VOL 23 | ISSUE 6 | JANUARY 2026 | MUMBAI | TOTAL PAGES 44 | PRICE ₹ 150

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PHARMA BIO WORLD
R.N.I. No.: MAHENG/2002/08502

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Annual Subscription: ₹ 1620/-, Foreign: USD 180

Registered Office: 26, Maker Chambers VI, 2nd Floor, Nariman Point, Mumbai 400 021, INDIA.
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PLACE OF PUBLICATION
JASUBHAI MEDIA PVT. LTD.
210, Taj Building, 3rd Floor, Dr. D. N. Road, Fort, Mumbai 400 001, Tel: +91-22-4037 3636

Published by Mr Hemant K. Shetty
Address: 406-D, The Karachi Citizens Co-Op Hosg Soc Ltd., Juhu Varsova Link Road, Andheri West, Mumbai - 400053.
Printer: Harilal Gangaji Patel
Printing Press (Name & Address): The Great Art Printers
25, Unique House, S A Brelvi Road, Fort, Mumbai 400 001.
Published from Jasubhai Media Pvt .Ltd. 3rd Floor, Taj Building, 210, Dr. D N Road, Fort, Mumbai 400 001.

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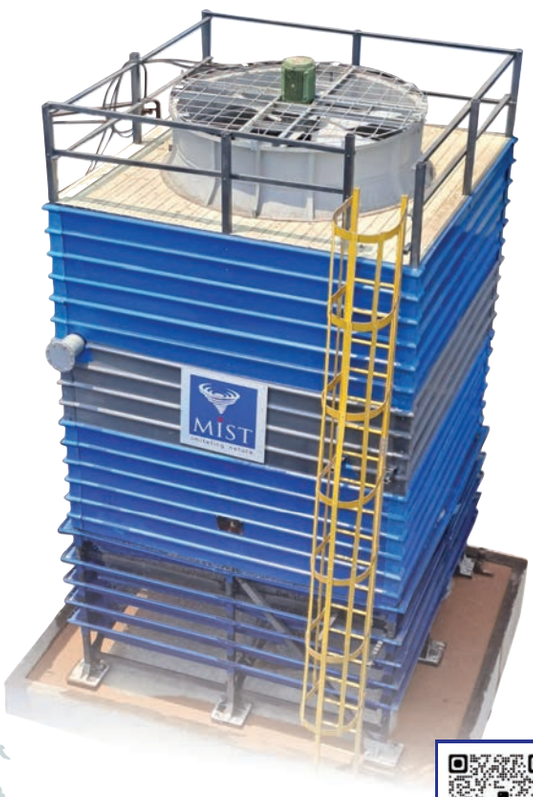

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GUEST COLUMN

Essential Phospholipids: A Promising Candidate for Easing Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by persistent and chronic inflammation of tissues within the gastrointestinal tract. The two predominant forms of inflammatory bowel disease are ulcerative colitis and Crohn's disease. As many as 10% of cases of IBS show the symptoms of both Crohn's disease and ulcerative colitis.

While Crohn's disease affects the small and large intestines, mouth, oesophagus, stomach and anus, ulcerative colitis mainly impacts the colon and rectum, leading to superficial mucosal damage.

Arun Kedia emphasizes about the use of Phospholipids in Inflammatory Bowel Disease (IBD) Management.

Arun Kedia
Managing Director, VAV Lipids

The occurrence of IBD shows geographical variations, with higher rates observed in Europe and North America, in contrast to lower rates in Asia. In India, recent research conducted by the IBD Center of the Asian Institute of Gastroenterology (AIG) has indicated a significant increase in the prevalence of IBD, showing a surge from 0.1% in 2006 to over 5% in 2023. The study also highlights that IBD now constitutes more than 5% of individuals experiencing lower gastrointestinal symptoms, including chronic abdominal pain, alterations in bowel habits, and persistent diarrhoea.

Currently, there is no definitive cure for IBD. The approach typically involves the lifelong use of maintenance drugs. Traditional treatment methods often lack the accuracy to target specific inflammatory sites, resulting in limited effectiveness. Often, these

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treatments also carry the risk of severe side effects due to the systemic redistribution of drugs.

To find an effective solution to these challenges, continuous research is underway that increasingly delves into developing targeted drug delivery systems. These cutting-edge strategies aim to transport drugs directly to inflammation sites, improving the drug's effectiveness while reducing side effects.

Use of Phospholipids in IBD Management: An Overview

During research, one approach that has shown immense potential in addressing IBD and ulcerative colitis is phospholipids. These complex lipids, consisting of phosphoric acid, a nitrogen base, alcohol, and fatty acids, have shown remarkable biocompatibility and distinctive amphiphilic properties. An amphiphile is a chemical compound with both hydrophilic (water-attracting) and lipophilic (fat-attracting) properties. These distinct characteristics are why phospholipids are so well-suited for use as essential pharmaceutical excipients.

A specific category of phospholipids that have attracted interest due to their potential to reduce inflammation is marine phospholipids. These phospholipids are filled with beneficial polyunsaturated fatty acids (PUFAs). They naturally occur in a tightly packed form, making them very stable and resistant to damage, and the body can use them efficiently.

What's more, these phospholipids play a significant role in reducing inflammation. They achieve this by influencing specific elements regulating inflammation and producing substances that contribute to calming inflammatory responses.

The distinctive structure of these phospholipids, featuring a water-repelling tail and a water-attracting head, allows them to form tiny structures known as micelles or liposomes when mixed with water. These structures, coupled with the inherent stability and resistance to damage intrinsic in marine phospholipids, offer an exciting possibility for therapeutic applications.

Recent research has also focussed on phosphatidylcholine (PC) in marine phospholipids for managing ulcerative colitis. People with ulcerative colitis exhibit a noticeable deficiency of PC in the colonic mucus. Clinical trials supplementing PC to the colonic mucus have shown reduced inflammation.

Two-pronged Benefits of Phosphatidylcholine

The notion that PC could have a role in ulcerative colitis originated while studying the mucus in the rectal wall during rectoscopy. In patients with ulcerative colitis who were in remission, the levels of PC were significantly lower compared to healthy individuals. This pattern persisted in people with active ulcerative colitis when studying mucus during colonoscopy. These findings prompted researchers to initiate clinical studies to investigate whether supplementing the deficient phosphatidylcholine in the mucus could alleviate inflammation in ulcerative colitis.

PC's protective functions include establishing a hydrophobic barrier on the mucus surface providing a shield for underlying tissues against harmful substances. Tests on samples of ulcerative colitis patients showed that they have less of this protective shield. This hydrophobic barrier acts as a frontline defence mechanism, preventing the attachment and penetration of substances that could serve as invasive agents.

Additionally, the phospholipids in the mucus become integral to the outer layer of cells in the intestines, influencing signal processes in the mucosa. PC has demonstrated the ability to reduce inflammatory responses, such as stopping the assembly of specific cell structures and preventing the activation of certain inflammatory genes.

In a nutshell, PC brings double benefits: it not only possesses anti-inflammatory properties but also reinforces the protective qualities of the mucus layer. This dual functionality makes it a promising panacea for treating inflammatory bowel diseases.

Within the digestive system, PC exists in two forms – within mucus structures and as a surface layer. It engages with mucins (proteins in the mucus) to create a protective barrier that thwarts bacterial invasion.

PC also controls cell signalling associated with inflammation, impacting receptor locations, signal activation, and production of inflammatory substances. The interaction of these actions plays a crucial role in regulating the body's inflammatory response.

Role of Supplements in Managing IBS

Given these findings, the prospect of oral supplements with marine phospholipids emerges as a feasible method to reduce inflammation in ulcerative colitis and IBS. This supplementation is a rich source of both phosphatidylcholine and Omega-3 fatty acids.

The possible advantages extend to integrating phospholipids into cell membranes, restoring phosphatidylcholine content in colonic mucus and providing the essential nutrient choline.

On a broader scale, adopting approaches centred around phospholipids can transform the treatment ecosystem for individuals dealing with inflammatory bowel diseases. As research in this domain continues, the possibilities for tailored treatments harnessing the distinctive properties of phospholipids are poised to grow.

Understanding the properties of essential phospholipids, notably phosphatidylcholine, brings forth several pathways for IBD management. With their unique properties and capacity to regulate inflammation, phospholipids have immense potential for targeted drug delivery and therapeutic supplementation.

Further research in the field will continue to show how their use in conventional treatments may offer hope and respite to people struggling with IBD.■

Challenges & Opportunities in Global Regulatory Compliance for Biologics

Dr. Nirdosh Jagota
Founder & Managing Partner
GRQ Biotech Advisors LLC

Ensuring regulatory compliance is a critical business requirement for Biotech industry to succeed. They need to stay current with the latest regulations, guidelines, and trends in ever changing regulatory environment. FDA, EMA, WHO, PICS and ICH guidance documents provide basic framework. While each country/region has its own legal framework and enforces its own requirements, basic principles remain about the same. The basic principle is that a patient receives a medicine, which is safe, effective and has appropriate quality. Companies need to have "patient centricity" as the focus.

Dr. Nirdosh Jagota spoke about the challenges in Global Regulatory compliance for biotech industry. He also spoke about the Good manufacturing practice (GMP) and Good Distribution Practice (GDP) for development and manufacturing quality.

Aspects of Quality and Compliance

Good Laboratory Practice (GLP) and Good clinical Practice (GCP) establishes framework around safely and efficacy of the medicines. Safety is defined by non-clinical toxicology, safety pharmacology. Drug interactions, special populations, and timing of these studies. Pharmacovigilance, clinical safety data management, trial design and analysis, clinical study protocols and reports, bioequivalence, periodic safety reporting and other studies define effectiveness of the medicine.

Good manufacturing practice (GMP) and Good Distribution Practice (GDP) provide important framework for ensuring development and manufacturing quality. During development, analytics, impurities (other safely considerations), stability and specifics for biologics are important. Phase appropriate GMP is the concept during development, however data integrity requirements remain the same during

development and manufacturing. These data audits are even more critical for biologics and advance therapy products. Recent FDA compliance actions for at least two large US based companies resulted into delay of product approval because of potential data integrity issues during development. From last few years FDA has a requirement for listing development testing and manufacturing sites in the biologic license application (BLAs).

