

# Indian companies board Lead Optimization bus

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The growth of lead optimization outsourcing continues to be fueled by the need for drug developers to bring down costs and speed products to market

The drug discovery and development process is getting longer and more expensive. The industry suffers from the same clinical attrition and safety-related market withdrawal rates today as it did 20 years ago. Industrialization of drug discovery from target selection through lead optimization scrutinizes these problems in detail, contrasting the promise of technology and industrialization with the challenges of using the tools available to their best advantage.

"Lead **Optimization** refers to the structural and functional optimization of drug-like molecules having the potential to be developed mathematication of the structural and functional optimization of drug-like molecules having the potential to be developed mathematication optimization of the structural and functional collaboration and information transfer between wet lab and dry labies optimization output. Largely known as computer aided drug design (CADD), a multitude of structural analysis domains interact in this area of research," said MN Manoj, CEO, Jigsaw BioSolutions Ltd, a Bangalore-based start-up. Docking, virtual screening, QSAR, molecular dynamics and real time molecular dynamics (hybridized with quantum mechanics) are some of the latest advancements in the field of structural bioinformatics and to the most they directly or indirectly participate in realm of drug discovery.

The pressure is on to get better lead compounds faster and at less cost. The amount of money wasted on leads that fail is very high. And the attrition rate to get a lead is huge. One estimate is that for every 100,000 compounds screened, about 100 hits are identified of these 100 hits, only one makes it to the lead compound stage. Between 40 percent and 60 percent of these lead compounds fail ADMET testing. Only 10 percent of IND submissions get approved. Over 72 percent of the costs for drug development are wasted on failures.

#### Evotec OAI AG Company initiatives

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Strand Life Sciences, a premier in silico technologies innovation company focused on developing technologies for drug discoveryeand have a launched its SAR modelling and deployment platform-Sarchitect this year. Sarchitect addresses the challenge of taking the model building prowess of computational chemists through to decision support in medicinal chemistry. Two editions of the Sarchitect product have been launched-Designer - for use by computational scientists and technology-based consulting in predictive modeling for lead optimization.

Accelrys<sup>rans</sup>Eading provider of scientific business intelligence solutions, has launched Discovery Studio 2.0, an advanced modeling and similation software environment for drug discovery. The new release features a fully integrated work environment for life science researchers allowing them to go from project conception to lead optimization using a diverse set of sophisticated software applications in a single, easy-to-use environment.

Albany Molecular Research (AMRI) which provides extensive resources for drug discovery and lead optimization helps customers identify and optimize lead compounds. Its diverse natural product-based and synthetic chemical libraries which include hundreds of thousands of diverse compounds provide an excellent starting point for a drug discovery program.

"We complement our medicinal chemistry lead optimization expertise with technologies in metabolism and biotransformation, including our proprietary combinatorial biocatalysis technology. Our in vitro biology capabilities enable us to identify biologically active compounds from our extensive collections efficiently and rapidly," said Dr Mark Sawicki, director, business development, AMRI.

AMRI has a three-year natural products research collaboration focused on screening and lead identification with Eli Lilly and Company. The goal of the collaboration is to discover and develop potential therapeutic agents for diseases of interest to both companies. AMRI has also entered into a two-year natural products-based drug discovery collaboration with Bristol-Myers Squibb Company. AMRI may provide follow-up medicinal chemistry hit-to-lead optimization, biocatalysis or chemical synthesis support on compounds of interest to Bristol-Myers Squibb. AMRI has also recently set up its subsidiary in Hyderabad.

Tata Consultancy Services (TCS), a leading global technology services company, assists drug discovery processes from target identification to lead optimization. It addresses four major functional areas-genomics, protein modeling and structural analysis, simulation and drug design, helping researchers with sequence analysis, genome analysis, comparative genomics, 3D modeling, 3D structure manipulations, structural analysis and simulations.

In August 2005, Tata Consultancy Services entered into an agreement with Congenia, a biotechnology start-up promoted by Italy's Genextra SpA group, to provide advanced lead optimization solutions for drug discovery.

The agreement marked the first of its kind for an IT services company. The Life Sciences R&D Division of TCS works on "P66", a target protein identified by Congenia as a key protein involved in several age-related diseases and will develop optimized drug leads based on the protein. TCS is using modules of its own product, "TCS Bio-Suite," to work on the target protein.

Jubilant Chemsys has been offering chemistry based drug discovery and development services ranging from early stage lead discovery and optimization to the identification of viable synthetic routes required to manufacture kilogram quantities of NCE for pre-clinical and clinical studies. Jubilant's services integrate the expertise of its scientists in the areas of drug discovery, drug development and analytical chemistry.

Jigsaw Bio Solutions (JBS), a Bangalore based new enterprise, is focused on providing quality end-to-end solutions in bioinformatics domain, including custom software and high performance computing hardware, bundled with professional training. JBS is also exploring the possibility of tapping the contract research projects in various bioinformatics domains including lead optimization.

## Novel approaches

Lead optimization could create a time saving of 18 percent during the drug discovery process, representing significant cuts in R&D expenditure, according to several reports. The key to successful lead optimization lies in adhering to stringent selection criteria during hit generation whilst embracing new technologies that can lead to improvements in screening.

