. P1030-01) was transferred to Alexion Pharma International Operations Limited & AstraZeneca Ireland Limited.

A detailed description of the operations at the main buildings and elements of the existing Biopharma manufacturing facility is included in Section 3 of this report.

1.3 Overview of the API Expansion Development

Planning permission was received in June 2023 for the expansion of the existing Alexion and AstraZeneca campus at College Business & Technology Park to include a new small molecule Active Pharmaceutical Ingredient (API) manufacturing facility and ancillary buildings/works (together referred to as the API Expansion development) (Planning Ref. No. FW22A/0300).

The API Expansion development will comprise a new five-storey production building and supporting facilities including a four-storey extension to the existing labs and a four-storey extension to the existing warehouse which will manufacture small molecule API products to meet Alexion and AstraZeneca's future product needs.

A planning application (Planning Ref. No. FW23A/0230) was submitted in August 2023 to amend and alter the API Expansion development granted under Planning Ref. No. FW22A/0300.

The proposed amendments included: change in the locations of the permitted Solvent Tank Storage Area and the permitted Waste Management Facility; slight increase in size of the API Manufacturing Building and Chemicals Material Store; reduction in the size of the new Laboratory Building and the Warehouse expansion; repositioning the approved thermal oxidiser abatement unit and its associated c. 46 m high flue stack; and other ancillary amendments, including

amendments to the façade of the permitted API Manufacturing Building. A decision to grant planning permission for the amended development was issued by Fingal County Council in Sept 2023.

It is envisaged that the site expansion will add approximately 105 No. personnel to the current campus workforce when operational.

The API Expansion permitted under planning ref. numbers FW22A/0300 and FW23A/0230 and comprises the following (as illustrated in Figure 1.1):

- a new 5 storey Active Pharmaceutical Ingredient (API) manufacturing building;
- a new single storey chemical materials store;
- a new 4 storey laboratory building;
- extensions to the existing warehouse building;
- a bunded solvent tank storage area including tanker loading and unloading yard;
- a chemical materials yard including liquid nitrogen storage tank, scrubbers, and a thermal oxidiser abatement unit complete with flue stack;
- a manufacturing building utilities yard including chillers and other miscellaneous plant and equipment;
- a medium voltage electrical building and solvent area control building;
- an extension to the existing high level pipe rack connecting all existing and new buildings and yard areas;
- 3 No. new diesel generators and 3 No. new bunded diesel storage tanks;
- modifications to site infrastructure, including; addition of 200 new car park spaces on the eastern side of the site, expansion of the site's existing storm water attenuation / fire water retention pond, and alterations and extensions to internal site roads, paving and underground services;
- enhancements to the site internal and boundary landscaping; and
- a new Waste Management Facility Building & roofed drum wash area

The API expansion which will be located on the northern side of the existing campus and will comprise a total gross floor area of approximately 21,530 m^2.

The overarching approach to the site integration strategy is a 'one site' philosophy. Where practical and safe general site functions will be shared with the existing manufacturing facility.

The API Manufacturing Building will be accessed through the existing main administration building reception / spine corridor.

A Just in Time (JIT) warehouse will be included in the API manufacturing building with the central warehouse expansion providing shipping/receiving; sampling; storage and weigh/dispense and movement of materials between buildings.

An In Process Control (IPC) lab will be located in the API Manufacturing Building with the new laboratory building providing central labs for Quality Assurance/Quality Control (QA/QC) functions. There will be an office area and kitchenette within the API Manufacturing Building with the existing main administration building providing canteen, town-hall and large conference facilities.

The new Laboratory Building will be connected to the existing Laboratory on its western site, while the existing Warehouse will be extended to its eastern side. A new car park will be constructed to the east of the site, and there will be an extension to the existing attenuation pond in the southeast of the site. There will also be a hazardous Chemical Material Store in close proximity to the API building, and a new tank farm for bulk solvents located to the east of the campus.

The European Communities (Control of Major Accident Hazards Involving Dangerous Substances) Regulations, 2015, S.I. No. 209 of 2015, or COMAH Regulations will apply to the site post expansion as the new API manufacturing facility will result in increasing the hazardous material inventory of the site above the thresholds set out in the COMAH Regulations, making the site a 'Lower Tier' establishment. Management of storage of hazardous materials at the site will be described in detail in the site's COMAH Risk Assessment which will be submitted to the HSA prior to the operation of the API Manufacturing facility.

As a lower tier establishment, the site will be required to establish a safety management system detailed in a Major Accident Prevention Policy (MAPP) and compile a Safety Report which identifies the chemicals of concern and must include an assessment of the extent and severity of the consequences of each identified major accident possibility.

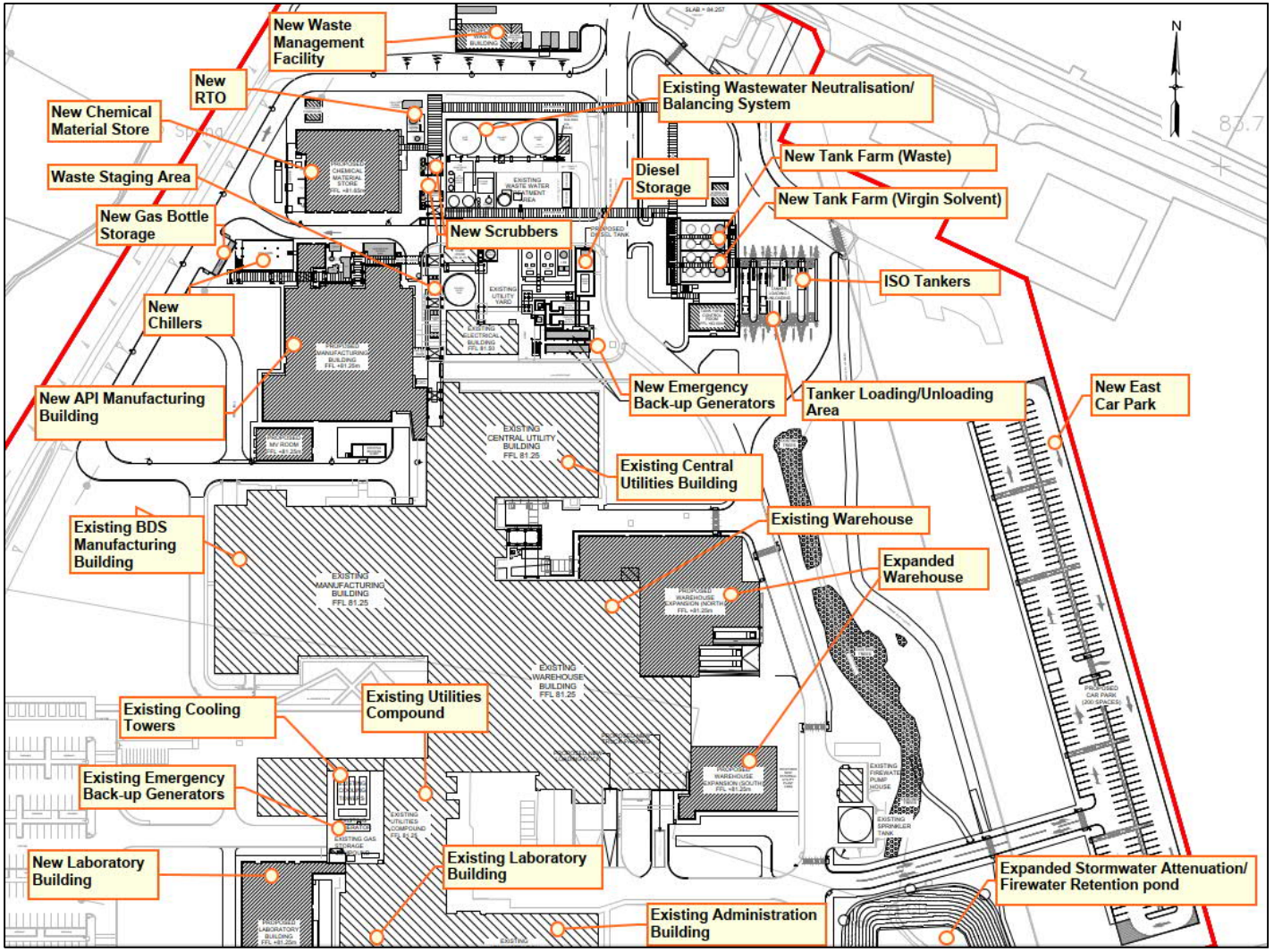

Figure 1.1: Alexion and AstraZeneca Campus Layout (Excerpt from IE0313009-22-DR-0002 Site Layout Plan annotated for report)

2 Description of Plant, Methods and Processes

2.1 Overview of the Existing Biopharma Main Process Steps and Systems

2.1.1 Introduction

At the existing Bulk Drug Substance (BDS) manufacturing building, there are currently two seed trains for cell culture and one train for purification. The plant can accommodate one additional seed train for cell culture and one additional train for purification for future installation.

Process Flow is product dependent with some degree of variance from product to product. Representative process flow diagrams (Figures 2.1, 2.2 and 2.3) and process descriptions (Section 2.1.2 to 2.1.4) are provided here.

The primary process steps per production train are as follows;

- Upstream: Inoculum Preparation, Cell Culture & Harvest (refer to Figure 2.1)
- Downstream: Purification and Product Formulation (refer to Figure 2.2)

The overall process is represented in a block flow diagram in Figure 2.3.

All of these primary process steps are located within cleanrooms constructed within the footprint of the four storey BDS manufacturing building. These operations are supported by the following process areas;

- Media preparation (internal);
- Buffer preparation (internal);
- Column packing (internal);
- Component preparation (internal);
- Wastewater management (internal and external);
- Process utility supplies (internal and external).