For manufacturing and life-cycle management, all aspects from raw material procurement to processing and facilities are important. Quality management system, personnel. Building and facilities, process equipment, documentation and records, material management, production, and in-process controls. Packaging and labeling, storage and distribution, lab controls, validation all are critical aspects. Controls over rejection and reuse of materials, change control. complaints and recalls, oversight of contract manufacturers, agents, brokers, traders, distributors, replacers and relabellers are equally important. Quality risk management and knowledge management are key pillars.

To ensure compliance, Biotechnology companies should

- Implement quality control systems that ensure compliance with regulatory requirements, including robust documentation practices.
- Provide comprehensive training to employees on quality and compliance requirements.
- Conduct regular audits identify potential compliance issues.
- Establish effective communication with regulatory bodies, and other stakeholders,
- Maintain data integrity throughout development, manufacturing, and distribution.
- Keep patient centricity, scientific excellence, and robust documentation as a focus.
- Seek expert advice from regulatory consultants when facing complex compliance issues.

Key Regulatory Agencies

- Food and Drug Administration (FDA): FDA is US regulatory agency responsible for regulating biotechnology products such as drugs, biologics, and medical devices.
- European Medicines Agency (EMA): The EMA is the regulatory agency responsible for evaluating and approval biotechnology products in the European Union. Each country in Europe also has its own regulatory agency.
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH): ICH is an international organization that develops guidelines for the development, registration, and post-approval of pharmaceuticals, including biotechnology products.
- World Health Organization (WHO): The WHO guides and supports countries in developing their regulatory systems for biotech products.
- National Regulatory Bodies: Each country's regulatory body regulates biotechnology products. Examples include Drug Controller General of India (DCGI), The federal institute for drug and medical devices (BfArM), the Pharmaceuticals and Medical Devices Agency (PMDA/JAPAAM), and the National Medical Products Administration (NMPA-China).
- The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation scheme (PIC/s) are two international instruments between countries and pharmaceutical inspections authorities.

Regulatory agencies use a risk-based approach to evaluate product quality. The regulatory requirements for biotech products are complex and vary depending on the product type and the regulatory body responsible for its oversight. In addition to compliance with regulatory requirements, companies need to pay attention to reputational aspects. Reputation is critical for business success and important for patients and other stakeholders such as shareholders and investors.

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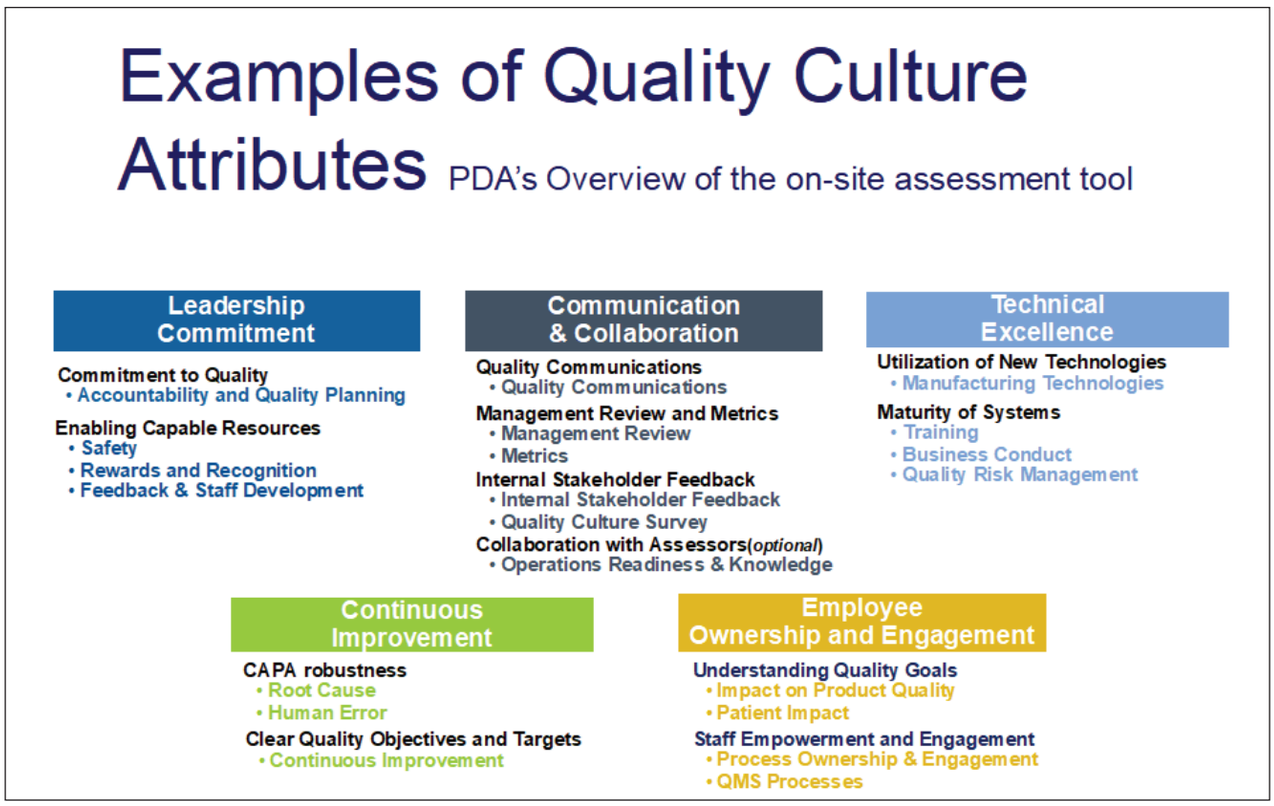

Some of the key points of quality paradigm are:

- Quality must be built and will not improve by additional testing and inspection. Refer to Quality by Design (QbD) guidances from ICH
- Better utilization of modern science throughout product lifecycle is a must.
- Robust Quality System (QS) assures quality throughout product life cycle
- Quality risk management (QRM) is the critical enabler throughout product lifecycle/
- Quality culture. Attached diagram from PDA provides a good summary of Quality culture attributes.

Some hypothetical case studies

Although building and sustaining quality is the most important aspect. Sometime a situation can happen which needs relevant scientific and compliance expertise to manage.

A Company found some trace particles in an injectable drug product. Immediately risk-assessment was performed and further supply of product was placed on interim hold. Global regulatory agencies were immediately informed and teleconferences were arranged with key agencies. Internally team did a comprehensive risk-assessment based upon patient risk-benefit and safety as the key factors. Technical team worked with a speed of light and identified the particulate matter. An approach was developed which ensures the patients have the safe and effective supply. A temporary solution of "point of use filter" was proposed to the regulatory agencies with commitment to solve the problem in intermediate time frame. A data package was provided demonstrating identity of particles and filtration data from point of use approach. Most regulatory agencies agreed with the interim approach while company had to scientifically solve the issue in the long term.

Company was informed by regulatory agency about potential data integrity failure. Company decided to inform global regulatory agencies immediately and developed a risk-based approach to continue the supply of life-saving critical products which did not have any substitute or were in short supply. The approach required utilization of third party to individually review each batch record and provide certification before release of the product. Several regulatory agencies accepted the approach based on risk-benefit analyses. The approach also required simultaneous restructuring of staff and robust talent management, extensive certified third-party training and audits at the plant.

Good manufacturing practice (GMP) and Good Distribution Practice (GDP) provide important framework for ensuring development and manufacturing quality. During development, analytics, impurities (other safely considerations), stability and specifics for biologics are important. Phase appropriate GMP is the concept during development, however data integrity requirements remain the same during development and manufacturing. These data audits are even more critical for biologics and advance therapy products. Recent FDA compliance actions for at least two large US based companies resulted into delay of product approval because of potential data integrity issues during development.

A new variant was observed in a drug product. The risk-benefit analyses indicated potential safety issue. Company immediately stopped the flow of product, and a product recall was issued. The product reintroduction took more than six months as company had to fix the process issues first.

As one can notice that each compliance issue requires careful understanding and expert input. There is no templated answer to these challenges. An understanding of global regulatory requirements, trends and deep scientific knowledge, and unbiased input from an expert consultant can help in such a situation. ■

The Pharma Revolution: How Artificial Intelligence is Reshaping the Landscape

The quest for improved health and longevity has reached a pivotal point. Artificial intelligence (AI) is not just a futuristic buzzword anymore; it is actively transforming the pharmaceutical industry. In recent years, the integration of AI in pharmaceuticals has paved the way for groundbreaking advancements, offering new avenues for drug discovery, personalized medicine, and enhanced patient care. **Dr. Romel Bhattacharjee** explores the merging of AI and pharma, discussing its use cases, innovative prospects, and limitations associated with this technological revolution.

From clinical trials to supply chain management, AI has the potential to accelerate innovation, improve quality, and reduce costs across the pharmaceutical value chain. However, careful management of both opportunities and challenges is required to realize this potential.

Beyond the Lab: AI in Action

- **Drug Discovery and Development:** One of the most significant applications of AI in pharmaceuticals is in drug discovery and development. Traditional drug discovery is a time-consuming and costly process. AI, however, can significantly expedite this process by analyzing vast datasets, predicting drug-target interactions, designing novel molecular structures, synthesizing potential drug candidates, and predicting their efficacy. Atomwise, for instance, uses AI to analyze molecular structures and predict potential drug compounds, speeding up the discovery phase. Exscientia also uses AI to automate almost the entire drug discovery process. In 2021, it identified an Alzheimer's candidate that moved to Phase 1 trials in just 12 months versus the industry average of 4–5 years. AI drug design can also improve success rates in clinical trials.

- **Personalized Medicine:** AI allows to create personalized treatment plans based on individual patient characteristics. By analyzing genetic, clinical, and lifestyle data, AI algorithms can identify the most effective treatments for specific patients. For example, IBM Watson for Oncology employs AI to assist oncologists in recommending personalized cancer treatment options by analyzing vast amounts of medical literature and patient records.

- **Clinical Trials Optimization:** AI streamlines the clinical trial process by identifying suitable candidates, optimizing patient recruitment, and predicting potential challenges. AI can also help to optimize trial design, monitor safety, ensure protocol adherence via sensors and apps, to analyze complex trial data. Trials are expensive and time consuming, so AI efficiencies provide a major competitive advantage. Startup Mendel.ai uses AI and big data analytics to reduce trial costs by 10–50 percent. Tempus, a technology company, employs AI to enhance clinical trial design and execution, leading to more efficient trials and faster time-to-market for new drugs.

