GlaxoSmithKline Cork

– Capacity & Capability

November 2010

GSK Cork Presentation Contents

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Section 1

- Site Role
- Facilities Overview
- Key Strengths & Capabilities

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- Available Manufacturing Facilities & Capacity
- Pilot Plant and Milling Facilities

Section 3

- New Product Introduction Capability
- Operational Excellence Capability
- Supporting Technology & Physical Properties Laboratory Capability

Section 4

- Environmental & Solvent Recovery Capability

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Section 1

- Site Role
- Facilities Overview
- Key Strengths & Capabilities

GSK Cork - Background

Operations commenced 1975

Site role within GSK: **New Product Introduction & Global Supply**

- Clinical supplies and scale up in co-located R&D Pilot Plant
- Industrialisation of New Products to provide supplies for validation and launch and to develop the final most cost effective, robust and environmentally sustainable commercial process
- Global Supply site during growth phase of product lifecycle for key products
- Capacity available for Third Party manufacture
- High containment manufacture (30 nanograms/m^3)
- Intermediate Drug Product Manufacture for compounds with poor bio-availability through use of Wet Bead Milling and Spraydrying capability

Supported by Extensive Laboratory Facilities including state of the art Physical Properties Laboratory

Facilities Overview

Land in Use at GSK Cork – 70 acres

Land Available at GSK Cork – 85 acres

Facilities at GSK Cork – 155 acres

Central Milling Facility

Building 9
R&D Pilot Plant

R&D Pilot Plant

Environmental Facilities

Waste water treatment

Incinerators & one thermal oxidiser

VOC Abatement / Scrubbing System

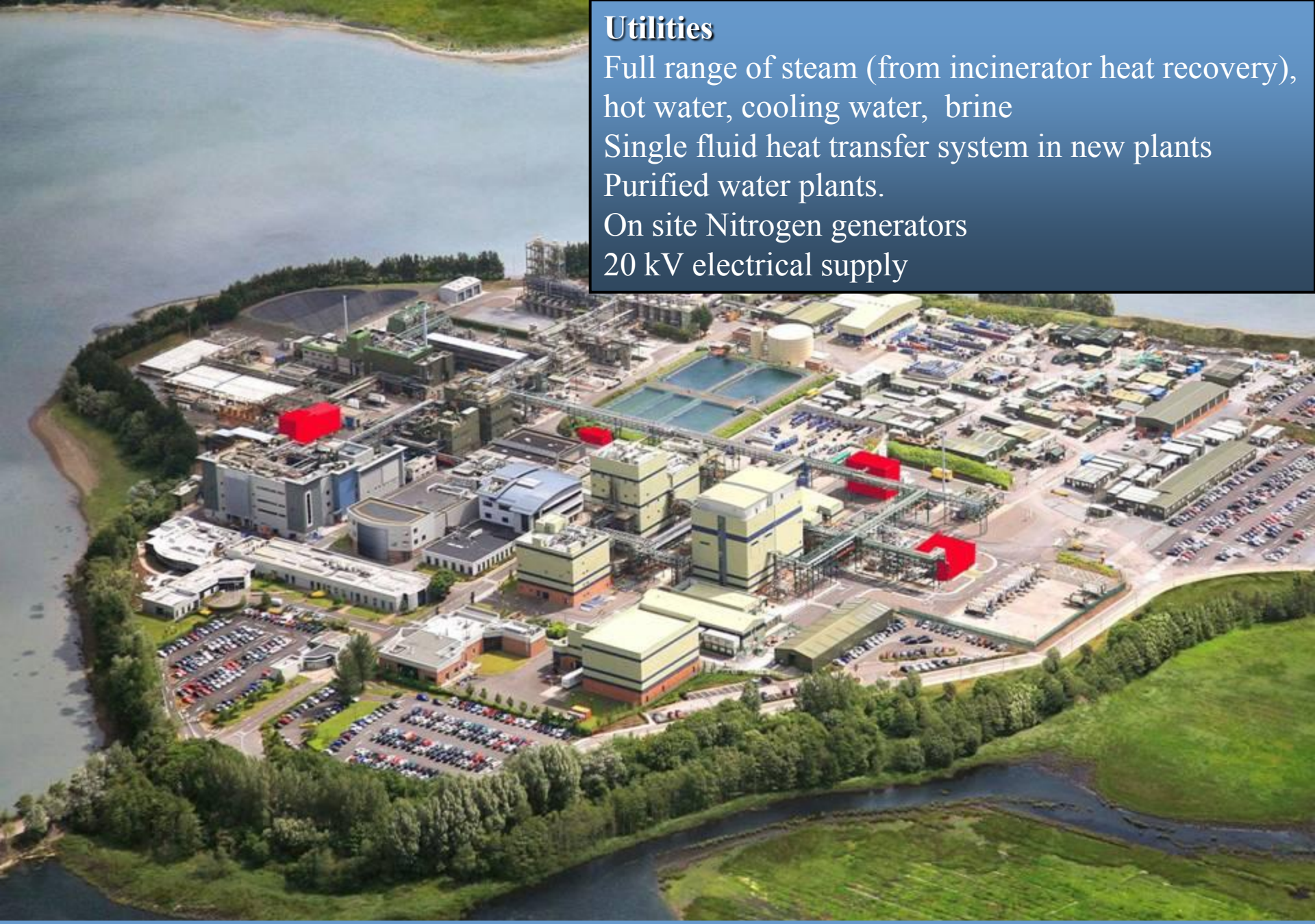
Solvent and waste storage

Solvent recovery plants

Chemical treatment

Waste heat to steam generation plant

Environmental Facilities



Utilities

Full range of steam (from incinerator heat recovery), hot water, cooling water, brine

Single fluid heat transfer system in new plants

Purified water plants.

On site Nitrogen generators

20 kV electrical supply

Utilities

Other facilities

Quality Control & development laboratories
Research & Development Lab
Physical Properties Lab
Offices / locker rooms
Cafeteria
Meeting Rooms