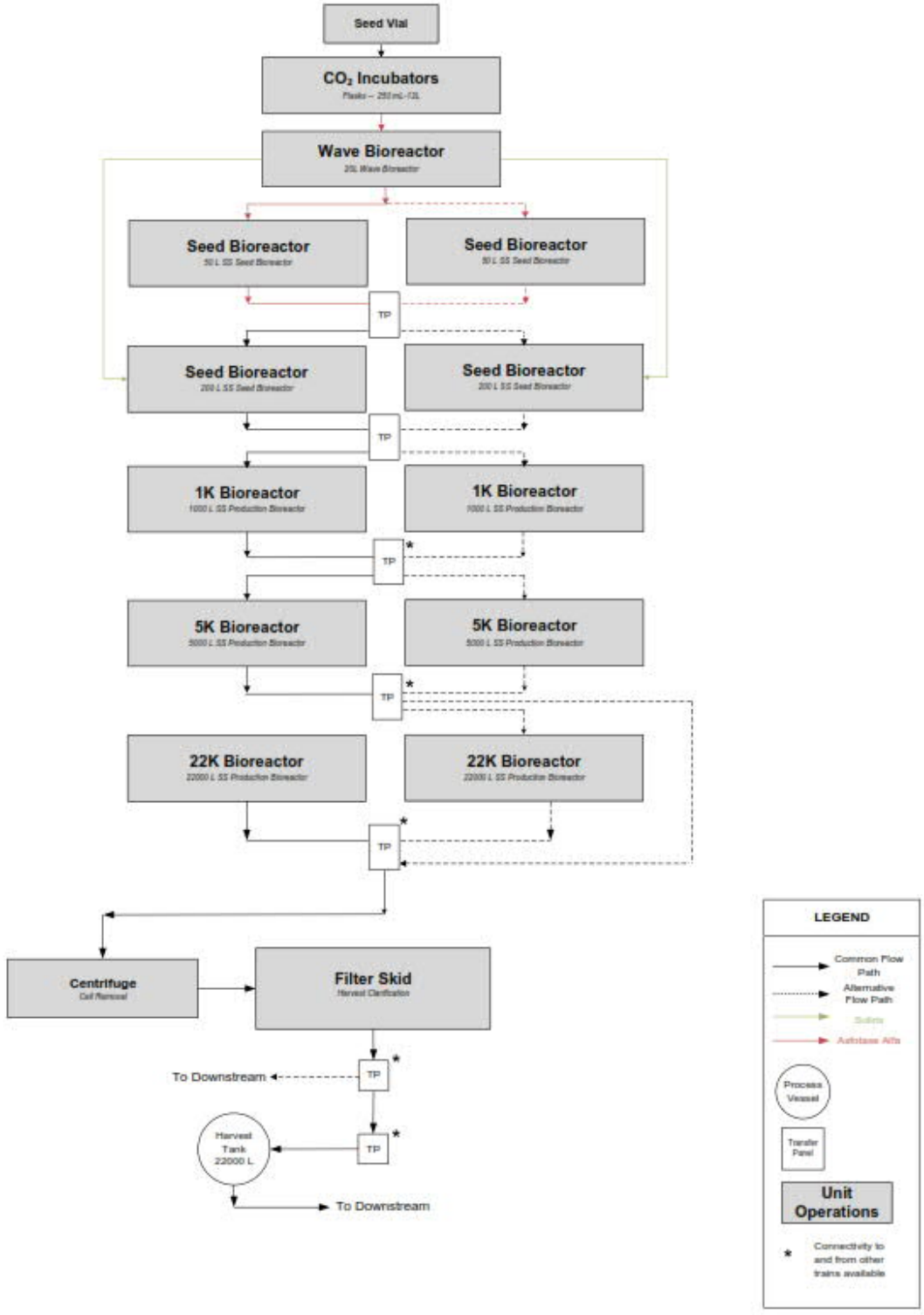

Figure 2.1: Upstream Block Flow Diagram

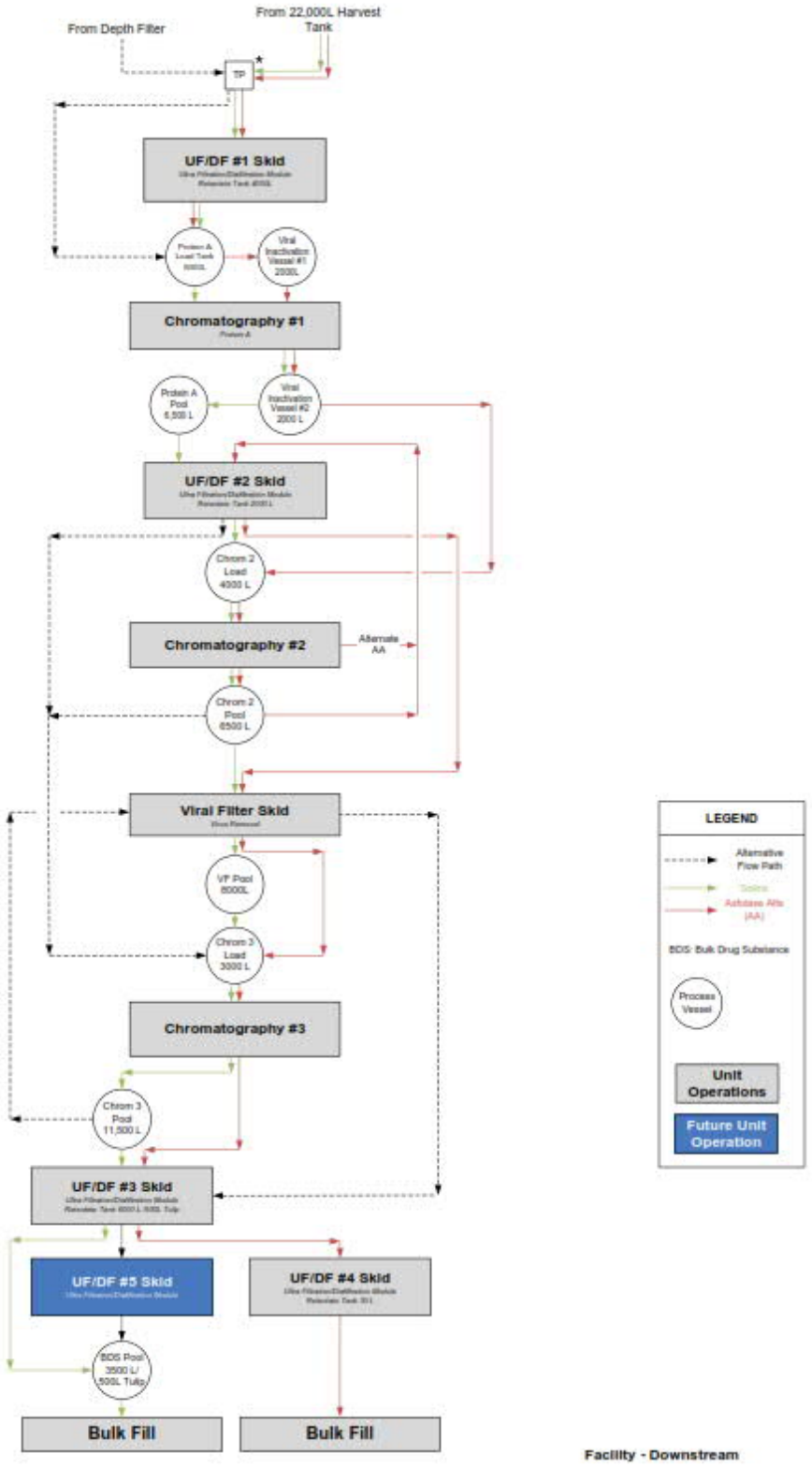

Figure 2.2: Downstream Block Flow Diagram

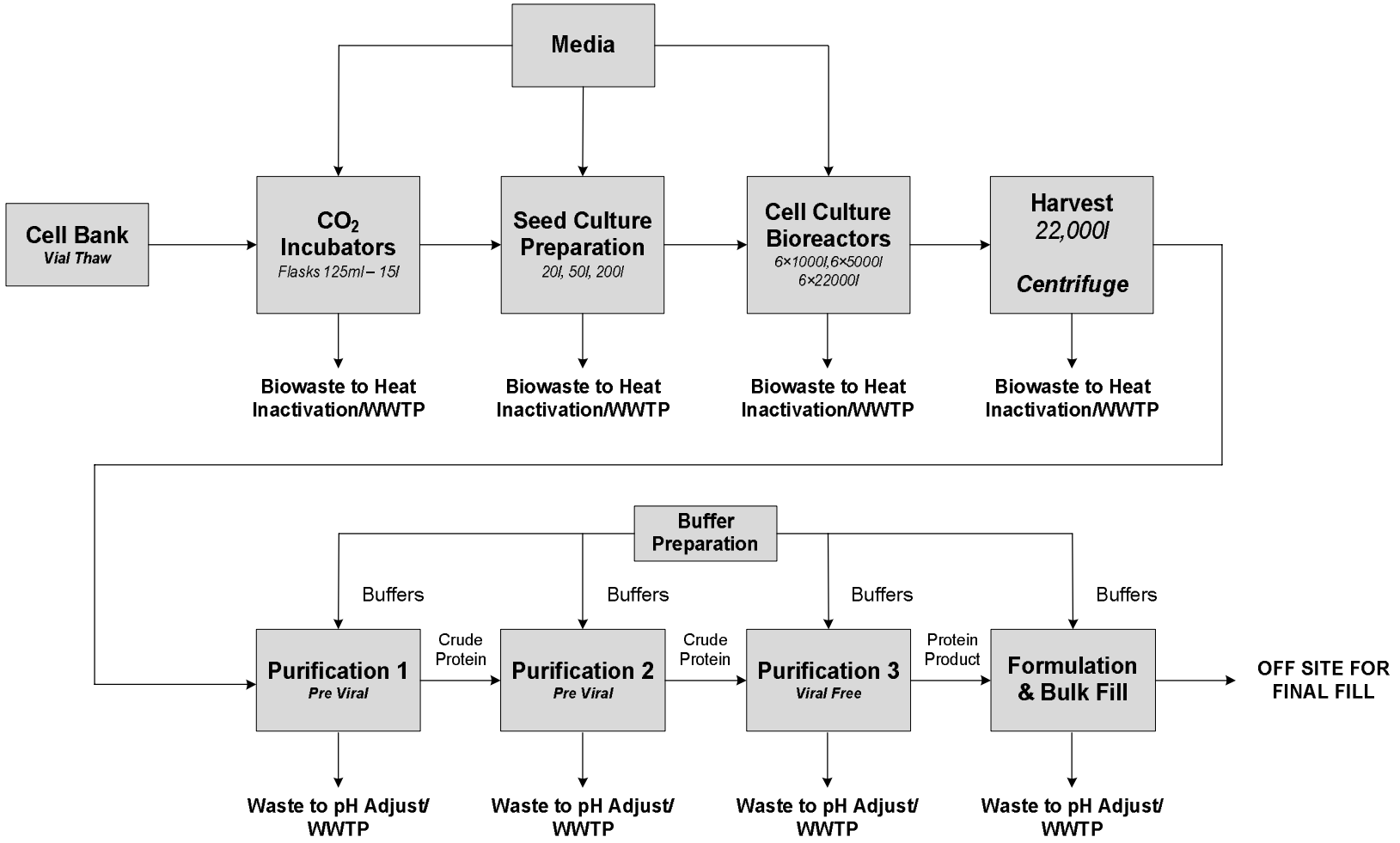

Figure 2.3: BDS Overall Process Flow Diagram

2.1.2 Upstream: Cell Culture (Inoculum Preparation, Bioreactor Suit (Seed Bioreactors & Production Bioreactors)

The manufacturing process starts with the growth of genetically modified mammalian cells (GMMs) in a series of shaker flasks and cell bag bioreactors to seed bioreactors of increasing size and on to three large scale (1,000L, 5,000L and 22,000L) production bioreactors. These are the cells that are used to produce the therapeutic proteins used as medical products.

Cell culture commences with thawing of the working cell bank vial and expanding the cells in suspension cultures containing growth medium. Cells are expanded in shake flasks, roller bottles and/or spinner flasks of increasing size until enough cells are available for transfer to a stainless steel bioreactor or cell bag bioreactor. Cells from multiple larger spinner flasks or a cell bag bioreactor can be used to inoculate a stainless steel bioreactor. The cell bag bioreactor and incubators and shakers for the shake flasks are located in the inoculum laboratory.

Continued seed expansion (three to five-day growth cycle per step) is completed in the bioreactor hall. The culture (spinner flask or cell bag) from the inoculum lab is used to inoculate the appropriate size stainless steel bioreactor. The culture from each stainless steel bioreactor is used to inoculate the next stage of cell growth. After inoculating the 22,000L production bioreactor, the cells continue to grow and product is expressed extracellularly. Protein expression may be continuous or may require an induction step (thermal shift, change in media, etc.). Growth phase is typically 11 to 14 No. days until target harvest parameters are reached. If required, the 5,000L bioreactor can be used as a production bioreactor and harvest from this vessel may be sent to the centrifuge.

2.1.3 Upstream: Harvest

The purpose of the harvest step is to remove cells and suspended cell debris from the product-containing conditioned media (from the 22,000L or 5,000L production bioreactors). Cells and cell debris are removed by centrifugation. Cell debris from the centrifuge is discharged to the biowaste system for decontamination. The process stream is then clarified by depth filtration and clarifying filtration prior to the first purification step in the downstream area.

2.1.4 Downstream: Purification

In the downstream area the harvested cell culture solution is purified using a series of chromatography skids and columns, a viral inactivation procedure, ultrafiltration skids (for concentration and diafiltration) and viral filtration skid. After purification, the product solution is then adjusted to the final bulk concentration and transferred to bulk drugs substance containers.

The purification process consists of four main areas:

- Purification Room 1 where Ultra Filtration UF-1, Virus Inactivation and Protein A Liquid Chromatography are located;
- Purification Room 2 where Chrom 2, UF-2 and Virus Removal by Nanofiltration are located;
- Purification Room 3 where Chrom 3 is located;
- Purification Room 4 where Final Formulation and Bulk Fill are located.

Purification Room 1

The primary objective of the ultrafiltration UF-1 step is to concentrate and diafilter (if necessary) the harvested cell culture solution. After the concentration and diafiltration step is completed the product solution is filtered into the protein A load vessel and viral inactivated in viral inactivation No. 1 vessel if required prior to performing protein A chromatography.

The primary objective of the protein A step is to remove cell-derived impurities, such as host cell proteins and nucleic acids. The protein A column is cycled multiple times to purify the entire batch of product. At the conclusion of the process, the column and skid are stored in a bacteriostatic solution. The eluate is then filtered and transferred to the viral inactivation No. 2 vessel, by cycle, if

required for virus inactivation. Virus inactivation is a low pH step. After virus inactivation, the solution is transferred to purification room 2 for the next purification step.

Purification Room 2

The primary objective of the ultrafiltration UF-2 step is to concentrate and diafilter the product solution for the next purification phase. When the product solution is ready it is transferred into the chromatography 2 load vessel. The primary objectives of the chromatography 2 step are the removal of host cell proteins and other process derived impurities. At the conclusion of the process, the column and skid are stored in a bacteriostatic solution. As required by the process, the UF-2 step can be completed before or after the chromatography 2 step.

The concentrated product is then transferred from the UF-2 retentate tank through the virus filtration skid and the filtered pool is collected in the virus filtration pool vessel, the chromatography 3 load vessel both located in purification room 3, or UF-3 retentate tank in purification Room 4 for further processing.

Purification Room 3

The primary objectives of the chromatography 3 step are the removal of impurities. The product is eluted from the column and collected into the chromatography 3 pool vessel or UF-3 retentate tank and diluted with buffer. At the conclusion of the process, the column and skid are stored in a bacteriostatic solution. As required by the process, the viral filtration step can be completed before or after the chromatography 3 step.

Purification Room 4 (Formulation and Bulk Fill)

The objectives of the final ultrafiltration/diafiltration purification step are to concentrate the protein from the previous step and to diafilter the product into the formulation buffer to the correct concentration, producing the BDS.

The final product is then filtered into a series of 1L BDS bags for product storage. The final product is then filtered and filled into 100L BDS bags for product storage.

Each product stored BDS is transferred to a 2-8°C cooler, quarantined and stored within cold rooms within the final product storage area of the warehouse until final release for filling at the off-site finish/fill facility.

2.2 Overview of the New Small Molecule API Manufacturing Process

The new API manufacturing facility has been designed to be a safe, smart, sustainable, Good Manufacturing Practice (GMP) compliant facility that is flexible and expandable with a mixture of traditional batch API and continuous flow API production processes. The APIs will be manufactured using small molecule technology which can only be completed using a chemical process.

The overall layout of the API Manufacturing facility and a description of the key unit operations for each of the processes are outlined in Figure 2.4 and Figure 2.5. It is noted that the design intent is for closed processing through-out the production areas regardless of the background environment / process step.

The new API manufacturing facility will be a multi-product facility targeting early commercialisation and late stage development of products, and as such, future products are not currently known. Therefore, the facility has been designed with flexibility to make it a multi-product, multi-functional facility. To assist with the design of the facility, the design envelope has been based on two API products (Osimertinib and Acalabrutinib) which may be produced when the plant becomes operational in early 2026.

This API Manufacturing facility will be a Good Manufacturing Practice (GMP) production facility and GMP standards of construction and finish will apply. All incorporated engineered containment systems and operational procedures will comply with the requirements of GMP standards and guidance.

2.2.1 Batch Processing

In the context of the API manufacturing facility, batch processing refers to the batch processing equipment set for small molecules that are chemically batch-synthesized in classical liquid-phase reactions from GMP starting materials, intermediates and reagents.

The batch equipment will be nominally segregated into a Medium Scale train and a Large Scale train, with the trains having potential for inter-connection via routing stations. The facility will include a range of typical equipment used for charging, synthesis, work-up, isolation, drying and pack-off. There will be 8 No. vessels in the reactor halls with space allocated for 1 No. additional reactor in the large scale. The trains will be based on medium scale with vessel size range from 1000l to 2500l and large scale with vessel size range from 2500l to 6300l.

Each reactor hall will be served by a dedicated charge room. There will be 2 No. flexible intermediate bulk container (FIBC) charge stations per room with space allocated for an additional 2 No. for medium scale and 3 No. for large scale. Below the reactor halls there will be a filter dryer / pack-off stack-up with in line de-lumping. There will be fallow space for a third stack-up which could be a centrifuge / spherical dryer / pack-off or a third filter dryer / pack-off.

A hydrogenator will be located in an annex connected to the main API Manufacturing Building. This will be connectable to each train.

Measure vessels, receivers and vessels for waste are required and will typically be located in a segregated process technical space.

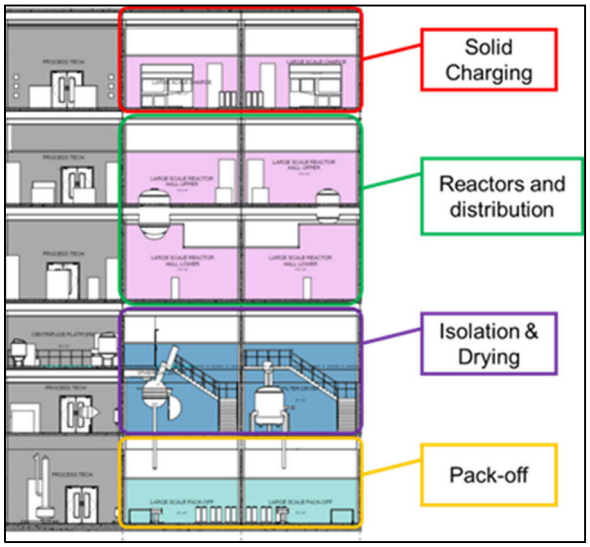

Figure 2.4: Section through the New Manufacturing Building.

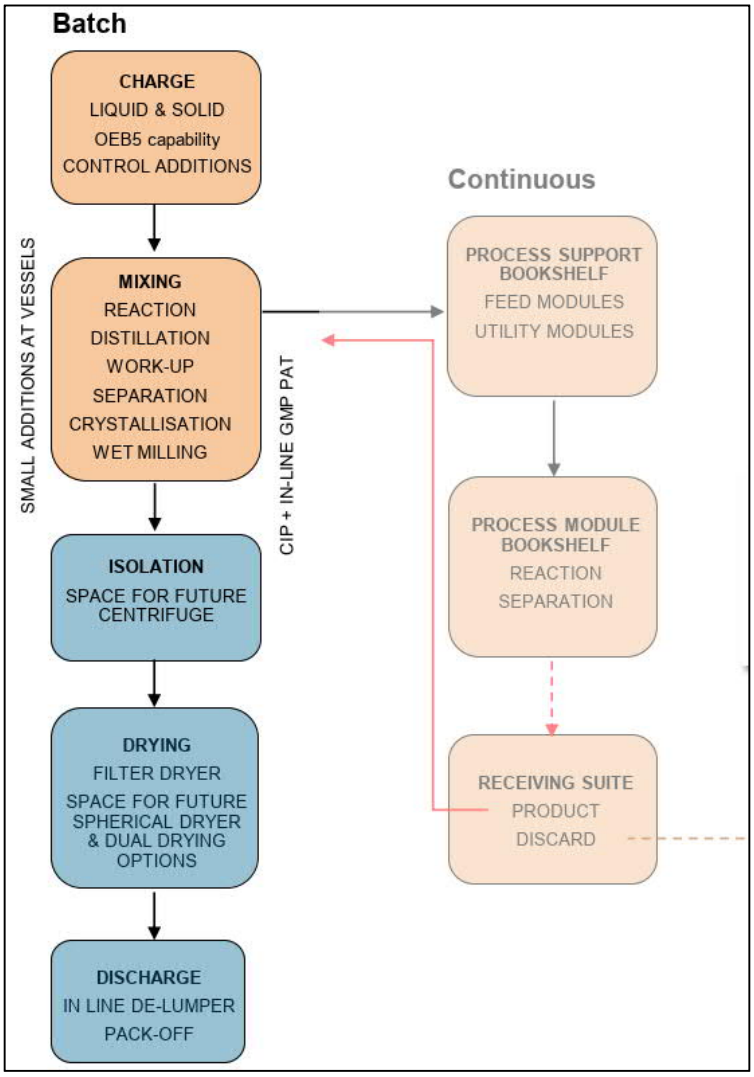

Figure 2.5: API Manufacturing facility Unit Operations

The Batch plant design will allow for a significant degree of configurability and flexibility. The incorporation of routing stations will provide the ability to easily configure process trains to meet the demands of a new manufacturing process.

The design of the new API manufacturing facility will allow for a series of GMP intermediate products that can be manufactured in sequence, on a campaigned basis, using a standard range of reaction chemistries. These intermediate products will be crystallized, isolated, dried, filled and stored in FIBCs for further processing. Subsequently, the intermediate molecule will be returned and further modified, by chemical synthesis until the final API is produced. The final API will be filled into the appropriate containers and stored prior to shipping for drug product processing.

An overview of these batch process unit operations is provided below:

Solid Charging

FIBCs will be used for the handling of large powder charges (> 25 kg) to reactors. FIBC discharge stations located in charging rooms will be used to charge large volume solids to reactors via a stainless steel charge chute. The FIBC discharge station will employ a glovebox to achieve occupational exposure band rating 5 (OEB5) containment during the docking, discharge and undocking processes.

Small volume solids (< 25 kgs) charging includes seed charge to the Crystallisation vessel or small solid additions to other reactor vessels such as catalyst or small volume reactant materials. Small volume solids charging to certain reactors will be enabled by the use of split butterfly valves (SBV) of proven OEB5 containment performance attached to flexible charge bags. The passive half of the SBV will be attached to a flexible charge bag or rigid container. Holders/bag support frames will be employed to assist in charging material from the bag.

After charging, the split valve attached to the charge bag will be recovered and re-used after cleaning.

Liquid Charging

A hard piped, fully automated solvent supply manifold will be provided per batch train. Solvent manifolds are located in the process technical area on the fourth floor. The following liquids may be charged to batch reactors, measure vessels and filter dryers from the manifold:

- Bulk solvent from the tank farm fresh solvent tanks;

- Bulk solvent from the tank farm iso-tankers;

- Solvent from IBC charging stations;

- Water For Operations (WFO).

A flow totalizer located on each inlet to the manifold will enable transfer of a measured amount of solvent to the target vessel. Each inlet will be connected to each vessel via an actuated valve. The transfer line from the solvent manifold to the receiving vessel will be blown through with nitrogen to ensure complete transfer following the liquid charge.

Drum Booths

Drum Booths will provide a contained enclosure from which solvents and liquid reagents in drums may be charged to reactors, measure vessels and filter dryers. A dedicated drum booth will be provided for each batch train. Drum booths are to be located in the process technical area on the fourth floor.

