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Big ambitions for India's contract research firms

The country's CROs want a seat at the global drug discovery table

by **Vanessa Zainzinger**, special to **C&EN**

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Credit: Sai Life Sciences | Sai Life Sciences employs upward of 2,000 people at its facilities in India.

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Amid the economic turbulence and supply chain upsets of the past 2 years, big pharmaceutical companies have been quietly moving some of their drug discovery projects from research outsourcing partners in China to partners in India.

The diversification effort started before the pandemic, says Ramesh Subramanian, chief commercial officer at Aragen Life Sciences, one of India's leading contract research organizations (CROs). "What we're seeing is a significant focus from companies on diversifying their geographical footprint," he says. "It goes both ways: companies that are fully ensconced in India look to China for diversification. Companies that are fully ensconced in China look to India."

But India is the clear winner in the drive to diversify, executives in the country say. Pharmaceutical companies have historically been more invested in China—Asia's largest market and home to the **world's largest CRO**, Shanghai-based WuXi AppTec—and are now expanding into India. And China's tensions with the US are helping fuel the shift.

Hyderabad, India-headquartered Aragen is already profiting. The company, which employs 3,200 people, just celebrated its best year yet, Subramanian says, and local reports peg the company's value at \$1 billion. Formerly known as GVK Biosciences, the company recently rebranded as Aragen, the name of its US subsidiary. The change was motivated in part by a desire to appeal to a customer base that is almost exclusively Western, according to Subramanian.

IN BRIEF

India's contract research organizations (CROs) are no longer just low-cost compound synthesizers. Over the past 15 years, they have asserted themselves as world-class chemistry-service providers. Now, the country's top CROs are setting up labs in the West, fostering global teams, and courting biotechnology companies. The goal of their executives is nothing less than becoming integrated partners for global drugmakers and going head to head with China as the world's powerhouse drug discovery partner.

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Western drug companies have been looking seriously at India for research help since 2005, when the country started to comply with the Agreement on Trade-Related Aspects of Intellectual Property Rights, or TRIPS, a globally recognized intellectual property pact, says Nailesh Bhatt, CEO of the US specialty pharmaceutical company Vgyaan. The new law roused the drug industry's interest in India for cheap access to highly qualified scientists and the potential for selling patented drugs in India, Bhatt says.

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Part of the industry is still low cost, Bhatt says, but India's largest CROs have evolved since then from cut-rate service providers to powerhouses for high-quality chemistry and biology serving the Western market. "The evolution of the Indian drug discovery services has been quite drastic," Bhatt says. "If you look at the number of contract development and manufacturing organizations (CDMOs) that were in India in the late 2000s versus what is there now, the clear winners have really emerged."

Now, India's top CROs and CDMOs are asserting themselves on the global stage. They are courting biotechnology companies by setting up satellite labs in the US and Europe. And they are hiring managers with Big Pharma or chemical experience. Their goal: go head to head with China while becoming less of an assistant and more of a partner for their drug industry customers.

Credit: Syngene International

Syngene International offers drug discovery biology services at its facility in Bangalore, India.

WESTERN STANDARDS

Jonathan Hunt, the CEO of Syngene International, says the window of India's operating cost advantage is narrowing. The country's successful CROs have had to keep up with globally recognized processes, quality standards, and operating models to compete in the world market. State-of-the-art facilities and top-notch teams are not compatible with offering low-cost services, he says. But if India's cost advantage is fading, the country's place in the outsourcing industry is holding firm, Hunt says.

Founded in 1993 by Biocon, a leading Indian drug company, Syngene is one of the Indian CROs that have moved beyond the rote performance of research tasks and into fuller discovery collaborations.

Hunt credits the company's success in part to a relationship with Bristol Myers Squibb that dates back to 1998. Syngene established a dedicated research facility for the US drugmaker in 2009. Earlier this year, Syngene **announced** the addition of a 4,600 m² lab to the facility. The company will additionally add 200 researchers to the facility's staff as part of an extension of the contract with Bristol Myers Squibb.

“**T**here aren't many places on the planet where you can access that volume of young talent regularly.

— **Jonathan Hunt**, CEO, Syngene International

The partnership, Hunt says, has committed Syngene to processes and quality standards that are equal to global ones. In hindsight, this commitment was key to Syngene's success with future clients. "From day 1, we gained a well-founded reputation that if you go inside our walls in Bangalore, our operations reflect the quality and safety standards that you find in the global markets," he says.

