MSD opens new R&D facility

Michael Sweetman reports on the opening of the new pharmaceutical formulation R&D facility at MSD in Ballydine

The new €100m pharmaceutical R&D facility at MSD in Ballydine, Co. Tipperary was recently officially opened by the Taoiseach, Enda Kenny TD; Willie Deese, executive vice president and president, Merck Manufacturing Division; and David O'Connell, general manager, MSD in Ballydine.

Construction on the 9,300 m^2 facility began in September 2007, and as a result 70 new high-calibre positions have been created.

It is anticipated that this number could increase to 120 as further innovative medicines are developed at the facility. An additional €6m investment is currently in progress, in order to extend the new facility and add extra capacity. MSD employs 2,300 people across eight operations in Ireland including Ballydine and has invested over €2.2bn in Ireland over the last five decades. The Ballydine site, which celebrates its 35th anniversary this year, was established in 1976 in Co. Tipperary, where the operation now employs 450 people. In recent years, the plant has expanded its business from producing active pharmaceutical ingredients (APIs) for use by Merck & Co., Inc. subsidiaries throughout the world to include the development of late stage clinical APIs which has resulted in the development of the new R&D facility.

Facility mission

The new facility's mission is to develop innovative methods for the formulation of new medicines from pilot to commercial scale and supply tablets for late stage clinical trials, launch and early stage supply, and it is currently in validation/start-up. It uses innovative technology platforms in order to develop processes for the formulation of solid dosage pharmaceutical product candidates used in late stage clinical trials. The formulation manufacturing facility will also enable the plant to manufacture initial launch quantities of newly-approved medicines.

The Taoiseach, speaking at the official opening of the new facility stated: "This strategically important development for MSD, which brings R&D and high-value jobs to our economy, is a significant endorsement of Ireland's wealth of talent and expertise."

David O'Connell also stated that this new facility "underpins Ballydine's strategic importance within the MSD global network and significantly increases and diversifies the level of high profile research and development conducted at the site which, in turn, is the lifeblood for the growth of the company and the life sciences industry as a whole."

There are currently six new innovative medicines in development at MSD in Ballydine, including a new candidate medicine for the combined treatment of high cholesterol and Type II Diabetes, which affects 90 per cent of the 346m people worldwide who have diabetes (WHO, Aug 2011) and a new candidate medicine for the treatment of Hepatitis C, which accounts for more than 350,000 deaths each year worldwide (WHO, June 2011). The other candidate medicines

An Taoiseach, Enda Kenny TD (right) with Willie Deese, executive vice president and president Merck Manufacturing Division (centre); and David O'Connell, general manager, MSD in Ballydine cutting the ribbon at the official opening of the facility.

Analytical development and commercialisation lab.

in development at Ballydine for unmet medical needs cover such diverse areas as insomnia, osteoporosis and cardiovascular illness. MSD in Ballydine also supplies material in support of MSD's clinical research programme worldwide. MSD, which has a worldwide annual R&D budget of $8.6bn, has five top priority candidate medicine research programs worldwide and three of these are now being developed at the Ballydine facility.

Overview of the facility

The pharmaceutical facility is a two-storey structure with a three-storey roller compactor module. The facility is designed to streamline material and personnel flows for the planned operations and be highly adaptable, flexible and capable of expanding to accommodate multiple technology platforms in the future with minimal disruption to ongoing operations. There are five main unit operations in the facility.

In addition to the main unit operations, the formulation facility has a flexible design to facilitate the addition of new evolving formulation technologies.

The facility concept included both development and manufacturing unit operations along with production support areas integrated into a single facility.

Some key attributes of the facility are as follows:

- flexible, responsive, capability of handling short campaigns with rapid turnaround, to meet clinical, launch, and supply needs;
- ability to accommodate variable batch size ranges to support development and full scale production (typically 100 to 1000 kgs);
- expandability to support introduction of new process technologies; and,
- design to accommodate specialised instrumentation to support R&D.

The new facility also makes use of existing and evolving process analytical technologies (PAT) to assist with process development/optimisation. Such PAT applications include real-time determination of blending endpoint, and rapid tablet assay methods allowing direct measurement of product potency. PAT enables quality by design (QbD) to ensure product quality in real time, with a process control strategy that in some cases does not require laborious and time consuming laboratory analysis.

Project design and construction

The overall building is 9,300 m^2, made up of a 6,500 m^2 process building, 900 m^2 warehouse (400 pallets) and 1,900 m^2 lab/offices. The conceptual design was done in MSD's head-office in the US, with the detailed design and construction management being executed by PM Group from their Cork office. Construction started in September 2007, with all equipment installed by late 2008. The design leveraged standard module designs for the main process modules from prior MSD projects. The construction was conventional stick-build using modular wall systems, and had a peak construction manpower of approximately 300.

Green plant

The building has incorporated the latest energy efficient design (EED). The plant has intense HVAC requirements, as it can facilitate a wide range of environmental conditions to meet the varying product environmental requirements. The HVAC incorporates a highly sophisticated building automation system (BAS), which includes relative humidity (RH) and temperature controls with the use of free-cooling and heat recovery in a number of the air handing units (AHU) in order to maximise energy efficiency. The HVAC is controlled through internal to external environment enthalpy control, ensuring the most efficient amount of heating and cooling energy is used to meet internal production requirements. Coupled with the BAS, the plant utilises the latest energy efficient motors and variable speed drives (VSD), which are controlled specifically to each area's specific requirements. The facility also has the latest energy efficient lighting control system with occupancy and daylight controls incorporated in non-GMP areas. The overall envelope of the building is built to the highest finish ensuring minimal building leakage and excellent building integrity.

Michael Sweetman Chartered Engineer, B.E., Eur. Ing., MIEI, Dip. C.L. C.A., is a certified LSS Black Belt and is currently senior LSS leader with MSD Ballydine. After graduating from UCD with a BE in Electronic Engineering, he spent eight years based in the Netherlands. Returning to Ireland in 1995, he worked with both Jacobs Engineering and PM Group, before joining MSD in 1999 where he worked in both capital projects and global planning roles. Michael has mentored more than 25 Green and Black Belt candidates to certification. He has recently started on his Master Black Belt (MBB) certification. He is also a committee member of the Chemical and Process division of Engineers Ireland.

The main companies involved in the design and delivery of the project:

Architecture, Engineering, Detailed Design, Procurement, Construction Management & Commissioning / Installation Qualification (IQ)	PM Group
Civil Contractor	Sisk
Structural Steel Contractor	Siac Butler
Roofing Cladding and Glazing	Siac
Electrical & Instrumentation Contractor	Suir Engineering
Mechanical Piping Contractor	BMD
HVAC contractor	Rockwell
Cleanroom Contractor	Asgard
Building Finishes	John Paul Construction

Main unit operations in the facility

1. **Dispensing:**
   Subdivision of the API (the chemical drug) and all the excipients into the exact quantities required for a batch of tablets. The excipients are basically inert materials such as lactose which are combined with the chemical drug to form a tablet. A typical tablet contains 20 per cent to 40 per cent API with the rest made up of inert excipients.

2. **Blending:**
   Blending of the materials to ensure a consistent blend.

3. **Roller Compaction:**
   Compaction of the blend into rolls which are then broken up using a coarse mill to give small granules which are suitable for compression into tablets following addition of a lubricant. These small granules are then blended. For some products roller compaction is not necessary and the blended mix can be directly compressed into tablets.

4. **Tablet compression:**
   Compression of the blended granules into tablets.

5. **Film Coating:**
   Coating of the tablets with an aqueous based dye to add a coloured coating to the tablet.