Document Archive

Other Facilities

GSK Cork – Key Strengths and Capabilities

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Compliance
- 12 FDA Inspections, 11 with zero findings on form 483
- Strong audit compliance with Environmental Protection Agency and Health & Safety Authority

Integrated R&D/Product Transfers
- Co-location of R&D Pilot Plant - 7 yrs of Phase 2/3 manufacture and scale-up/development
- Capability for internal transfers - 20 multi-stage new products validated since 1990
- Capability for external transfers - 35 projects outsourced in last 3 years

Manufacturing / Technology
- Wide range of chemical reactor scale (30 - 16,000 Litres)
- Experience of manufacturing 400MT+/annum to less than 10kg/annum (per product)
- Wet Bead Milling / Spraydrying Pharmaceutical Development plant for scale-up of poorly bio-available compounds, producing drug product intermediate for clinical / commercial supply
- High containment facilities for highly potent cytotoxic compounds, pioneers in glovebox technology
- State of the Art Automation and PAT systems
- New Laboratory Information System installed Q2 2010

Sustainability
- Best Available Technology (BAT) for solvent recovery, incineration and waste water treatment
- Solvent emissions less than 1% of licensed limits (< 1MT per annum)
- Largely self sufficient regarding treatment of waste

Government support
- Low Corporation Tax rate (12.5%)
- Government support for R&D capital/research projects and R&D Tax Credits
- Unique network of Industry/Government/Academic linkages
- Networked cluster of Big Pharma in Ireland - strong collaboration and sharing of best practice

GSK Cork – Employees

Total Number of employees:

- GSK Cork Site employees: 367
- Technical Shared Service employees based at Cork: 40
- R&D Cork employees: 32
- Others (above site, universities, etc): 24

Qualifications*:

- PhD/Masters degree ~ 56
- BSc/3rd level ~ 130
- Process Operators/Crafts ~ 180
- Staff turnover rate ca. 1% (but 4% historically)

*GSK Cork Site employees only

GSK Cork Presentation Contents

Section 2

- Available Manufacturing Facilities & Capacity
- Pilot Plant and Milling Facilities
- Slides 18 to 37 give a summary of the facilities that could be made available for external / sharing business. These facilities are backed up by significant technical capability and expertise that resides on the site.