If Indian companies' cost advantage is narrowing, what still sets them apart from CROs in the West is the benefits of the country's population of more than 1

Snapshots of some of India's leading CROs

billion. Syngene has more than 5,400 employees, of whom 87% are scientists. "There aren't many places on the planet where you can access that volume of young talent regularly," Hunt says.

Large pharmaceutical companies turn to India to fill a gap between the type of R&D that they need and the number of people at their companies who are qualified to do it, Aragen's Subramanian says. His company has around 1,600 people dedicated to drug discovery. "Scale is something very tough to reproduce. And companies' needs evolve dramatically. You might need x number of people today and twice as many tomorrow," he says.

Not all of India's drug discovery talent is local. Western scientists have long been hires at companies like Syngene and Aragen. And increasingly, the top CROs are hiring outside managers with large pharmaceutical or chemical experience.

One example is Marcel Velterop, president of drug discovery and CDMO services at the Bangalore, India-based CRO Jubilant Biosys. Velterop held positions with DSM and Dr. Reddy's Laboratories before joining the CRO. And before Hunt, who is British, was appointed Syngene's CEO in 2015, he was an executive at AstraZeneca.

Vgyaan's Bhatt says the recruitment of such leaders proves companies are serious about playing the global field. "They need credibility, leadership expertise, and a real global perspective if they want to be able to sit with the head of R&D at AstraZeneca or GSK [GlaxoSmithKline] and say, 'Not only should we work for you; we should be partners in drug discovery,'" he says.

Hunt, who lives in Manchester, England, and travels between the continents when COVID-19 restrictions allow, says his appointment represents not a strategy to increase Syngene's ties with Western customers but rather the global nature of top-tier CROs. Most of Syngene's clients are from outside India. "It's no surprise that your talent base and your leadership increasingly represent the geographical spread and diversity of the customers in the industry," he says.

WESTERN FOOTHOLDS

To Syngene, the company's geographic presence doesn't need to mirror this diversity. The firm has been strengthening its sales staff in key markets like the US and UK, but all its discovery and manufacturing facilities are in India. While Hunt says Syngene is open to establishing a base in the West, he says the absence of one "hasn't held us back so far."

Other Indian CROs consider a site in the West necessary if they are to form more integrated relationships with their clients—especially relationships that extend

Aragen Life Sciences

- ▶ **Founded:** 2001
- ▶ **Employees:** 3,200
- ▶ **Sales:** \$160 million
- ▶ **Sites:** Bangalore, Hyderabad, and Vishakhapatnam (India), and California (US)
- ▶ **Services:** Discovery, development, and manufacturing of small molecules, and discovery and development of large molecules

O2h group

- ▶ **Founded:** 2003
- ▶ **Employees:** 500
- ▶ **Sales:** \$12 million
- ▶ **Sites:** Ahmadabad (India) and Cambridge (England)
- ▶ **Services:** Integrated drug discovery; synthetic chemistry; biology; absorption, distribution, metabolism, and excretion; process R&D; and scale-up

Sai Life Sciences

- ▶ **Founded:** 1999
- ▶ **Employees:** 2,200
- ▶ **Sales:** \$105 million
- ▶ **Sites:** Bidar and Hyderabad (India), Massachusetts (US), and Manchester (England)
- ▶ **Services:** Discovery, development, and manufacturing of drug substances

Syngene International

- ▶ **Founded:** 1993
- ▶ **Employees:** more than 5,400
- ▶ **Sales:** \$304 million
- ▶ **Sites:** Bangalore, Hyderabad, and Mangalore (India)
- ▶ **Services:** Research, development, and manufacturing across modalities, including small and large molecules, antibody-drug conjugates, and oligonucleotides

beyond preclinical drug discovery and encompass the manufacturing of drug candidates that might enter clinical trials. "At some point, not having a site in the West was really hurting us," says Tuneer Ghosh, global head of chemistry, manufacturing, and controls business development at Sai Life Sciences.

Hyderabad-based **Sai** opened a development and manufacturing site in Manchester, England, in August 2020. Despite challenges posed by the pandemic, the site was a success. Less than 6 months after opening, Sai announced plans to double its head count and expand the site to offer active pharmaceutical ingredient (API) production, particle science and engineering, in silico modeling, and flow chemistry. A further expansion later this year will add a kilogram-scale lab that follows good manufacturing practice (GMP) standards.

