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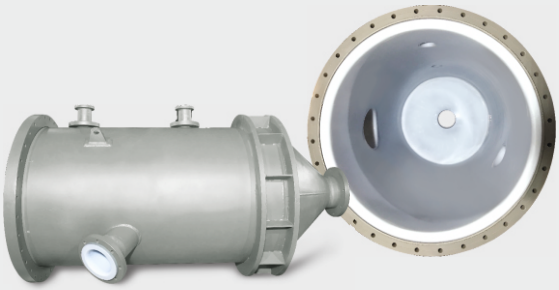


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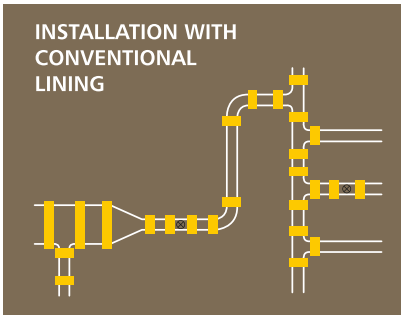

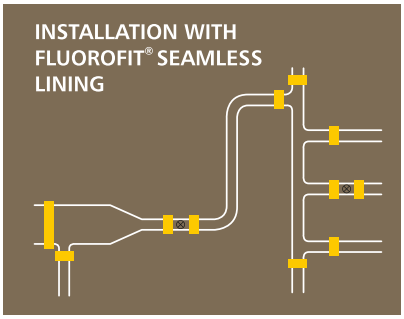

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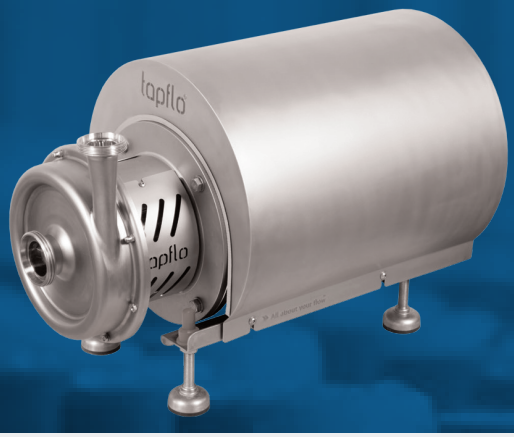

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Ocugen & Bharat Biotech Announce Execution of Definitive Agreement to Commercialize Covaxin™ in the US Market

Dr. Krishna Ella, CMD, Bharat Biotech International Ltd

Malvern, PA & Hyderabad, India - Ocugen, Inc., a biopharmaceutical company focused on discovering, developing, and commercializing gene therapies to cure blindness diseases and developing a vaccine to fight COVID-19, and Bharat Biotech, a global leader in vaccine innovation, today announced they have entered into a definitive agreement to codevelop, supply, and commercialize Bharat Biotech's COVAXIN™, an advanced stage whole-virion inactivated COVID-19 vaccine candidate, for the United States market.

Under the terms of the agreement, Ocugen will have US rights to the vaccine candidate and will be responsible for clinical development, regulatory approval (including EUA) and commercialization for the US market. Bharat Biotech will supply initial doses to be used in the US upon Ocugen's receipt of an EUA. In addition, Bharat Biotech will support the technology transfer for manufacturing in the US. In consideration for the exclusive license to the US market, Ocugen will share the profits from the sale of COVAXIN™ in the US market with Bharat Biotech, with Ocugen retaining 45% of the profits.

The collaboration will leverage the vaccine expertise of Ocugen's leadership team. In preparation for the development of COVAXIN™ in the US, Ocugen's Vaccine Scientific Advisory Board and Ocugen management have initiated discussions with the U.S. Food & Drug Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA) to develop a regulatory path to EUA and, eventually, biologics license application (BLA) approval in the US market for COVAXIN™. Ocugen is also in active discussions with manufacturers in the US to produce a significant number of doses of COVAXIN™ to support its US immunization program.