The drum booth will be serviced by an extract fan, which will exhaust air with trace solvent vapours to atmosphere. A vision panel with glove-ports will be incorporated on each door to facilitate critical operations (which require containment) being carried out from outside the drum booth. These will include opening of containers, inserting and removing a lance to drums and opening/closing certain valves.

Measure Vessels

The purpose of the measure vessels will be to provide additional reagent preparation vessels for use in the API reaction section particularly for when controlled rate additions are required. Measure vessels are non-jacketed, non–agitated glass-lined carbon steel tanks that will be employed to prepare and hold liquid solutions for use in the process. They are located in the process technical area on the fourth floor.

Measure vessels are to be supplied with solvent or reagent from the associated batch train solvent manifold or drum booth via an angled dip pipe or sprayball (for vessel flush). Vessels are to be enabled for automated inertion, venting and pressure/gravity transfer to a reactor.

Reactors

Reactions will take place within multi-purpose reactor vessels which have a range of capacities and pooled into trains based on general capacity. The vessels will be industry standard reactors made from either Glass Lined Carbon Steel (GLCS) or Hastelloy. They will be agitated, jacketed, pressure vessels (-1 to 6 barg) equipped with a range of instruments to allow fully automated, recipe driven control of the equipment and Process analytical technology (PAT) determinations. The Reactors will be connected to the routing stations and will be capable of being configured in an arbitrary manner, based on the requirements of the batch.

Each reactor will have a dedicated vertical shell and tube condenser on the reactor overheads. The condenser will be supplied from the cold glycol system via local “tempered” loop with local pump per condenser. This arrangement enables independent temperature control per condenser.

Distillate from the vent condenser may be refluxed back to the reactor or routed to the receiver via the upper routing station. The off-gases from the condenser are routed to an acid or base vent collection header or process vacuum supply. Two reactors per train will have the capability to vent hydrogen off gases (or other flammable gases) direct to external atmosphere.

The reactor heating, cooling and temperature control will be provided via a local jacket services tempered loop drawing from the hot and cold glycol systems.

Additionally any reactor within a train may be employed as a crystalliser.

Receiver vessels

There will be one receiver vessel per batch train. The receivers will be sized based on 60% of the nominal volume of the largest reactor in a train. They will be jacketed, glass lined carbon steel (GLCS), pressure vessels (-1 to 6 barg) with the capability for future agitator installation. They will be located in the process technical area on the first floor.

Receivers are primarily intended for use as distillate receivers and phase separation receivers.

The following inlet routes to receivers are to be provided:

- From Upper routing station (for distillate transfers from reactor condenser);

- From Lower routing station (for phase split transfers from reactor outlet);

- Recirculation route from receiver pump (for receiver cleaning);

Inlets are to be directed to a short dip pipe or a spray ball (for cleaning operations).

Pressure inerting and blanketing functionality with nitrogen is to be provided per receiver. Receiver off-gases are to be routed to an acid or base vent collection header. A “vapour balance” route will be provided to the Upper routing station. This will allow connection of the receiver overheads to a reactor vent route to enable pressure equalisation between the receiver and reactor during a vacuum distillation operation.

Receiver heating, cooling and temperature control will be provided via a local jacket services tempered loop drawing from the hot and cold glycol systems.

Filter Dryer

There will be two Nutsche filter dryers included in the new API manufacturing facility. Each filter dryer will be located in a dedicated GMP Grade D room on the first floor.

Separate heating and cooling circuits will be provided on the filter dryer side, top, base, dust filter and agitator. Heating, cooling and temperature control will be provided via a local jacket services tempered loop drawing from the hot and cold glycol systems.

Operations associated with the filter dryer are: Vacuum/Pressure test; Inertion; Filtration (Deliquoring); Cake wash; Vacuum or convective drying; Product discharge; Cleaning.

A slurry of crystallised product in solvent will be transferred to the filter dryer via the product inlet line direct from the crystalliser or via the lower routing station.

Product will be discharged from the filter dryer to the Pack off station located on the ground floor via a chute arrangement.

Mother Liquor Receivers

Each batch train shall have a single mother liquor receiver associated with it, for purposes of capturing the filtrate from the filter dryer. The Receivers will be non-jacketed, glass-lined carbon steel vessels. They will be located in the process technical area on the ground floor.

Inlet lines from the filter dryer and vacuum skid will be directed to a short dip pipe or a spray ball (for cleaning operations).

Pressure inerting and blanketing functionality with nitrogen will be provided per receiver. Receiver off-gases will be routed to an acid or base vent collection header.

Pack Off

Dried product from the Filter Dryer will be discharged, via a stainless steel chute, to a pack off station.

Dedicated pack off stations will be provided for the medium and large scale trains. They will be located in segregated, Grade D rooms on the ground floor. Product will be charged by weight to FIBCs or drums. The pack off station will be designed to handle a range of FIBC and drum capacities.

The Pack off station will employ a glovebox to achieve OEB5 containment during the filling and undocking process.

(Process) Routing Stations

The Batch processing area of the facility will be configured with routing stations (process manifolds) that will allow for a high degree of plant configurability.

As this will be a high-potency materials plant, connections at the routing stations will only be made/broken during campaign setup and post end of campaign cleaning. During cleaning, some re-configuration may be allowed based on outcomes of risk assessments.

Bag Filters, Extract booths, Wet Mills

Two off Bag filters are to be employed in the Medium and Large Scale Trains for filtration of process fluids. The Bag filters will be located in a once through air extract booth during processing and bag change out. Connections will be made to/from reactor transfer lines via hard piped spools and hoses. An electric heating jacket will be employed when necessary for hot filtrations.

A dedicated extract booth will be provided for each batch train. The extract booth will provide a contained enclosure where filter bags can be changed out. The extract booths will be located in the reactor halls (third floor for medium scale and second floor for large scale). A hoist will be located within the extract booth to enable removal of filter bags.

A single Wet Mill (high shear mixer) will be used in both Medium and Large scale batch trains. The unit will be mounted on a base and moved by pallet truck.

Hydrogenation

A batch hydrogenation reactor will be installed as part of the new API manufacturing facility. The reactor will be located within a separate building located north of the main API Manufacturing Building. The hydrogenation enclosure will be accessed from the ground floor of the API Manufacturing Building via a link corridor. The hydrogenation reactor will be connected to the Large scale batch train via hard piped transfer routes.

The hydrogenation enclosure includes the following equipment:

Catalyst slurry vessel

This will be a stainless steel, non-jacketed vessel complete with a top mounted agitator. The vessel will be located on a platform level above the hydrogenation reactor.

The catalyst slurry for the hydrogenation process will typically be nickel, palladium or platinum. Catalyst slurry will be dispensed to the required weight in one of the drum sampling booths within the Hazardous Material Store. Dispensed catalyst will be charged to the pre-inerted Catalyst slurry vessel via a glovebag. The catalyst will be mixed with water or solvent by agitation within the slurry vessel. The catalyst slurry will then be transferred by gravity to the hydrogenation reactor.

Hydrogenation reactor

This will be a Hastelloy jacketed reactor with top mounted agitator. Process fluids are to be transferred to the reactor from the Large Scale lower routing station. Solvent will be transferred from the Large Scale solvent manifold. There will also be a solvent/reagent inlet from the hydrogenation drum booth.

Hydrogen (or alternative gas for other gas liquid reactions) will be supplied to the reactor from an external hydrogen gas manifold. Catalyst slurry will be charged via a transfer line from the catalyst charge vessel.

The reactor will be fitted with a top mounted agitator with a 2 stage impellor and a dry running nitrogen pressurised double mechanical seal. A gas seal monitoring panel will be provided to control and monitor the agitator seal gas supply.

Samples can be taken from a top mounted educator sampler via a sampling dip pipe. The reactor will have a dedicated vertical Hastelloy shell and tube condenser on the reactor overheads. The condenser will be supplied from the cold glycol system via a local “tempered” loop. Distillate from the condenser will be refluxed back to the reactor.

The off-gases from the condenser will contain hydrogen with potential for solvent vapour and are routed to discharge to atmosphere via a dedicated vent route. The vent line will have a nitrogen sweep and oxygen analyser to ensure it is inert during the venting step.

The reactor heating, cooling and temperature control will be provided via a local jacket services tempered loop drawing from the hot and cold glycol systems. Pressure inerting and blanketing functionality with nitrogen will be provided.

Following completion of the hydrogenation reaction, the reactor contents will be recirculated via a bag filter to remove the catalyst from the process fluid. Process fluid will then be transferred back to a nominated reactor in the Large or Medium Scale process trains via the Large Scale Train Upper Routing Station.

The filter bags containing catalyst will be removed in a drum booth and placed in a drum which is to be sent off-site for catalyst recovery with an appropriately licensed waste vendor.

Hydrogen Charging

The Hydrogen charging arrangement will consist of 2 no. Hydrogen Manifolded Cylinder Pallets connected in a duty/standby arrangement to a gas supply manifold. The hydrogen supply manifold will be located external to the Hydrogenation building. The gas manifold will control the hydrogen supply pressure to 8 Barg. It will also enable automatic change over from the duty to the standby gas supply when the duty gas supply is depleted.

A separate nitrogen supply cylinder will be employed to pressure test the hydrogen transfer line prior to the introduction of hydrogen.

Drum Booth

A drum booth, similar to the design of batch drum booths, is provided to allow contained transfer of drummed solvents and reagents to the hydrogenation reactor. It is also employed for removal of filter bags from the bag filter.

Hydrogenation Emergency Relief Receiver

Emergency vent routes from the Hydrogenation Reactor and Catalyst Slurry vessel are directed to the Hydrogenation Emergency Relief Receiver located external to the Hydrogenation Enclosure.

This is a 5,000L horizontal vessel designed to capture liquid from the process vessels in an over pressure scenario. In this abnormal event, vapour and gases would pass through the receiver to a vent outlet located to the roof of the main API Manufacturing Building.

2.2.2 Continuous Processing

The new API manufacturing facility will also provide the capability for the production of GMP pharmaceutical intermediates by continuous processing.

The continuous processing train will consist of a number of small unit operations (reactors, columns, etc.) arranged per product manufacturing campaign basis (See Figure 2.6). This type of continuous processing of intermediates will provide for rapid turnaround between products and ultimately quick access to products for patients. It is anticipated that approx. 50% of future new product will have more than one stage deploying continuous flow chemistry.

The continuous processing area will be integrated with the batch process trains for dissolving and feeding the starting intermediate and for crystallising, isolating, drying and packing-off the pharmaceutical intermediate manufactured. The Medium Train Batch Upper and Lower Routing Stations will be the interface between the batch process trains and the continuous suite. At a high level, continuous manufacturing will constitute process flow from a batch reactor hall into the process support room through the continuous flow bookshelf and back to the batch reactor hall (via the process support room) for crystallisation prior to isolation, drying and pack-off for the representative process.

The new API manufacturing facility will include for a modular, reconfigurable continuous line for multistep continuous processes containing up to 3 No. reaction steps and 2 No. separation or purification steps. Modules will be swapped in and out depending on the configuration required for each process.

The continuous processing area will consist of 3 processing rooms arranged by a vertical stack-up over first, second, and third floors. A process support room will be located on the third floor and will be used to feed dissolved starting intermediates and other reagents via a transfer-in routing station into the second floor continuous processing room, where arrayed flow modules are housed in bookshelves (Figure 2.6).

The chemical transformations and purification will occur in flow as the molecule passes through the modules. Product streams and divert streams will be collected in vessels below in the first floor process support room for further processing.

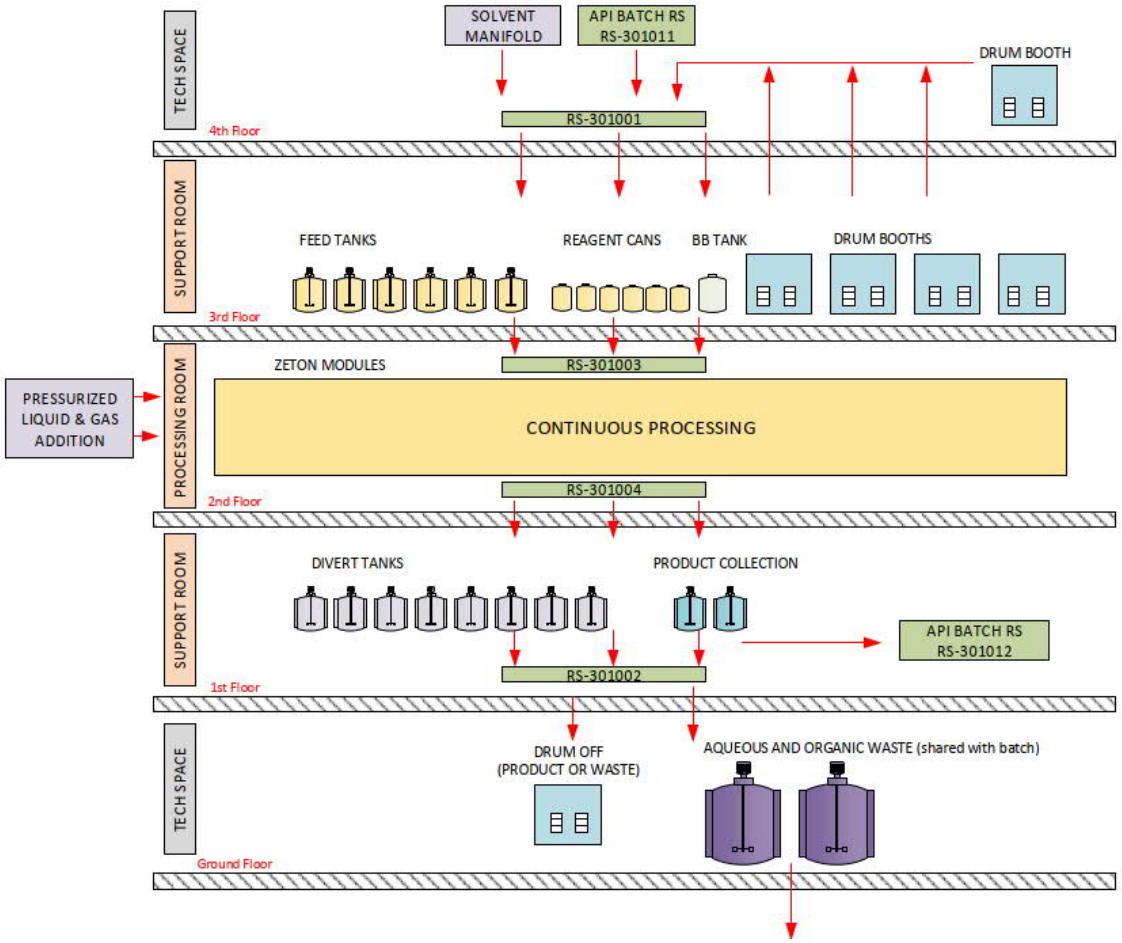

Figure 2.6: Continuous Suite Vertical Stack-up Schematic Diagram

Pressurised Liquid and Gas Addition

The continuous modules may require pressurised gases and pyrophoric material addition. The design includes for 2 no. Gas manifolds for duty-standby charging of process gases from Manifolded Cylinder Pallets or single cylinders. The gas manifolds / cylinders are located externally adjacent to the Heat Transfer Fluid (HTF) chillers. The current design provides for High Pressure Nitrogen and Oxygen to be supplied to the 2nd Floor continuous manufacturing (CM) processing room.

The pyrophoric skid will be equipped with weigh scales and Nitrogen manifold and will be housed in a dedicated enclosure located immediately north of the API Manufacturing Building. The pyrophoric storage footprint provides for a burn trench to be installed at the rear of the enclosure to remove liquid and prevent pooling in the event of a leak from the storage containers.

Continuous Manufacturing Heating/Cooling

The heating and cooling duties for continuous processing suite unit operations will be achieved with dedicated temperature control units (TCUs). The TCUs supplying the 200L Feed/Divert/Product Collect tanks are intended to maintain a constant set temperature in the range 10 to 50°C. The operator will specify the tank temperature control by selecting a temperature set point on the TCU unit human machine interface (HMI).

Feed/Divert/Product Collection Tanks

The following design intent / functionality will be provided on the continuous processing Feed / Divert / Product Collect tanks:

Agitation: The ability to control the speed of agitation accurately, utilising multiple set points during a feed tank batching, will be critical in maximizing product formulation and yield.

Pressure / Vent Control: Pressure inerting and blanketing functionality with nitrogen will be provided on all 50 L and 200 L vessels with provision for venting to either the acid or base vent collection headers.

Feed Tanks Small Solid Additions: The continuous processing feed tanks will be provided with small solids charging capability. The design will allow solid reagents to be added to the feed tank, while maintaining both containment and an inert atmosphere within the tank.

Liquid Charging (Via Drum booths)**:** Liquid charging drum booths will provide a contained enclosure from which solvents and liquid reagents in drums can be automatically charged to Feed Tanks, Reagent Cans, Divert and Product Collect Tanks. The Drum booth will be serviced by an extract fan, which exhausts air with trace solvent vapours to atmosphere.

2.2.3 Containment

The range of materials to be handled in the new API facility will include a wide range of potent compounds and products up to and including Occupational Exposure Band (OEB5)[1].

Compounds may include: APIs, raw materials or intermediates that may be classified as hazardous and/or carcinogenic, mutagenic, reproductive hazards (CMRs) materials.

As is typical during the manufacturing of APIs and associated intermediates, there will be large scale usage of organic solvents at the facility. It is noted that there will be no halogenated Volatile Organic Solvents (VOCs) used at the API manufacturing facility.