Located in Alderley Park, a former country estate that is now a 160-hectare life sciences center, Sai's site in Greater Manchester has opened new opportunities with UK- and European Union-based drug companies and biotechs, Ghosh says. "Historically, Sai has been doing really good business with large pharma in the West, but for critical projects, which need speedy delivery, or for complex chemistry, they would still look to CDMOs that are closer to them."



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Echoing other executives in India, Ghosh says that some customers are nervous about taking their intellectual property to CROs or CDMOs in India but are happy to hire a team in the UK. Last year, Sai began working with a drug industry client that has a policy of not outsourcing the synthesis of new chemical entities to India. The Manchester site, Ghosh says, "gave us a direct cutting edge. We had been trying to get into that big pharma for several years."

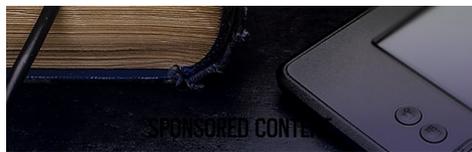
The Manchester team comes mostly from Big Pharma and Western CDMOs, creating a cultural link to customers, says Dean Edney, Sai's global head of process R&D. Edney, who came to Sai after 26 years at GlaxoSmithKline, divides his time between Manchester and Hyderabad when the pandemic doesn't thwart travel.

Credit: Sai Life Sciences

Sai Life Sciences opened this development and manufacturing site in Manchester, England, in August 2020.

Sai wants to create teams on two continents that can tap into each other's expertise. The talent pools in Manchester and Hyderabad are different, Edney says, and the transfer of knowledge is "absolutely key" in Sai's strategy to build a global organization. The plan to expand into flow chemistry in Manchester, for example, will be aided by the team in Hyderabad, where flow-chemistry experience is more readily available. And once travel is possible again, team members will rotate between sites.

Sai is not the only Indian CRO that sees advantages to a Western base. In 2014, before the rebranding, GVK Biosciences acquired the US CRO Aragen. Officially, the



rationale was to get involved on the biologics side of the drug industry. But Subramanian says GVK was also keen to gain access to US-educated talent and strengthen its relationships with Western pharma.

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Similarly, Kolkata-based TCG Lifesciences established a US subsidiary, TCG GreenChem, earlier this year. It currently occupies 5,000 m² of laboratory space across sites in Ewing, New Jersey, near Princeton, and Richmond, Virginia. TCG GreenChem's CEO, Chris

Senanayake, who previously worked at Boehringer Ingelheim, Sepracor, and Merck & Co., became the chief science officer of TCG Lifesciences in 2019 before founding TCG GreenChem.

The idea, Senanayake says, is to make TCG GreenChem the drug development engine for TCG Lifesciences and its clients, with innovation spearheaded in the US and most manufacturing done in India. If used well, this system will allow TCG Lifesciences to engineer complex molecules at low cost, he says.

Newer, smaller CROs are also taking this approach. Naresh Jain founded NJ Bio with the aim of leveraging India's R&D expertise and bringing it to the US. "The expertise in CRO work, large-scale manufacturing, and APIs that India has grown over the last decades is stronger than that in the US now," Jain says.

The cost of labor is still an incentive for an Indian base, he says: the annual price of employing a scientist in India is as low as \$30,000, compared with \$180,000 in the US. India's chemists "produce similar results, if not better," Jain says. But he also speaks highly of chemists trained in the US who bring a more innovative approach. Working together on sites in India and the US, the two sides bring a lot of value for NJ Bio's clients, Jain says. "Whenever you mix two different cultures, it's very refreshing. Diversity brings innovation."

Founded in 2019, NJ Bio occupies about 3,200 m² of a former Bristol Myers Squibb facility in Princeton. Jain also helped to launch an affiliated company, Amar Chemistry, in Mumbai, India, around the same time. Between its sites in India and NJ, the CRO specializes in bioconjugation, nucleotide chemistry, custom synthesis, biomolecular nuclear magnetic resonance, and flow chemistry. Jain's ambition is to grow it into one of the largest niche-expertise CROs in the US.

