Plant 3, Cork

- Plant 3 design criteria
- Modules 1 & 2
  - Alternative technologies reviewed
  - Technologies selected
- Module 3
  - Technologies selected
External Layout

JANSSEN PHARMACEUTICAL LTD.
PLANT 3 API MANUFACTURING FACILITY

Plant 3, Containment Technology

Mark Hassey
Plant Overview

- All transfers designed for High Containment. (370ng/m3 -8hr TWA)

- Material to be charged to each module will originate from:
  - Plant 1, 2, or 3, Janssen Belgium, External Suppliers

- Product from Modules 1 & 2 will go to:
  - Existing D6, M1, M3, M5 or S001
  - Plant 3, Modules 1, 2 or 3

- Aseptic pack-off from Module 3 product transferred to Belgium.
**New Technology**

- **Contained Materials Handling**
  - **Design** -
    - Minimise Occupational Exposure levels for current and future \textit{pbOEL Category 3B compounds}; i.e. OEL Range (TWA-8hr) 10-1000 ng/m$^3$.
    - Minimise dependence on PPE
    - Minimise Manual Handling
    - Protect the Product from Contamination

- **Acceptance Criteria** (as per SOP-WW-IH-013.00)
  \[= 0.5 \times \text{Worst Case Product OEL (Paliperidone; R076477)}\]
  \[= 0.5 \times 740 \text{ ng/m}^3\]
  \[= 370 \text{ ng/m}^3\]
MODULE 1: pbOEL Category 3B Processes

- Filter
- Solvent
- Contained Discharge System
- Primary Filter Unit
- Secondary Filter Unit
- Dosing Vessel
- Reactor 4 m³
- Heating/cooling skid
- Contained Charging Sampling & Seeding
- Decanter
- Condenser
- Distillate Receiver
- Waste Receiver
- CENTRIFUGE DRYER
- Mod 2 Gas Handling
- Contained Discharge System
- Filtrate Receiver
- M5 or D6
New Technology

- Design Excellence approach
  - Focus Group to establish Internal Customer requirements
  - Philosophy document produced and circulated to key stakeholders
  - Internal and external benchmarking and vendor information gathering to identify suitable technology options
  - Options tabulated against Customer requirements, weighted and scored. (by Site strategic planning process group).
# Summary of Options for Consideration

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
<th>Containment Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Buck Valve, ANO to supply hoist, transport frame,</td>
<td>Based on three operations each of 30-minute duration, the indications are that the DEL is achievable.</td>
</tr>
<tr>
<td>2</td>
<td>Isolator c/w αβ connection</td>
<td>Proven technology with 75L FIBC’s to 150ng/m³</td>
</tr>
<tr>
<td>3</td>
<td>Hecht c/w PTS on Reactor, Packing Head for make / break</td>
<td>Standard design achieves &lt;1µg/m³. Confident that required levels can be achieved</td>
</tr>
<tr>
<td>4</td>
<td>Hecht c/w PTS on Reactor, Buck valve for make / break</td>
<td>Based on Buck</td>
</tr>
<tr>
<td>5</td>
<td>Bohle to supply Bohle Valve, hoist, transport frame, etc.</td>
<td>Estimated 8 hr TWA of 0.6µg/m³ based on readings of 1.3 to 2.9µg/m³ over a 106-minute operations</td>
</tr>
<tr>
<td>6</td>
<td>ILC Dover</td>
<td>Standard design achieves &lt;1µg/m³.</td>
</tr>
<tr>
<td>7</td>
<td>PSL Vortex Charge point valve (not developed as similar technology to Buck Valve)</td>
<td>Standard design achieves &lt;1µg/m³.</td>
</tr>
<tr>
<td>8</td>
<td>IDC (not developed due to size limitation)</td>
<td></td>
</tr>
</tbody>
</table>