API & Intermediate Plant - Building 3 Module 2

Building 3
Module 2

- A large scale multipurpose processing plant for API's and Intermediate stages
- Built in 2007 at a cost of €70M
- Highly flexible processing module – API or Intermediate finishing areas
- 1 Glass Lined and 1 Hastelloy reactor vessels
- 4,000L to 16,000L scale of wet end processing
- 2 Hastelloy Filter Dryers available – each $6m^2$
- Sieve available on discharge train
- PAT devices installed
- Remote manual or batch sequence operation with electronic batch record
- OHC 3 (>10$\mu g/m^3$) capability installed for charging
- OHC 3 (>10$\mu g/m^3$) capability for offload
- Batch size 720kg to 1680kg (Process dependant)
- Typical Capacity 200 to 1100MT (Process dependant)

API & Intermediate Plant - Building 3 Module 2 Processing Equipment

Building 3 Module 2

3rd

Bulk Solvent Manifold

Plant Room (Combivac Vacuum Pumps/ Nitrogen Recirculation System)

Solids Charging Room (Visual Contained Charging System)

WHTK 1
1000L
316L SS

Dedicated Purified Water Generation Plant [Located External]

2nd

Venting to Lean Gas & Zone 0 Headers

Lasentec & on Crystalliser

RV-2
16000L
GLCS

RV-1
12500L
Hast C22

Control Room

FDR-3501
6 m²
Hast

Mass Spec for Dryer & Blowback End-Point Detection

FDR-3502
6 m²
Hast

1st

Dowtherm Skids

API Polishing Filter Skid

Low Shear Slurry Transfer Pumps

Ground Floor

Drum Charge Station

RCV - 1
4000L
GLCS

RCV - 2
8000L
GLCS

RCV -3
8000L
GLCS

Heel Reslurry Vessel

Mother Liquor Receivers

SI-1
Hast

SI-2
Hast

API & Intermediate Plant - Building 2

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- A medium/large scale multipurpose processing plant for API's and Intermediate stages
- Highly flexible processing module – API and Intermediate finishing areas
- 4 Glass Lined and 3 Hastelloy reactor vessels
- 1,500L to 7,500L scale of wet end processing
- 2 Hastelloy Filter Dryers available – each $3m^2$ - 1 API and 1 Intermediate
- API discharge train sieve installed
- PAT devices available
- Remote manual or batch sequence operation with electronic batch record
- OHC 4 (>1$\mu g/m^3$) capability installed for charging
- OHC 3 (>10$\mu g/m^3$) capability installed for offload
- Batch size 315kg to 750kg (Process dependant)
- Typical Capacity 40 to 250MT (Process dependant)

API and Intermediate Plant
Building 2 Processing Equipment

Building 2

Roof

Bulk Solvent Manifold

Vent Manifolding to Scrubber / Incinerator

2nd

HTK-1
250L
GLCS

RV-1
6300L
HC22
PTS
Temp Loop

RV-2
8000L
GLCS
Lasentec
or
Turbidity

1st

HTK-2
1600L
GLCS
Sampler

HTK-3
900L
316L

RV-3
6300L
GLCS

RV-4
6300L
GLCS

RV-5
4500L
GLCS

RV-6
6300L
HC22

GB-1
316L

RV-7
6300L
GLCS
Sampler

FDR-1
3.0 m²
HC22

FDR-2
3.0 m²
HC22

GB-2

Ground Floor

RCV-1
6300L
GLCS

RCV-2
4000L
SS

Receiver

Drum
Charge Stations X 3

Location for
CUNO, Calmic Filter,
Polishing Filters

CT-1
600mm bowl
316L
Chilled solvent

Pall
Box

Discharge Room 3

RCV-3
4000L
GLCS

RCV-4
4000L
GLCS

Mother Liquor & Wash
Receivers

Lumpbreaker

Sieve

Bags

Discharge Room 1

Bags

Discharge Room 2

API or Intermediate Plant - Building 7

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- A medium scale multipurpose processing plant for API and Intermediate stages
- 2 Glass Lined reactor vessels
- 1000L to 4000L scale of wet end processing
- 1 Stainless Steel Filter Dryer (1.5m^2)
- 1 glovebox for contained charging
- 1 glovebox for contained sampling of reactor vessels
- Remote manual or batch sequence operation with electronic batch record
- OHC 4 (> 1$\mu g/m^3$) containment for charging
- OHC 3 (> 10$\mu g/m^3$) containment for offload
- Batch size 158kg to 400kg (Process dependant)
- Typical Capacity 20 to 130MT (Process dependant)

