SCRIP
CITELINE COMMERCIAL

09 Oct 2024 | **Interviews**

How Syngene Is Revving Up Capabilities In ADCs, PROTACs

by Anju Ghangurde

Syngene's CEO talks to *Scrip* about how the firm is deepening capabilities in areas like ADCs, PROTACs and why the US Inflation Reduction Act may not necessarily shrink outsourced small molecule work. The executive also shares his view on the China 'rebalancing' trend amid geopolitical tensions and the US BIOSECURE Act.

There's a lot going on in the external operating environment for contract development and manufacturing organization (CDMOs) and firms like *Syngene International Ltd.* are navigating the turbulence resolutely, gearing for wins when opportunities emerge alongside deepening their expertise in new modalities.

In an interview with *Scrip*, Jonathan Hunt, managing director and CEO of Syngene outlined how the firm was shaping its suite of capabilities in platforms such as antibody drug conjugates (ADCs) and proteolysis-targeting chimeras (PROTACs) and also discussed some of the ground realities against the backdrop of geopolitical tensions and the advancement of the US BIOSECURE Act. (*See side box*)

Hunt believes that new technologies like

BIOSECURE Act, Comparative Pilots

Frontline CRDMOs like Syngene see momentum in dual sourcing and the China rebalancing trend no matter which way things go for the US BIOSECURE Act. (Also see "*Syngene Chief: Large Cap Biopharma Taking China 'Rotation' More Seriously*" - Scrip, 1 May, 2024.)

SCRIP
CITELINE COMMERCIAL

ADCs are a “really nice fit” with Syngene’s capabilities, given its “depth in chemistry to do the warheads”, experience with linkers and end-to-end discovery, development and manufacturing of biologics. (Also see "*Podcast: Syngene CEO On Sub-Dynamics As US Biotech Funding Finds New Normal, ADC Capabilities*" - Scrip, 17 Nov, 2023.)

“If you put those three together, you've got all the components that you need for ADCs. I think the market is increasingly recognizing that. We're seeing reasonable progress in that area,” the CEO said.

The Indian CRDMO has been advancing a cutting-edge ADC that is in Phase I trials for advanced solid tumors. The first-in-class ADC is expected to provide superior dosing accuracy and an improved safety profile versus conventional ADCs.

In another instance, one of Syngene’s clients, a leader in ADCs, faced challenges in acquiring a crucial raw material for drug-linker synthesis, with the Ukraine war disrupting global supply chains, leading to spikes in costs and product shortages. They then tapped Syngene for assistance, prompting the Indian firm’s process research and development team to design and implement an innovative approach by utilizing a different route of synthesis. That enabled a significant reduction in raw material consumption and the new method also eliminated the use of toxic and expensive reagents. (Also see "*Syngene COO On Delivering Cost Gains For mRNA Products*" - Scrip, 15 Aug, 2022.)

Syngene’s MD and CEO Jonathan Hunt maintained that the Act to him is a piece of legislation that's sitting on top of a trend that was already there and the tone of conversations with clients is much more around “long term supply chain planning, resilience, dual sourcing capabilities and best value”.

“They were discussing those things years before the BIOSECURE Act was put forward and I suspect they may be looking at those things year after year after the Act passes or doesn't pass,” he asserted.

While they may be independent variables, the trends appear aligned and headed in the same direction, he noted, adding that the rise of the Chinese economy and its competition with the US and the resulting geopolitical tensions creates a landscape that business leaders need to run operations within.

COVID-19 too delivered some tough lessons around the need for supply chain design resilience. (Also see "*Califf: Not Wise To Create Problems Related to Chinese Pharma Supply Chain Dependence*" - Pink Sheet, 2 Oct, 2024.)

“It showed us where we'd overoptimized so that we had very taut but very efficient supply chains and sometimes if they're too tight, they break and there's a general learning in many industries not just pharmaceuticals. Sometimes that extra little bit of fat or flexibility in the system is what protects you when the environment changes suddenly,” he

SCRIP
CITELINE COMMERCIAL

The impressive delivery apparently saw the client entrust Syngene with a non-GMP (good manufacturing practices) scale-up project, where the Indian firm optimized processes by "minimizing synthetic steps, improving yields, and employing crystallization techniques to avoid column purification". This was followed by another project involving a scalable process that reduced processing time and reagent consumption while simplifying isolation methods.

