Non-GMP investment expands pharmaceutical product development services

In a £13.7 million investment, pharmaceutical CDMO Almac has expanded its commercial manufacturing facilities and completed a new non-GMP product development facility at its Craigavon, UK site to meet further demand for its pharmaceutical services in new markets. We report on how the facilities will complement existing operations and what this means for the company's business.

The Almac Group, with UK headquarters located in Craigavon in Northern Ireland and a North American headquarters in Souderton, PA, USA, comprises a number of integrated business units: Almac Diagnostics, which is focused on biomarker discovery and development; Almac Sciences, offering API and analytical services; Almac Pharma Services, offering pharmaceutical development, analytical services, and commercial services; Almac Clinical Technologies for clinical technology support; and Almac Clinical Services, which provides clinical trial supply services. The group is owned under the McClay Foundation, represents an asset investment of $740 million and employs more than 3300 staff at seven global sites, generating $443 million in services revenues.

Pharmaceutical product development is provided by Almac Pharma Services which has 450 direct employees. The division occupies floor space of almost 243,000 sq ft at Craigavon and about 100,000 sq ft at Almac's Audubon, PA, USA commercial packaging facility. Its capabilities include development and manufacturing of oral dosage forms, as well as packaging & release for oral dosage forms, topicals, and steriles. The business unit has a strong regulatory record with approvals from MHRA, FDA, JPMHLW, ANVISA and others.

New non-GMP product development facilities

In January of this year Almac doubled its pharmaceutical development capacity with the creation of a new non-GMP facility complete with two new analytical laboratories at Craigavon. "This allows us to meet the growing demand for our services, primarily through repeat business with existing customers, but also adding new customers," says Brian Eastwood, Senior Business Development Manager of Almac Pharma Services.

The new non-GMP formulation development facility has been added to offer greater flexibility and speed in formulation and process development, creating an environment where development work can be progressed quickly and then easily transferred to the GMP environment. Although the new facility is dedicated to non-GMP work, it has all the technical capabilities of the company's existing GMP pharmaceutical development facility, including high levels of control over environmental conditions, as well as extending current capabilities in processing potent compounds with low occupational exposure limits (OELs).

Whereas the existing GMP facilities can support drug product manufacturing from Phase 1 up to registration and commercial scale, the new non-GMP facility will primarily focus on lab-scale experiments, with batch sizes ranging from less than 1 kg up to an expected maximum of 15-kg scale for most technologies.

John McQuaid, VP of Technical Operations explains: "Our priority was to ensure we had good integration of all technologies in both the non-GMP and GMP facilities. Duplicating equipment trains means that we can conduct non-GMP work efficiently and then transfer rapidly to GMP manufacturing for clinical and registration batches. We are finding that demand for non-GMP process development work has increased as clients seek to better understand their processes in line with the principles of Quality by Design. This type of work also creates large sample sets for analytical testing and multiple stability studies

Almac's UK headquarters site at Craigavon combines and integrates activities across the whole range of pharmaceutical discovery and development to commercial production.

which is why it was also important that we doubled our analytical capacity in parallel."

The non-GMP development and Almac's GMP production equipment deliberately use the same principles of operation with duplicate technology in the two facilities enabling seamless transition between the development and GMP phases of projects. Processes transferable from non-GMP to GMP facilities include dry blending in tumble blending systems, dry granulation using roller compaction, high-shear granulation, fluid bed drying employing top spray granulation plus Wurster coating, compression employing an instrumented single station and rotary tablet presses, encapsulation using capsule boards and automated encapsulation technology, and a coating process using side-vented pan coating. Both facilities can also handle solvent granulation and coating processes.

Expanded commercial manufacturing

Almac also recently announced the expansion of its UK commercial manufacturing facilities. Together with the recent completion of the non-GMP drug development facility at Craigavon, this dual expansion represents a total investment of £13.7 million, which includes financial support from Invest Northern Ireland. Over the next three years, up to 229 jobs will be created across the two projects.