As the facility will be multi-product and intended for use in late stage development and commercialisation of new products, a range of process materials, reagents and solvents may be used in the facility and they will have a variety of hazardous properties, including flammability, toxicity, carcinogenic, mutagenic, reproductive hazard, respiratory/skin contact sensitizers etc. The facility has been designed against reference solvent hazards.

During normal operation, the plant environment design basis is for all equipment with high-potency compounds to be fully contained.

The following features will be incorporated in the design of the API Manufacturing facility to ensure appropriate containment and protection of the environment:

- Process vessels are to be nitrogen inerted, with process vent streams being routed to end of line treatment by wet scrubbing and VOC abatement system (regenerative thermal oxidiser (RTO)). It is noted the off-gases from hydrogenator system vessels will contain flammable gas (i.e. hydrogen) with potential for trace solvent vapour and must be discharged to atmosphere via a dedicated vent route for safety reasons.
- Waste aqueous and solvent streams from processing are to be segregated and routed to the waste tank area in the tank farm. No solvents or potent API products and raw materials will be directed to the existing site neutralisation/balancing system. These materials will be segregated and transferred to road tanker from the tank farm waste vessels for offsite disposal.
- It is the design intent that spilled materials (liquid or solid) shall not inadvertently enter the API Manufacturing Building and Chemical Materials Store floor drainage systems. Dry powder spills will be collected into lined drums. Drums to be used for discharging or filling liquids will be positioned on bunds to contain potential spills and to prevent liquid entering the floor drains. Any liquid going to the floor drain will go to the API Manufacturing Building floor drain weak effluent sump tank and then be directed to the aqueous waste tank in the tank farm. The

[1] OEB 5 products have an occupational exposure limit of 0.1 to 1 µg/m^3 8 Hour Time Weighted Average (TWA).

building floor drain weak effluent sump tank can be isolated in the event of a spill, the contents sampled and pumped to IBCs if required. All floor drains will be open, with a liquid seal. Sealed floor drains will not be used due to the pooled solvent risk following a possible incident and the associated fire risk.

- Waste streams will be filtered within the API manufacturing facility or at mother liquor vessel outlet prior to transfer to waste collection tank in the tank farm area.
- During normal operations, APIs shall be contained via the use of primary containment equipment including gloveboxes/isolators/glove bags and downflow booths. Each downflow booth will be fitted with a coarse filter, pre-HEPA (high efficiency particulate arrestor) and HEPA to collect any particulates generated during the dispensary operations.
- Areas with higher risk of product exposure are to be separated from the main processing areas by use of airlocks and control of room pressure differentials to provide secondary containment. These areas will have Heating, Ventilation, and Air Conditioning (HVAC) exhaust high efficiency particulate air (HEPA) filtration. Entry to these areas is to be via gowning / de-gowning airlocks. This is to reduce the spread / loss of containment of pharmaceutical compounds in the event of a breach condition occurring.
- Mitigation for ground water and stormwater protection will include external storage vessel bunding, spill containment, vessel overfill protection, and emergency response systems.
- Product containers being removed from the production areas will be wiped cleaned externally before leaving the facility.
- Solid waste materials with potential potent material contamination or constituents shall be sealed in lined drums or kegs and appropriately labelled before removal from the facility.

3 Ancillary Processes & Support Systems

3.1 Existing Biopharma Manufacturing Facility Ancillary Process & Support Systems

The main support systems to the Biopharma manufacturing facility include:

- Media preparation;
- Buffer preparation;
- Column packing;
- Weigh and dispense;
- Equipment cleaning / CIP;
- Equipment Wash; and
- Waste Management Area.

3.1.1 Media Preparation

The purpose of the media preparation area is to make up and supply media, nutrient feed solutions, and other supplemental feeds (e.g., alkali and antifoam) for the cell culture bioreactors and inoculum labs. *Attachment 4-6-2* of the IE Licence Review Application provides a comprehensive list of all raw materials used in the process.

3.1.2 Buffer Preparation

The purpose of the buffer preparation area is to make up and supply buffer to the buffer hold vessels. Buffer prep and supply solutions of inorganic salts and other solids are mixed with water in the buffer preparation area. Mix tanks are used to prepare aqueous buffer solutions used in the purification steps for chromatography and ultra and diafiltration. These solutions are used for cleaning and conditioning of the chromatography resins as well as for containing the products in a stable solution. *Attachment 4-6-2* of the IE Licence Review Application provides a comprehensive list of all raw materials used in the process.

3.1.3 Column Packing

Downstream includes areas for column packaging and column storage.

3.1.4 Weigh and Dispense

In the dispensary located in the warehouse, powders for media and buffer solution make up are weighed out from vendor provided raw material containers for each process solution (media or buffer). The powders are directly weighed into stainless steel transfer containers or into small plastic bags that are placed inside the stainless steel containers.

3.1.5 Equipment Cleaning / CIP

The following cleaning strategies are implemented within the Biopharma manufacturing facility:

- Clean-In-Place (CIP) systems;
- Clean-Out-of-Place (COP) systems;
- Manual cleaning (minimal);
- Autoclave sterilization; and
- Steam-In-Place (SIP).

In order to maximise productivity, all of the major processing equipment is cleaned via an automated CIP system. The equipment is rinsed with purified water and residual material is removed by use of recirculating cleaning solutions. All aqueous wastewater is recovered from the

cleaning systems and directed to the site wastewater treatment area. SIP is employed after CIP when process sanitisation or sterility is required.

3.1.6 Equipment Wash

Equipment preparation upstream and downstream areas is provided containing necessary COP systems, autoclaves and sinks with utility drops for manual cleaning.

Dedicated washrooms are provided to cell culture, to downstream, and a dedicated wash for media and buffer Prep on Level 3 of the BDS manufacturing building.

3.1.7 Heat Inactivation

Biowaste, defined as liquid process waste that could contain live cells, is collected from the Cell Culture and Harvest areas of each of the production trains in under slab drain piping and flow by gravity through a sump and pumped to the Biowaste Treatment Area. Biowaste is held in the Biowaste Hold Tank, and fed to the heat inactivation system. The Hold Tank provides enough retention capacity to temporarily store an off-spec bioreactor batch and allow production to continue on a temporary basis.

The biowaste is processed through the heat inactivation system, designed to heat treat the waste at a suitable temperature which will kill any live cells that may be present. Direct steam injection is used to heat the biowaste in the steam jet. Downstream of the steam jet, the retention tube ensures that the biowaste is kept at elevated temperature for a long enough period to kill any organisms i.e. 10 second contact time. The system operates continuously to heat up and cool down the waste as opposed to using a batch type system.

Post-treatment cooling is provided to minimise steam consumption and cool the treated waste to a safe level for recombining with other process waste at the onsite wastewater neutralisation/balancing system.

3.2 New API Manufacturing Facility Ancillary Process Support Systems

Process support equipment required for the new API Manufacturing facility include:

- Solvent Storage and Distribution;
- Equipment Cleaning;
- Weigh and Dispense; and
- Production Waste Management

3.2.1 Solvent Storage and Distribution

Bulk Solvent Storage and Distribution

Bulk solvent storage at the facility will include:

- 2 x 50m^3 bulk solvent storage tanks for the batch and continuous processes;
- 2 x 20m^3 bulk solvent ISO tankers for the batch and continuous processes.

The 2No. Bulk solvent storage vessels will be used to supply vessels in the API production building via a solvent manifold system. The bulk tanks will be refilled as required from road tankers using a dedicated road tanker unloading bay.

The bulk solvent storage tanks will be manufactured in 316L stainless steel, of vertical orientation and be installed above ground. Each tank will be fitted with level transmitter and high level switch, provided with nitrogen for inerting and will have a connection to the lean vent collection header which will be routed to the RTO for abatement of fugitive emissions. Additionally, each tank will be fitted with a duty pump to transfer the solvent into the API production building.

The tanks will be located within containment bunds in the new tank farm. The bunds will be sized in accordance with the EPA Guidance Note '*Storage and Transfer of Materials for Scheduled Activities'*, 2004).

A new road tanker loading / unloading facility will be provided as part of the new API manufacturing infrastructure. The bays within the tanker facility will allow for:

1. The unloading of bulk solvent to the 2 No. Bulk Solvent Storage vessels; and
2. Short term parking of fixed ISO tankers which are intended for specialty waste collection and to feed directly to the solvent manifold in the API Building. This is to provide flexibility in terms of changeover of solvent between campaigns. These tanks will be nitrogen inerted.

Venting of fugitive emissions from the ISO tankers which are used for temporary storage and supply of solvents is not required as the these tanks will not be re-filled on site. The ISO tankers are provided with a nitrogen blanket that will replace the solvent as it is removed from the tank. This will ensure no solvent vapours are generated/released. There will be venting of fugitive emissions from the waste ISO tanker which will be routed to the RTO for abatement.

Solvent transfer lines will be kept above ground, made of single walled construction and will be fully welded outside of any bunded areas.

Refer to Section 4.1.3 of this report for details of spill protection measures for the tank farm and loading/unloading areas.

In addition to bulk solvent charging from the tank farm, 2 No. IBC charging stations will be provided on the ground floor of the API production building. Each of these stations will provide space for 2 No. IBCs.

3.2.2 New Chemical Materials Store

The new chemical materials store located directly north of the proposed API manufacturing facility will provide secure, protected and managed storage facilities for chemical materials to be used within the new API Manufacturing Building. The building will consist of segregated chemical material storage areas, fire protection, sampling areas, workstation and external fork truck charging.

In the Chemical Material Store, heating of 200L drums will take place in a drum heating cabinet to heat the drum contents to ensure they are in the liquid phase.

Sampling of 200L drums containing liquid will take place in drum sampling cabinets in the sampling room within the Chemical Material Store. This will involve removing the filling cap, taking a sample and refitting the filling cap.

Vapours released during drum heating and sampling operations will be captured within the cabinets and extracted to vent externally to atmosphere. These emissions will contain only trace amounts of solvent vapours given the low volumes of solvents involved, short duration of the activities and the atmospheric conditions.

The Chemical Materials Store will have floor drains which will collect potential leaks/spills and directed to the Aqueous Waste Tank in the tank yard via the API Weak Effluent Sump. There will also be spill bunds underneath the storage racking in the store (sized to 110% of the largest container on the racked locations overhead) to capture potential spills.

3.2.3 Equipment Cleaning

The following cleaning strategies will be implemented within the API manufacturing building:

- Clean-In-Place (CIP) facilities: For the decontamination and cleaning of equipment in a closed manner before opening;

- Clean-Out-of-Place (COP) systems: This will take place in the 2nd Floor Wash Room where contaminated parts will be cleaned in a contained 'Wash Isolator'
- Manual cleaning (minimal).

Cleaning may deploy a combination of solvents, Water for operations (WFO), detergents and cleaning chemicals.

CIP

The intent of the cleaning systems will be to reduce, reuse and recycle CIP fluids as much as possible. This may involve using final rinse CIP fluids from a CIP cycle as the first rinse of another CIP cycle or using spray washing rather than soaking to remove contamination. 1 No. CIP fluid regeneration skid is provided per train to allow removal of particulates and dissolved components from the CIP fluid so that they can be reused in the same or next CIP cycle.

The efficient use of the CIP process will allow for quicker turnaround times in between batches and campaigns. Cleaning turnaround times will be optimised. This will include starting the cleaning of vessels as they become free rather than waiting until production is complete within the whole process train. Most modules have a transfer out pump that will operate as a CIP pump for the module to allow the module to be cleaned in place without CIP set up as soon as the module comes free.

COP Wash Isolator

Small parts that cannot be cleaned in situ such as passive valves will be washed in the COP (Clean Out of Place) Wash Isolator. This will consist of a two chamber unit to be located in the wash room on the second floor. Wrapped parts will be brought into the first chamber by opening the hinged door of the chamber. The wrapped parts will then be transferred to the second chamber via glove ports for unwrapping and cleaned with process water using a spray gun. When cleaning is completed, the parts will be taken back into the first chamber, bagged and removed from the Isolator. A Rapid Transfer Port (RTP) port will be installed on the second chamber to allow a continuous bag liner or RTP to be connected for removing solid waste materials from the isolator. This solid waste will be placed into a drum and brought downstairs through the Just In Time warehouse for staging in the external waste staging area to the east of the API manufacturing building prior to transfer to the Central Waste Management Facility where it will be collected for off-site recovery/disposal at an appropriately licensed waste facility.

Any solvents or detergents required for cleaning will be brought into the isolator in small bottles. The COP wash isolator will have a dedicated extract fan with double safe change high efficiency particulate air (HEPA) filter prior to being discharged back into the wash area. The drain will be pumped out via a bag filter.

3.3 Warehouse

3.3.1 Existing Warehouse

The existing warehouse provides storage and logistics support for Biopharma manufacturing & packaging operations onsite.

- Shipping;
- Receiving;
- QC material storage;
- Ambient GMP warehouse storage;
- Chemical storage (Acid & Base) for GMP materials;
- Warehouse locker/toilet facility;
- Weigh & dispense;

- QC Sample management;
- 18% Ethanol storage;
- HVAC plant room and electrical distribution;
- Retain sample storage (2-8 degree cold room);
- Waste Handling (Hazardous & Non-Hazardous); and
- Fork truck charging.

Packaging Operations

The packaging area has been designed to cater for all commercial and clinical products. With the introduction of combination products and medical devices the packaging area has introduced automated device assembly to its capabilities.

It is required that the packaging area has the flexibility to handle a large variation in lot/batch sizes across all products. As a result the packaging area has taken the following approaches:

- Fully automatic packaging, labelling and serialization/aggregation;
- Semi-automatic packaging, labelling and serialization/aggregation;
- Manual packaging and labelling;
- De-labelling and rework; and
- Device Assembly.

The building also contains an internal mezzanine floor that houses the mechanical plant and storage for retain samples.

3.3.2 Warehouse Expansion

The expansion of the Warehouse associated with the site's API Expansion development is located to the east of the existing warehouse.

The proposed warehouse expansion will consist of both a northern and southern extension. The southern extension consists of 2-8°C cold rooms and the northern proposed extension will be an ambient warehouse with a weigh and dispense area.

The proposed warehouse facilities for the API operations include:

- Receiving/shipping;
- Ambient GMP warehouse staging;
- A bunded area suitable for segregated storage of pallets is to be provided;
- Freezer modules;
- CSafes Packaging;
- Offices;
- Washrooms and changing;
- Retain sample storage (2-8 degree cold room);
- Weigh & dispense; and
- Stand-Up workstations.

The Warehouse expansion will be used by both the existing Biopharma manufacturing facility and the new API manufacturing facility for storage of raw materials and products.

A very narrow aisle (VNA) racking system is proposed for the warehouse extension. This will use Turret Trucks which allow the operating aisles to be narrower than conventional vehicles and are capable of higher lift heights.

The expanded warehouse will include ambient storage, cold storage (2˚C - 8˚C), freezer storage (-20˚C to -75˚C), acid and base storage, Engineering Stores, Quality Control (QC) sampling and storage, and an API materials weigh and dispense area including QC sampling also.

Weigh and Dispense

A weigh and dispense (W&D) facility for the preparation of batch input materials for the API manufacturing facility and quality control sampling area are to be provided within the warehouse expansion to the north of the existing warehouse at ground floor and Level 1 overhead. Suitable equipment and facilities are to be provided for the dispense of dry API batch inputs into correct ready to use bags and containers.

Dispensed dry API batch inputs shall be prepared into Split Butterfly Valve (SBV), Charge Bags and FIBC / Big Bags. Materials received (raw materials and Intermediates) will be in a wide variety of sacks, drums, bags, big bags.

A link / staging area will connect the proposed sample and weigh/dispense area to the central area of the existing warehouse.

An overview of the material flow through the API section of the warehouse expansion is provided in Figure 3.1.

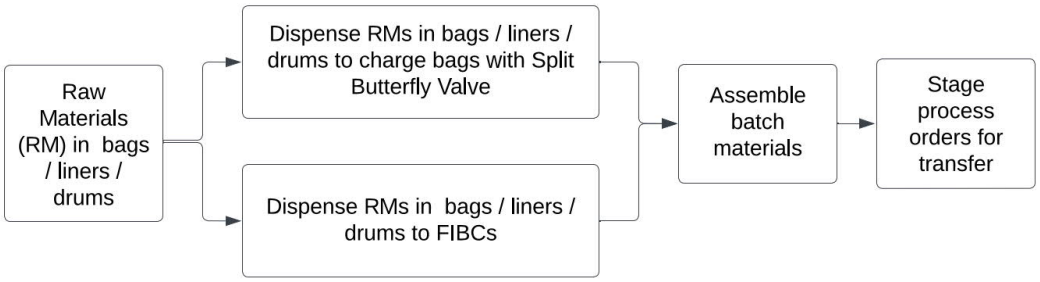

Figure 3.1: Overview of the material flow through the API section of the warehouse expansion.

Secondary Containment for Weigh and Dispense Rooms

Materials and Personnel Movement

Areas will be provided with airlocks with appropriate pressure differences to contain potential emissions;

- All material containers and surfaces will be cleaned before removal from areas;
- Materials air lock (MAL) & personal air locks (PAL) will be provided for the use of personal protective equipment (PPE) when required;
- Mist safety showers at PAL to be provided based on proposed PPE use
- Breathing apparatus will be self-contained with no requirement for breathing air supply piped to area; and
- PPE storage and cleaning facilities will be provided.

