

# NEW WORKING MODELS WITH PHARMA

The 21<sup>st</sup> century pharmaceutical and biotech sector has come a long way from its heritages in 19<sup>th</sup> century pharmacy, with differentiated contract testing services business models. Traditional contract research testing services that follow the outsourcing model offer low-cost options to pharma that come with advantages and disadvantages. With New Approach Methodologies (NAM) being developed and encouraged by the FDA and CDER, there is a new business process and markets emerging parallel to outsourcing models. These new business processes impregnated with robotic process automation through artificial intelligence (AI) and machine learning (ML) tools, framework is forecast to build the bandwidth to create a new working equation with pharma industry. NeuroSAFE is one such breakthrough (NAM) with the power to democratise the safety and efficacy testing of pharma and biopharmaceuticals from R&D stage till manufacturing.

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## Traditional operating style

Over the last three decades pharma companies have increasingly relied on outsourced research to minimise costs, and incorporate new science relating directly to the better understanding of biology. The outsourcing trend led first to smaller, service-oriented companies taking up portions of early pre-clinical research contractually. These contract research organisations (CROs) arose in silos based on disparate skills employed along the complex drug developmental process. CROs specialising in chemistry provided services for synthetic and medicinal chemistry, whereas those with expertise in biology, separately, provided services in cell biology and animal studies. These pre-clinical CROs generated data for the investigational new drug (IND) application dossiers submitted by pharma clients, to the FDA, for commencement of human clinical trials. Clinical trials are conducted by another set of service providers that specialise in human studies. Today CROs conduct almost all of the R&D that leads to pharma product approvals.



Over the last decade or so the CRO industry has been driven by acquisitions to amalgamate skills to (i) improve financials, (ii) assuage client concerns of having to deal with too many vendors, and (iii) play a seminal role in intellectual property generation to ask for risk-sharing rewards that are multiples above the cost-plus models associated with plain vanilla silo services. Even more recently, acquisitions in the space show a clear key trend, CROs are acquiring their peers for innovation, not just expanding top-lines or geographies. Testament to this is the fact that valuations of innovation-led acquisitions were almost double the rest over the past five years.



A closer look shows that the intellectual property (IP) is primarily generated in early pre-clinical stages of drug development. Importantly, a lot of this IP emerges from cell-biology research, relating to biochemical pathways, genes and proteins as drug targets. Later animal studies serve to help validate early hypotheses. But it is of note that animals is not where IP is generated. Animal studies are, however, integral to drug discovery as they allow testing at an organism level, and FDA approval is unthinkable without these. But now there is an emerging paradox: failures during human trials are mostly due to data from animal studies not translating to humans! Disease and drug response mechanisms at the genetic level are different in animals. The rise of animal models with humanised diseased parameters have helped translatability but the overall failure rates are still >75 per cent for drugs under development, (albeit with better rates for biologics). Exacerbating the 'non-translatability' problem is the recent movement against animal research. In the Cosmetics sector, for example, a European commission has banned the use of animals altogether. Even for the pharma sector animal-research capacities are strained, due to which costs have nearly tripled over the last decade.

'Inaccurate animal science' and 'animal rights' is driving cell-biology efforts (both academic and commercial) to come up with solutions that are better indicators of experimental drug performance. Leading cell-biology service providers today are not only providing better mechanistic details to understand safety and efficacy profiles, the bleeding-edge now is human cell systems. The cream of the crop here are companies that deal with human induced pluripotent stem cells (HiPSCs) that bring totally next generation benefits to the assay system. It is interesting to note that leading CROs like Charles River Laboratories started as an animal supplier to the pharma industry in the 1940s and went on to acquire Hemacare in 2021 for access to stem cells, cells, tissue like in vitro systems yielding human relevant readouts.

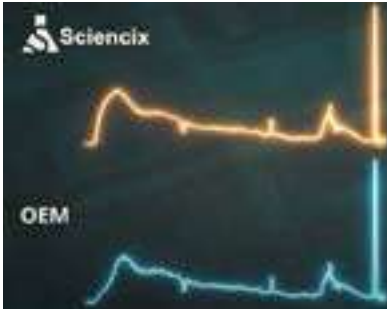
In parallel, information technology, AI/ML are also making significant strides in drug discovery, crunching big and voluminous data that is spewed all along the process of drug discovery. In the pre-clinical stages combining IT with human cell biology is creating realistic models for safety and efficacy testing akin to human systems. Moreover with the massive computing power available now, testing and modelling is done in a high throughput manner saving time and cost while increasing accuracy of insights that are relevant for human biology.