API or Intermediate Plant – Building 7 Processing Equipment

2nd Floor

Solvent Manifold:
IMS; THF; EtAc;
Toluene; Acetone;
Methanol;
Process Water

RV-2
4000L
GLCS

GB-2
316L
Sampling G'Box

RV-1
7000L
GLCS

GB-1
316L

Vent Manifolding to Incinerator

HTK-12
1300L
GLCS

Building 7

1st Floor

Operator Control Area
[DeltaV Automation]

Location for
GAF,
Polishing Filters

RCV-1
200L
316L SS

Area Guard
Receiver

FDR-1
1,5 m²
316L SS

Ground Floor External

Note: External Road Tanker Loading
Waste disposal facility

Note: External Drum Staging Area

Ground Floor

Drum Charge
Station
(2 pumped routes)

RCV-2
7080L
316L SS

RCV-3
4000L
316L SS

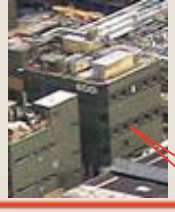
Receivers

Discharge
Room

ML1
316L SS

Continuous
liner

Intermediate Plant - Building 6



- A medium to large scale multipurpose processing plant for Intermediate stages
- 4 Glass Lined reactor vessels
- 2,000L to 8,000L scale of wet end processing
- 1 Hastelloy Filter Dryer ($3m^2$) and 1 Stainless Steel Filter Dryer ($3m^2$)
- 2 gloveboxes for contained charging
- Wiped Film Evaporator
- Large in - process solids filter
- Remote manual or batch sequence operation
- OHC 4 (> $1\mu g/m^3$) containment for charging
- OHC 3 (> $10\mu g/m^3$) containment for offload
- Batch size 360g to 840kg (Process dependant)
- Typical Capacity 50 to 275MT (Process dependant)

Intermediate Plant – Building 6
Processing Equipment

Building 6

2nd Floor

HTK-1 2165L 316L SS

HTK-2 450L GLCS

HTK-3 1600L GLCS

HTK-4 600L 316L SS

GB-1 316L

GB-2 316L

Vent Manifolding to Incinerator

1st Floor

Wiped Film Evaporator 698L 316L

RV-1 6300L GLCS

Filter-1 1.6m2 316LSS

RV-2 8000L GLCS

RV-3 7000L GLCS

RV-4 7000L GLCS

FDR-1 3.0 m² HC22

FDR-2 3.0 m² 316L SS

Ground Floor

Location for CUNO,, Polishing Filters

Discharge Room 1

Discharge Room 2

Continuous liner

RCV-1 2039L 316L SS

RCV-2 5500L GLCS

RCV-3 6000L 316L SS

Mother Liquor & Wash Receivers

RCV-6 4500L 316L SS

Drum

Drum Charge Stations X 2

RCV-4 14200L 316L SS

RCV-5 7000L 316L SS

Receiver

Ground Floor External

Intermediate Plant - Building 1 Module 33

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- A medium/large scale multipurpose processing plant for Intermediates stages
- 1 Glass Lined and 1 Hastelloy reactor vessels
- 1,500L to 6,000L scale of wet end processing
- Can operate with module 32 or as a stand alone module
- 1 Stainless Steel Filter Dryer – $3m^2$
- OHC 3 (>10$\mu g/m^3$) capability installed on FDR discharge
- Remote manual or batch sequence
- Batch size 300kg to 735kg (Process dependant)
- Typical Capacity 40 to 240MT (Process dependant)

Intermediate Plant - Building 1 Module 33 Processing Equipment

Building 1
Module 33

Venting available to HCL Scrubber & incinerator

Bulk Solvents:

Third floor

FDR1
3m2
316L

HTK1
1000L
GLCS

Second floor

Discharge Area

RV1
6300L
GLCS

First floor

Drum Charging booth

RV2
6300L
Hast C22

HTK2
500L
316 SS

Ground floor

RCV1
3400L
GLCS

RCV2
6300L
GLCS

Intermediate Plant - Building 1 Module 3

- A medium/large scale multipurpose processing plant for intermediate stages, currently used for GSK products with up to 50% capacity available
- 4 Glass Lined and 2 Hastelloy reactor vessels
- 1,000L to 6,300L scale of wet end processing
- 6m^2 Stainless Steel Filter Dryer + 4m^2 Hastelloy Filter Dryer available
- 2,000L off-line Agitated Pan Dryer available
- PAT devices installed
- Remote manual or batch sequence operation
- OHC 3 (>10$\mu g/m^3$) capability for charging and offload
- Batch size 315kg to 1680kg (Process dependant)
- Typical Capacity 40MT to 550MT (Process dependant)

