Integrating R&D and cGMP kilo-scale synthesis for new therapeutic products

TCG Lifesciences is a contract research services company headquartered in India and with a worldwide presence offering technical support ranging from specific solutions to integrated discovery projects across multiple therapeutic areas. This article describes how the company's platform technologies and expertise in process development and scale-up provide solutions for the discovery and development of new drug candidates including new chemical entities (NCEs).

Founded in Kolkata, India in 2001, TCG Lifesciences (TCGLS) has developed into a company providing the international pharmaceutical industry with integrated drug discovery services, outsourced chemistry services, and process development and scale-up for new NCEs and drug products. Dr Subho Roy, the company's director of chemistry and head of process development and scale-up, says that the chemical and pharmaceutical industries are under increasing pressure to bring new products to market faster, at lower costs and with higher quality: "The design and delivery of a safe, sustainable and robust process that can be used at production scale is a critical step in bringing a new product to market. Designing a chemical process involves building a comprehensive knowledge and understanding of the chemical reactions being used, as well as the associated critical process parameters," he says.

"During early phase development, it is important to quickly provide a few kilograms of material, while working to establish cost-effective synthetic routes," Roy continues. "This can be achieved in the laboratory with integrated analytics during early-phase development. At the same time, it is also important to quickly evaluate the merits of a batch, semi-batch or continuous approach to manufacture the product at scale.

"As the process is continually developed, quality process knowledge is gained through the combined use of synthesis workstations with integrated real-time analytics providing chemical, particle, thermodynamic and kinetic information. Finally, the process is optimised by improving troublesome steps, and by reducing the cost of goods by removing poorly performing or expensive steps or by the re-design of an entire route. Multiple kilograms of the desired compound can be synthesised following this optimised route to meet the requirements of the development team."

TCGLS undertakes custom development of clients' processes from preliminary research findings or at any later stage through to multiple kilo quantities. The work is carried out in the company's fit-for-purpose kilo laboratory in Kolkata in the East of India, which is equipped with the latest technology, state-of-the-art laboratories and analytical equipment. TCGLS has a highly qualified and experienced staff of more than 50 chemists for process scale-up and kilo-scale manufacturing.

Reaction calorimetry in the kilo lab at TCGLS provides essential data.

"The ability to scale up chemical processes is a significant feature of our business, and we have a long track record of successful projects involving scale-up," says Roy. "At all stages we employ scalable and representative unit operations. Typical projects would involve one or more of the following stages: bench-scale chemistry; process concept and evaluation; process validation; basic engineering; and HAZOP reviews."

TCGLS has the capabilities and experience to produce material for IND-enabling studies, and this includes synthesis of material for both non-GLP and GLP toxicity studies. Typically, a GMP-compatible process is developed that can later be refined and scaled to deliver higher amounts of product. Candidates are advanced from milligram scale to multi-kilo scale, establishing robust process design and achieving high-quality GMP supplies, and a dedicated analytical team develops methods for release and control of drug substances. "These capabilities enable us to assist our discovery partners from the early synthesis stage through candidate selection up to regulatory toxicology supplies and the supply of 'first-in-man' study quantities," says Roy.

Strategic collaborations

This year, TCGLS achieved two separate milestones in the company's drug discovery partnership with Endo Pharmaceuticals. In one of its fully integrated discovery programmes with Endo, aimed at identifying novel small-molecule drug candidates for an unmet medical need, TCGLS delivered a preclinical development candidate in early

2012. Working with Endo, the TCGLS team conducted all aspects of laboratory research for the programme involving medicinal chemistry, in vitro biology, ADME, preclinical pharmacology and early toxicology studies. Two lead compounds resulting from the collaboration have been selected by Endo for cGMP manufacturing and GLP-toxicology studies. The required quantity of material was produced quickly by following a procedure developed by the R&D department at TCGLS. This process was later modified and some troublesome steps and reagents were eliminated, thereby making the process ready for the next level of scale-up.

In the second discovery programme, initiated in 2011, TCGLS has achieved a discovery milestone following the company's design and delivery of novel fast-follower hit structures within set timelines. This multi-year, three-stage project aims to identify potent in-vivo active novel blockers of an undisclosed target for eventual clinical development.