"The evaluation of COVAXIN™ has resulted in several unique product characteristics including long-term persistence of immune responses to multiple viral proteins, as opposed to only the spike protein, and has demonstrated broad spectrum neutralizing capability with heterologous SARS-CoV-2 strains, thus potentially reducing or

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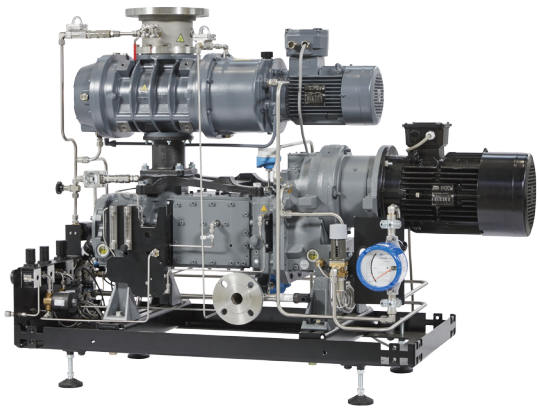

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eliminating escape mutants. Requiring only a standard vaccine storage temperature of 2-8oC and with the potential to treat all age-groups, COVAXIN™ may offer an important option to protect lives across America," said Dr. Shankar Musunuri, Chairman, CEO, and Co-Founder of Ocugen.

The Central Licensing Authority in India has granted permission for the sale or distribution of COVAXIN™ for restricted use in emergency situations in the public interest, in clinical trial mode. With the kickoff of what is likely to become the biggest national vaccination campaign in India's history, COVAXIN™ is being administered as one of the two COVID-19 shots available under emergency authorization with the first batch of 30 million doses being administered to health professionals and front-line workers. "The COVID-19 pandemic has affected humanity at large. As a company determined to protect global public health, it has always been important for us to develop vaccines for a global cause. Our goal for all vaccines developed at Bharat Biotech is to provide global access. COVAXIN™ has generated excellent safety data with robust immune responses to multiple viral proteins that persist. With the recent progression of COVAXIN use under EUA in India, I am confident that we will be able to work with Ocugen to develop a plan to bring COVAXIN to the US market," said Dr. Krishna Ella, Chairman & Managing Director of Bharat Biotech.

Yokogawa and ICQ Consultants Enter into Partnership Agreement for Biopharmaceutical Business

Tokyo, Japan, & Southborough, MA, USA: Yokogawa Electric Corporation (TOKYO: 6841) (Yokogawa) and Integrated Commissioning and Qualification Consultants, Corp. (ICQ Consultants) of Southborough announce that they have entered into a partnership agreement under which ICQ Consultants will provide consulting and engineering services for the installation, maintenance, qualification, and support of Yokogawa's bioreactor systems and related products in the United States.

As a result of the COVID pandemic, the global biopharmaceutical market has been growing at an unprecedented rate, with significant investments being made in diagnostics, vaccine development, and medical devices to test and treat the coronavirus. These investments have driven demand for infrastructure in developing and manufacturing monoclonal antibody drugs and products that require mammalian cell bioreactor technologies.

Since 2007, ICQ Consultants has played an important role in the commissioning and qualification of manufacturing plants in the major life sciences hubs in the United States, including some of the world's largest bio-manufacturing facilities. As part of

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Yokogawa's Advanced Control Bioreactor System BR1000

this partnership agreement, Yokogawa will leverage ICQ Consultants' engineering and laboratory expertise in the biopharmaceutical segment to deploy its new bioprocess technologies in the United States. The first portfolio product, the Advanced Control Bioreactor System BR1000 was recently released on January 8, offering significant performance advantages over existing methods for biologics development.

The automation of manual processes is a rapidly advancing trend in the biopharmaceutical industry. For complete automation of the fed-batch mammalian cell culture process, the control of glucose -- a key nutrient source -- is critical. Through in-line sensing and model predictive control software, and automated feeding, a stable concentration of glucose in bioreactors can be achieved. The BR1000 automates lab-scale mammalian cell culture with highly accurate real-time monitoring and advanced process control.

Michael Bogan, president of ICQ Consultants, commented, "We are very excited to join Yokogawa in this strategic partnership agreement to help facilitate the support of their bioreactor systems and related products throughout the United States. As ICQ Consultants continues to expand operations across the country, we are poised to further develop lasting relationships, which has been a key factor in our ongoing success. I look forward to working with Yokogawa on this unique and collaborative opportunity."

Hiroshi Nakao, a Yokogawa vice president and head of the company's Life Innovation Business Headquarters, added, "Driven by a clear business vision and recent successes in the life sciences, food, and pharmaceutical sectors, Yokogawa Corporation of America is also turning its attention to biologics development and manufacturing. Alliances with industry experts like ICQ Consultants are vital to gain expertise and penetration in the high growth biopharmaceutical market. ICQ Consultants' engineering and technical knowledge in drug manufacturing will support our innovative new bioreactor and bioprocess technologies and help position Yokogawa for rapid sales and market leadership in the emerging bio-industrial autonomy sector."