Many efforts are underway to make lead optimization less time-consuming and more linear, as well as to bring down the cost of drug discovery and development. The major trend in lead optimization is the different strategies to accelerate the process, such as in silico and high-throughput in vitro approaches. Computational methods can be applied to chemical structures to predict ADMET properties even before the compound is synthesized so that only favorable compounds need be synthesized for screening. Whole cells are also increasingly being used in high-content screening mode to provide selectivity information along with other valuable data concerning the effects of compounds on cell function. New approaches for predicting cytotoxicity, blood brain barrier permeability and active transports in the early stages of drug discovery have also been developed.

Technological advances in the development of nanotechnology, miniaturization and systems biology are driving improvements in the refinement of the lead optimization process and cost-effectiveness of drug development.

There are more than 25 companies that provide high quality services to the pharma industry helping to improve the lead optimization process. The increasing availability of cheap lead optimization services will benefit pharma companies, enabling more new targets to be investigated without significantly increasing R&D budgets.

The formation of strategic alliances will continue to aid drug and technology development as smaller companies license out drugs to bring in revenue. Equally, in-licensing will enable larger companies to sustain and improve profitability but there will be an increasingly high price attached to these projects. In the race to market, companies that provide technologies that go beyond simple data generation to providing knowledge that drives informed decisions will be the most successful.

## "AMRI is flexible in addressing clients' specific discovery needs"

-Dr Michael Trova, Senior Vice President, AMRI

-Dr Mark Sawicki, Director, Business Development, AMRI

#### What is the global scenario in lead optimization activity?

Lead optimization is a global market. Lead optimization services are coming from the US, EU, Japan and increasingly coming from parts of Asia. The market is spreading across the globe. It has grown successfully over the last 10 to 12 years that we have been associated with this business.

The growth in Asia in particular is increasing significantly and this is probably why we have established operations in Asia

over the past few years.

Lead optimization is a discipline whereby medicinal chemists synthesize one molecule at a time to address specific biological issues, bioavailability, toxicology, absorbtion and distribution. In order to address these biological objectives, medicinal chemists conduct lead optimization process. We need to have experience in addressing such issues and experience is something that AMRI has tremendous in amount.

#### How is AMRI positioned to serve this sector?

The real major know-how in experienced lead optimization is something that AMRI has uniquely set up as a service provider to provide something different from its competitors.

What we have done to address the global market needs is seen in some of our expansions and growth of our business over the last few years. We had growth in the US but probably not explosive growth as we had 10 years ago. We had significant growth in the lead optimization business and other parts of our business in Asia and Europe as well. AMRI established a subsidiary in Singapore in 2005 and now have around 50 people employed there.

The subsidiary in Singapore is focused on lead optimization activity for its customers around the world including the US, Europe and Asia. We also established a subsidiary in Hyderabad in 2005, which has a similar size today and has similar and subsequent growth opportunity and plans. The Indian subsidiary mainly focuses on medicinal chemistry support, intermediate synthesis and also scale-up and chemical development activities. Just last year AMRI bought a company, formerly known as ComGenex, in Budapest, Hungary in Central Europe. It specializes on compound libraries for the lead optimization activity. We incorporated a new location in Budapest as well to assist our global discovery services and activities.

Today we have discovery services and activities being operated out of the US, Budapest, Singapore and to some extent India as well.

#### Is there any market figure which you can quantify for this kind of services?

Drug discovery and development is a growing market. In particular most of the large pharma are re-evaluating what they exactly want to do internally versus what they want to outsource and that trend has been continuing since the late 1990s. In many cases, a lot of these organizations including large pharma and biotech companies have entered sites and virtual sites they want independently to support all their outsourcing efforts to decide what is their physical sites and outsourcing budget level. The pharmaceutical industry is continuing to grow and they are making decisions to what additional resources they can outsource to give more flexibility to their budgets. The figure at a physical level is very difficult to quantify, but yes, there is a tremendous market.

#### Elaborate on the products that AMRI has been offering for lead optimization?

Lead optimization as a discipline is intellectual property driven. The tools used in lead optimization today in many cases are very similar to lead optimization tools we used 5-10 years ago. They include parallel synthesis, ability to make huge number of compounds, new techniques in microfluidics, new tools in computational chemistry as well. All these tools help in selecting targets and validating clinical selection, but the tools in the synthesis side are very largely intellectual based and experimental based.

AMRI helps contribute to place dozens of compounds into preclinical and clinical denominants for pharmaceutical partners. For confidential reasons, we cannot disclose who we work for. We cannot disclose what specific targets we work on. That would be violation of their confidentiality.

#### What are the current trends and how do you foresee the future of this industry?

The industry will continue to grow with globalization of these types of services and capabilities That is also something we focus on. Now you even see some of our competitors in India are doing the same. They are purchasing facilities in the US and Europe to give themselves a more global presence. As the Asian pharmaceuticals market matures over the coming years, it is going to be more critical to have a global presence.

Jahanara Parveen