Note 1 – Test is required.
Modules 1 & 2 - Alternatives considered

- ILC Dover
Modules 1 & 2 - Alternatives considered

- ILC Dover
  - This technology was already in use on site
  - Reduced capital investment
  - Reduced space requirements in process areas
    - This technology had a DEL of 1000ng/m³
    - Expertise required to achieve DEL (considerable amounts of retraining on a regular basis)
    - Increased operating costs
Modules 1 & 2 - Alternatives considered

- Total Containment Buck Valves
Modules 1 & 2 - Alternatives considered

- Total Containment Buck Valves

3D View showing the surface area being cleaned
Modules 1 & 2 - Alternatives considered

- Total Containment Buck Valves

Active & Passive TC in the Open position with product transferring

Drive Unit in the fully Open position 180°
Modules 1 & 2 - Alternatives considered

- Total Containment Buck Valves
  
  + Used a cleaning cycle to achieve a DEL in the region of 100 ng/m³
  + Reduced space requirements in process area
  + Passives could be fitted to FIBCs that could be used elsewhere on site
    - Had only been fabricated in DN 100
    - Significant development work required for successful DN200 units
    - Significant investment required for adequate supplies of passives
    - Additional operation required to remove passive from spent FIBC
Isolators

- Advantages
  - Proven in achieving required level of containment with FIBC’s (Pfizer LI)
  - Similar operation currently in D6 on site
  - Small charge quantities easily accommodated through RTP
  - Can be used with FIBC’s / IBC’s

- Disadvantages
  - Impact on layout, additional services, etc.
  - Initial capital cost above budget
  - Ergonomics of carrying out operations through gloveports
Technology selected

- Customised FIBCs (twin-necked) from Hecht.
- Transported in rigid frame
- Skan glovebox used for making and breaking connections.
- Seeding materials can be added via a canister to the side of the glovebox
- Glove boxes can also be used with ILC Doverpacs and standard long-necked FIBCs from elsewhere on site
FIBC Typical details

Connection to charge / discharge chute in Glovebox
Neck (inner bag)
Connection to glovebox
Inner Liner
Outer Protection Shroud

FIBC Requiring Inversion

FIBC c/w inlet and outlet connections
FIBC in restraining frame
FIBC Glovebox

- Centrifuge dryer takes entire batch as single charge (minimise handling)
- CFD discharge is homogenised
- Discharged into heat sealed continuous liners
FIBC Glovebox
Plant 3: Module 1: Cat. 3b PbOEL Process
Plant 3, Containment Technology

ISOLATION / DRYING

PACKOFF ISOLATOR

CATEGORY 3 PROEL PRODUCT
In-Line Sampler
In-Line Sampler

- Supplied by Prosys Ltd.
- Used for collecting IPC samples
- Connected to recirculation line
Drum Charging Booth

- Used for charging non-bulk solvents to reactors - supplied by ACE
Module 3 Containment and Materials Handling

- Design principles will adhere to cGMP and Aseptic design principles.
- Acceptance criteria for containment systems 0.37µg/m³.
- Quantities of API handled ~ 30-40kg
- Clean in place systems to minimise exposure levels.
- Materials charging Charging with IDC Biosafe RTP system.
- Pack - off isolator at positive pressure.
  Note: Reverts to negative pressure in the event of Isolator failure.
MODULE 3: Aseptic API Process

Low Bioburden Grade

Dissolution Reactor

500L

Filter

Sterilising Filter

Crystalliser

500L

FIMA CENTRIFUGE/DRYER

Pack-off

PACK OFF G/BOX

Pack-off

Filtrate vessel (Media Incubator)

Aseptic Grade

Centrifuge-Dryer

G/BOX
New Technology

- Module 3 Charging
  - Smaller charge quantities.
  - Infrequent use
- IDC
  - Direct Connection (No glove box required)
  - Alfa Beta Technology with the unique ability to open the port from the outside
- Single use bags with connections
- IH testing has given results of < 50 ng/m³ (TWA)
Contained Charging to R331

IDC Charge
Contained Pack-off from Module 3

- Centrifuge dryer takes entire batch as single charge (minimise handling)
- CFD discharge is homogenised
- Discharged into heat sealed continuous liners