- **Drug Repurposing:** AI techniques like deep learning and machine vision can analyze vast sums of biomedical data to help in identifying existing drugs that can be repurposed for new therapeutic purposes. BenevolentAI, a technology company, utilizes AI to analyze biomedical literature and databases to find a potential target for treating COVID that led to a clinical trial in just months. AI can also model target interactions to validate and prioritize the most promising targets.

- **Healthcare Delivery:** AI chatbots, virtual nurses, and clinical decision support systems can provide guidance to doctors at the point of care. In time, they may help democratize cutting-edge treatment expertise across geographies and levels of care. Chatbots and virtual assistants can also personalize patient communication and medication adherence. In the near future, AI would presumably be used to analyze medical records to predict adverse drug reactions before they occur, ensuring patient safety.

- **Supply Chain Management:** AI improves supply chain efficiency by predicting demand, optimizing inventory, and minimizing disruptions. AI is also being applied across manufacturing for improving yields, monitoring quality, and predicting equipment maintenance needs before failures occur. Pharmaceutical companies can use AI to track medicines across complex global supply chains to enhance forecasting accuracy, ensuring a steady supply of medications and reducing the risk of shortages or overstock.

Opportunities Galore

- **Cost Reduction and Efficiency:** AI applications in pharmaceuticals can significantly reduce costs and boost efficiency. By automating processes, optimizing workflows, and accelerating drug development, pharmaceutical companies can streamline operations and allocate resources more effectively.

- **Enhanced Diagnosis and Treatment:** AI-powered diagnostic tools contribute to more accurate and timely disease diagnosis. This, in turn, facilitates the development of targeted and effective treatment plans, improving patient outcomes and decreasing healthcare costs associated with misdiagnosis or delayed treatment.

- **Predictive Analytics for Disease Prevention:** AI can analyze patient data to identify patterns and predict disease outbreaks, enabling proactive measures for disease prevention. By leveraging predictive analytics, pharmaceutical companies and healthcare providers can implement preventive strategies and allocate resources strategically.

- **Patient-Centric Healthcare:** AI facilitates the development of patient-centric healthcare solutions by tailoring treatments to individual patient profiles. This shift toward personalized medicine ensures that patients receive treatments that are not only effective but also minimize adverse reactions, ultimately improving overall healthcare outcomes.

Challenges

The incorporation of AI in pharmaceuticals largely depends on the scrutiny of extensive volumes of sensitive patient data. A pivotal concern revolves around the assurance of privacy and security for this data, given that unauthorized access or data breaches could yield severe consequences. Such incidents have the potential to weaken patient trust and impede the widespread adoption of AI technologies within the pharmaceutical domain.

Another significant challenge stems from the highly regulated environment in which the pharmaceutical industry operates. The integration of AI into various facets such as drug development and patient care necessitates strict adherence to regulatory standards. Navigating these regulatory hurdles is often time-consuming, posing a potential impediment to the swift adoption of AI technologies in the industry. It becomes imperative for regulatory frameworks to evolve and adapt to accommodate the nuances of AI-powered drug development and clinical trials.

Furthermore, the increasing sophistication of AI systems introduces ethical considerations, particularly in the healthcare sector. The transparency of AI processes becomes crucial, especially when dealing with black-box algorithms that raise concerns regarding trust and accountability. Addressing questions about potential biases in AI algorithms is paramount to ensure fair and equitable access to healthcare resources.

AI could increase barriers to market access and competition. The handful of large companies with vast data and AI talent can increase dominance over smaller players struggling to keep pace with the technical complexity. Policymakers should address these issues early to ensure developments benefit patients equitably while managing risks.

As AI continues to advance, a thoughtful approach to ethical considerations is essential to navigate the evolving landscape of healthcare technology responsibly.

Limitations

- **Lack of Human Intuition**: AI systems, while powerful, lack the human touch and intuition that is often crucial in healthcare decision-making. The reliance on algorithms may lead to a disconnect between technology and the nuanced, individualized care required in certain medical scenarios.
- **Limited Generalization:** AI models are trained on specific datasets, and their performance may be limited to the conditions present in those datasets. Generalizing AI models to diverse populations or unforeseen scenarios may result in discriminatory outcomes with reduced accuracy and reliability.
- **Overreliance on AI**: Overreliance on AI systems without proper human oversight can be risky. Healthcare professionals must remain actively involved in decision-making processes, utilizing AI as a supportive tool rather than a replacement for human expertise.

Outlook

AI adoption in pharma is still in early stages but advancing rapidly thanks to accelerating technical capabilities, lowered computational costs, and fierce market competition. Navigating AI's duality of opportunities and challenges will determine winners and losers. Stakeholders across the pharmaceutical and AI sectors must engage in open dialogue to address ethical concerns, foster collaboration, and build robust regulatory frameworks. Continuous R&D is crucial to unlock the full potential of AI while mitigating its risks. Companies focused closely on patient benefit as the guiding light while responsibly and proactively addressing AI risks have the best prospects to lead this next wave of biopharmaceutical innovation. ■

Author

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Sr. Analyst, Technology/IP
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Aranca

Navigating challenges : CRAMS Industry holds long-term growth potential

The Contract Research & Manufacturing Services (CRAMS) contribute approximately 15% to 20% of the Indian Pharmaceutical Industry, which has a total value of around USD 48 billion in FY23. Over the period of FY18 to FY22, the CRAMS segment experienced a robust growth rate of about 17%. However, due to geopolitical developments and recessionary trends in regulated markets, the growth rate of the segment decelerated to approximately 4% in FY23. This slowdown in growth has also impacted the operating profitability margins, causing a decline of about 350 basis points during the same fiscal year, based on industry aggregates representing over 70% of the CRAMS segment.

CareEdge Ratings anticipates that this contraction in the CRAMS segment is temporary and expects a recovery starting from Q3FY24. The palpable reason for this recovery lies in the resumption of research activities by innovator and biotech companies, gradually returning to normalcy. The following section highlights the factors that contributed to the slowdown and contraction in the CRAMS segment and outlines the expected evolution of the segment going forward.

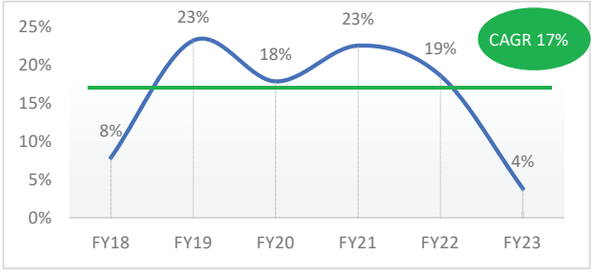
Factors for Higher Growth Rate during FY18 to FY22:

Discovery and development of a new drug is a quite lengthy and complex process, generally involving 10-15 years of time with investments running in billions (more than USD 5 billion). More than ever, the innovator companies are looking for partners across the pharmaceutical value chain to encourage innovation, optimise costs, enhance efficiency, flexibility and productivity through the various stages of drug discovery to development.

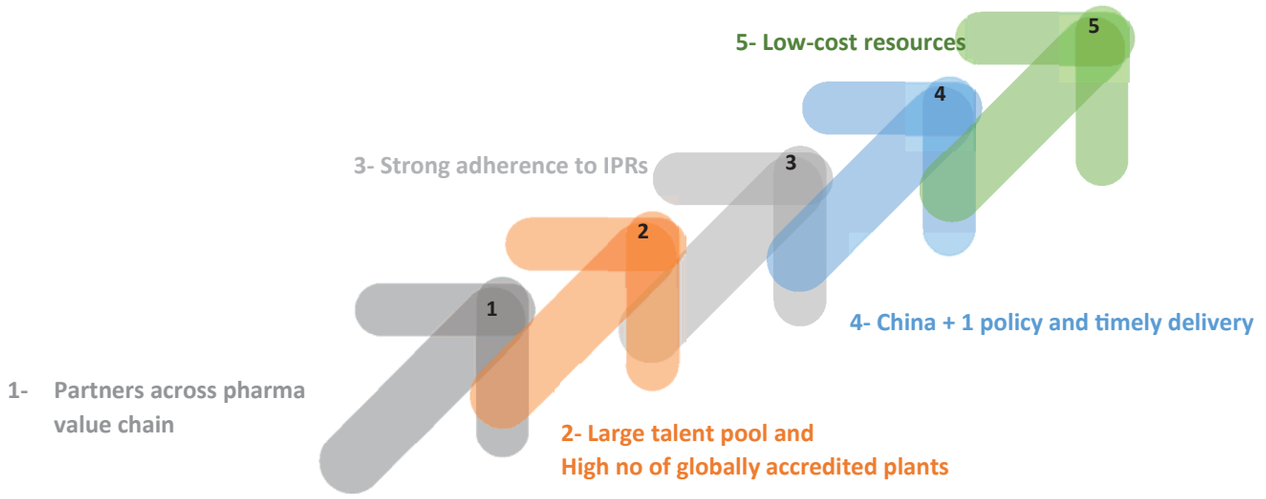
Indian CRAMS players offer a complete end to end solution viz. right from the drug discovery and preclinical studies to drug development and manufacturing. The segment has grown over time from simple molecule research and manufacturing to manufacturing of complex molecules requiring high end research. The presence of large talent pool, large globally accredited plants, strong adherence to Intellectual Property rights (IPR), efficient and reliable delivery timelines, China plus one policy, low cost and deep research acumen has made India as the preferred destination for global pharma innovators. The analysis of data of industry aggregates that represent over 70% of the CRAMS segment shows over a period of 7 years viz. FY18-FY28, the industry has registered a CAGR growth. of about 17%.