Extracts from the weigh and dispense area of the Warehouse expansion will contain air with potential for particulates/dust that will be exhausted to atmosphere through HEPA filters with 99.99% efficiency.

There will be a segregated HVAC system provided for the area with single pass or recirculation with double HEPA filtration. The HVAC system has been designed to ensure no dust leakage by

implemented negative pressures. Production and non-production rooms are to be near ambient with separation provided by positive pressure airlocks. There are provisions included for safe changing of extract HEPA filters at the weigh and dispense rooms.

Equipment will use Clean in Place (CIP) where possible.

Cleaning will be with aqueous solutions, not solvents. Final wipe down may use spray bottles of solvent e.g. IPA or impregnated wipes.

Wash sinks are also provided within the W&D area for cleaning out of place. Equipment will be cleaned within the operating rooms to remove gross contamination before being wetted down and/or bagged before removal from the operating rooms to the area wash room.

Shipping and Receiving

A new shipping/receiving area is to be installed as part of the warehouse extension to the north/east.

The existing shipping and receiving area to the south will primarily be used for cold chain and the area to the north/east for ambient materials. The north/east area will also be for primary transfers to/from the API manufacturing facility.

3.4 Centralised Waste Management Facility

A new Waste Management Facility will provide the Alexion campus with a centralised waste storage area for temporary staging of waste prior to collection for offsite disposal/recovery at an appropriately licensed waste facilities. It will be used by both the existing Biopharma manufacturing facility and the new API manufacturing facility.

Currently waste generated at the existing Biopharma manufacturing facility is stored in a waste management room in the warehouse. This waste will be stored in the site's new Central Waste Management facility following the site expansion.

Process solid wastes and waste liquids stored in 200 litre drums generated from the API manufacturing process will be temporarily staged in the waste staging area adjacent the API manufacturing building. Here solid wastes will be staged in covered waste bund and liquid waste drums will be staged in a bunded chemical store prior to removal to the new central Waste Management Facility.

The Waste Management Facility will include wheelie bins, waste skips, compactor cages, bunded self-contained chemical stores, a single storey waste building for storage of waste generated from the entire campus. This will include hazardous and non-hazardous waste which will be segregated and bunded as required according to the properties of the waste.

The facility will also include a sheltered drum wash station which will also be used for washing of drums from the existing Biopharma manufacturing facility only. Wastewater from the drum wash area will drain to the onsite wastewater management system and is controlled under the site's IE Licence (Licence Reg. No. P1030-01).

No other waste activities will be carried out in the Waste Management Facility.

All waste generated onsite is notified to and managed by the Total Waste Management (TWM) contractor on the site. All documentation is retained on site in accordance with legislative requirements.

3.5 Automation and Control Systems

3.5.1 Building Management System (BMS)

A Building Management System (BMS) exists on-site and all relevant existing plant is included on the BMS software. This will extend to the new API manufacturing facility once operational for building controls. The BMS system controls the following:

- Plant start-up and shut down;
- Monitor all plant operation;
- Relay plant alarms in accordance with agreed alarm hierarchy;
- Monitor outside ambient conditions;
- Monitor internal conditions;
- Sequencing and modulation to achieve and maintain design conditions;
- Pick up and relay alarms from plant and system not controlled by the BMS;
- Interface with fire-alarm and security systems to start-up / shut-down plant;
- Relay alarms via modem to external communications systems.

3.5.2 Manufacturing Control Systems (MCS)

As part of the new API manufacturing facility, a MCS will be installed to control and monitor the manufacturing process to ensure that the process produces a reliable product that meets all quality and other regulatory requirements.

MCS software for the new API manufacturing facility shall be implemented in accordance with S88. The ISA S88.01 standard (S88) defines a consistent set of terminology and models used to define the control requirements for batch manufacturing plants. Following the S88 standard, the software will facilitate in providing a common, consistent model for the design and operation of batch manufacturing plants and batch control systems.

The control system being installed to control the new facility process shall be a single digital control system (DCS). A DCS is a control system that processes signals coming from sensors by means of a computer. The process equipment will be controlled via this DCS, which is known as the Manufacturing Control System (MCS).

The MCS will control the following:

- Stick-built equipment;
- original equipment manufacturer (OEM) equipment;
- Clean utilities; and
- Recording of critical environmental parameters.

3.6 Power Loss to Site

In the event of the electrical power to site being lost, the BMS and production control systems will continue to operate on Uninterruptible Power Supply (UPS) so that managed shutdowns of critical equipment are achieved. There are a number of back-up emergency generators on site that will power up to take over from the critical UPS power sources, but its main function is to provide power to facilitate a safe evacuation of personnel (lights, sockets, environmental monitoring).

The control systems for abatement equipment (onsite neutralisation/balancing system, Stormwater Monitoring and VOC abatement system) will continue to operate on UPS power and back-up emergency generators.

4 Emissions and Abatement Systems

4.1 Aqueous Emissions (Wastewater/Stormwater/Potential Firewater)

This section describes the existing management of domestic/foul wastewater, process wastewater, stormwater and potential for firewater at the Alexion campus, and how the new API expansion will tie into these systems as appropriate.

4.1.1 Domestic/Foul Wastewater

Sanitary / domestic foul wastewater from the canteen, toilets, showers, lockers and canteen facilities in the existing Administration Building, BDS manufacturing building and Warehouse at the Alexion campus currently discharges from the site at wastewater discharge point (SE-1) into the local Uisce Éireann 450mm diameter foul sewer at the southern boundary of the site in accordance with Schedule B.3 of the site's current IE Licence (P1030-01). This wastewater is then conveyed to the Ringsend Wastewater Treatment Plant (WWTP) which in turn discharges treated effluent to Dublin Bay.

There is an existing canteen and kitchen in the Administration Building onsite which generates domestic wastewater that is passed through grease traps meeting the requirements of *BS EN 858 Separator systems for light liquids (e.g. oil and petrol) Selection of nominal size, installation, operation and maintenance. The grease trap* removes any oils, fats and greases prior to joining the foul drainage network on site. It is inspected and cleaned on a regular basis as part of the site preventive maintenance system.

Foul wastewater to be generated at the new API Manufacturing building, new Laboratory building and Warehouse extension will also join the existing foul network on site and discharge from the site via licensed discharge emission point SE-1.

There is no new canteen or kitchen facilities proposed as part of the expansion of the Alexion site. All personnel will utilise the existing on-site canteen facilities.

4.1.2 Process Wastewater

At the existing Biopharma manufacturing facility, contaminated process wastewater which potentially contains Genetically Modified Organisms (GMOs) is segregated upstream and treated in the heat treatment inactivation system prior to discharge to the onsite wastewater pre-treatment (neutralisation/balancing) system.

All process wastewater from the existing BDS Building, Warehouse, and Utility Yard floor drains is treated in the onsite wastewater pre-treatment neutralisation/balancing system before being discharged to the public sewer (at licensed sewer emission point SE-2) and on to Ringsend WWTP for further treatment. Prior to discharge at SE-2, the process drainage undergoes monitoring at licensed sewer emission monitoring point (SEMP-2).

The onsite equalisation/balancing system which provides pre-treatment to the existing Biopharma process effluent consists of the following component treatment steps (refer to Figure 4.1 for an overview of the onsite equalisation/balancing system):

1. ***Effluent Screening*:** Upstream coarse screening is employed which removes shoe covers, hair nets, gaskets etc., which can have a detrimental impact on downstream mechanical equipment.
2. ***Wastewater Balancing:*** The main purpose of the balance tank system is to provide buffering capacity to smooth out variations in the flow and pollution loads. This allows a uniform discharge to the public sewer, and provides natural buffering to pH fluctuations allowing the effluent feed to the downstream neutralisation stage to remain steady.

   An additional calamity tank is also provided to cater for periods of peak load or abnormal concentration requiring retention. Peak loads can be diverted to the calamity tank away from the balance tank and bled back into the system over time allowing for a more uniform treatment and discharge profile. The calamity tank will also cater for storing wastewater during specific

storm events where no discharge is permitted by Uisce Éireann to the external sewer network for periods of up to 7 hours. Once storm conditions have abated a maximum discharge rate of 81.9l/s from the site is permitted to facilitate emptying of the on-site storage.

3. ***Cooling:*** Process effluent from the BDS manufacturing building is at elevated temperatures due to the thermal deactivation of production wastes and the potential use of high temperature utilities such as Water for Injection (WFI). In accordance with Schedule B.3 of Alexion's current IE licence (P01030-01) the effluent temperature is restricted to a maximum of 40°C, therefore it is necessary to reduce effluent temperature. Cooling occurs naturally during effluent transfer and equalisation.
4. ***Neutralisation:*** The pH control is achieved utilising inline dosing, with a programmable logic controller (PLC) controlled chemical dosing system (acid and caustic). There are upstream and downstream pH sensors installed allowing for effective pH adjustment. The recirculation loop is provided downstream of the monitoring point to reverse wastewater back to the balancing tanks if the quality of the discharge waste water does not comply with licence requirements.
5. ***Odour Control*****:** Under normal circumstances odours do not arise from the waste water management system. The tanks associated with the existing WWTP (Flow equalization/balancing tanks) are fitted with a carbon based odour abatement system as a preventative measure to stop odours arising.
6. ***Monitoring:*** Wastewater flow and loads require monitoring at SEMP-2 to ensure compliance with the site IE requirements. Flow, temperature, TOC and pH require continuous monitoring via a 24-hour proportional flow composite sampler. Samples are also taken here for monthly monitoring of Chemical Oxygen Demand (COD), Biochemical Oxygen Demand (BOD), Suspended Solids (SS), Total Nitrogen, Total Phosphate, Sulphates, Oils, fats & greases, and toxicity, active pharmaceuticals, and respirometry (as requested) at licensed sewer emission monitoring point (SEMP-2).

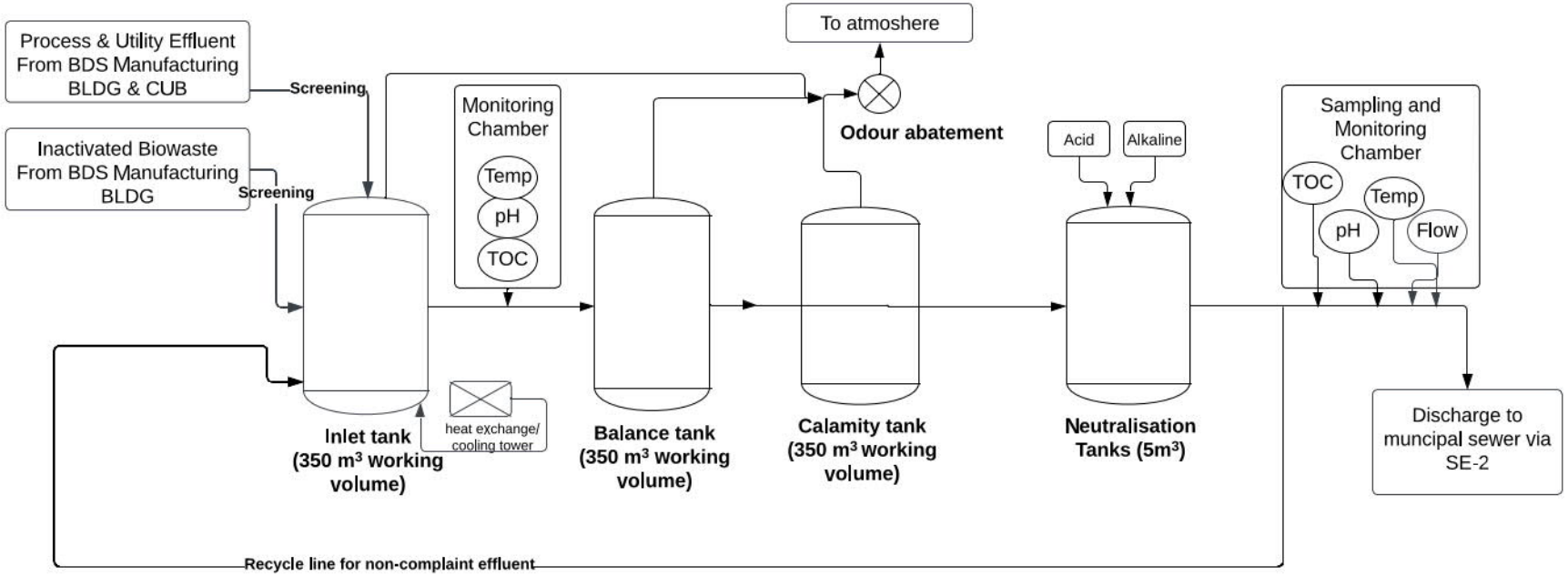

Figure 4.1: Overview of the Onsite Wastewater Equalisation/Balancing System

Process wastewater from the existing labs on site currently undergoes continuous monitoring of flow, temperature and pH and quarterly monitoring of COD, BOD, SS, Detergents (as MBAS), Orthophosphate, Sulphates, Oils, fats & greases, and toxicity (quarterly) at licensed sewer emission monitoring point (SEMP-1). From here the wastewater joins the site's foul drainage network and is discharged from the site at licensed sewer emission discharge point SE-1 to the Uisce Éireann Sewer network which goes to Ringsend WWTP for further treatment.

As part of the site API expansion development, the process drainage from the existing laboratory building will be re-directed to join into a new process drain and wastewater pumping station for the new Laboratory building. From here the existing and new laboratory process wastewater will be pumped to the existing BDS Process drainage system and into the onsite neutralisation/balancing system for pre-treatment prior to discharge from the site at SE-2. As a result, SEMP-1 is no longer required for monitoring of process wastewater at this point as only foul wastewater will be discharged from SE-1 following the expansion works. Therefore SEMP-1 will be decommissioned and removed from the site's IE Licence. The volumes of wastewater anticipated to be generated from the new Laboratory building is expected to be minimal and no other wastewater from the new API manufacturing facility will go to the existing process drainage system or neutralisation/balancing system. Alexion and AstraZeneca protocol does not permit the pouring of solvents or chemicals down a laboratory sink. All liquid solvent waste generated in Laboratories is collected in jerry cans or similar and transferred to waste storage where it is periodically collected for offsite treatment and disposal at an appropriately licensed waste facility.

There are a number of sources of process wastewater from the API expansion development including:

- API Manufacturing Building liquid solvent and liquid aqueous waste;
- Floor drains in the API Manufacturing Building, Chemical Materials Store, and the Warehouse extension weigh and dispense area;
- API Manufacturing Building neutralised acid from acid scrubber; and
- API Manufacturing Building spent caustic from caustic scrubber.

All of the above wastewater streams will be stored onsite and tankered off-site for third party recovery/disposal by a licensed waste collector as required.

The API process waste will be stored in 2 no. fully bunded 50m^3 capacity storage tanks (one for solvent wastes and one for aqueous wastes) located in the new tank farm area.

Wastewater from the drum wash area in the new Waste Management Facility will be directed to the onsite neutralisation/balancing system before joining the existing process drainage network on site and being discharged to the public sewer (at IE licensed sewer emission point SE-2) and on to Ringsend WWTP for further treatment. The drum wash area is only to be used for drums from the existing Alexion Biopharma facility and therefore will not handle any hazardous liquid from the API Manufacturing facility.

Refer to Figure 4.2 for an overview of the wastewater drainage system at the expanded Alexion and AstraZeneca campus.

