Early-stage Development, Xcelodose & Clinical Phases

Following the acquisition of Penn Pharma, PCI's comprehensive pharmaceutical development and clinical trial service includes the production of drug in capsule (DIC) using Xcelodose® technology, utilising the latest equipment for the processing of potent molecules.

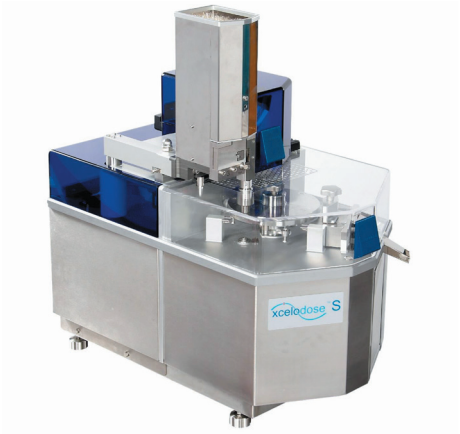
The pharmaceutical industry's ongoing demand to shorten drug development times, thus making significant cost savings, is driving technological advances forward at the same time as there are major changes happening in the research and development of high-value, and often potent, speciality medicines. Currently, more than half of research projects from pre-clinical to late clinical development fall into this category.

In the past, pharmaceutical companies have competed on the grounds of product innovation. Taking into account the high cost of R&D, coupled with the economic and political pressures for better end product pricing, finding ways to reduce overall costs becomes critical. But it is not just cost which is at the forefront of development – the size, timescales and complexity of clinical trials are all putting pressure on the industry to shorten the drug development process.

Research and development within the industry has the potential to transform patient care across a wide range of diseases through the use of an ever-increasing range of new chemical entities (NCEs). Since the supply and cost of these new chemical entities are of high value, the importance of accelerating the supply of drug product into the clinic for initial Phase I, first-in-man clinical trials becomes crucial.

But the traditional product development route of a formulated solid oral drug for Phase I clinical trials involves a range of complex activities. These include the initial compatibility studies; analytical method development; prototype development; short-term stability; process/formulation refinement; Phase I method validation; stability manufacture and finally clinical manufacture.

This process can take in excess of nine months to complete and with significant cost for product development alone – and such



costs do not take into account the cost of delivering the actual clinical trial. The ability of pharmaceutical companies to remain commercially competitive depends on transforming new chemical entities into clinical products and on to commercial launch. Filling an active pharmaceutical ingredient (API) directly into a capsule is potentially the quickest and preferred option for entering early-phase clinical trials.

Manufacturing drug in capsules (DIC) can reduce time and financial investment at the early stage of the drug development process. It can minimise the use of costly API and reduce the amount of formulation and analytical development necessary to support an investigation new drug (IND) application or investigational medicinal product dossier (IMPD).

As such, the timeframe for completion to early-phase clinical manufacture can be reduced to approximately four to six months

– potentially halving the time taken by the traditional product development route. The associated cost savings can be as much as 70 per cent, though once again this is dependent on the cost of the API and does not include the cost of the actual clinical trial. However, as the biological activity and the specificity of the API increases, the dosage strengths are decreasing, making the APIs more potent in terms of occupational handling for drug product manufacture.

Therefore it is not suitable to use methods of manufacture such as hand filling, semi-automatic filling and traditional automatic encapsulation for the accelerated development pathway of DIC for low dosage strengths. Such processes may also lead to inconsistent capsule filling, and are often time-consuming and inefficient in terms of cost.

Automated powder precision dosing at very low powder fill weights, less than 50mg, was not possible until recently. Manual hand filling using human operators was very time-consuming, requiring an enormous amount of concentration to accurately weigh such low fill weights.

Xcelodose® technology was first introduced into PCI in 2010 with the installation of the Xcelodose® 120S – a semi-automated process. This required capsules to be manually separated and loaded into the dial plate; filling was automatic and acceptable capsules would be manually capped and closed.

In December 2015, PCI invested in the latest **Xcelodose® 600S** microdosing system. This new technology has the capability to fill amounts as low as 100 µg at speeds of more than 600 capsules an hour, and is fully automated and controlled by a programmable logic control (PMC) system.

The system does away with the need for initial formulation screening and associated stability testing, enabling faster times to first-in-man, and informs the key go/no-go decision point of Phase I clinical studies for the development of new molecules.

Capsules are loaded into the feed hopper and a dispense head is selected and fitted on to the system. Drug powder is placed into the dispense head, or the operator can use the integral high throughput unit for longer runs and greater fill weights.

Once product batch data is entered into the control PMC, the system auto handles and fills the capsules, separating and then realigning the base and cap before closure. The capsules are then checked for length and sorted automatically. The fully programmable system provides exceptional levels of accuracy and precision. There is very little waste of expensive drug product and batch production is recorded, allowing traceability of samples that meet GMP requirements.

As the industry continues to focus on products to treat more specialist disease areas, the trend will be towards the development of more potent, expensive molecules, putting even greater pressure on the need for greater cost-effectiveness and shorter development and production timescales.

There is a distinct lack of early toxicity data available when initiating the DIC process. Potent compound development therefore requires a focus on safety through the use of contained processing. Potent compounds include drugs aimed at oncology, immunosuppressants, antivirals and opioid-based analgesics.

The new technology ensures safety and prevents operator exposure to potent products by the installation of a **Xceloprotect** isolator. The high levels of containment afforded by this equipment ensures an occupational exposure limit (OEL) down to <0.1µg/m^3 over an eight-hour time weighted average, meeting the intended regulations for Safebridge 3 and 4 applications.

David O'Connell, PCI's Director of Scientific Affairs, said:

"By involving our experts early in the strategic development of a client's new product, we can assist in optimising the process, ensuring that regulatory hurdles are minimised and that the most efficient routes to clinic are delivered."

All new project enquiries are based on the principles of lean manufacture, and follow a process which examines safety, quality, delivery and cost (SQDC). An initial questionnaire is issued to potential clients to assist with this process. Only when all elements of this process are fulfilled will a proposal be prepared and sent to the client.

If a project is subsequently awarded, a second questionnaire is completed to further inform the process, following which each molecule is awarded a 'potent passport'. During the production cycle, all information is constantly reviewed and updated during the product development and clinical trial lifecycle.

During the process, health and safety is a primary driver; great attention is given to on-site security and safety with four levels of secure access to the containment facility, with only qualified staff being permitted in the production unit.

With the pharmaceutical industry targeting more specialist niche medicines with ever-increasing potency, PCI is able to offer clients a state-of-the-art facility and the latest contained technology, adhering to industry guidelines for the processing of potent molecules, delivering contained manufacturing which offers speed-to-market of the highest quality.

David O'Connell

Director of Scientific Affairs at PCI Pharma Services, an integrated full-service provider expertly delivering a seamless transition from development to commercialisation.

After graduating from Glasgow Caledonian University with a Bachelor of Science degree in applied bioscience, David spent seven years as a Supervisory Scientist working for Aptuit in Edinburgh, before moving to Penn Pharma as Head of Formulation Development in 2009. Here he played a vital part in the design of the potent Contained Manufacturing Facility (CMF), which won the ISPE Facility of the Year award for Facility Integration (2014). In 2013, David took on the role of Director, Pharmaceutical Development at the PCI site in Tredegar, South Wales.

In his current role, David aids clients with formulation development, technical transfer and scale-up of solid oral, oral liquid and semi-solid products for clinical trials and/or commercialisation.

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