Factors Denting Growth Rate and Profitability Margins in CRAMS Segment during FY23:

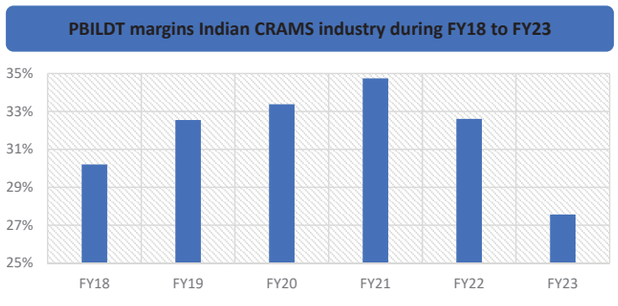
Revenue growth rate of CRAMS **industry during FY18 to FY23**



Despite the promising long-term growth potential of the Indian CRAMS market, the industry is currently grappling with several challenges that have affected the performance of key players in FY23. The slowdown can be attributed to the impact of rising inflation and recessionary pressures in the US and European markets. Leading innovator and biotechnology companies have reduced their investment in research and development for drug discovery and development, which has directly impacted the Indian CRAMS segment, predominantly reliant on exports.



Specifically in the European market, energy prices have surged by over 30%, logistics costs have increased by over 100%, and there has been a more than 50% rise in the input cost of raw materials due to geopolitical tensions. These factors have resulted in significant cost inflation. Notably, CRAMS players with manufacturing units overseas have been more severely affected, experiencing deeper margin reductions compared to those with manufacturing units in India. Furthermore, leading CRAMS players in India have witnessed an overall increase



in raw material and freight costs, amounting to approximately 20%, thereby denting their margins by around 350 basis points during FY23.

Way Forward

The credit quality of Indian CRAMS players has demonstrated stability and is expected to continue in the future. This is primarily due to their low-leveraged balance sheets and moderate capital expenditure plans. According to CareEdge Ratings, the CRAMS segment is projected to experience robust growth of around 10% in the medium to long term. This growth will be driven by the increasing trend of outsourcing by innovator.

CareEdge Ratings anticipates that innovator and biotechnology companies will regain momentum in their research and development spending during the current fiscal year, gradually returning to normal levels by Q3FY24. This is crucial for them as each stage of the drug discovery process is time-bound and critical. Looking ahead, CareEdge Ratings expects the PBILDT (Profit Before Interest, Taxes, Depreciation, and Amortization) margin of CRAMS players to improve and remain within the range of 29-30%, aligning with the normalization of revenue growth.'■

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Innovations in Drug Delivery Systems

An oral solid dosage (OSD) form, comprising tablets, capsules, and powders, is considered the most attractive drug delivery mechanism due to its convenience and cost-effectiveness. Within these, capsules have gained prominence owing to their simplicity, ease of manufacturing, and patient acceptance. **Kinjal Shah** emphasizes about the drug delivery mechanism to enhance the therapeutic efficacy of the drugs.

Capsules were traditionally being manufactured from animal-based gelatin, also known as empty hard gelatin capsules (EHGC). However, lately, the industry has started manufacturing hydroxypropyl methylcellulose (HPMC) capsules, which are made from wood pulp and thus vegetarian in nature. The demand for HPMC has increased in export markets such as the US and Europe as well as in the domestic market owing to changes in consumer dietary and religious preferences. The oral solid dosage forms have also evolved over time with respect to the release of the active ingredients – from immediate release to extended release or sustained release and even controlled release.

The global pharmaceutical generics industry has been lately witnessing significant challenges, such as intense pricing pressures, especially in the US market, increasing competition, rising costs of raw materials and manufacturing, regulatory uncertainties and supply chain disruptions. The pricing pressures in the US generics market, which started in 2014/15, have been more pronounced lately for the oral solid dosage form due to its high competitive intensity. Thus, in recent years, the pharmaceutical industry has seen a surge in innovation in drug delivery systems. The industry is constantly endeavouring to improve the drug delivery systems to enhance the therapeutic efficacy of the drugs, reduce side effects and improve patient compliance.

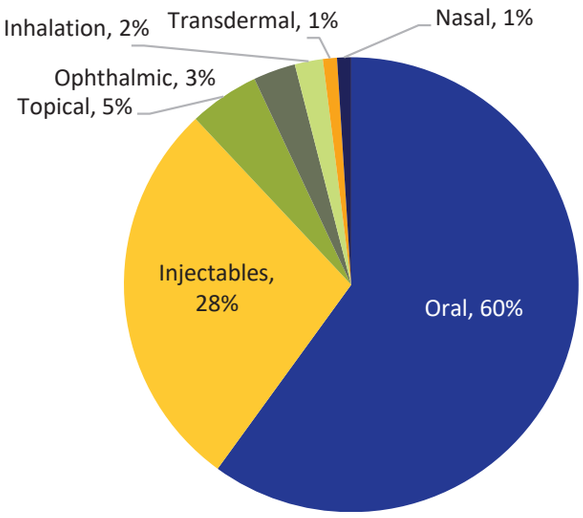
As the therapeutic landscape has evolved from small-molecule drugs to a new generation of therapeutics and even live cells, drug delivery technologies have also evolved to meet their unique delivery needs. Driven by increased investment in research and development (R&D) and consistent regulatory support, the pharmaceutical industry is constantly advancing the processes and technologies from the earlier conventional processes.

The industry currently has developed various other dosage forms or delivery systems, such as injectables, transdermal patches and inhalers. Each of these delivery systems has its own benefits and challenges depending on the drug and targeted outcome. Thus, the delivery system is selected taking into account factors such as drug solubility, stability, and bioavailability. Combination drug delivery is also a growing trend. This strategy of

combining different drugs with different delivery mechanisms is expected to lead to a synergistic effect with better treatment outcomes. It enables the constituent drugs to function together, offering an overall enhancement to the therapeutic effect.

Exhibit: ANDA approvals by USFDA for the global pharmaceutical market in CY2022

According to ICRA Research, of the total 742 abbreviated new drug approvals (ANDAs) approved by the United States Food and Drug Administration (USFDA) in CY2022, oral dosage forms accounted for 445 or 60%, followed by injectables at 28% and others at 12%. Within the oral dosage form,

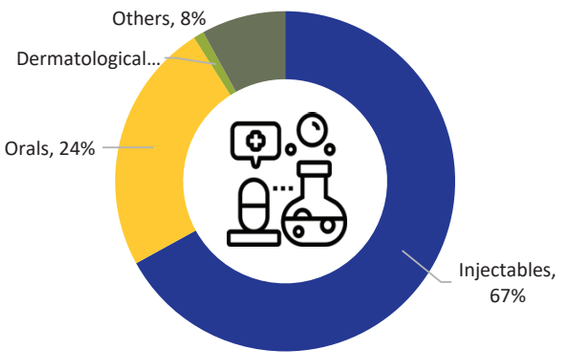


Source: ICRA Research

~16% were extended-release/ delayed-release formulations. For India, of the 355 ANDA approvals received in CY2022, 69% were for oral formulations, and a little less than 20% were for injectables.

Exhibit: Product shortages in the US – Drug Administration type

More recently, the US pharmaceutical market has been witnessing product shortages across therapy areas, including pain/ anesthesia, cardiovascular, infectious diseases, central nervous system, and oncology. Considerable pricing pressure, discontinuation of operations by some local pharmaceutical companies, and tightening USFDA scrutiny have continued to result in product shortages in the US pharmaceutical



Source: IQVIA, ICRA Research

market. Injectables accounted for 67% of the drug shortages, with oral solids accounting for 24%.

ICRA believes that as the current therapeutic landscape shifts from small molecules to biologics, drug delivery systems will continue to evolve. ■

Author

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Internet of Things (IoT): The New Prescription for Pharmaceuticals Manufacturing and Supply Chain

The application of Internet of Things (IoT) in the pharmaceutical industry will be the next phase of growth for pharma companies. IoT refers to the networking of physical objects through the use of embedded sensors, actuators, and other devices that can collect or transmit information about the objects. Advances in wireless networking technology have made it possible to collect data from these sensors almost anywhere at any time.

Imagine running a pharmaceuticals manufacturing company. You are not only managing the complexities of the batch manufacturing process, but also looking at plugging all gaps in your logistics chain, and ensuring complete quality to your customer. Although industrial automation and control technologies are well established in life sciences manufacturing facilities, integral information on real-time status of equipment is still not readily available to the management to take timely decisions. Moreover, stringent CGMP (Current Good Manufacturing Practice) regulations expect top quality compliance across all your equipment.

A rising number of biologics drugs (temperature-sensitive, short shelf-life drugs) in the market would mean that you have to ensure temperature consistency and loss-free shipping from the source to the point where the drug is administered. Operating costs run high due to expensive cold chain logistics, and also because of losses due to bad handling.

The challenge is accentuated in the manufacturing and distribution of generic drugs, which constitute up to 80 percent of today's pharma market. To handle the stiff competition in the market for generics, you also need highly developed logistics capabilities with the highest efficiencies at the lowest cost.

Warehousing, a vital component in the manufacture of pharmaceuticals, is costly, and its efficiency and quality are crucial for the company's survival. Many companies choose to manage the processes internally, given the sensitive nature of the products. A McKinsey study says that warehousing accounts for 95 per cent of all pharma logistics costs.

Today, pharmaceutical companies have a compelling opportunity to adopt and profit from the game-changing technological advancement called the Internet of Things (IoT) that promises to fix all the aforementioned gaps. In an IoT environment, every 'thing' is equipped with a sensor that allows it to intelligently communicate and interact with other objects and systems within the IoT ecosystem. The IoT environment helps pharmaceutical companies to automate and revitalise their manufacturing and supply chain management operations.

IoT extends visibility into every area of the business from development through manufacturing, transport, distribution, dispensing, and consumption. On the shop floor, real-time data from sensors will allow visibility across all areas of work, and result in improved productivity, efficiency, reduced cycle time and manufacturing costs.

Smart warehouse management systems enabled by IoT integration will bring in increased visibility, provide

real-time data to track and report inconsistencies (for example, storage temperature), and ensure that the right data is available at the right time to enable the right people to act when it truly matters. In logistics, tracking drug inventory movements in real time can save billions of dollars. Smart pharma packaging can help ensure that shipments and medications are accurately tracked, and the supply chain remains fluid, efficient, and cost-effective.

According to IDC, there were 9.1 billion IoT units installed in 2013, which is predicted to increase to 28.1 billion in 2020. In such a fast-changing world, connected equipment, men and material tracking, sample lifecycle management, smart packaging, and cold-chain monitoring are among the top IoT applications suited for the pharmaceuticals industry. Investing in these transformational technologies comes with its challenges. Below are some recommendations and best practices for pharmaceutical companies to fully benefit from their IoT integration.