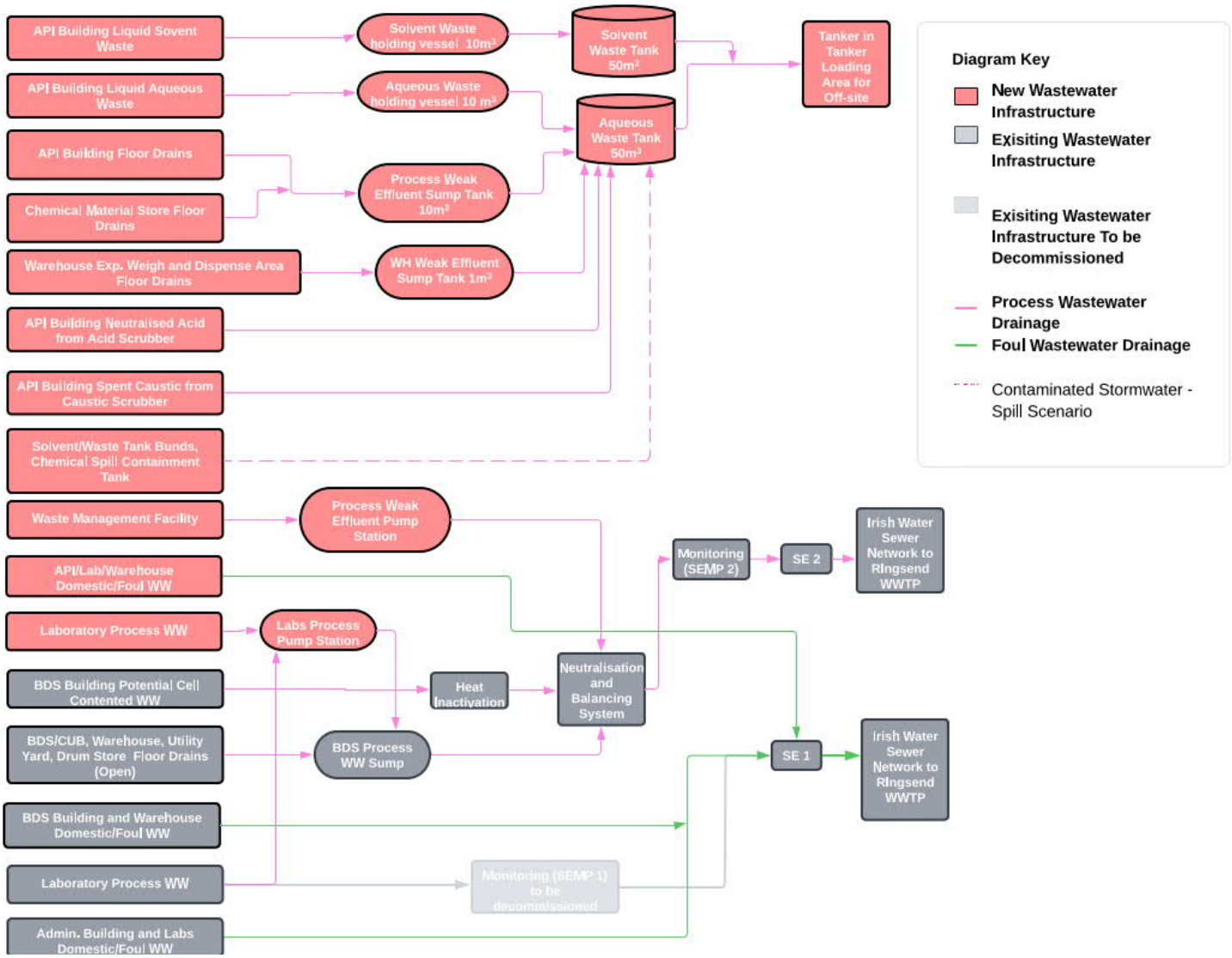

Figure 4.2: Overview of Wastewater Drainage System at the Alexion and AstraZeneca Campus

4.1.3 Stormwater

Stormwater run-off arising from the within the existing Alexion campus (roof and hardstanding / paved areas) is managed as part of the existing Sustainable Urban Drainage System (SuDS) infrastructure within the site, as described below and shown schematically in Figure 4.3.

Discharge of all stormwater run-off from the existing site is to the existing Fingal County Council 1,050mm diameter surface drain at the southeast of the site (via the site stormwater attenuation pond). A Class 1 bypass oil separator is installed on the surface water drainage line prior to the attenuation pond.

Stormwater discharge from the site is attenuated as per the requirements of Fingal County Council (FCC). The permissible discharge of 3.4 l/s/ha was agreed with FCC as part of the Phase 1 planning application (March 2014, Planning Refs. FW14A/0020 & FW14A/0138). In accordance with this, the hydrobrake from the attenuation pond discharges at a rate of 27.4 l/s. No change to this is required as part of the API Expansion development.

The existing stormwater attenuation pond has a capacity of 3,600m^3 to accommodate storm events relating to the existing campus. The current pond is lined with a fully welded High Density Poly Ethylene (HDPE) liner to ensure that it does not interfere with the groundwater in the surrounding area.

There is also an existing stormwater attenuation tank (280m^3) in place at the Phase 2 carpark to the southwest of the site.

At the existing Alexion campus, there is a procedure in place (*SOP-0119669 Bund Emptying Procedure*) which includes a checklist to follow to confirm no contamination prior to discharge to stormwater drainage system if verified as clean.

Stormwater run-off arising from the new expansion areas within the Alexion and AstraZeneca campus (new roof and hardstanding / paved areas) will be managed as part of the existing SuDS infrastructure within the site.

For the new hardstanding areas relating to roads and the new buildings associated with the site expansion, discharge of all stormwater run-off will be to the existing Fingal County Council 1,050mm diameter surface drain at the southeast of the site via the site stormwater attenuation/firewater retention pond. A new continuous Total Organic Carbon (TOC) monitor will be installed at the inlet to the pond which will be linked to the shut-off valve on the outfall of the pond. In the event of an elevated TOC reading, the actuated valve on the outfall from the pond will close automatically to contain the stormwater until further investigations can be made to determine the cause of the elevated TOC. There is also existing continuous pH monitoring on the outlet of the pond which will close the actuated shut-off valve on the outlet of the pond if an elevated pH reading is detected.

To mitigate the risk of pollution resulting from a chemical spill at the ISO tanker loading/unloading yard area, the yard area itself will be locally bunded by kerbing and will be sloped towards a linear drainage channel which will collect the stormwater drainage and potential spills from the ISO tankers and/or road tankers. The linear drainage channels will drain via double contained pipework to an underground chemical spill containment tank (sized to 110% of the volume of an ISO tanker) equipped with continuous TOC monitoring and an automatic shut-off valve on the outlet of the tank which will be closed in any of the following circumstances:

- during all loading/unloading events (manual);
- upon an elevated TOC reading (automatic);
- during a fire alarm (automatic).

Once loading/unloading operations have ceased, the shut-off valve will be re-opened once the operator is satisfied that no spill has occurred.

In normal circumstances (i.e. no chemical offloading operations) the clean stormwater run-off from the tanker loading/unloading area will flow through the underground spill containment tank and discharge into the existing stormwater network via a new hydrocarbon interceptor and underground stormwater attenuation storage located to the south of the new tanker loading/unloading yard.

Once verified as uncontaminated via TOC monitor, stormwater collected in the new tank farm bunds will be pumped to the new stormwater drainage system for the tanker loading/unloading area which will flow to an underground stormwater attenuation tank (65m^3 capacity sized for 1 in 100 year return period) via a new Class 1 By-Pass Separator. From here, the stormwater will be released at a controlled rate via a flow control valve to the existing stormwater network to flow towards the existing pond at the southeast of the site.

In the event of an elevated TOC reading which would indicate a spill or leak in any of the tank farm bunds, the contaminated stormwater will be automatically re-directed by pumps to the Aqueous Waste Tank in the tank farm area for disposal/recovery offsite by a licensed waste contractor as appropriate. It is noted that these pumps will be deactivated in the event of a fire alarm and potentially contaminated stormwater will fill up the bunds eventually overflowing to the stormwater gullies nearby and drain to the stormwater attenuation/firewater retention pond in the southeast of the site for retention (Refer to Section 4.1.4).

Stormwater collected within the new Scrubber and Chiller bunds installed as part of the site expansion will be manually released to the stormwater gullies near the bund via a drain valve once verified as clean by TOC monitoring. If contamination is noted in the bunds, the contaminated Stormwater will be transferred to IBCs for off-site reuse/recovery.

Local stormwater attenuation is proposed for the Waste Management Facility in the form of an underground Aquacell tank (82m^3 capacity sized for 1 in 100 year return period). Stormwater from the area will flow through a Class 1 bypass interceptor prior to the attenuation tank. From there it will connect into the existing stormwater network onsite. There will be a shut-off valve installed on the stormwater drain from the Waste Management Facility yard which can be closed in the event of a spill in order to prevent any potential contamination of the stormwater network. Hazardous liquid waste is to be temporarily staged at the Waste Management Facility in self-bunded Chemical Store containers pending collection for off-site disposal/recovery.

For the new eastern carpark facility and associated access road, permeable paving is proposed which will provide stormwater attenuation and also retention of any suspended solids and hydrocarbons in the stormwater. There will also be a stormwater drain from the carpark to the stormwater attenuation pond through a new interceptor at the car park.

All stormwater discharge from the site's stormwater attenuation pond via licensed discharge point SW-1 will continue to be attenuated as per the requirements of Fingal County Council.

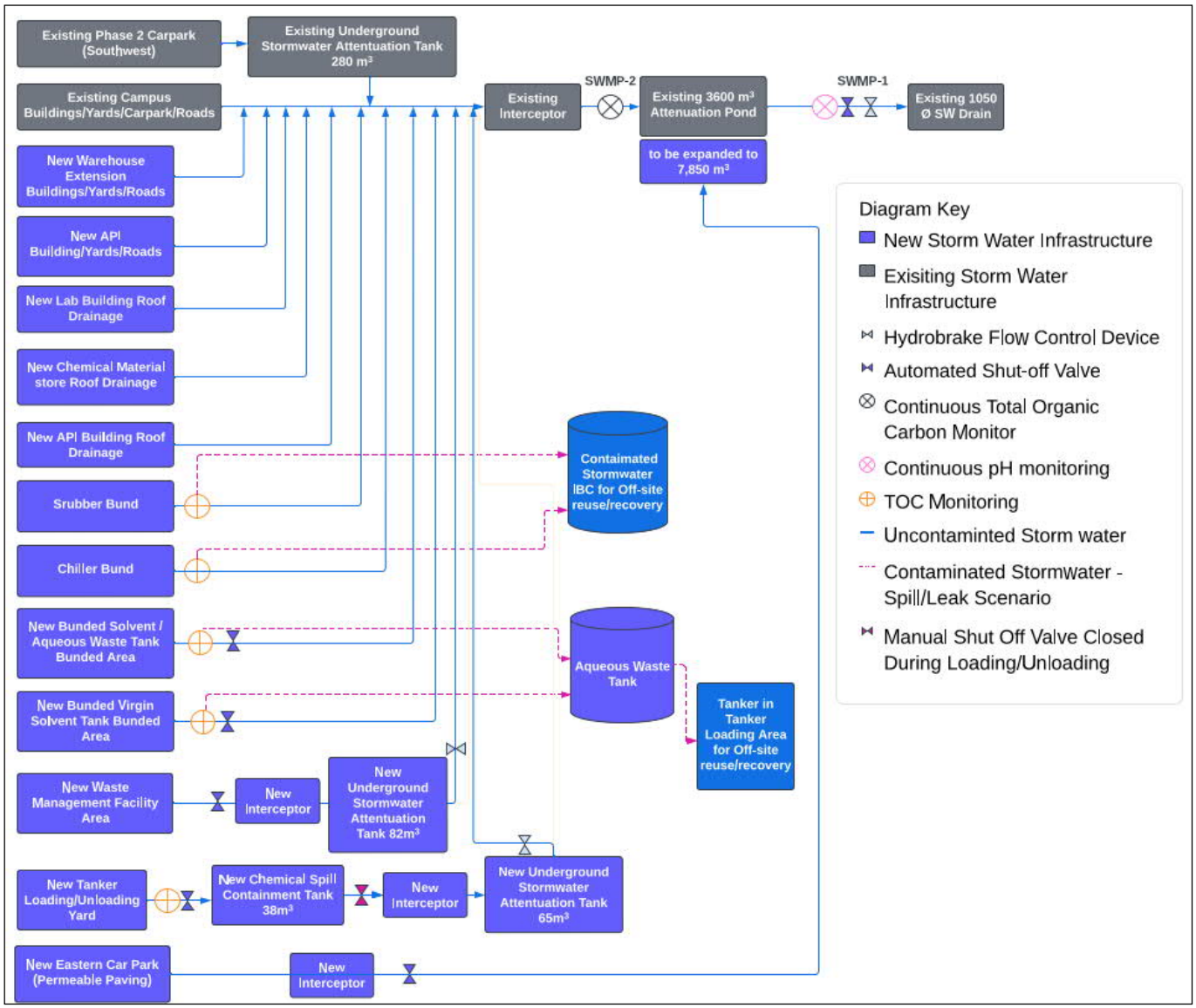

Figure 4.3: Overview of Stormwater Drainage System at the Alexion and AstraZeneca Campus

4.1.4 Potential Firewater Run-off Retention

The site expansion works include for an extension to the existing stormwater attenuation pond in the southeast of the site to accommodate the volume of firewater run-off retention required for the site in accordance with the methodology outlined in the EPA's *Guidance on Retention Requirements of Firewater run-off* (2019).

In the event of a fire at the site, potentially contaminated firewater run-off will drain through the site stormwater drainage network to the expanded lined attenuation pond for containment. The shut-off valve on the outfall of the existing pond will close automatically if a fire alarm is triggered, ensuring that no potentially contaminated fire water runoff can leave the site via the outfall from the pond.

Following the fire event, the fire water runoff in the pond will be analysed to determine the options for proper disposal. If adequate treatment is available on site final disposal via normal licensed emission point SE-2 may be permissible. Approval with the EPA And Úisce Éireann will be sought prior to this option. If the testing indicates that the water cannot be released then the contaminated water will be removed from site by an approved contractor and disposed of appropriately.

As part of the firewater management at the site there will also be a risk management programme prepared and implemented for the site.

4.2 Land, Soil and Groundwater

There are no emissions directly to soil or groundwater from the existing facility or as part of the API expansion development.

Groundwater monitoring is completed annually at the on-site monitoring wells: AGW-1, AGW-2, AGW-3, AGW-4 and AGW-5 by Alexion in accordance with Schedule C.5.1 of the site's current IE Licence (P1030-01). It is proposed to relocate AGW-2 to a new location as it must be moved from its current location (307926E, 241238N) due to overlap with the site's new tanker loading/unloading area. Once agreed as part of this IE Licence review application, the borehole will be drilled in the approximate new location proposed (Refer to Drawing '*IE0311488-22-DR-0010_A_01 Monitoring locations'*).

The potential effect on soils, geology and hydrogeology during operations at the campus is limited to accidental spillage of substances such as fuel, oils, and raw materials at the site. Hazardous materials used on site will be stored in bunded areas in accordance with EPA guidance and integrity testing of pipework will be carried out as per the site's IE Licence requirements.

Further, the spill control procedures that are already in place at the Alexion facility will be applied to the operations relating to the site expansion.

There is no historic soil or groundwater contamination issues associated with the Alexion College Park site. Refer to *Attachment-4-8-2-Baseline-Report* included with this IE Licence review application for further details on existing conditions and control measures to be implemented on site for protection of land, soil and groundwater.

4.3 Noise Emissions

In accordance with its current IE Licence, the Alexion and AstraZeneca campus is subject to noise limits at 5 No. nearby noise sensitive locations (NSLs) outlined in Table 4.1 for day, evening and night-time operations.

Table 4.1: Operational Noise Limits for the Alexion Facility

Daytime dB(A) $L_{A,rT}$ (30 minutes)	Evening-time dB(A) $L_{A,rT}$ (30 minutes)	Night-time dB(A) $L_{A,rT}$ (15-30 minutes)
55	50	45

The site carries out an environmental noise survey of the site annually, in accordance with Condition 6.13 of their IE Licence.

There will be new external noisy plant added to the site as part of the API expansion development. The noise emissions for the development have been included in predictive noise modelling software which has demonstrated that noise levels arising from the operation of the API expansion development in addition to the operation of the existing Biopharma manufacturing facility will be in accordance with the noise limits as per IE Licence P1030-01 (Refer to *Attachment-7-1-3-Noise Emissions Impact Assessment*).

Operation of the existing Biopharma manufacturing facility and the new API manufacturing facility will be in accordance with Best Available Technique (BAT) principles, and in accordance with the IE licence requirements for the site.

Noise monitoring will continue to be carried out annually to demonstrate operations of the site does not exceed the site's noise emission limits.

4.4 Air Quality

4.4.1 Main Air Emission Points

The main emission points associated with the existing combustion plant on the site consist of the following (specified duties quoted relate to rated net thermal fuel input Megawatt thermal MW_{th}) (refer to *Attachment-7-4-1-Emissions to Air-Main and Fugitive* for further details):

- 8.8 MW_{th} Plant Steam Boiler 1 (Emission point ref. no. A1-1);
- 8.8 MW_{th} Plant Steam Boiler 2 (Emission point ref. no. A1-2);
- 8.8 MW_{th} Plant Steam Boiler 3 (Emission point ref. no. A1-3);
- Future Plant Steam Boiler 4 (Emission point ref. no. A1-4) (not yet installed);
- 1.55 MW_{th} Low Pressure Hot Water (LPHW) Boiler 1 (New Emission point ref. no. A1-5);
- 1.55 MW_{th} LPHW Boiler 2 (New Emission point ref. no. A1-6);
- 1.55 MW_{th} LPHW Boiler 3 (New Emission point ref. no. A1-7).

It is noted that the 3 No. existing Low Pressure Hot Water Boilers (LPHW) listed above had previously been classed as minor air emission points (previous emission ref. no.'s A3-1, A3-2, A3-3). These LPHW boilers are being reclassified as main air emission points in this IE Licence review as they have a rated thermal input over 1 MW_{th}.

Air emissions monitoring is carried out for the main emission points on site in accordance with Schedule C.1.1 of the current IE Licence (P1030-01).

Emissions from the natural gas fired Steam Boilers and the LPHW Boilers include the products of combustion, oxides of nitrogen and other nitrogen compounds (NO_x) and carbon monoxide (CO).

Each Steam Boiler is designed for low NO_x emissions (NO_x emission concentration less than 100 mg/Nm^3 dry basis, 3% O_2). The low NO_x emission design are achieved through fuel-air ratio control.

There is provision under Regulation 13 of the European Union (Medium Combustion Plant) Regulations 2017 (S.I. 595/2017) for the use of an alternative fuel for short periods under emergency circumstances in the event of an interruption to natural gas. In accordance with this, diesel / hydrotreated vegetable oil is proposed as an emergency fuel for the Steam Boilers only to be used exceptionally in the case of a sudden interruption to the supply of the primary fuel natural gas to the site.