Intermediate Plant - Building 1 Module 3 Processing Equipment

Building 1
Module 3

2nd

Bulk Solvent Manifold

HTK1
250L
GLCS

HTK 2
2500L
GLCS

RV 1
4000L
GLCS

HTK3
2500L
GLCS

RV2
6300L
GLCS
Turbidity

Venting to Incinerator

2 X Charge booths
2X PTS Charge Booths
316L SS

FDR1
6.0 m²
316L SS

Mass Spectrometer on Vent and Run 0ff

OHC 3 Containment

316L SS

1st

Discrete Services

RV3
4800L
GLCS
Single fluid

RV 4
6400L
GLCS

RV5
6300L
HC22

RV6
4800L
HC22

Ground Floor

RCV1
6000L
316L SS

Receiver

RCV2
6500L
304SS

Mother Liquor & Wash Receivers

1 X Drum Press
(Drum Heater)

1 X Contained Drum Discharger
1 X Booth

Small Scale High Containment Plant - Building 5

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- A small scale multipurpose processing plant for API's and Intermediate stages
- OHC 5 (< 1μg/m^3) capability and highly flexible processing module
- 6 Gloveboxes
- Dedicated development & QC analytical laboratory
- 2 Glass Lined and 1 Hastelloy reactor vessels
- Hydrogenator
- 5L to 44L scale of wet end processing
- 1 Hastelloy Filter Dryer
- Remote manual or batch sequence operation with electronic batch record
- Batch size 300g to 4.5kg (Process dependant)

Small Scale High Containment Plant - Building 5 Processing Equipment

Dispensing Area	3 x Gloveboxes and 2 x fumehoods Solvent Charging fumehood (pressure kettles)	GMP QC Analytical Lab + Development Lab	Utilities area