The product, a laxative drug contract manufactured by Almac, has recorded strong sales growth year-on-year in Europe.
The company said that with existing facilities at full capacity and further demand forecast in a number of new markets, it has decided to focus all production in Northern Ireland with additional equipment and resources in Craigavon. The investment will deliver blending equipment, and an automated packing and integrated cartoning line, which will enable high-volume bulk commercial manufacturing, scheduled to begin in November this year.

Almac Pharma Services has also invested in a new US commercial packaging facility at Audubon, PA, offering bottling, blistering, and cartoning services, as well as walleting and vial labeling. The facility was approved by the FDA in January.

Project management

Almac's pharmaceutical development services at Craigavon are headed by McQuaid, and comprises three departments:
Formulation Development,
Analytical Development and Project Management. For new projects, enquiries are received and logged by the company's Business Development department, which completes an initial review assessing how the project fits into Almac's operations and capabilities. The initial enquiry assessment covers technical, safety and quality aspects, and following this a detailed proposal and an indicative timeline response is generated and issued. Once a project has been awarded, a dedicated project manager is assigned to it. The project manager coordinates and manages activities of a multidisciplinary team, including organising a 'kick-off meeting', team roles and responsibilities, and a communication plan. Also completed will be a documentation schedule and overall project plan. The project manager reviews performance against the plan, tracks milestone completion and ensures budgetary terms are monitored.

Eastwood explains: "Strong project management is one of the advantages clients leverage when they work with Almac. With a dedicated project manager for each project, the client has a single point of contact throughout"

GMP development facility

Almac Pharma Services also has a GMP development facility built in 2006. The facility is designed around containment and flexibility, and operates independent temperature and humidity controlled zones (RH > 20%). Technical capabilities of the facility include pre-formulation; early-stage development; scale-up and later-stage development; and contained processing.

Preformulation capabilities range from polymorph screening, crystal engineering and crystal form selection, to solid state characterisation performed by a dedicated solid state group. Other studies include solubility investigations, studies of formulation vehicles eg polymers, lipids, surfactants, co-surfactants, and organic solvents, excipient compatibility studies, and the determination of BCS classification (BCS 1,2,3,4).

Early-stage development includes oral liquid formulation studies, co-solvent screening, API in capsule shells; development of solid oral dose presentations; manufacturing of prototype tablets, capsules and powders; blending process investigations using a range of technologies; solubility enhancement; batch analysis and IP testing. Early-stage work also includes clinical supply for Phase 1 studies, GMP manufacture, end-of-line packaging and labelling as a time-saving measure, release testing, and shipment to the relevant CRO or client.

Scale-up and later-stage work includes development of immediate release oral dose formulations, covering tablets, capsules and powders; development of modified release oral dose formulations; manufacture of prototypes; PK studies; probe stability studies; scale-up and process investigations; GMP manufacture for Phase 2 and Phase 3 studies; manufacture of commercial-scale process validation batches; and technical support after commercialisation.

Non-GMP potent processing at Almac Pharma Services' new facility in Craigavon, UK.

Almac's contained processing capability enables the handling of Safebridge Category 1-3 compounds with operator exposure levels (OELs) in the range of 0.03-10µg/m^3/8hrs. Development and GMP batches of clinical supplies, as well as low-volume commercial products, can be produced in batch sizes ranging from 0.1 to 100 kg.

"Whether client requirements are for First in Human supplies or later-phase development and registration batches, Almac has access to a wide range of innovative technologies for solid oral dose products," says McQuaid.

Analytical development

From state-of-the-art analytical laboratories, Almac has over 200 analytical scientists delivering comprehensive analytical solutions to support drug substance (API) and drug product development programmes, as well as providing analytical and microbiological testing solutions for clinical and commercial drug product supply.

Over 80 analytical scientists are dedicated to its pharmaceutical development operations providing support services that include analytical method transfer; comparative analysis; method development, optimisation and validation; registration, clinical and development stability studies; testing and QP release of clinical supplies and CMC regulatory support including IMPD/IND preparation; and CTD preparation.