In February, TCGLS announced the nomination of a preclinical development candidate under a research and development collaboration entered into in 2009 with Pfizer. Under the agreement, Pfizer will own the compound and other back-up candidates, while TCGLS will receive a milestone payment having moved these compounds to the candidate nomination stage. The development candidate is a small-molecule NCE meeting the criteria set by Pfizer, including potency, pharmacokinetics, preclinical pharmacology, toxicology and related properties. TCGLS contributed synthetic chemistry, in-vitro pharmacology, DMPK, in-vivo pharmacology, and preliminary safety studies to the project.

Other examples of work carried out by TCGLS where efficient process research and scale-up have resulted in meeting desired end points include a project in which multiple kilogram quantities of a new chemical entity were prepared for a multinational company and the material used for preclinical development. Within a short timeframe of four months, a GMP-compatible process was developed along with analytical methods to support scale-up. The initial stages were telescoped and some critical parameters were optimized: finally, a robust process was established which was followed to produce the API consistently at consistent quality.

In another project, TCGLS successfully synthesised a natural product for a USA-based natural product company. The product is currently being used by a leading cosmeceutical company for one of its branded products. Once the efficacy was established, it took about six months for TSGLS to develop a GMP-compatible process for this five-step synthesis sequence. The company is currently producing this material in multiple kilogram quantities every month in its cGMP facility.

Flexible business model

"The global pharmaceutical market is expected to grow at a five to eight per cent CAGR up to 2014, taking into account the impact of the changing mix of innovative and mature products, increased access to emerging markets, and, on the other hand, price pressure due to regulatory requirements in developed countries," says Roy. "Consequently, the global pharmaceutical market is expected to expand to $1.1 trillion in that period. The 'pharmerging' countries are expected to grow by 13-16 per cent over the next five years. Process development and scale-up will continue to play a crucial role in bringing the cost of generics down to an affordable level, and at the same time deliver processes for the new chemical entities entering the market.

"This is one area of our business that has seen significant growth in the past few years, so much so that we are seriously considering building our own larger-scale production facility to meet the increase in demand," he says. "It has become a common occurrence that we produce a research quantity of a material, a few hundred grams, and then within a short time multiple kilograms of the material are produced and delivered. Where the product requirement exceeds our current capacity, with the client's permission we work with carefully selected partners at a larger scale to ensure a successful outcome. Thus on the one hand TCGLS is helping clients to develop processes that will enable the synthesise of material required for IND-enabling studies in a safe and cost-effective manner and at the same time we are working with a small number of generic companies, helping them file DMFs with EU and US regulators.

"Increasing understanding of molecular complexity coupled with advancement of knowledge of biological pathways and processes has resulted in old working principles being challenged. Control of impurities present in the drug substances at trace concentration levels has also increasingly become important to meet regulatory specifications, making process research and development and scale up functions of critical importance in developing a new drug. To meet these new demands we have often seen CMC starting at an early stage of development. Capabilities in developing new and efficient synthetic routes, infrastructure and downstream instruments to mimic production at a laboratory scale coupled with strong analytical infrastructure, has put TCGLS strategically in a sound position to leverage market demand. Because of the long term relationships TCGLS already enjoys with the discovery activities of its multinational clients and the fact that the market is looking for a broad range of services from single company, TCGLS is ideally positioned for long-term growth in the area of process research and development and scale up," concludes Roy.

Meet Subho Roy of TCGLS

Dr Subho Roy has been one of the key scientific leaders at TCG Lifesciences and has been with the company since 2002. He has more than 16 years of industrial experience and is a specialist in new process development and process optimisation, and played a key role in conceptualising and designing the company's kilo laboratory. Dr Roy has several publications to his credit and holds several European patents. He obtained his PhD from the Indian Institute of Chemical Technology based in Hyderabad, India, working with Dr A.V. Rama Rao in the field of total synthesis of natural products with biological interest. After a brief period with AVRA Laboratories, he joined the University of Kansas for his post-doctoral work under Dr Gunda I. George, where he was involved in the total synthesis of various natural products of marine origin, and subsequently joined TCGLS.

Further information

Dr Subho Roy
Director Chemistry & Head Process Development & Scale-up
TCG Lifesciences Ltd
Block BN, Sector V, Salt Lake City
Kolkata 700 091
India
Tel: +91 33 2367 3151
Fax: +91 33 2367 3058
Email: contact.prd@chembiotek.com
Web: www.tcgls.com