- Invest in supportive IoT infrastructure and be future-ready.
- Invest in IoT-based security solutions because security is paramount and workarounds are costly.
- Focus on robust change management to make sure people, processes, and responsibilities adapt seamlessly and make the transition successful.
- Think big, start small, fail fast, and scale quickly.
- Make sure that key decision-makers are on board and success criteria in project lifecycle are defined early.
- Perform pilots, establish business benefits through proofs-of-concept (POCs), employ Agile methodologies, choose suitable partners, and leverage expert teams to effect this digital transformation.

Looking ahead, the advances in digital technologies, ubiquity of mobile computing, dominance of social media, and a growing portfolio of smart products are sure to bring real-time actionable intelligence. Enterprises must constantly use emerging technologies to innovate, stay relevant, constantly hone competitiveness and make profits. The risks of doing nothing must be evaluated. The time for pharmaceutical companies to accelerate implementation and use of IoT platforms and solutions is now. ■

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Building Cell Culture Capacities

In the dynamic crucible of biological and medical research, the technique of cell culture stands as an indispensable tool, providing scientists with the ability to meticulously study and manipulate cells outside their natural milieu. In the context of a rapidly evolving biotechnological landscape, the imperative to establish robust and scalable cell culture capacities has become not just a scientific pursuit but a strategic necessity.

Sushil Suri, Chairman & Managing Director, Morepen Labs spoke about the nuanced intricacies involved in building cell culture capacities, navigating through the labyrinth of facility design, equipment selection, process optimization, and the exacting realm of quality control, with a particular focus on real-world applications.

Facility Design

Cleanroom Requirements : The cleanroom, akin to a controlled biosphere, demands meticulous planning. Adherence to ISO classifications, particularly ISO 5 for critical areas, is not a mere guideline but a foundational requirement. The layout must transcend functionality; it should embody unidirectional airflow patterns, advanced gowning procedures, and a meticulous segregation of work zones. The objective is not just to prevent contamination but to create an environment where cell cultures thrive in a state of absolute purity, devoid of external interferences.

HVAC Systems: The Heating, Ventilation, and Air Conditioning (HVAC) system, often relegated to the background, is the silent conductor orchestrating the symphony of the cleanroom. Beyond the basic functions of temperature and humidity control, this system must be designed with a surgeon's precision. Regular maintenance isn't just a routine; it's a ritual. Rigorous validation protocols ensure that the air circulating within the cleanroom is not just sterile but an optimal habitat for the delicate ecosystems of cell cultures.

Facility Layout: The facility layout is not a mere blueprint; it is an architectural narrative designed for versatility. It must not only cater to an array of cell culture processes, from the delicate dance of small-scale experiments to the grand orchestration of large-scale industrial production, but also possess the elasticity to adapt to the ever-evolving needs of scientific exploration and bioproduction. The application-driven design ensures that the facility can seamlessly accommodate diverse research and production goals.

Equipment Selection

Bioreactors : The bioreactor, the crucible for cellular life, requires more than just careful selection; it demands a marriage of science and engineering. Scalability is not a feature; it is a fundamental requirement. Agitation mechanisms, whether sparging or impeller-driven, are not just components; they are the conductors of cellular symphonies. Control systems, sophisticated and nuanced, are not just interfaces; they are the guardians ensuring the optimal conditions for cellular flourishing. The application-oriented selection ensures that the chosen bioreactors align perfectly with the specific needs of the research or production at hand.

Incubators and Shakers: Incubators and shakers, often viewed as mere vessels, are the architects of a cell's environment. They are not just instruments; they are the custodians of life. Precision in controlling variables such as temperature, CO2 levels, and humidity is not a luxury; it is a mandate. The scalability of these systems isn't just an add-on feature; it's an essential characteristic ensuring seamless transitions between scales. The real-world application demands that these systems provide not just controlled conditions but an optimal setting for the specific cell culture under study or production.

Monitoring and Control Systems: Advanced monitoring and control systems are not just technological novelties; they are the vigilant sentinels safeguarding the sanctity of the cell culture environment. Automation is not a convenience; it is a necessity. These systems, overseeing parameters like pH, dissolved oxygen, and nutrient levels, are not just tools; they are the guarantors of a consistent and controlled habitat. They transcend the realm of efficiency; they are the architects of precision. In the real-world application, these systems ensure reproducibility and reliability, critical for the success of experiments or the production of consistent batches.

Process Optimization : Media and Supplements : The alchemy of cell culture media isn't a routine; it's a symphony of biochemical precision. The quest for optimization transcends the realm of formulas; it's a journey of adaptation. Serum-free or defined media options aren't just alternatives; they are the next frontier in enhancing reproducibility and scalability. Continuous refinement isn't a choice; it's an imperative in the quest for the perfect nutritional milieu. In real-world applications, media formulations are tailored to the specific needs of the cells, whether for basic research, drug development, or bioproduction, ensuring optimal growth and productivity.

Cell Line Development : Investing in cell line development isn't a transaction; it's a commitment to the very essence of cell culture. Techniques such as genetic engineering, exemplified by CRISPR/Cas9, aren't just tools; they are the architects of genetic landscapes. The focus isn't just on productivity; it's on creating cell lines that aren't just stable but exhibit consistent performance across the diverse scales of scientific exploration. Real-world applications demand cell lines with specific traits for the development of therapeutics or the study of complex cellular processes.

Scale-Up Strategies: Scaling up isn't a linear progression; it's a multidimensional puzzle. Feasibility studies and pilot trials aren't just prerequisites; they are the overtures to a grand symphony of industrial production. Transitioning seamlessly from small-scale research to large-scale production demands more than just planning; it requires the harmonious collaboration of scientific acumen and engineering finesse. It's a choreography of precision and adaptability. In real-world applications, scaling up ensures that the benefits of research findings are translated into tangible outcomes, be it the production of pharmaceuticals, vaccines, or bio-based materials.

Quality Control

Contamination Prevention: The battle against contamination isn't just a skirmish; it's an unrelenting war. Aseptic techniques aren't just protocols; they are a way of life within the cell culture facility. Personnel training isn't just an initiation; it's a continuous evolution. Stringent cleaning procedures and routine environmental monitoring aren't just tasks; they are the fortifications protecting the sanctity of cell cultures. In real-world applications, the prevention of contamination is not just a theoretical concern; it's a practical necessity to ensure the validity and reliability of research outcomes or the safety and efficacy of produced biopharmaceuticals.

Analytical Methods: The analytical journey is more than a quest for data; it's a deep dive into the health, viability, and productivity of cell cultures. Real-time monitoring isn't just observation; it's orchestration. In-process controls, whether it's cell counting, metabolite analysis, or genomic profiling, aren't just checkpoints; they are the conductors of a symphony ensuring not just consistency but a crescendo of reliable results. In real-world applications, analytical methods are the eyes and ears of the scientific process, providing insights into cellular behaviour or confirming the quality attributes of produced biological products.

Regulatory Compliance: The world of cell culture doesn't exist in isolation; it's bound by the strings of regulatory frameworks. Meticulous documentation isn't just paperwork, it's the chronicle of excellence.

Processes, procedures, and quality control measures aren't just guidelines; they are the code of ethics in the scientific narrative. Regular audits aren't just evaluations; they are the reflections on a commitment to not just compliance but excellence. In real-world applications, regulatory compliance is not just a bureaucratic hurdle; it's the assurance of safety, quality, and efficacy, essential for bringing novel therapeutics or biotechnological products to market.

Building cell culture capacities is not a task; it's an odyssey that demands more than just technical prowess. It requires meticulous planning, substantial investment, and an unwavering commitment to excellence. From the design of state-of-the-art facilities to the selection of equipment that transcends functionality to the optimization of intricate processes and the implementation of stringent quality control measures, each step is not just a process; it's a brushstroke in the masterpiece of scientific exploration. In an era of biotechnological renaissance, the ability to establish and adapt cell culture capacities is not just a strategic advantage; it's a transformative force propelling scientific research and bioproduction into uncharted realms of innovation and discovery, where every challenge is not an obstacle but an opportunity for scientific transcendence. Real-world applications are the litmus test for the success of these endeavours, where the intersection of scientific ingenuity and practical outcomes defines the true impact of building robust cell culture capacities. ■

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The Hybrid Trials Revolution

India's robust healthcare infrastructure – and highly trained professionals – make it a cost-effective haven for international clinical trials. Sponsors can expect significant savings in the conduct of clinical trials through process and technology-driven efficiency that drives faster trial completion thanks to India's efficient recruitment capabilities. **Sanjay Vyas** emphasizes about landscape of clinical trials is undergoing rapid transformation with remote and Patient-Guided approaches.

Boasting a diverse population of over 1.4 billion people representing a wide range of demographics and disease profiles, India simplifies patient recruitment and offers a wealth of data for research. This combination of factors has propelled India to the forefront of global clinical trials, making it the ideal partner for international sponsors seeking high-quality research with exceptional value.

Decentralized Clinical Trials changing the course of CT in India

Although the concept of decentralized clinical trials (DCTs) has been under exploration in the industry the COVID-19 pandemic has significantly accelerated the adoption of such trials with an elevated sense of urgency.

Traditionally, participants in clinical trials have been required to visit a physical site for various activities such as study visits, assessments, and data collection. However, with evolving times and the advent of decentralized clinical trials, the participants are empowered to engage in the trial comfortably from their homes or local healthcare settings. DCTs harness digital technologies and remote processes to enhance patient convenience, streamline data collection, and improve the overall efficiency of the trial.

Countries like India emerge as ideal locations for the effective implementation of DCTs due to their promotion of integrity and inclusivity in healthcare treatment. India also presents advantages for establishing DCTs, including a diverse patient pool and a growing talent base in clinical research.

DCTs have gained strategic importance in the field of clinical research as patient-guided approaches continue to be a key focus. DCTs have the potential to remove geographical barriers for clinical trial participants, making them an appealing option for a nation like India. However, to fully unlock the potential of DCTs in India, navigating the evolving regulatory landscape is crucial.