Upper Level

Lower Level

Vent to Inert Header via HEPA filter

GB-1
316L SS
1 x gaf
Duty/Standby
filters

GB-2
316L SS

GB-3
316L SS
2 x cartridge filters

FDR-1
0.035 m²
Hast

HTK-1
25L
GLCS

RCV-1
200L
GLCS

RCV - 2
200L
GLCS

RV-1
44L
Hast C22

RV-2
44L GLCS

RV-3
44L GLCS
r

GB-4
316L SS

Receivers

External

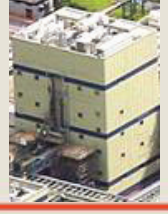
Drum Charge
Stations X 4

Waste Drum Filling
Containment System

Hydrogenation
manifold

Summary of Pilot Plant & Milling Facilities Available

R&D Pilot Plant



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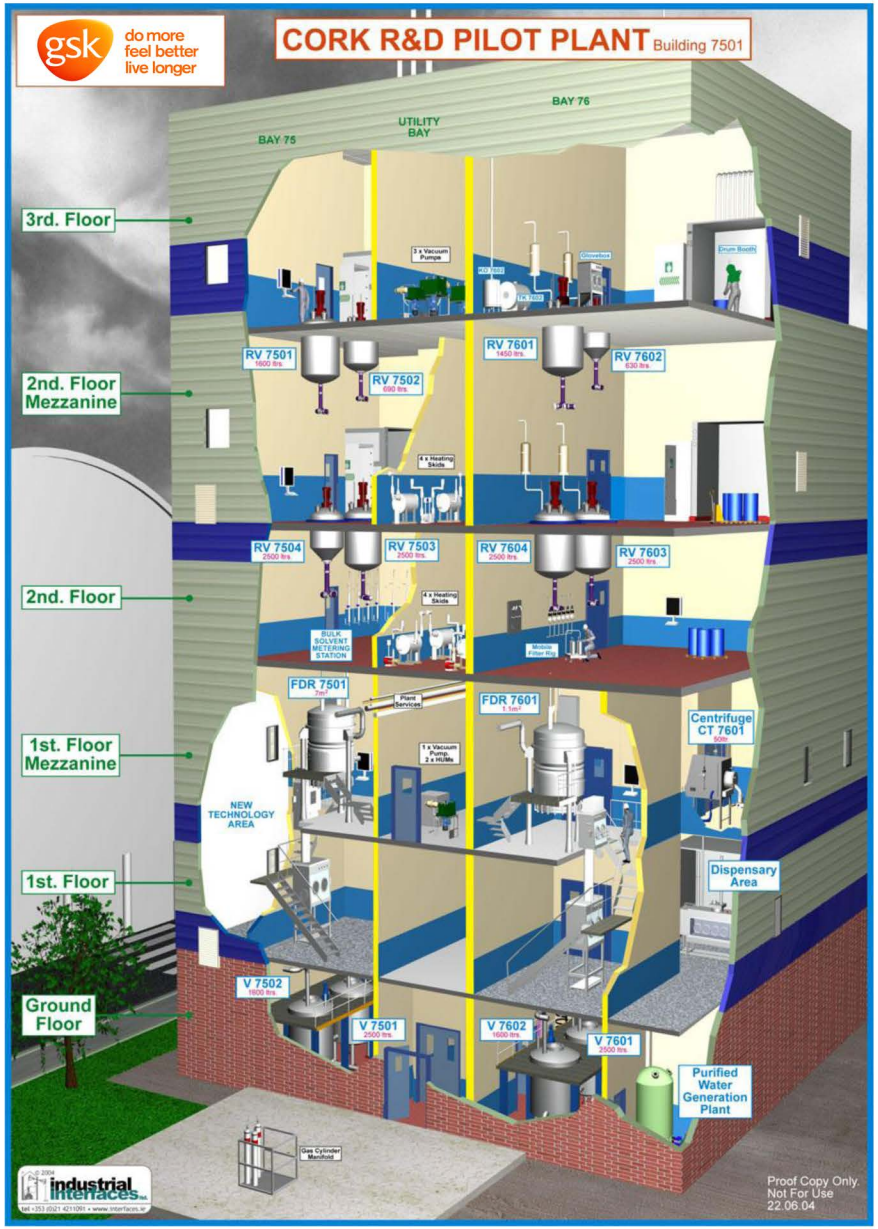
- Contains 2 modules with up to 2,500 Litre reactors
- Highly flexible for multiple chemistries– can introduce products within 4 weeks and at less than €50-100K capex
- Suitable for introducing new products to the site, scale up/development and clinical supplies
- Flexible quality systems that can be used for validation and launch supplies.
- Plant has manufactured API for commercial markets
- Supported by the R&D technical team and R&D site laboratory