<u>API Manufacturing Facility Integrated Waste Gas Management System</u>

An integrated waste gas management system is proposed for the new API Manufacturing facility which includes a system of solvent condensers, acid and base (caustic) scrubbers, and a regenerative thermal oxidiser (RTO) as the end of line abatement technology (Refer to Figure 4.4).

Further details on the integrated waste gas management system being installed for the new API manufacturing facility are provided here:

1. *Solvent Condensers*

   As described earlier, each reactor will have a dedicated vertical shell and tube condenser on the reactor overheads which will condense solvent entrained in waste gases generated within the vessels. Solvent distillate from the vent condenser may be refluxed back to the reactor or routed to the receiver via the upper routing station. The off-gases from the condenser will then be routed to an acid or base vent collection header or process vacuum supply and then to the new RTO for abatement. It is noted that the solvent condensers are not shown on Figure 4.4 as they are located at individual reactors.

2. *Acid Gas and Base Scrubbers*

   As the API manufacturing plant will be a multi-product facility, there are numerous recipes possible which can have acid or base components involved. Depending on the product recipe, the vent from process equipment can have either acid components or base components. There will be dedicated wet scrubbers included in the integrated waste management system to remove the acid gas and base gas components from the respective vent headers.

   Dedicated extract fans located downstream of the wet scrubbers will ensure that the vent headers operate under negative pressure. The combined vent streams from the extract fans will then be sent to the VOC abatement unit (RTO) for final treatment.

   The scrubber solution will be recirculated in the scrubbers for as long as possible to fulfil the function of the scrubbers (removing acidic and caustic vapours from waste gases to ensure optimum operation of the RTO). Water will be sampled for conductivity/pH to indicate when it must be replaced with fresh water.

3. *Regenerative Thermal Oxidiser (RTO)*

   As part of the integrated waste management system, a new thermal oxidiser abatement unit complete with flue stack will be installed as an end of line abatement system. The RTO is to be installed for controlling and reducing Volatile Organic Compound (VOC) emissions from the new API manufacturing facility.

   The RTO represents the most appropriate environmental solution for VOC abatement at the API manufacturing facility. The type of thermal oxidiser to be employed at the site is a regenerative thermal oxidiser. The regenerator columns are to be filled with a ceramic packed bed and will be lined with an insulation layer to resist the high reaction temperature. The combustion chamber will also be lined with fibre material and will connect the regenerator columns with each other. The burner system which is designed with separate combustion air connection is to be located at the side to allow easy access. The air collection system will comprise the raw and clean gas ducts with integrated tight closing valves at exhaust air inlet and clean gas outlet and the dampers at the purge air inlet. The fans will transfer the exhaust air through the RTO system. The exhaust air stream will be fed alternatively by time-controlled dampers into one of the regenerator columns. It will flow through the hot packed bed from bottom to top and will be pre-heated in the process. In the oxidation chamber the exhaust air will be brought to the required final reaction temperature. The oxidised hot clean gas will then flow through the other columns from top to bottom, transmitting its heat to the packed bed in this process.

   There are two methods of heat recovery used in the RTO: The system is equipped with an integrated regenerative heat recovery (RTO) performed with ceramic honeycomb blocks; and the exhaust flue gas goes through a heat exchanger with the incoming gas to preheat it.

The following vent streams from the API Facility are routed to the RTO as separate feeds:

1) Inert Vent Feed Stream

The waste gas streams from the various process equipment in the various manufacturing process in the API Building are vented to either the acid vent header or the base vent header. The individual equipment are operated in an inert atmosphere and the vent headers are also continuously vented with nitrogen. The acid vent header is routed to the caustic scrubber and the base vent header is routed to the acid scrubber for removal of inorganic acid and base components respectively. Each scrubber has dedicated extract fans to ensure that the vent header operate under negative pressure. The scrubbed vent streams are combined downstream and routed to the RTO as the Inert Vent Feed Stream.

2) Lean Vent Feed Stream

Vents in the Tank Farm area from the bulk solvent storage tanks, aqueous waste storage tank, organic waste storage tank, tanker loading/unloading operations and waste ISO tanker will be collected in a dedicated header. This header is operated below the lower explosive limit (LEL) including approved margin by addition of fresh air from the atmosphere for dilution at the start of the header and hence is called the Lean Vent Header. The lean vent extract fans located at the

end of the header will ensure that the header operates under negative pressure. These fans will feed the lean vent to the RTO as a separate stream from the scrubbed combined acid and base vent stream. This lean vent feed stream will not be routed via scrubbers, as it is not expected to have any inorganic acid or base components.

RTO Package

Inside the RTO package, the inert vent feed stream is first mixed with dilution air and then with the lean vent feed stream. The purpose for addition of dilution air (fresh air from the atmosphere) is to ensure that the volatile organic compound (VOC) concentration is below the lower explosive limit (LEL) and approved margin. A minimum airflow to ensure safe operation will be maintained in the RTO header irrespective of RTO operating inline or in bypass mode.

Downstream of this mixing, a LEL monitoring system is installed to control the dilution air intake and monitor the VOC concentration of the diluted vent gas of max. 25% LEL for the downstream positioned RTO.

The RTO process air fan located in front of the RTO will ensure that the ductwork with both Vent Streams operates under negative pressure. These fans will feed the diluted vent stream to the RTO. The RTO process air fan conveys the Lean Vent Stream and Inert Vent Stream through the RTO system.

In case of high LEL alarm the RTO Process air damper will close and Bypass damper will open. Bypass fan will start to feed the Vent stream via Bypass line direct into the Stack. The RTO will run in stand-by mode in the meantime. Until the VOC concentration in the ductwork is below the defined LEL limit, a duct purge timer will start (time required to purge the duct 5-times of duct volume). After this timer is finished, the LEL Alarm has to be acknowledge and first then the diluted Vent stream can be flow through the RTO again. This is the required safety scenario for the RTO.

In the unlikely event of the RTO failing, a bypass scenario will occur as described above. During this abnormal event, an alarm will be generated to alert the API operations team. The procedure of shutting down processes generating emissions will be initiated immediately and completed as soon as practicable and, in a manner consistent with safety and protection of the environment. For the air dispersion modelling assessment included with the IE Licence review application (*Attachment-7-1-3-2-Emissions to Air Impact Assessment),* the time between the initiating alarm and stopping any unabated emissions to atmosphere was assumed to be 60 minutes. During this time, operators will work to safely shut down the process and waste gas emissions will reduce significantly as the duration of the bypass elapses.

Control parameters to be measured to ensure the Acid Gas Scrubber and Base Gas Scrubber are working correctly include continuous monitoring of the scrubber Solution: Circulation Flowrate, pH, and/or conductivity. Fan speed and differential pressure across the scrubber will also be measured continuously.

Control parameters to be measured to ensure the RTO is working correctly include continuous monitoring of the chamber temperature, inlet temperature, outlet temperature, inlet pressure, lower explosion limit on the inlet header.

During start-up operations, the feed in to the RTO will not commence until it is ensured the RTO has reached the appropriate temperature and all other parameter are within the correct specification. During shut-down of the RTO, all fans drawing vents to the RTO will cease prior to the shut-down of the RTO.

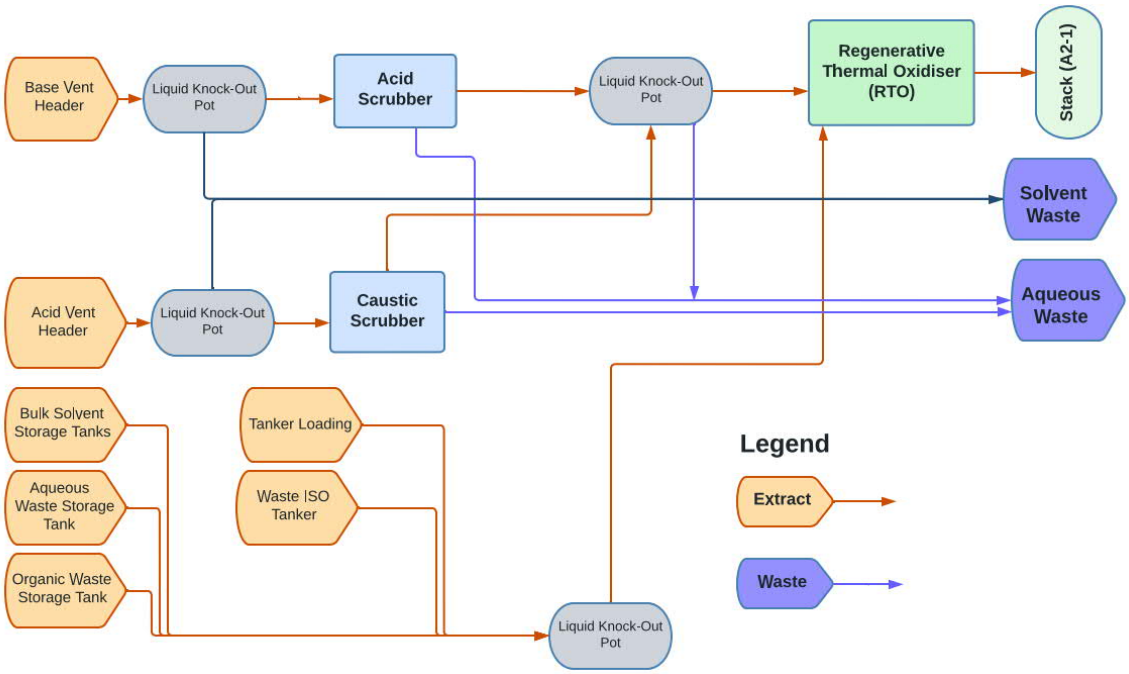

Figure 4.4: Overview of the API Manufacturing Facility Integrated Waste Gas Management System

The knock-out pots shown in Figure 4.4 will be in place to remove any entrained liquid which may have been swept up vent lines in the waste gas management system.

An assessment of the potential impact of the new VOC abatement system emission point (Ref. No. A2-1) to atmosphere is detailed within *Attachment-7-1-3-2-Emissions Impact Assessment* of this IE Licence Review Application.

4.4.2 Minor Air Emission Points

Biopharma Manufacturing Facility

There are several minor emission points on the existing Alexion site, relating to laboratory operations, production emissions, diesel tanks, ethanol storage room exhaust and HVAC emissions (clean building air) (refer to *Attachment-7-4-2-Emissions to Air-Minor and Potential*).

A number of abatement technologies are utilised to prevent emissions of pollutants to atmosphere from the minor emission points on site including:

- *Biologics Safety Cabinets*

Biologics Safety Cabinets (BSCs) are fitted with a high efficiency particulate arrestor (HEPA) filter.

- *Bioreactors*

All the cell culture vessels (seed bioreactors and production bioreactors) are fitted with a sterile filter (0.2µm) preventing particles and Genetically Modified Microorganisms (GMM) greater than 0.2 µm from exiting the vent lines. The Bioreactor feed vessels is also fitted with a 0.2µm filter on their vent line.

- *Harvest, Purification & Media/Buffer Prep Vessels:*

The Harvest, Purification, Media Preparation and Buffer Preparation vessels are fitted with a 0.2µm vent filter preventing particles and Genetically Modified Microorganisms (GMM) greater than 0.2 µm from exiting the vent lines. Passive vents to atmosphere from buffer preparation vessels will contain trace solvent vapours.

- *Material Sampling/Dispensing:*

Operations involving solids are carried out on a small-scale manual basis in dispensing booths which operate 100% recirculation of air i.e., no external exhaust point to the atmosphere. Each downflow booth are fitted with a coarse filter, pre-HEPA and HEPA where required to collect any particulates generated.

- *Lab Fumehood Emissions*

Minor fugitive VOC emissions can also arise from Lab fumehoods (including the Small Scale Media and Buffer Prep Fumehoods) emissions. The levels of VOC fugitive emissions are deemed to be very minor. As such, no particular abatement technology is required.

API Manufacturing Facility

As part of the API manufacturing facility there will be several new minor emission points added to the site relating to production emissions, new laboratory operations, breathing losses from diesel tanks and clean air HVAC emissions (refer to *Attachment-7-4-2-Emissions to Air-Minor and Potential*).

A number of abatement technologies are utilised to prevent emissions of pollutants atmosphere from the following operations at the new API manufacturing facility:

- *Glove Boxes / Isolators / Glove bags*

Glove-boxes, Isolators and Glove bags are proposed to provide OEB5 containment at a number of locations in the API manufacturing facility. Extracts from this equipment with potential for particulates/dust will not be exhausted to atmosphere. Instead, the extracted air will be recirculated to the manufacturing building rooms following double HEPA filtration.

Extracts from the Weigh and Dispense area of the Warehouse expansion will contain air with potential for particulates/dust that will be exhausted to atmosphere through HEPA filters with 99.99% efficiency.

- *Drum booths / Drum Cabinets / Glove Boxes*

Exhaust from liquid charging/handling containment equipment (e.g. drum booths, drum heater/sampling cabinets and glove boxes) will be vented to atmosphere. These will not contain any particulates and therefore are not fitted with HEPA filters. Given the low volumes of solvents involved (< 200L drums) and atmospheric conditions, these exhausts will contain trace solvent vapours.

- *Production / Process Vessels*

Any sources of significant solvent vapours from the production process reactors and vessels is routed to the integrated waste gas treatment system for abatement.

Process vessels from the hydrogenator system containing hydrogen will have condensers which will remove the majority of solvent vapours generated. Distillate from the condenser will be refluxed back to the vessel. The off-gases from the condenser will contain flammable gas (i.e. hydrogen) with potential for trace solvent vapour and must be discharged to atmosphere via a dedicated vent route for safety reasons.

- Lab Fumehood Emissions

At the new Laboratory building there will be a combined extract system from fume cupboard exhausts, ventilated cabinet exhausts, LEV (Local Exhaust Ventilation) and laboratory equipment vents and building HVAC system. Given the low volumes of solvents to be used on a laboratory scale, there will only be trace amounts of levels of VOC emissions from this system. As such, no particular abatement technology is required.

4.4.3 Potential Air Emission Points

There are a number of potential emission points at the existing Biopharma manufacturing facility and the new API manufacturing facility relating to pressure relief valves on vessels/storage tanks and backup emergency generators and sprinkler pumps.

Emergency relief routes from the bursting discs on the Batch and Continuous vessels to be installed as part of the new API Manufacturing Building will be directed to the Emergency Relief Receiver located external to the API Manufacturing Building. This is a 30,000L horizontal vessel designed to capture liquid from the process vessels in an over pressure scenario. Vapour and gases pass through the receiver to a vent outlet located above the roof of the main API Manufacturing Building.

There are three existing diesel fuelled emergency back-up generators installed at the existing Alexion facility which would be used to provide electricity to the site in the event of a power outage. As part of the API Expansion development, 3 No. 2,500kVA emergency back-up generators will be installed to provide emergency power in the event of a failure of the electricity mains supply. During normal operations, the back-up generators are/will not be operational, with the exception for testing/maintenance which occurs for a maximum of 10 minutes every two weeks and is completed individually (not at the same time). Low sulphur diesel (maximum 0.1% sulphur by mass) is/will be used as the primary fuel for the emergency generators. The emergency generators emit combustion exhaust gases containing NO_x/NO_2, CO, and SO_2 to atmosphere.

There are two existing sprinkler pumps at the Alexion facility: 1 diesel fuelled and 1 electric pump that has an uninterruptible power supply (UPS) and emergency back-up generator for power in the event of a power outage, which would be used to provide electricity to the fire sprinkler system in the event of a power outage. During normal operations, the sprinkler pumps are not operational, with the exception for testing/maintenance which occurs for a maximum of 10 minutes every two weeks.

4.4.4 Odour

Odour emissions from the existing Biopharma facility do not cause a nuisance on site or off-site. The tanks associated with the existing WWTP (Flow equalization/balancing tanks) are fitted with a carbon-based odour abatement system as a preventative measure to stop odours arising. It is noted that there have been no odour complaints received by the site since the beginning of operations there.

No odours are foreseen as part of the site API Expansion development due to the nature of the development. In addition, all new storage tanks on site will be appropriately sealed.

5 Laboratory Activities and Facilities

5.1 Existing Biopharma Laboratory

The existing Biopharma laboratory area is located attached the campus administration Building.

The laboratories support the product from the Alexion supply chain and have expanded as the site has developed to support the drug substance manufacture, drug product manufacture, and development facilities.

The laboratories and functional areas include the following:

- Sample receipt and Sample preparation (Stability);
- Stability storage;
- Microbiology laboratory;
- Immunology laboratory;
- Sterility laboratory;
- PCR lab (DNA testing);
- Chemistry laboratory;
- Instrument laboratory;
- Metrology;
- Glass wash.

Office write-up areas are also provided in the laboratory area.

5.2 New API Laboratory

The new API manufacturing facility will require laboratory services that are not already available on the Alexion site including the following:

- Chemistry Lab;
- Quality Control (QC) Analytical Lab;
- Storage;
- Write-Up areas;
- Offices;
- Circulation, and
- Plant space.

The new four-storey laboratory building will be located west of the existing labs on the Alexion site. This new laboratory will serve API operations for AstraZeneca and will also provide expansion space for Alexion Biopharma laboratory operations. The new laboratory building will be connected to the existing laboratory building via a link corridor.

As part of the site expansion, there will also be an In Process Control (IPC) Test Laboratory located in the new API Manufacturing Building. The IPC lab will carry out required tests and analysis for the confirmation of active pharmaceutical ingredients from the products generated during the production process.