"The successful process optimization allowed for efficient technology transfer for GMP manufacturing, culminating in a completed GMP campaign," Syngene, which is a publicly listed arm of *Biocon, Ltd.*., explained.

While the first ADC, Mylotarg (gemtuzumab ozogamicin), arrived on the market over two decades ago and there were some setbacks along the road, the class has been in the spotlight over the recent past with significant investment flow and deal appetite from big pharma. 2023 saw the $22bn *Merck & Co., Inc.*-*Daiichi Sankyo Co., Ltd.* alliance, *Pfizer Inc.*'s $43bn acquisition of *Seagen Inc.* and *AbbVie Inc.*'s $10.1bn takeout of *ImmunoGen, Inc.* all with an eye on the hot ADC space. (Also see "*It's Official: The Merck-Daiichi Deal Has The Biggest Upfront Ever*" - Scrip, 23 Oct, 2023.)Deal interest in the segment continues in 2024, with *Johnson & Johnson*'s $2bn buyout of *Ambrx, Inc.*. being among the prominent transactions this year. (Also see "*Five Recent Deals Show ADCs Aren't Cooling Off For Summer*" - Scrip, 23 Aug, 2024.)

explained.

Hunt had earlier indicated that "China switchers" are setting up "pilots" across a broad range of services and often placing them with a select short list of suppliers.

"They then intend to run these comparative pilots through the year and use this as a way of selecting a longer-term partner," the CEO said in a statement on the impact of the proposed BIOSECURE legislation on Indian CRDMOs. (Also see "*Who Will Reap The BIOSECURE Spoils? US Industry Boost Not Guaranteed*" - Pink Sheet, 13 Sep, 2024.) (Also see "*BIOSECURE Act: Pfizer To Lilly - Where Are The Likely Sourcing Gaps?*" - Scrip, 23 Sep, 2024.) (Also see "*Geopolitics, US BIOSECURE: Pharma Looks To Redistribute CDMO Footprint*" - Scrip, 13 Sep, 2024.)

"We have made good progress and I get a sense we are winning our fair share of these pilots."

Request for proposals (RFPs) at Syngene are up almost 50% year-on-year in terms of value in the first quarter of fiscal year 2025 – the best Q1 in the last four years.

Hunt underscored that one of the things that Syngene can do for clients is to make sure that they've got "resilience and flexibility" in dual sourcing in where they do their science, development, and manufacturing.

He, though, cautioned that changes in how

SCRIP
CITELINE COMMERCIAL

Expertise In PROTACs

Hunt also spotlighted Syngene's deepening expertise in the area of PROTACs, where the Bengaluru-based firm has built "quite a sophisticated capability"; it has a team about 500 scientists engaged in the area for developing targeted cancer treatments.

PROTACs are highly specific medicines that can break down undesirable or detrimental proteins in cells, though formulating these compounds into dosage forms is complex due to their poor solubility or permeability and chemical stability issues.

In one instance, Syngene worked with a global biopharma company to develop a PROTAC molecule aimed at targeting a specific oncogenic protein implicated in various cancers. The collaboration saw the lead PROTAC molecule advance into preclinical development, which helped identify a drug candidate to progress to the clinic, demonstrating its potential as a therapeutic candidate for cancer treatment.

Syngene has also made important strides in other areas, developing a novel method for perineural injection, leading to new projects in its kitty. The firm has also conducted a repeat dose intrathecal injection study for a novel oligonucleotide.

Intrathecal administration, a specialized route for delivering drugs into the spinal cord, is vital for treating conditions affecting the central nervous system; such

firms do their R&D and manufacturing are "very cautionary, steady and thoughtful and not overnight changes". (Also see "*What's In Store For CROs, CDMOs – "Stay In Your Swim Lane", Consolidation, Divestitures*" - Scrip, 7 Nov, 2023.)

For instance, if you tech transfer a product from one manufacturing site to another, that could be "24 months of very structured work".

"It is a positive wind, and I do think it's going to be a five to10 year long positive enabler for companies like Syngene and India. But if it's two years to tech transfer something, there's going to be no overnight sensations," he added.

Syngene is also recalibrating its own China dependency for procurement of certain requirements but is "happy to use China supply when it makes sense and that's about risk management". Developing a local partner network in niche chemistry areas for development services, for instance, has helped the firm reduce dependency on China.

"We're becoming less China dependent than we were in the past and we want that choice," Hunt added.