To achieve this, NJ Bio has to convince its potential clients that it is safe to entrust their intellectual property (IP) to a team that works partially out of India, Jain says. "When we try to sell our services to most clients, their main concern is their IP," he says, as US companies are nervous about sending sensitive information to other continents. NJ Bio's model gives clients the option to get early-stage work done in India and later-stage work in the US. "For example, a compound that requires a 25-step synthesis has the first 10 steps done in India and the other 15 in the US," he explains. "Clients are much more comfortable with this model."

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Miles Congreve, chief scientific officer at the biotech firm Sosei Heptares, is an example of such a client. He is used to working with Asian CROs on drug discovery but draws the line at the manufacturing of drug candidates under GMP standards.

"We would struggle with using Indian and Chinese groups for GMP just because you can more easily audit sites in the West," he says. "You don't want an issue with manufacturing that you don't have control over." This is a common hurdle for CROs that want to become one-stop shops offering both research and manufacturing services.

If Syngene, for example, had a site near Sosei Heptares's base in Cambridge, England, then Congreve would consider the company a one-stop shop, he says. As it is, Sosei Heptares employs a jigsaw puzzle of CROs and CDMOs, picking them for different projects according to their individual strengths and locations.

“**O**nce you start getting professional investors, I think the doors will open wide for India.

— **Ramesh Subramanian**, chief commercial officer, Aragen Life Sciences

Last year the biotech worked with six CROs on designing inhibitors of the SARS-CoV-2 main protease to find an oral drug for the treatment of COVID-19. Syngene supported chemical synthesis, enzyme inhibition screening, and characterization of pharmacokinetic properties of key compounds. UK-based Domainex and Croatia-based Fidelta contributed to assay development and screening. Piramal Pharma and WuXi contributed to the synthesis work alongside O2h Group, a CRO based in India and Cambridge, England.

O2h is Sosei Heptares's biggest external team and receives a budget of more than \$1 million each year. Run by the Indian British brothers Sunil and Prashant Shah, O2h was built on a premise similar to NJ Bio's. "We saw the strength in chemistry that India had in the early 2000s and the emergence of the biotech scene in Cambridge and put those two observations together," Prashant Shah says.

The brothers geared their business to help start-up biotech companies from the get-go. Besides drug discovery services, they offer seed funding and incubation support, as well as mentoring and connections to clients in the vibrant Cambridge scene.

Credit: Syngene International

All of Syngene International's research facilities are in India, including this one in Bangalore.

"Having a presence in the UK was essential for building those relationships with customers and supporting them with their drug discovery requirements," Prashant Shah says. The advantage of doing most of its chemistry and biologics in India, he says, is the ability to scale up a project quickly.

Sosei Heptares started working with O2h in 2008. It was the first CRO the young biotech hired. Would the relationship have been this successful if O2h had only had a site in India, or only in the UK? "That's a good question," Congreve says. "It was certainly a factor in the beginning because I liked being able to go to their office in Cambridge and visit the site. But today we work with companies where we've never even seen their site."



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COZYING UP TO BIOTECHS

To India's CROs, courting biotechs like Sosei Heptares is arguably the biggest part of their business plans, and the biggest motivation behind setting up shop in the West. "Yes, we are absolutely going after biotechs," Sai's Ghosh says. When biotechs stopped partnering with Big Pharma firms for all their promising compounds and began taking some drugs to market themselves, Sai changed its business model to cater to them, he says.

Like NJ Bio, O2h, TCG, and Aragen, Sai is leveraging its multiple sites to provide biotechs with speed, infrastructure, support, and reassurance that their IP is secure and in a familiar setting. Besides the Manchester site, Sai has placed business development representatives in Massachusetts, San Francisco, and European hubs like Barcelona.

The focus on biotechs also gives CROs a chance to shake off their reputation as rote makers of compounds. Rather than settle into the service role often expected by big drug companies, CROs can enjoy relationships that are more symbiotic, as young companies take help from experienced contract research partners to craft their strategies for drug development.

The desire for more equal client relationships runs through all of India's most successful CROs, although none go as far as to say that gaining access to intellectual property is a part of the plan. Syngene's Hunt says the leap from providing simple, repeatable chemistry tasks to doing integrated drug discovery is natural for the industry. "We're just a biotech company in disguise," he says. "We don't need to own the IP, but we create IP in a way that's indistinguishable from a biotech or pharma."

The difference may be indistinguishable, but it continues to be important. CROs typically charge their customers for an agreed-upon number of full-time equivalent (FTE) employees. Under an FTE contract, the client pays the CRO a fixed amount without regard for the project's eventual success or failure.