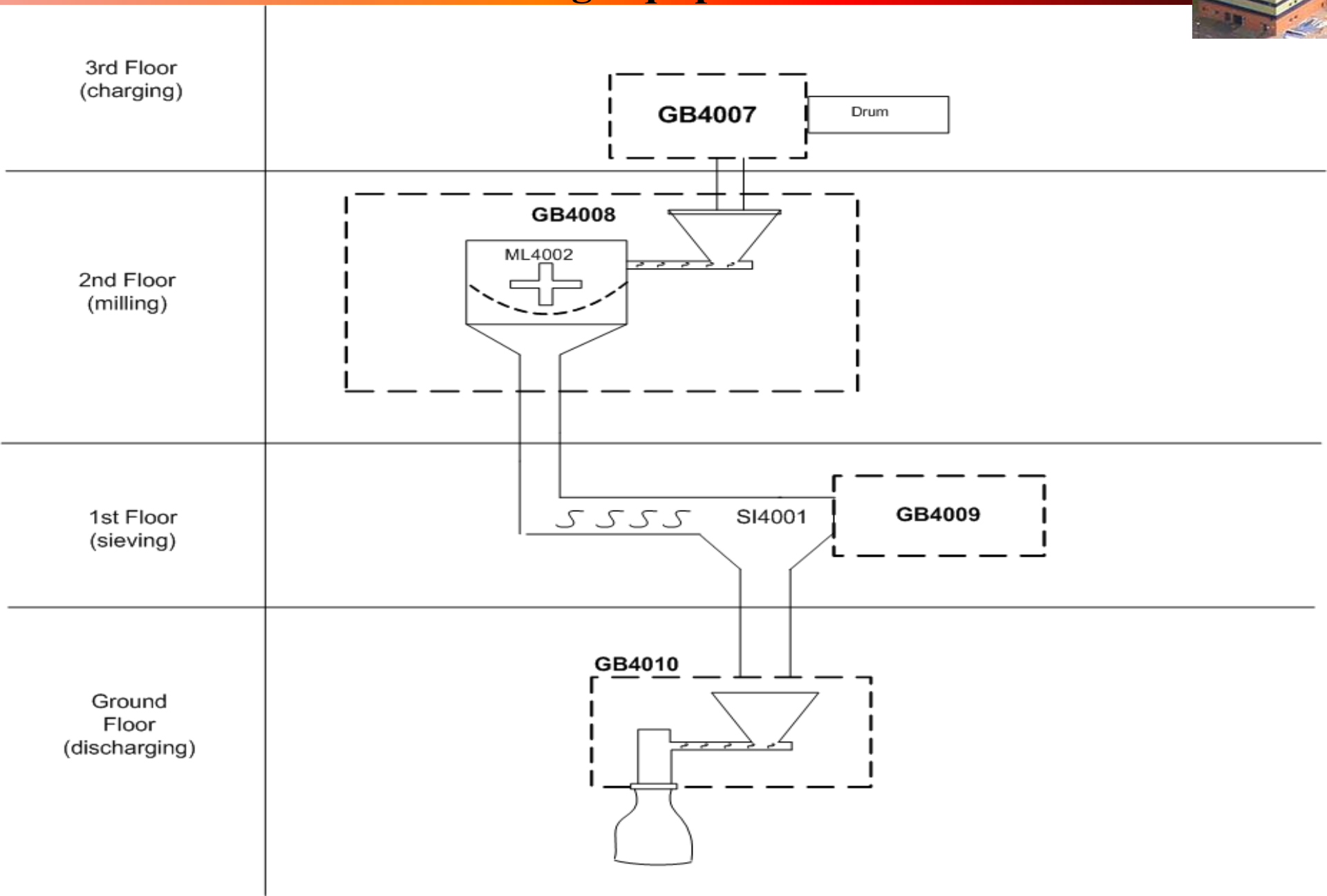
R&D Pilot Plant
Processing Equipment



Dry Milling Suite

- Meets GMP standards for final milling and handling of API (class 100,000)
- Segregated suite with 3 Floors
- Air Classifier Mill (316L SS) and final kegging/packaging through a glovebox
- Suitable for products with exposure limits to 10 micrograms/m^3

Dry Milling Suite
Processing Equipment



Wet Bead Milling / Spraydrying Suite

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- Segregated suite suitable for wet bead milling and spraydrying of API and excipients
- Patented GSK Technology
- 3 Floors
- 11 Wet Bead Mills
- Spray drier (316L SS PSD3 NIRO)
- Capacity of 15 - 20MT API equivalent per annum

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Section 3

- New Product Introduction Capability
- Operational Excellence Capability
- Supporting Technology & Physical Properties Laboratory Capability

New Product Introduction Capability

- **Very strong record for introduction of new products**
  - Experienced technical staff

- **Co-located R&D Pilot Plant**
  - Clinical Manufacture for phase 2/3 and validation to support launch
  - Highly flexible facility, suitable for process development and scale up

- **Flexible industrialisation facilities**
  - Manufacture of New Products to provide supplies for validation and launch and to develop the final most cost effective, robust and environmentally sustainable commercial process

- **Excellent site support infrastructure**
  - Synthetic chemistry & analytical labs
  - Engineering lab
  - Physical Properties laboratory to assess suitability for formulation

- **Experienced in working closely with secondary customers to minimise DP impact**

- **Strong relationship with R&D**

- **Strong links to academia in Ireland and abroad**

Operational Excellence Capability

- Master Blackbelt: 2
- Blackbelt Certified: 3
- Blackbelts in training: 4
- Greenbelt Trained: 94
  - Certified: 62
- Advocate* Trained: >220
  - Certified: 180