Evolving Regulatory Landscape for Decentralized Clinical Trials (DCTs) in India

During COVID-19, unanticipated deviations to clinical research protocols became unavoidable, as subjects were unable to attend study visits due to travel restrictions, clinic closures, and quarantine requirements. Regulatory bodies around the world were forced to quickly revise their regulations or guidance to minimize disruptions to clinical research.

Many of these clinical research companies turned to Direct to and from Patients (DTP/DFP) distribution to

enable continuation of drug delivery to their patients. Another successful implementation of DTP/DFP was in India, where home delivery of clinical trial medications was not previously available before the outbreak of COVID-19. However, given the critical need to keep patients in their clinical trials, the Indian government permitted DTP services.

In May, the FDA released draft guidance for implementing DCTs, sparking a wave of excitement and anticipation within the field of clinical trials. The much-awaited guidance marks a significant milestone in the evolution of clinical trial methodologies, signalling clear support for the global shift toward expanded trial models. By releasing the guidance, the FDA reaffirms its commitment to promoting innovation in clinical trial design and emphasizes the need for careful consideration, training, oversight, and risk management for the successful implementation of DCTs.

Bridging the gap between centralized and decentralized CT - The Rise of Hybrid Trial Designs

A hybrid clinical trial is a type of medical research study that incorporates both traditional face-to-face elements and virtual or remote components, such as those delivered over the internet or via a mobile device. This approach allows for greater flexibility in conducting clinical research and can have benefits such as reduced costs and easier recruitment of participants. However, it also presents challenges related to data security, patient privacy, and oversight. Hybrid trials can offer greater efficiency, engagement, and the generation of stronger evidence for clinical trial sponsors. They are particularly effective for studies with difficult-to-recruit patient populations. The integration of digital health technologies, in-home clinical visits, and agile monitoring are key components of decentralized and hybrid clinical trial designs.

The use of hybrid clinical trials has become more prominent due to the rising cost and time to bring new drugs to market, as well as the impact of the pandemic outbreak. These alternative trial models are being leveraged to address challenges and improve the efficiency of the drug development process.

Deployment of Digital Tools to Leverage Hybrid Clinical Trials

Given the advancements in digital tools and technology, several segments in the field of clinical research have growth potential. These breakthroughs addressed challenges encountered during the

pandemic and had a significant impact on clinical research. Digital tools are increasingly being used to leverage hybrid clinical trials, allowing for more convenient, accurate, and efficient data collection. Some of the key digital tools used in hybrid clinical trials include eConsent, ePRO (electronic patient-reported outcomes), telemedicine, wearable devices, and remote patient monitoring.

The use of digital technology in clinical trials benefits patient recruitment and retention, data collection, and ultimately, the speed at which new therapeutics can be brought to market. Digital tools, such as wearable devices, remote monitoring, and electronic data capture systems, have the potential to change the way clinical trials are conducted. These digital tools increase patient engagement, allow for real-time data collection, improve data accuracy, and alleviate logistical challenges. Integrating digital solutions into clinical trials can help increase recruitment, improve patient compliance, and simplify data management processes.

The future of clinical trials will be defined by the adoption and implementation of powerful artificial intelligence technologies to handle the growing volume of data in standard and non-standard formats. Predictive analytics can help with disease detection, pattern recognition in medical images, genomic data analysis, and faster data analysis and inferences.

Hybrid Clinical Trials and Global Capability Centers

India has become an attractive choice for pharmaceutical and biotechnology firms conducting clinical trials due to its extensive and varied patient population, cost-effectiveness, and proficient medical workforce. The digitalization of clinical trials is poised to boost market expansion by optimizing processes like data collection, regulatory compliance, logistics, and supply management. The integration of digital therapies has further streamlined the collection of real-time safety and toxicity data, enabling swift adjustments to trial designs and fostering market growth.

The establishment of Global Capability Centers (GCCs) in India plays a crucial role in facilitating these hybrid trial models. Equipped with advanced technology infrastructure and a skilled workforce, GCCs enhance the efficiency of clinical trial operations. They are well-positioned to support the intricate requirements of hybrid trials by offering specialized services in data analytics, regulatory affairs, and quality assurance. This integration of GCCs not only reinforces India's status as a hub for clinical trials, but also provides global pharmaceutical and biotechnology companies with the technological expertise and adaptability needed to conduct research and development activities efficiently in the evolving landscape of hybrid clinical trials.

As India embraces the future of hybrid clinical trials, propelled by its robust infrastructure, diverse population, and digital prowess, it stands poised to revolutionize medical research. The hybrid approaches, coupled with the expertise of GCCs, promise faster drug development, wider patient access, and ultimately, healthier lives for all. ■

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The Gap & Need for Innovative Point-of-Care Bio-Diagnostic Technology Solutions

The healthcare landscape is currently undergoing transformative shifts, with a primary focus on enhancing patient outcomes. However, it is marked by exigencies that necessitate a profound revaluation of conventional methodologies, particularly in the diagnostics area. While giant strides have been made in advancement of treatment and mitigation of life-threatening diseases, there still is a compelling need for ground-breaking Point-of-Care (POC) bio-diagnostic technologies, steering clear of conventional paradigms and emphasizing the imperative for innovation in advancing diagnostic capabilities.

Dr. Praful R Naik, Director & CEO, Prashak Techno Enterprises Pvt. Ltd. spoke about the significance of point-of-care technologies (POCT) in delivering cost-effective solutions that effectively tackle numerous unmet healthcare needs.

Traditional bio-diagnostics while commendable in their contributions, confront formidable challenges including protracted turnaround times, logistical intricacies, and inherent financial burdens. These limitations are particularly pronounced in underserved areas, where access to advanced medical facilities is restricted. The need for rapid, decentralized, and cost-effective diagnostics has fuelled the development of POC bio-diagnostic solutions. The exigent demand for innovative POC bio-diagnostic technologies emerges as an incisive response to these limitations, propelling the scientific community towards novel avenues of exploration.

This evolution has propelled research and development on point-of-care tests which has grown steadily over the last 20 years, and the global point-of-care diagnostic market is expected to surpass US$30 billion in the year 2030. POCT signifies the utilization of technology directly at the location of patient care to elevate healthcare outcomes. Point-of-care technologies (POCT) detection in bio-diagnostics is a critical frontier in healthcare, with a profound impact on patient outcomes, when healthcare providers deliver services to patients in real-time, ensuring immediate and effective care, especially in resource-limited settings and will play pivotal role in healthcare delivery and life-saving procedures.

Key Offerings and aspects of Point of care bio-diagnostics Solutions

▪ Unleashing rapidity and precision at the point-of-care with a resolute focus on temporal dynamics, affording real-time results that are indispensable for informed clinical decision-making. It explores the precision in diagnostic methodologies with advancements aimed at unravelling the intricacies of biomolecular interactions at unprecedented levels.

- Bio-diagnostic POCT carve a niche in the proactive interception of infectious agents, critical for mitigating the dissemination of contagions and enabling effective containment.
- POCT can offer solutions to early detection of multifaceted nature of infectious diseases through a holistic analytical approach capable of deciphering intricate biomarker profiles.

- Innovations in bio-diagnostic POCT is marked by an emphasis on genomic interrogation, laying the foundation for personalized medicine and bespoke therapeutic interventions.
- Continuous and dynamic monitoring of biochemical parameters becomes the focal point, presenting a departure from static diagnostic snapshots towards a fluid understanding of physiological states.
- Bio-diagnostic POCT necessitates harmonious amalgamation of diverse scientific disciplines—engineering, biochemistry, and clinical expertise—to catalyse the inception of ground-breaking technologies. The interconnectedness of disparate scientific realms—physics, chemistry, and engineering will converge in the journey towards an evolved and refined diagnostic future.
- Veracity and reliability of the diagnostic outcomes drives continual evolution of technological innovations in bio-diagnostic POCT.

Technological Innovations In point-of-care bio-diagnostics

- Miniaturization of diagnostic processes through microfluidic systems and Lab-on-chip technologies (LOCT) resulting in integrating sample preparation, analysis, and detection on a single chip and enabling portability for on-the-spot testing.
- Polymerase Chain Reaction (PCR) and other nucleic acid amplification techniques have brought molecular diagnostics to the POCT realm, enabling rapid and accurate detection of genetic material for infectious diseases and genetic disorders. The advent of Next-generation-sequencing technologies (NGST) has further expanded bio-diagnostic POCT by allowing comprehensive genomic analysis at real-time speeds.
- Internet of Things (IoT) and wearable devices allowing seamless data transfer between diagnostic devices and healthcare system play a crucial role in continuous monitoring, providing real-time health data for improved diagnostics and personalized treatment plans.
- AI algorithms have been integrated into bio-diagnostic POCT for data analysis, interpretation, and decision-making. Machine learning enhances the accuracy of diagnostic results, particularly in complex datasets, and contributes to the evolution of intelligent diagnostic systems.
- Simple to use yet effective, bio-diagnostic POCT offer cost-effective and user-friendly solutions, particularly advantageous in resource-limited settings. For example, microfluidic paper devices enable a range of tests, from blood typing to pathogen detection. Advent of 3D printing has also facilitated the customization and rapid prototyping of bio-diagnostic devices. This technology will accelerate the development and deployment of bio-diagnostic POCT, enabling development of tailored solutions to specific healthcare challenges.
- Other noteworthy examples of POCT include the use of urine dipsticks, rapid strep tests, and blood glucose monitors. It reflects the pivotal role these technologies play in providing accessible, timely, and economically viable healthcare solutions, aligning with the broader objective of meeting diverse healthcare challenges on a worldwide scale.

Significance stems from the increasing demand for immediate results, essential for informed decision-making by healthcare professionals. Beyond addressing emergency situations, bio-diagnostic POCT can contribute significantly to preventive healthcare, enabling swift screening and early disease detection. POCT market's growth is evident in its enabled reach to remote areas, reducing healthcare disparities, and aligning with industry goals of cost-effectiveness and resource optimization. Their integration with digital health enhances connectivity, making them pivotal in shaping the future healthcare landscape.