Some Indian CROs are keen to establish risk-sharing agreements with their customers under which they receive less money than in a straight FTE contract but qualify to earn royalties if their contribution helps the customer launch a new product.

But biotechs tend to be skeptical of these contracts, which rely on the CRO's providing input that is worth its share of the profit. "True risk means true money on the table, and sometimes the CROs overvalue the input they can give," says Robert Boyle, the CEO of Sentinel Oncology, a biotech in Cambridge, England, that outsources all its chemistry research. Sentinel has done one risk-sharing agreement, with O2h, in the 16 years since its foundation. Sentinel paid for five FTE chemists. O2h provided another five for free and took a share of royalties in the program.



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Although Boyle was happy with the project, he is not convinced that CROs can cross the bridge from being a set of helping hands to becoming a true partner for biotechs. "It's a different business model. Contract research was driven by being a cost-efficient, professional outsourcing arm," he says. "I can see more risk sharing as some CROs try to differentiate themselves as a one-stop shop, but I think it's proven hard to get that off the ground."

Indeed, Boyle still sees the financial advantage of Indian CROs as their main draw. "It would be very hard for us to suddenly flip to a UK chemistry service provider who would want to charge \$200,000 for an FTE agreement when we pay \$75,000 in India," he says. "That's a lot of money for a young biotech."

“ True risk means true money on the table, and sometimes the CROs overvalue the input they can give.

— **Robert Boyle**, CEO, Sentinel Oncology

If money is the deciding factor for biotechs, China's CROs are as competitive as India's. Sentinel uses both, and Boyle says he has no preference for doing business with one or the other, although he says working with Chinese firms can be hampered by the language barrier.

Industry watchers name language as China's biggest hurdle for contract research dominance. India, with its English-savvy population, has the upper hand. And while it's not challenging for big corporations to employ translators or local staff, smaller companies, such as most biotechs, will struggle to create a partnership with a Chinese CRO, TCG's Senanayake says. "Communication is the only downside to China. This is where we can differentiate ourselves and support the biotech industry."

If India's CROs have ever had a chance to eclipse China's, this is the time. Political tensions between the US and China and the drive to **reclaim the manufacturing supply chain** by the pharmaceutical industry and government during the pandemic highlight the extent to which China dominates the world's supply of pharmaceutical chemicals. These tensions have tempted some potential customers to edge away from the contract research giant.

But although some business may move to India, the shift doesn't seem to be making a visible dent in China's prominence. WuXi, for one, recently forecast its net profit for the first half of 2021 to increase by more than 50% from a year ago. Another leading Chinese player, Pharmaron, said its profit shot up 140% in the first quarter of 2021 from last year.

Aragen's Subramanian is optimistic that India will gain more business from China in the near future. The ingredient missing to propel India's contract research industry to the top is investment, he says. And here, private equity companies are beginning to fill the gap.

Last year, the Carlyle Group took a 20% stake in Piramal Pharma, a CDMO headquartered in Mumbai. In November, Syngene signed a 5-year agreement with the drug discovery and development subsidiary of Deerfield Management, a venture capital firm. And Goldman Sachs took a significant stake in Aragen this year. Subramanian says there are "several other deals that we know are in the works."

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One of the things that differentiated China from India when research outsourcing took off between 2001 and 2010 was China's access to government-provided capital, Subramanian says. Without it, Indian companies were unable to scale in the same way. "The science was always there. The talent was always there. What was lacking was financial capital," he says. "Once you start getting professional investors, I think the doors will open wide for India."

Sosei Heptares's Congreve expects consolidation over the next decade, with at least some of India's star players being bought by or acquiring companies that will give them wider global reach. It would be good news for their clients, Congreve says. "It's attractive to work with companies that are widening their network so you can access their services around the world," he says. "Clearly, in another 10 years from now, there will be huge corporations that have swallowed up others as part of a group."

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And financial machinations aside, O2h's Prashant Shah adds that Indian CROs themselves have become "extremely confident" in their ability to drive the country's industry forward. "They've got very strong balance sheets. They can invest and make decisions and move quite aggressively to take up new opportunities across the entire pharmaceutical landscape," he says. "India is genuinely a powerhouse in terms of its capabilities now."

Vanessa Zainzinger is a freelancer writer who covers the chemical industry.

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