As described under Section 4.4.2 of this report, fume hoods within the new and existing laboratories discharge to atmosphere. Small quantities of hazardous material are handled in these fumehoods for various testing purposes. Emissions of these materials to atmosphere are negligible given the quantities involved (Refer to *Attachment-7-4-2-Emissions to Air-Minor and Potential*).

6 Utility Requirements

The principal utility demands for the Alexion facility are as follows:

6.1 Electricity

All of Alexion's current electricity supply is from renewable sources and its electricity supplier provides a '*Certificate of renewable source Electricity Supply*' to assure this. The site is currently serviced through a medium voltage supply. The maximum import capacity (MIC) for the site is 8,000 kVA, and the maximum recorded electrical consumption on site is approximately 3,150 kVA.

6.2 Natural Gas

Natural gas enters the site via a natural gas distribution supply line to the south of the site for Phase 1 and a separate AGI at the north of the campus which supplies Phase 2.

Supply to the API manufacturing facility will tie into existing site infrastructure and distribution main, which is confirmed to have adequate capacity to meet the requirements of the site expansion.

6.3 Liquid Nitrogen

Liquid Nitrogen is needed for the existing Working Cell Bank (WCB) freezers located in the BDS manufacturing Building. A Liquid Nitrogen storage tank ($1m^3$) is located in the compound to the east of the BDS manufacturing building. This storage vessel pressure transfers the liquid to the WCB Freezers. The tank has the necessary equipment for regulating pressure, pressure relief and road tanker connection for tank refill.

Liquid nitrogen will also be required for the new API manufacturing facility and will be supplied from a new 35 m^3 liquid nitrogen tank and vaporizer system located externally to the new API manufacturing building.

6.4 Plant Steam

The plant steam system at the existing campus consists of 3 No. 8.8 MW_{th} natural gas fuelled steam boilers located in the Phase 2 Central Utilities Building (CUB).

The steam is generated from each boiler at 8barg and piped to a common header and then distributed out to the BDS manufacturing building. There is also some local pressure reduction within the boiler house (i.e. for deaerator and Low Temperature Hot Water (LTHW)). A dual pressure reducing station steam supply is located in the BDS manufacturing building to provide low pressure (4 barg) steam to BDS facility users in addition to 8barg users.

The condensate recovery/make up system is composed of a surge tank skid and deaerator tank skid which supply feedwater to boilers. Each skid is factory-assembled and consists of vessels, pumps, piping, valves, and dedicated controls. Bypass piping is provided around the deaerator to allow feedwater from the surge tank to be delivered to the boilers during periods of inspection or maintenance. A blowdown skid is also provided for each boiler which includes a blowdown vessel and controls for water temperature exiting to drain.

No new steam boilers are required to support the site expansion. Steam required for the new API manufacturing facility will be generated by the existing 3. No steam boilers.

6.5 Cooling Tower Water and Chilled Water

An extensive chilled water system is in place to provide the cooling requirements for the existing BDS manufacturing facility.

The existing cooling water system consists of 5 No. single cell open cooling towers, distribution pumps and piping, chemical treatment system and a side stream filters located in the recessed part of the roof of the Phase 2 CUB for the BDS manufacturing building. The cooling towers are located directly above 3 No. water cooled liquid chillers. Each tower fan is equipped with a variable

frequency drive which adjusts the speed of the fan to match the cooling demand. The distribution pumps operates at variable speeds and circulates the water between the cooling tower and the user points, which includes the chillers and Biowaste cooler heat exchangers and miscellaneous heat exchangers. The tower fans and distribution pumps are sequenced to match the operation of the chillers etc.

Make-up water is supplied from the water for operation storage tank to make up for the blowdown, evaporation, and drift losses.

Chillers are also installed within the Phase 1 CUB north of the existing laboratory building, within a dedicated chiller plant room. Externally located dry air coolers are located adjacent to the utility plant room in a plant compound to the west of the utility plant room, at ground level.

HVAC chilled water is generated through the use of 6 No. magnetic gearing centrifugal chillers (3 no. in the Phase 1 CUB and 3 no. in the Phase 2 CUB. Chilled water is distributed to the use points via a primary-secondary pumping arrangement. Variable speed drives (VSD's) are included with each pump. The primary pumps are set at a predetermined speed using the VSD's and the secondary pumps modulate the speeds to maintain the required user flow rate through the system. Chilled water is distributed throughout the existing campus via a spine rack and network of piping.

The cooling services provided in the Phase 2 CUB will be extended to the API manufacturing facility.

6.6 Low Temperature Hot Water (LTHW)

LTHW for the existing Biopharma manufacturing facility is generated through the use of 3 No. steam to LTHW plate heat exchangers which are factory-assembled with dedicated controls. LTHW for the existing Lab, Administration building & Phase 1 Warehouse is generated through the use of 3 no. LTHW Gas Boilers with dedicated controls.

The LTHW is distributed throughout the facility to the air handling units, reheat coils and unit heaters via a network of piping. The LTHW distribution utilises variable frequency drive (VSD's) pumps to meet the building demand.

The LTHW provided in the Phase 2 CUB will be extended to the API manufacturing facilityty

6.7 Compressed Air

Compressed air is supplied across the entire site via 4 No. air compressors (3 Duty and 1 Standby) and associated filters. The system will provide compressed air to 2 No. headers, 1 No. for process air and 1 No. for instrument air in the existing Biopharma manufacturing facility.

Compressed air for the API manufacturing facility will be supplied via tie-in from the existing BDS manufacturing facility at a pressure of approximately 7 barg. A single compressed air supply will be used for driving instruments, valves and pumps.

6.8 Water

6.8.1 Water Supply

The existing water supply in the local area is provided and serviced by Irish Water's water supply infrastructure. It is provided by a 400mm diameter public watermain located outside the eastern boundary of the site. A 200mm diameter internal main distributed water within the site. This mains supplies a 940m^3 capacity on-site process water storage tank as well as the 718m^3 on-site fire water storage tanks. There is also a separate 100mm diameter metered connection from an Uisce Éireann main located at the southeastern corner of the site.

The API expansion development does not require a new potable water supply connection. It is intended to utilise the existing Uisce Éireann connection to facilitate the slightly increased supply.

The 940m^3 site water storage tank is designed to ensure a minimum of 24 hours back up storage is available in the event of any interruption to service supply.

6.8.2 Water Treatment

Chemical Dosing (Closed Systems)

A number of the existing campus water systems require chemical dosing to prevent corrosion and minimize bacterial build up. These include:

- Low Temperature Hot Water Systems;
- HVAC Chiller Water Loops ;
- Glycol Chiller Water Loop;

A water treatment vendor was appointed by Alexion to supply chemicals and maintain all of the water treatment systems on site. No bulk storage is required on site for these water treatment chemicals as the appointed water treatment vendor maintains these systems and ensures that they are continuously topped up as required.

For the open cooling tower and steam boiler systems the water treatment vendor provides the necessary controls, operational tanks, quills, pumps, etc. to satisfy the requirements of the water being treated.

6.9 Biopharma Manufacturing Facility Specific Utility Requirements

6.9.1 Gaseous CO_2

CO_2 is required for pH control in bioreactors within the existing BDS manufacturing building. This is supplied by pressure transfer through a vaporiser from a Liquid CO_2 storage vessel in a dedicated compound within the CUB yard. The tank has the necessary equipment for regulating pressure, pressure relief and road tanker connection for tank refill.

There is no large bulk tank required for CO2 for the new API manufacturing facility.

6.9.2 Gaseous O_2

O_2 is required for maintaining dissolved oxygen levels in bioreactors within the BDS manufacturing building. Liquid O_2 is pressure transferred through a vaporiser from a storage tank ($20m^3$) located in a dedicated compound within the Phase 2 CUB yard. The tank has the necessary equipment for regulating pressure, pressure relief and road tanker connection for tank refill.

There is a small speciality supply of O2 required for the new API manufacturing facility which will be supplied in gas bottles.

6.9.3 5m (20%) Sodium Hydroxide (NaOH) (Product Contact)

Sodium Hydroxide(NaOH) (pharma grade) is used throughout the BDS manufacturing building for various processing steps. It is delivered to site in $1m^3$ IBCs and stored in the Base store in the Warehouse.

There is a Sodium Hydroxide skid in the BDS manufacturing building level 0 plant room. IBCs are moved from the Warehouse Base store as required and pumped from this skid to the points of use throughout the BDS building.

6.9.4 CIP 100 , Proklenze Two & Proklenze Booster

Clean in place (CIP) cleaning solutions CIP 100 , Proklenze Two & Proklenze Booster are used for CIP activities within the existing Biopharma manufacturing facility. These CIP solutions are delivered to site in $1m^3$ IBCs and stored in the Warehouse Acid and Base stores.

There is a dedicated CIP Supply Skid for each of the CIP chemicals located in the BDS Level 0 Plant Room, IBC's are connected to the CIP supply pump that delivered CIP chemicals to the CIP Skid.

6.9.5 Ethanol

Ethanol (18% w/w concentration in water) is delivered to the site in 1m^3 IBCs and stored in the existing ambient warehouse. It is used for the sanitisation and storage of chromatography resins.

IBCs are supplied to the Ethanol room in BDS manufacturing building from the Warehouse as required. IBCs are placed on the upper level of the Ethanol Skid, connected to the storage tank via pipe and the IBC is drained. The ethanol solution is pumped from here to the purification area via a closed pressurised loop to the chromatography suite for column regeneration (cleaning) and storage of the columns.

6.10 Chilled Glycol

Chilled Glycol water is generated at the existing campus through the use of 2 No. screw variable speed drive (VSD) chillers. The fluid is a mixture of 10% propylene glycol with water. A primary / secondary pumping arrangement is utilized to distribute chilled glycol water to users throughout the existing BDS manufacturing facility.

The primary pumps set a predetermined speed using the VSD's and the secondary pumps modulate the speeds to maintain the required user flow rate through the system. Chilled Glycol water is distributed throughout the Biopharma manufacturing facility via a spine rack and network of piping.

The chillers have heat pump capability on the condenser side to generate LTHW 45/35°C water when required. Cooling tower water is also available via a plate heat exchanger on the LTHW heat recovery circuit if no heating is required to keep the chillers in operation.

Chilled Glycol water pipe sizing is based on a maximum velocity of 3.0 m/sec and a maximum pressure drop of 300 Pa/m. By maintaining the pipe velocities and pressure drops within these parameters, the noise generated from these fluids is minimized.

50% Ethelyne glycol provided in drums will be used in a closed system at the new API manufacturing facility for production cooling requirements.

6.11 API Specific Utility requirements

6.11.1 Process Air

Process air will be required for blow down of Process Water user points post use. There will be a process air take off from the compressed air distribution on each floor with 1 micron hydrophobic filters and sample points for quality sampling.

6.11.2 Breathing Air

A dedicated compressed air generation system will be installed to supply breathing air to user points within the API manufacturing building and the chemical material store. The BDS building compressed air supply is not suitable for breathing air due to the supply dew point of -70°C. The current sizing basis for the breathing air distribution is for two breathing air suits to be connected simultaneously i.e. 48m^3/h at 4barg. The air quality should align with the requirements of EN12021.

Standby compressed air cylinders will be installed as backup in case of failure of the breathing air system. The breathing air suit manufacturer will need to be agreed at detailed design. A suit with in-built pressure regulator similar to the following example from Dräger will be used.

No external breathing air points will be installed as any external hazardous spills will be dealt with by the Emergency Response Team (ERT).

6.11.3 Vacuum Pumps

Vacuum pumps are required for vacuum distillation operations in reactors and crystallisers. Two dry running vacuum pump skids will be installed to provide vacuum to both medium and large trains

as well as a connection to the continuous backbone. Each vacuum pump skid will include vacuum pump, condensers, knock out pots and associated piping and instrumentation as required.

It is expected that only one vessel will be connected to the vacuum at any one time. A manifold arrangement allows the user to switch one of the trains to a different pump in case of a failure of one of the vacuum pumps.

A dedicated vacuum system will be provided for each filter dryer.

6.11.4 Heat Transfer Fluid

As part of the new API manufacturing facility, a centralized heat transfer fluid system will supply the process heating and cooling requirements to the batch process suites and vacuum pumps. The heat transfer fluid will be an ethylene glycol/ water mixture which will be pressurized. The heating and cooling requirements for the processes are as follows:

- Maximum Process Operating Temperature 120°C
- Minimum Process Operating Temperature -10°C

Hot Heat Transfer Fluid (135˚C)

The hot heat transfer fluid will be generated using 8 Barg plant steam from the central distribution system.

The hot heat transfer fluid will be provided with duty/standby distribution pumps and duty/assist heat exchangers to provide redundancy of the equipment. The system will also be provided with a buffer tank to smooth out the return temperature of the inlet of the heaters.

Cold Heat Transfer Fluid (-25˚C)

The cold heat transfer system will be chilled by 2 no. ammonia chillers cooled with cooling water. Each chiller will be sized to provide the entire peak low temperature chilling load of 460 kW. Thus providing N+1 redundancy. The chillers will be located external to the API building within a ventilated enclosure. The enclosure will be provided with an ammonia gas detection system to detect any ammonia released into the room due to a leak. If a leak does occur a dedicated extract system will remove the ammonia.

The cold heat transfer system will be provided with a buffer tank. The buffer tank will be divided into a warm well and a cold well. These wells will be separated by a perforated baffle. The chillers will take heat transfer fluid warm section of the tank, chill the fluid and return it to the cold section of the tank. The cold heat transfer fluid distribution pumps will take fluid from the cold section of the tanks.

Both the chiller circulation and the cold heat transfer fluid loops will be provided with duty/stand-by pump-sets.

7 Main Alternatives

Discussion on the alternatives considered during project design phase of the existing Biopharma manufacturing facility and new API manufacturing facility is included in this IEL review application in *Attachment-4-7-1iv-REF ECM.*

As part of the Environmental Impact Assessment Report (EIAR) submitted to Fingal County Council (Planning Ref. No. FW22A/0300) in December 2022, there were a number of alternatives considered for the new API Manufacturing Facility, including an explanation of what environmental factors were considered and influenced the selection of the preferred option. Please refer to the EIAR for further details on the alternatives considered. The EIAR is included with this IEL review application as *Attachment-6-6-1-EIAR-Planning-Dec-2022.* A summary of the consideration of alternative from the EIAR is included here.

7.1 The Need for the Project

As a leading global healthcare company AstraZeneca requires *'state of the art'* production facilities containing the latest technology and digital innovation to expand their internal capability for late stage development and early commercial supply of small molecule Active Pharmaceutical Ingredients (APIs) to meet the future growing drug pipeline. To meet this objective it was decided that a new API facility was required, to target the high value, low volume, highly potent products within AstraZeneca's future portfolio. 'Do-nothing' scenario does not apply.

7.2 Manufacturing process

Traditionally the manufacture of pharmaceutical products is carried out either through a chemical or biological process. To support the production of small molecule APIs, small molecule technology is required which can only be completed using a chemical process.

7.3 Selection of Preferred Site/Location for the Development

7.3.1 Alternative Sites

It was deemed necessary to co-locate the additional manufacturing capacity adjacent to an existing pharmaceutical supply chain facility, to ensure logistical efficiency and environmental sustainability. The option of developing at a new greenfield or brownfield site, not already within Alexion's ownership, was considered an 'unreasonable alternative' for this project principally due to the increased timeframe associated with developing a new site which would significantly impact the ability to serve AstraZeneca's patients.

The selection of the preferred location for this project involved careful consideration of a broad range of factors, all of which were deemed critical to the success and viability of the project. Key factors amongst these considerations were factors with potential environmental consequences, in particular;

1. Support and Capacity
   The availability of a site with existing supporting business functions capable of accommodating the proposed expansion;
2. Access and Connectivity
   The availability of sustainable access to the site capable of supporting traffic associated with the site development and future manufacturing operations;
3. Environmental Setting
   An environmental setting consistent with and compatible with the nature of manufacturing proposed, in terms of zoning policy and adjacent land uses; and
4. Utility Capacity
   A site with established or available utility connections capable of supporting the proposed biopharmaceutical manufacturing processes, including; power, natural gas, water, wastewater, surface water, and communications.

On the basis of the factors above, it was determined that the preferred location for the new API manufacturing facility is the Alexion Biopharmaceutical Manufacturing Camus located at College Business and Technology Park, Blanchardstown, Dublin.

7.4 Alternatives Conclusions

Locating the project within Alexion's existing Campus provides the opportunity to draw from established practices and competencies available at the existing facility. The campus has the space to accommodate the required scale of production and lands to surrounding the existing facility are optimum from both operational and environmental perspectives. The selection of this site ensures logistical efficiencies are achieved while linking well with services, car parking and the administration functions in the campus. The selected lands are well located in respect of adjacent receptors. Consolidated building forms are proposed; that visually match the existing facilities and provide a coherent visual appearance that supports the campus feel of the overall complex.

Alternatives were considered as part of the site selection, layout, design and process for the project. The preferred project solution achieves the project objectives in respect of operational and environmental requirements.

An outline description of the main alternatives to the proposed technology, techniques and measures which were studied by Alexion and AstraZeneca during the design of the new API manufacturing facility, has been prepared against the BAT reference document on Economics and Cross-Media Effects (2006), and is included in this Licence Review application as *Attachment-4-7-2-4-REF-ECM.*