One such innovative startup - FastSense Innovations, is at the forefront of bio-diagnostic POCT innovation, with a focus of transforming healthcare through cutting-edge technologies. FastSense vision is driven by its steadfast commitment to affordable and accessible healthcare diagnostic support at a consumer's doorstep. The ideation and development expertise at Fast Sense has been aptly recognised and supported with prestigious government grants which has propelled FastSense in its pursuit of innovation. FastSense has been able to

blend interdisciplinary experts comprising seasoned scientists, renowned doctors, and industry experts which has resulted in a holistic approach to addressing critical gaps in diagnostics, from conceptualization to the development of tangible, impactful solutions. FastSense innovations and advancements deploy molecular diagnostics, biosensor technologies, and artificial intelligence resulting in technology solutions with highest standards of diagnostic efficacy. Its flagship development comprises the Sepsis Screening solution - 'Sepsis-S', which stands as a testament to its commitment to early detection by enabling doctors with better decision making and improved patient outcomes. FastSense is also working on Cancer and liver bio-diagnostic POCT, specifically aiming to enable early detection of Hepatocellular Carcinoma (HCC) and liver ailments which has the potential to address a significant challenge in underserved populations. FastSense development pipeline includes accessible diagnostic solutions for the early identification of pancreatic cancer as well as bio-diagnostic solutions for Women-Centric Health issues.

The Epilogue

In conclusion, the imperative for novel bio-diagnostic POCT transcends the routine and beckons the scientific community towards uncharted territories. The quest for innovation in this realm is not merely an aspiration; it is a categorical mandate dictated by the exigencies of contemporary healthcare. Bio-diagnostic POCT have the potential to transform healthcare outcomes globally, more particularly in the developing and least developing regions of the world, making a meaningful difference in the lives of individuals and communities. ■

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Navigating the Transformative Landscape of Stem Cell Technology in Medicine and Biotechnology

Stem cell technology is an advancing field that holds immense promise for effective disease treatment through the unique characteristics of involved progenitor cells. Stem cells, distinguished by their unlimited yet controllable proliferative potential and multipotency, exhibit the capacity to undergo prolonged self-renewal through cell division and can, under specific conditions, differentiate into specialized cells such as cardiac muscle cells or pancreatic insulin-producing cells. **Subhadra Dravida and Praveen Parkali** talks about the transformative landscape of Stem Cell Technology and key trends and applications of Stem cell technology.

To fully harness the potential of stem cell technology, decoding mechanisms underlying stem cell proliferation, differentiation into tissue-specific cells, role in repair and regeneration, identifying the combination of signals directed towards the functions is fundamental biology.

Key trends and applications of Stem cell technology

Stem cells in treatment and disease management: Stem cell-based therapeutic modalities represent a paradigmatic advancement in the treatment and management of various chronic diseases. This approach harnesses various types of viable human stem cells, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells (ASCs), for both autologous and allogeneic therapies. These cells exhibit the capacity to generate therapeutic proteins or facilitate the restoration of tissue function. Conditions such as macular degeneration, strokes, osteoarthritis, neurodegenerative diseases, and diabetes are particularly managed by stem cell-based therapies. Notably, ESCs and ASCs are produced from natural sources for the repair of diseased tissue or organs under both physiological and pathophysiological conditions. The multifaceted potential of stem cell-based therapies positions them as significant contributors to the advancement of medical treatments.

Stem cells in safety and efficacy testing

Drug discovery and development is a protracted, expensive, and high-risk process, spanning 10-15 years with an average cost exceeding USD 1-2 billion per approved drug to reach the markets. Approximately 40-50 percent of clinical failures are due to insufficient clinical efficacy data and adverse safety related concerns, prompting substantial efforts to change the strategy of assessing safety or efficacy concerns during preclinical and clinical investigations. In vitro methodologies offer high-throughput, in-depth screening, surpassing the capabilities of animal models. Commercially available human-derived cell lines, including

those for astrocytes, neurons, microglia, and oligodendrocytes, permit the study of specific cell types, overcoming limitations associated with animal models . A paradigm shift towards human surrogate cell and tissue-based microphysiological models particularly human induced pluripotent stem cells (hiPSCs), is evident in being adopted with the latest FDA modernization act 2.0 coming into force. Replacing hiPSCs obtained from patient-derived fibroblasts with human MicroPhysiological Systems (hMPS) composed of primary and progenitor cells harvested from human biological discards provide a scalable and flexible approach, allowing for large-scale, in vitro studies that can be repeated any number of times for meaningful insights. The hMPS models ensure relevance without the need for extrapolation to the human species, offering closer mimicry of human physiology.

Vaccines and biotherapeutics, derived from biological sources, undergo rigorous testing at various stages of development including routine testing during manufacturing stages to ensure batch consistency, safety and potency owing to their labile components. The World Health Organization's guidelines play a pivotal role in setting international standards and influences global regulatory practices especially in assessing Critical Quality Attributes (CQAs). While historically, quality control relied on animal tests; recent advancements including non-animal technologies (NATs), new approach methodologies (NAMs) have reduced animal-based testings in in-process controls, and testing CQAs. Despite the viability of these technologies, awareness remains a key barrier to the widespread adoption of 3R's (Replacement, Reduction, Refinement) approaches, with organizations like the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3R's) actively addressing this gap through engagement with the scientific community.

Stem cells in artificial organs

3D bioprinting stands as a promising edge in artificial organ fabrication and advancements in regenerative medicine, Throughout the evolution of tissue engineering, diverse cell types have been utilized, with traditional methodologies involving either in vitro seeding of scaffolds with cells and biomaterials

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or direct cell therapy through stem cell injection into the native tissue or organ. The criticality of selecting an appropriate cell type cannot be overstated, as it profoundly influences the functionality and design of the tissue-engineered model. Stem cells, with their self-renewal and potent properties, emerged as a widely employed cell source for 3D bioprinting and regenerative medicine, offering an expansive reservoir for cellular materialization. Stem cells, sourced from embryonic or mesenchymal origins, exhibit differentiation potential, with demonstrated versatility in generating blood or nerve cells, and differentiating into diverse cell lineages such as bone or cartilage cells. Stem cells, particularly mesenchymal stem cells, are pivotal for clinical applications, contributing to the regeneration of diseased tissues through tissue-engineered implants composed of stem cells and biodegradable scaffolds. Moreover, mesenchymal stem cells, amenable to genetic modification, present promising prospects for somatic gene therapies targeting systemic or local diseases.

Stem cells in Cellular Agriculture

Cultured meat (CM) involves the invitro production of meat from animal cells cultivated outside of the living organism. This innovative process occurs in a bioreactor, where animal cells undergo two distinct phases: proliferation, aimed at achieving the maximum cell yield, and differentiation and maturation, wherein cells are seeded onto scaffolds and guided to mature into skeletal muscle cells for optimal protein production. Stem cells, specifically adult and pluripotent stem cells, emerge as

prime candidates for initiating the cultured meat production process due to their ability to self-renew and differentiate into mature cell types essential for meat composition. The ideal cells for invitro meat manufacturing should exhibit robust self-renewal capabilities and the capacity for continuous division . Despite embryonic stem cells possessing pluripotent features ideal for culturing meat, practical challenges and consumer controversies surround their use. Nevertheless, undifferentiated progenitor cells such as mesenchymal stem/stromal cells (MSCs) and fibro/adipogenic progenitors (FAPs) present in organs and tissues are good contributors to meat components, underscoring the significance of stem cells in the production of cultured meat. Ensuring the palatability, nutritional value, texture, and safety of cultured meat necessitates the utilization of cell lines derived from species familiar to consumers, such as chicken, turkey, duck, geese, cattle, or pigs .

Integration of artificial Intelligence in stem cell technology

Artificial Intelligence (AI), leveraging Machine Learning (ML), deep learning, and other methodologies, represents a powerful approach to addressing complex data analysis. Notably, AI has demonstrated exceptional proficiency in image recognition, marking its initial foray into the field of biology. This has been particularly evident in providing advanced tools for the description and classification of cellular morphology.

3D bioprinting stands as a promising edge in artificial organ fabrication and advancements in regenerative medicine, Throughout the evolution of tissue engineering, diverse cell types have been utilized, with traditional methodologies involving either in vitro seeding of scaffolds with cells and biomaterials or direct cell therapy through stem cell injection into the native tissue or organ. The criticality of selecting an appropriate cell type cannot be overstated, as it profoundly influences the functionality and design of the tissue-engineered model

Conclusion

Stem cell technology stands as a transformative force with groundbreaking impacts in medicine and biotechnology. It has potential and proven applications in disease treatment, in safety and efficacy testings, artificial organ creation, cellular agriculture, and integration with artificial intelligence. From addressing neuro degenerative diseases to accelerating drug/vaccine development, sourcing cells for bioprinting and shaping the future of cultured meat production, stem cells technology has got midas touch in translating the applications for real time use. ■

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Meeting sustainable health commitments through ESG

In the pharmaceutical industry, a sector fundamental to safeguarding global health, there is a growing commitment towards innovation and improvement, as being realised through the adoption of Environmental, Social and Governance (ESG) principles. **Saransh Chaudhary** talks about shift towards impactful actions that intertwine with global health and sustainability. The Adoption of Environmental, Social and Governance (ESG) principles in pharma industry marks a journey of constant innovation and improvement

The Imperative of ESG in Pharma

The pharmaceutical sector is undergoing a transformative shift towards ESG, driven by public consciousness and evolving regulatory frameworks. This change is fostering a revaluation of manufacturing practices, prioritising resource efficiency and embracing circular economy models. Furthermore, the industry is adopting a more transparent and ethical approach, underscoring the significance of these elements in its core values.

Proactive ESG Implementation

In response to these emerging demands, pharmaceutical companies are intensifying their efforts towards environmental stewardship, such as optimizing energy use and minimising carbon footprint. Socially, the focus is shifting towards ensuring more equitable access to medicines and upholding ethical standards in clinical trials. In terms of governance, there is an increased commitment to maintaining high standards of business ethics, compliance and risk management.

Aligning ESG with UNSDGs

The convergence of ESG principles with the United Nations Sustainable Development Goals (UNSDGs) is particularly pronounced in the pharmaceutical industry. ESG initiatives correspond with several UNSDGs, including those focusing on health, clean water, and responsible consumption and production. A prime illustration of this alignment is the industry's approach to antibiotic resistance. This effort not only supports various UNSDGs but also showcases a deep obligation towards global health and responsible antibiotic usage.