The China derisking effort across industry comes against the backdrop of ongoing US-China tensions and the progress of the US BIOSECURE Act, which would curtail US government contracts and grants for services provided by a "biotechnology company of

capabilities were generally, in the past, limited to studies conducted primarily in the US and Europe.

More widely, the advancement of new modalities is opening up a multitude of opportunities for small and large biopharma firms to develop new treatments; CRDMOs that can keep pace with the scientific advances and evolve their suite of offerings alongside will likely also have much to gain.

Last year, Boston Consulting Group said that it expects new modalities to continue to be a big driver of biopharma revenue growth. In 2023, four of the six top-selling biopharma products led by Keytruda (pembrolizumab) were based on new modalities—in 2028, that is expected to hold true of all top six products, executives from the consulting group said in an article.

concern." The bill is seen as a bid to rein in growing Chinese influence in the country and targets firms such as the BGI Group, *WuXi AppTec.*, and *WuXi Biologics*, among others. The US House of Representatives earlier voted 306 to 81 in favor of the bill, which now heads to the Senate.

The *Financial Times* recently reported that WuXi AppTec may be considering the sale of certain units and sites, though *Scrip* could not immediately verify where things stand on this front.

IRA, Small Molecules And Outsourcing

The promise of new modalities notwithstanding, small molecules are currently at the core of industry's innovation efforts even as it remains unclear whether legislation like the US Inflation Reduction Act (IRA) could trigger a shift in R&D budgets away from this segment in due course.

A senior McKinsey executive recently pointed out that the pipeline of innovators firms, on average, has anywhere between 6,000 to 7,000 assets under development and close to 50% of those assets still continue to be small molecules. Of the 50% which are large molecule and new modalities, more than half of it counts as plain vanilla mAbs.

On whether the IRA could prompt a definitive shift away, in time, from small molecules in US biopharma, which can then put some negative pressure on demand for CRDMO services, Syngene's

Big Pharma R&D Chiefs On IRA's Unintended Casualty, Product Life Cycle Compression

By Anju Ghangurde

15 May 2023

R&D heads of Takeda, Amgen, Lilly and Novartis discuss some of the tectonic forces shaping the biopharma sector and the unintended consequences of the IRA on small molecule innovation. Advances in the

Hunt brought in the element of counter intuitive logic.

The CEO explained that R&D heads at innovator firms, particularly the bigger ones, are typically "platform neutral" in the sense that they want to have all of the technology and the science available when addressing a particular target or disease area.

neurodegenerative diseases segment amid impressive data from donanemab was another key talking point.

Read the full article here

"It's hard enough to find and innovate a drug that you're going to throw away a good small molecule which you think would have an impact on the disease state because it's a small molecule. It's almost missing the magnitude of the scientific challenge in the first place of finding a drug," Hunt asserted.

Nevertheless, decisions around new or renewal of capital allocation, he believes, are going to increasingly sit with the CFO in the company as much as the head of R&D.

"If you think the prospective returns from small molecules are going to be less attractive than the equivalent returns from large molecules, you may choose not to deploy your own balance sheet, but increasingly to outsource that," Hunt maintained.

"So, you're still using the full technology toolkit when doing the science, but you might start to accelerate the rate at which you actually outsource some of that small molecule work if your own assets were coming to the end of their life and you had the choice of renewing them or not. So in a strange way, it may actually quicken the pace at which you see small molecule externalization."

Additionally, Syngene believes that the IRA's effect on the economics of small molecule manufacturing could fuel an increase in outsourcing, especially when additional capital investment for small manufacturing is warranted.

The IRA and it's "unintended consequences" when it comes to areas like small molecules has been much discussed. The Act enables Medicare to negotiate drug prices for small molecule drugs nine years after US Food and Drug Administration approval and 13 years after FDA approval of biologics. Industry experts believe that such uncalled-for distinction could see companies defocus small molecule programs. (Also see "*Amgen's Ian Thompson On Payer Shifts, Obesity Opportunity And The Future Of Blockbusters*" - Scrip, 28 Jun, 2024.) (Also see "*Former VA Secretary, Biogen Exec On IRA And Politics, Price Clamps In Europe*" - Pink Sheet, 10 Oct, 2023.)

Big pharma firms like *Amgen, Inc.*, among others, have underlined how the IRA is curbing

innovation. Amgen was earlier reported to have has shelved some of its own small molecule R&D programs because of the shortened timeframe to recoup its R&D investment before it would have to negotiate drug pricing with Medicare.