Meet John McQuaid and Brian Eastwood of Almac Pharma Services

John McQuaid is VP Technical Operations for Almac Pharma Services, having joined the company in 2003. He is responsible for the Pharmaceutical Development Department which brings together Formulation Development, Analytical Support and Project Management. He has extensive product development, quality assurance and validation experience including hosting product pre-approval inspections by the FDA as well as inspections from other regulatory authorities. He has more than 20 years' experience in the industry, including expertise in dosage forms, as well as in packaging of a wide range of dosage forms for international clinical trials. He holds a BSc in Science with Business from the University of Ulster and a Diploma in Industrial Studies.

Brian Eastwood is a senior business development manager at Almac Pharma Services, which he joined in May 2010. His role is to develop the business and marketing strategy for the company's Pharmaceutical Development, Clinical & Commercial Manufacturing and Product Launch services.

Prior to joining Almac, he worked as Corporate Business Manager for a local health care company for four years after gaining almost ten years' experience working within the R&D department at Norbrook Laboratories Ltd. He holds a BSc (Hons) Degree in Biochemistry from Queen's University, Belfast and a MSc Degree in Biotechnology from the University of Ulster.

Scale-up and product launch

With Almac having both development and commercial facilities at the same site, one of the advantages clients can benefit from is an ease of scale-up into product launch and ongoing commercial supply.

A technical project manager and matrixed team manage scale-up and manufacture of process validation batches, together with a dedicated Product Supply Manager acquiring product knowledge and planning for commercial launch including printed packaging components, distribution and other commercial considerations. Product and process knowledge is transferred to commercial production/QC personnel, with the technical group providing continued support for process optimisation and trouble-shooting. Routine commercial supply and client management is by the dedicated PSM.

Eastwood explains: "Our clients enjoy the ease of engagement when working with Almac. Having dedicated project management teams interfacing seamlessly from transfer into commercial supply saves time, reduces costs and management time, and ultimately de-risks the overall process."

Formula for success

"Almac is fully aware of the financial constraints that pharmaceutical companies now operate within, thus we seek to expand our services in such a way as to make the client engagement as easily managed, cost-effective and risk-mitigated as possible. Coupling the capabilities and talent within our Pharmaceutical Development team to our long and successful history of providing commercial services provides an integrated and seamless approach to clients that has seen the successful launch of multiple products.

"The recent £13.7 million investment represents a strengthening of our presence across the pharmaceutical development and commercial sectors," he concludes.

Further information

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DoE Case Study: Phase 2 process validation manufacture

A 'virtual' company approached Almac in 2009 after completing some early development work at another CDMO to put in place a strategy for formulation and process development. This was led by consultants in conjunction with Almac. An enteric coated, controlled release erosion matrix formulation was chosen.

The initial project consisted of optimising the process for Phase 2 supplies with the final project scope of work involving full-scale formulation and process development, clinical supply, registration and process validation batch manufacture. The timescale for the project was as follows:

2009 – Formulation and process development
2010 – Phase 2 drug product manufacture
2011 – Process investigation studies
2012 – Phase 3 manufacture
2013 – Final process investigation studies, registration batch manufacture and process validation manufacture
Future – Scale-up and commercialisation

For this tablet it was critical for the API to release rapidly upon transit to the upper small intestine for efficacy and the regulatory strategy for the product. It was also critical to minimise release of drug in the stomach.

The API presented numerous operational difficulties including inconsistent physical properties and high-containment requirements. Previous formulations had already been assessed in a Phase 1 study resulting in a target dissolution profile but the change in scale and process was found to alter the dissolution profile. Therefore Almac employed an extensive Design of Experimentation approach to this project to investigate the relationship between formulation and process variables and product Critical Quality Attributes, with dissolution being the most important.

For projects such as this, it is typical for the Formulation Development department to prepare eight to ten development batches in a two-week timeframe. Quick turnaround of dissolution profiles from the development tablets was critical to the success of the project.

The result was that by employing a Quality by Design formulation and process development approach, Almac converted a variable and poorly understood process into a robust manufacturing process suitable for process validation. A number of assumed critical process parameters were found not to be critical and others that were not considered critical became better understood, thus being taken into account in further scale-up. Almac's technical capability, development experience and containment facilities were instrumental in the success of the project.