Antibiotic Sustainability: A Focal Issue

Central to this discussion is the sustainability of antibiotics, a key element in combating the escalating challenge of antibiotic resistance (AMR). Efforts to address AMR resonate with UNSDG 3, which aims to diminish infections and deaths caused by communicable diseases.

The Broad Impact of Addressing AMR

Under UNSDG 3, which signifies health, the focus on effective management of resistant infections can significantly enhance global health outcomes. Likewise, combating AMR can contribute to the protection of water sources from contamination, thus meeting the objective of UNSDG 6 concerning water sources. The responsible use of antibiotics is also in line with sustainable consumption and production patterns, which are associated with sustainable practices (UNSDG 12). Similarly, we can meet UNSDG 17 relating to global partnerships through cooperative initiatives in

AMR research by fostering international collaborations and developing collective responses.

Sustainable Antibiotic Research

The issues concerning ESG are so intertwined that working towards one priority area of UNSDGs can enable progress across multiple related fields, including antibiotic research where the end results should be directed towards ensuring equitable access and sustainable use through policy interventions and coordinated efforts of all stakeholders led by the government.

Challenges and the Way Forward

Integrating ESG principles into core business strategies remains a complex task that necessitates a paradigm shift at every level of the organisation. The industry is also tasked with the challenge of maintaining consistent, transparent ESG reporting to provide substantial insights. Moving forward, the establishment of robust ESG governance structures and the use of technology for ESG data analysis will be pivotal.

Toward a Healthier, More Sustainable World

The pharmaceutical industry is on a journey to cultivate a culture of sustainability, educating its workforce about the importance of ESG principles and their role in ongoing sustainability efforts. While significant strides have been made in ESG initiatives, the journey towards a healthier and more sustainable world is ongoing. It demands continuous effort and a focused approach on identified areas. ■

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Drug Development in the 21st century

Bringing a new drug to market is a daunting journey - 10+ years and $1.1 billion for 100 candidates, with only 6 reaching the finish line. Success rates plummet at each stage, from 32% in early tests to 58% in Phase III. This high attrition highlights the need for innovation, and researchers like **Subrahmanyam Vangala** and **Uday Saxena of Reagene Biosciences** propose 3D human systems as a potential game-changer for efficient, cost-effective drug development.

Analysis of reasons for clinical failures suggest - poor PK (10-15%), unmanageable toxicity (~30%) and lack of efficacy (40-50%) top the list. Traditionally, Phase IND-enabling trials are conducted in animal models (rodents, canines and non-human primates), before introducing into Phase I trials, yet >90% clinical trial failures questioned the validity of animal trials for safety and efficacy evaluations resulting in poor clinical outcomes. The "fail early-fail fast" high-throughput screens (HTS) deployed in Early Drug Discovery (EDD) did not improve the productivity in RDD. Failing in Phase III trials is thus a costly failure. Worldwide, exploratory research and development of Alternatives to Animal models are being developed which can be used for Safety and Efficacy (S&E) evaluations of NCEs. In specific, the focus is on developing human model systems such as 3D Micro Physiological Systems (MPS) also known as Non-Animal Models (NAMs). Organ-on-a-chip, Human-on-a-chip models with spheroids, organoids combined with tools such as microfluidics and 3D-bioprinting techniques are being developed to mimic physiological communications of various cell types and organs in humans. These are not typical HTS models used in EDD but Limited Throughput or Higher-Throughput systems. More importantly these models must be customized to enable investigative and mechanistic approaches for human relevance.

Current Approaches in First in Human (FIH) SAFE Dose Selection

The FIH dose is critically important in ensuring that the PK predicted from animal data is accurate and gives confidence to further escalate the doses to the maximum tolerated dose (MTD - derived from animal toxicology studies). Briefly, FDA guidance (download (fda.gov)) requires conversion of Animal Doses to Human Equivalent Doses (HED) for both therapeutic and toxic doses. Most sensitive species toxic MTD dose is used for these extrapolations. Allometric scaling, animal PK-PD data are used to calculate a maximum safe dose for humans and a conservative dose is used for FIH studies. Nevertheless, species differences in physiology, drug distribution & delivery, drug target pharmacology, ADME, properties of the drug candidate limit the accuracy of these extrapolations from animals to humans.

FIH dose corrections may be made using human in vitro data - target binding affinity, functional pharmacology in human derived cells, intrinsic clearance (Clint) in human liver microsomes, human plasma protein binding etc. Additionally, metabolic profile in humans is sometimes different from animals with higher exposure of metabolites in humans than animals and/or new metabolites in humans those not found in animal species. In such cases, the role of metabolites in pharmacology and toxicology of drug candidate may be underestimated and regulatory agencies require additional studies using animal models/in vitro human models.

Biomarkers of Efficacy and Toxicity in Preclinical and Clinical Development

Standard biomarkers of safety (e.g., liver enzymes) and efficacy (e.g., phenotypic expression of the disease) used in clinical trials did not impact clinical trial outcomes.

With rapidly evolving technologies (transgenic animals, LC-MS/MS, LC-NMR, Next Generation Sequencing, etc,) and availability of patient biopsies - there has been a lot of emphasis on using surrogate markers of disease diagnosis, efficacy and safety for optimal clinical trial designs. However, the progress has been very slow as the clinical validation and deployment of these emerging novel biomarkers for regulatory satisfaction is quite rigorous. To date, ery limited biomarkers have been approved for use in regulated clinical trials.

The Bottle Neck of Drug Development: Poor Translation of Animal Models

Although scientists across the globe, continuously debate, many scientists agree that Phase 0 and Phase I trials do not translate effectively to Phase II and Phase III S&E outcomes. Dissecting the reasons, the following disconnects are noticed in the strategy employed for clinical trial designs.

Animal models of disease do not reproduce human disease. The primary reason is that the genetics, biochemistry and molecular biology of disease initiation and progression are different from animals and humans. The phenotype of disease (e.g., symptoms, histopathology) may be similar between animals and humans, but the underlying molecular pathways, targets and target pharmacology are very different between animals and humans.

Healthy animals are used in safety evaluation of NCEs: Standard regulatory toxicology studies typically use healthy young animals which are kept in germ free rooms and given same food and water for the entire study period. These healthy animals do not have manifested disease and the safety outcomes reported from these studies may not be reliable for human patients with disease.

Healthy volunteers often used in Phase I trials who do not have the manifested disease pathology. For example, inflammation is a common underlying feature of many diseases. The expression of drug metabolism enzymes is often downregulated by inflammatory cytokines and thus ADME related factors are not same in patients with disease compared to the healthy volunteers. One of many reasons why Phase I trials may not translate to successful Phase II and III outcomes.

The chronic diseases in humans (average life span 70 years) may take 20-30 years to manifest. In contrast, many animal disease models are rodents with a life span of 2 years. To reproduce a 30-years of human chronic disease in rodents thus poses many challenges. Examples include: Chronic exposure at low doses of benzene, a human leukemogen, causes aplastic anaemia (pre-leukemia) in rodents but does not reproduce overt human leukemia in rodents. Chronic diabetic nephropathy takes 20-30 years to manifest in humans defined as End Stage Renal Disease. Several available rodent models (via chemical or genetic manipulation) do not reproduce ESRD similar to that in humans.

The regulatory agencies do acknowledge the poor outcomes of these flawed strategies and encouraging researchers worldwide to build alternatives to animal models to bridge the gaps in drug discovery and regulatory DD. US legislation in 2022 made a landmark decision by passing Senate Bill (BILLS-117s5002cps.pdf (congress.gov) to accept the data from alternatives such as organoids, spheroids 3D-bioprinted and other in vitro non-animal models for IND and NDA/BLA submissions .

Building in vitro Non-Animal Models using human derived tissues, cells and other recombinant models: Worldwide, there is an explosion of interest in these directions. Current major focus of the industry is to build in vitro Drug Induced Liver Injury (DILI) and Disease models those recapitulate human physiology, ADME and pathophysiology.

In vitro models of Drug Induced-Liver Injury: DILI is often a post-marketing problem. After successful safety outcomes in Phase III trials, and regulatory agency approvals, some drugs sometimes show fatal idiosyncratic DILI leading to drug withdrawals from the market. The mechanisms of these DILI are largely unknown but experts around the world believe both genetic and immune components related to the specific individual cause DILI. Troglitazone (Type 2-anti diabetic) as an example was withdrawn in 2000 due to fatal DILI, escaping preclinical and clinical trial detection. Post-marketing, at least two dozen cases of acute liver failures, deaths or requiring liver transplantation were identified. The second-generation rosiglitazone and pioglitazone were rare in inducing liver failure and patients recovered following treatment withdrawal. Some in vitro studies using human hepatocytes could

differentiate troglitazone and rosiglitazone, suggesting in vitro models can predict hepatotoxicity. Additionally, prototype human on a chip microfluidic models showed that the drug metabolism enzyme expression in human hepatocytes is several-fold higher in 3D microfluidics chips than the static single cell 2D hepatocytes. In the last two decades several companies are building organoids, spheroids of livers to mimic human liver microenvironment for DILI assessments.

Building 3D bio-printed Human Disease-In-A-Dish models (3D DIAD) for integrated ADME, Efficacy and Safety Evaluations: We, at Reagene Biosciences are developing models to mimic human diseases in vitro for a better efficacy evaluation and its modulation by ADME. More importantly, these models can be customized for PK-PD) and PBPK evaluations for effective FIH dose determinations and for safety related liabilities including DILI and Drug Induced Cardiotoxicity (DIC). To date, we developed various DIAD models as listed in Table1.

The future should employ more of in vitro 3D NAM/ MPS/DIAD models to decrease clinical failure rates from 90% down to at least 50%, saving costs, time and unnecessary use of animals and accelerate RDD process for successful drug launches into market. ■

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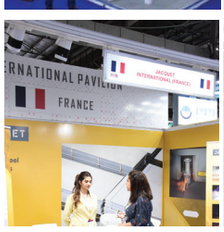

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R.N.I. No.: MAHENG/2002/08502. Date of Publication: 26th of every month. Poster Registration No: MCS/207/2023-25
Posted at Patrika Channel Sorting Office, Mumbai 400001. On 27th every month. Total Pages 44

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