*3 levels

- OE builds smarter, simpler and sustainable processes and ways of working

- OE reduces variation, eliminates waste and improves process efficiencies

Supporting Technology

- The plant is highly automated with Delta V batch software control. For some processes the eBR system is used to generate an Electronic Batch Report.
- Sophisticated temperature control
- The production plant is designed for quick changeover between products by allowing each vessel in the processing train to be cleaned independently.
- High containment facilities for highly potent cytotoxic compound - pioneers in glovebox technology
- **Process Analytical Technology**
  - Reaction Monitoring (solution spectroscopies **IR, NIR, UV**)
  - Crystallisation monitoring (in slurry: **Lasentech, Turbidity**)
  - Distillation monitoring (Solution Spectrocopies in the vessel, **Mass Spec and NIR** for distillate lines)
  - Isolation and Drying monitoring (**Mass Spec**)

Physical Properties Laboratory Capability

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Cork have a range of techniques that can be used to assess:

- Physical nature of the material
  - Optical Microscopy
  - Scanning Electron Microscopy (SEM)
  - X-Ray Diffraction
  - Tap Bulk Density (TBD)
  - Particle size measurement (Malvern and Sympatec instruments)
  - Air-jet sieving/ultra-sonic sieving
  - Viscometry

- Sorption Properties
  - Surface Area
  - Gravimetric Vapour Analysis (GVS)
  - Equilibrium Relative Humidity (ERH)

- Thermal Properties of the material
  - Differential Scanning Calorimetry (DSC)
  - Thermogravimetric Analysis (TGA)

Laboratories

Quality Test Laboratory	Physical Property Laboratory
• Classic wet chemistry techniques • TLC • Melting Point • FT-IR, ATR • Heavy Metals • Sulphated Ash (ROI) • Loss on Drying • Halogen Moisture Analysis • Karl Fischer (coulometric, volumetric) • Specific Rotation • Dionex • HPLC (including chiral HPLC etc.) • GC (direct injection, headspace) • UV Spectroscopy • LC-MS • LC-MS-MS • ICP-OES • NMR	• PSA – Particle size analysis (Malvern Mastersizer S, 2000 and Sympatec Helos) • SEM – Scanning electron microscopy (LEO EVO 40XVP) • XRPD – X-ray powder diffraction (PANalytical X'Pert PRO MPD) • DSC – Differential scanning calorimetry (TA Instruments Q1000) • TGA – Thermogravimetric analysis (TA Instruments Q500) • GVS – Gravimetric vapour sorption (Hiden Isochema IGA*Sorp*) • OM – Optical microscopy (Micron Optical E600POL) • SSA – Specific surface area (Micromeritics TriStar 3000) • TBD – Tap bulk density (Varian VanKel) • AJS – Air Jet Sieve (Hosakowa micron/Hosakowa Alpine) • Sonic Sifter – Classification/sizing • Viscometry

Other Laboratory Facilities

- Chemistry
  - Jacketed vessels
  - Multimax (facilitating DOE)
  - Hydrogenation facilities
- Engineering
  - 0.03m2 filter-dryer
  - 10Lt and 15Lt jacketed vessels
  - Solvent recovery rig
  - Facility to wheel equipment in for trials

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Section 4

- Environmental & Solvent Recovery Capability

Environmental Operations

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- There is an extensive environmental operation on site.
- The following activities are carried out:
  - High temperature Incineration (2 Plants) with surplus capacity
  - Waste Water Biological Treatment
  - Chemical Treatment
  - Solvent Recovery(see next slide)
  - Storage of liquid and solid wastes and raw materials

- The plant is operating under the terms of an EPA Integrated Pollution Control Licence and management and control of wastes / emissions is a significant part of the requirements.

Solvent Recovery

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- There are two large solvent recovery plants on site (1 Multi Purpose Unit & 1 Batch Recovery Unit) with extensive spare capacity.
- These units are fully automated.
- Solvents (e.g. Toluene, IPA, Methanol, Ethyl Acetate, Acetone, Heptane, Methylene Dichloride) have been recovered in these units.
- The Multi Purpose Solvent Recovery unit, with both columns fully operational, can process 25,000MT foul material per year.
- **Storage of Chemicals**
  - Both liquid and solid raw materials and wastes are stored on site.
  - The liquids are stored in large stainless steel tanks.
  - Each tank is contained in a bund or a walled enclosure which will take the contents of the tank in the event of a large spillage.
  - The tank operations are strictly controlled to prevent emissions.
  - All solids are stored in a special drum park which is designed to control spillages.
  - Cold storage is available on site for temperature sensitive materials