#### New Approach Methodologies Concept – Brewing New World Order

Even the FDA which is typically not concerned with approval of pre-clinical protocols is now recommending the use of NAM, which include cell biology methods that are more scientifically accurate. White papers from FDA and CDER encourage the global industry to embrace surrogate human in vitro pre-clinical models to improve the predictability of clinical outcomes. In line with this, international organisations including ICH, ICCVAM (NIH), ▶

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and OECD have outlined the principles of 3R (Replacement, Reduction and Refinement) framework for performing more humane animal research or do away with animal research completely. Current thinking from opinion leaders and multilateral institutions are strong signals for the imminent shift to “non-animal” methods through the use of NAMs. Current literature describe NAMs using micro-physiological systems (MPS) like organ-on-a-chip, tissue-on-a-chip, organotypic cultures like co-cultures, 3D organoids, in vitro/ in silico toxicity prediction tools, quantitative structure activity relationship (QSAR) computer-based models for toxicity testing. Wide-ranging developments of MPS models using human cells have been developed to improve toxicity and efficacy prediction in humans, and are understandably explored for use in both pre-clinical and drug development stages.

An example of a well-used NAM in vitro method utilising HiPSC is CiPA (Comprehensive in vitro Pro Arrhythmia) assay to predict risks associated with drugs on ion channels. The readouts of CiPA paradigm help profile the risk of candidate drugs before clinical trials are undertaken. Other assays like ALI (in vitro air liquid interface) cell culture model for studying structure and function of organs (including lung, intestine, kidney, lung, and liver) have been developed and validated for commercial applications.

### Indian CROs: A Historical Perspective

The ~25-year old Indian CRO industry has done well by achieving US\$1.8 billion in revenues in 2021, while growing at double digits over the last decade. However, the performance is mostly attributable to chemistry services. Indian CROs are predominantly offspring of the traditional Indian pharma industry or Indian corporate conglomerates, both financially and expertise-wise. Consequently, the industry is steeped in chemistry skills but less so for biol-

ogy. Chemistry skills, stemming from the reverse-engineering culture of traditional generics industry, have been well exploited for early research, providing services for synthetic and medicinal chemistry, and also later for large scale manufacturing, where CDMO services have come of age and form significant portions of CRO revenues. However, due to the chemistry-laden heritage, the Indian CRO industry has made only modest strides in biology services. In at least one case a top-10 pharma major, Eli Lilly cancelled an ongoing research services contract with an India CRO, and shifted to Pharmaron in China for access to better biology skills.

More recently (for less than a decade) Indian CROs are incorporating biology services through both organic and inorganic routes. Examples of this include GVK Biosciences acquiring Aragen in 2015, and Intox in 2021. The latter was acquired for the expressed purpose of incorporating animal toxicology services. But even these are mostly geared towards “non-human” cell biology or CDMO-type large scale biologics manufacturing, and not so much innovation and new discovery (intellectual property). To reinforce this take the example of the leading global CRO, Charles River Laboratories, that has played an equal part in the innovation of 70 per cent of the drugs approved by its pharma clients over the last 5 years. In line with this leading international CROs (CRL, Wu-Xi, Pharmaron, Eurofins) are all evolving not only from an increased focus on cell biology but also through embracing human cell biology.

Introducing NAM concept in Safety and Potency Testing Offered as a Solution

Non-clinical safety and potency testing on human MPS models is a reality to practice at industrial scale when digital tools and robotic process automation complement the in vitro system developed. One of the best features of this model is its seamless integration into the user’s workflow. The other advantages like user’s data privacy, access to human MPS based robust testing methodologies

integrated in the process to implement in R&D, pre-clinical, clinical and manufacturing stages are totally revolutionary.

Vaccine neurovirulence is a real safety concern of all the vaccines produced for neurotrophic viruses (eg: Polio, Covid-19, HIV, Yellow fever, Mumps, Measles) with history of mishaps associated with qualified vaccines in the immunised population. Monkey Neurovirulence Test (MNVT) is the gold standard method practiced for over 50 years to test neurovirulence. Likewise, Human data are generally not available for IND’s neurotoxicity profile, but when they are they take precedence over animal test results. ■

References are available at [www.pharmafocusasia.com](http://www.pharmafocusasia.com)



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