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Sun Pharma to introduce complete range of Brivaracetam at an affordable price for epilepsy treatment in India

Mumbai, India : Sun Pharmaceutical Industries Limited announced that the company will introduce the complete range of Brivaracetam dosage forms at an affordable price for epilepsy treatment in India. Sun Pharma's brand, Brevipil (Brivaracetam) tablet 25 mg/50 mg/75 mg/100 mg was launched in the market on Day-1 post patent expiry of innovator product (February 21, 2021). Brevipil oral solution (10 mg/ml) and injectable (10 mg/ml) will be available in the market over the next few weeks. Brivaracetam is approved by the Drugs Controller General of India (DCGI), as an adjunctive therapy in treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

Said, Kirti Ganorkar, CEO – India Business, Sun Pharma, "We are introducing the complete range of Brivaracetam in India at a competitive pricing which will improve patient access. This product reaffirms our commitment towards improving epilepsy care by bringing multiple treatment options to patients and health care professionals in India."

Brivaracetam belongs to the class of anti-epileptic drugs (AEDs) which have a unique or different mechanism of action compared to the existing treatment options. It has fast onset of action and promising efficacy1. Long-term studies indicate that the response obtained with the use of Brivaracetam is sustained, with favourable tolerability profile and compliance to the treatment2. While epilepsy is a common neurological disorder, because of the social stigma surrounding epilepsy, cultural practices and poor awareness of new treatment options, management of epilepsy in India continues to be a challenge3,4. It is estimated that around 5.7 million to 6.4 million people in India suffer from epilepsy5,6. BRIVIACT® is a trademark of UCB.

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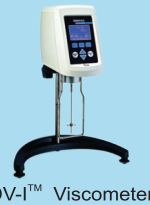
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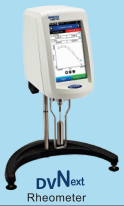
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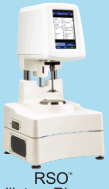
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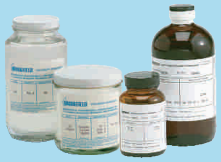
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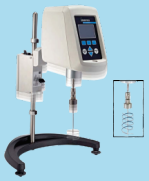
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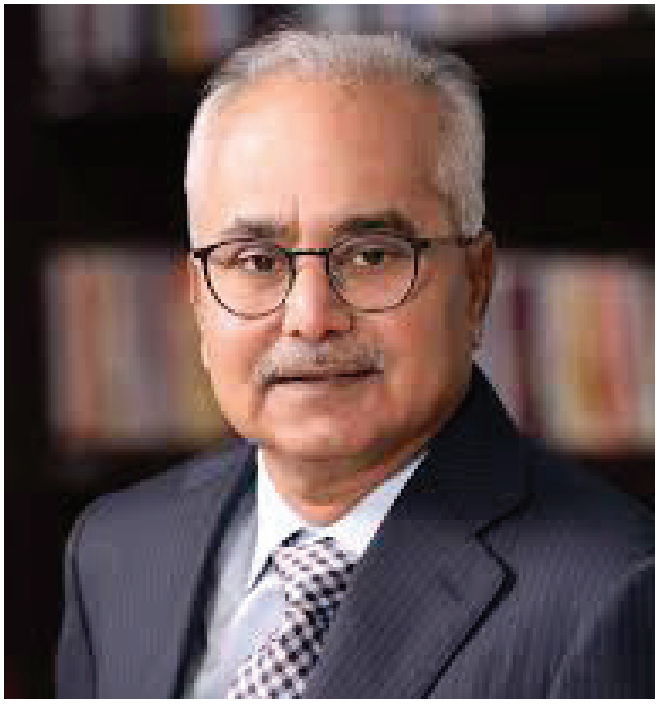
Dr. Reddy's initiates process for Emergency Use Authorization of Sputnik V



G V Prasad, Co-Chairman & MD, Dr. Reddy's Laboratories

Hyderabad, India: Dr. Reddy's Laboratories Ltd. announced that it has initiated the process with the Drugs Controller General of India (DCGI) for Emergency Use Authorization (EUA) of the well-studied human adenoviral vector-based platform vaccine candidate, Sputnik V. As part of the review process, Dr. Reddy's will present the safety profile of the phase 2 study, and interim data of the phase 3 study, which is expected to complete by 21st February 2021. In September 2020, Dr. Reddy's partnered with the Russian Direct Investment Fund (RDIF) to conduct the clinical trials of the Sputnik V and for its distribution rights in India. The vaccine is currently undergoing the phase 3 clinical trial in India. Sputnik V has demonstrated an efficacy rate of 91.6% in the interim analysis of the phase 3 clinical trial, which included data on 19,866 volunteers in Russia, who received both the first and second doses of the vaccine. Sputnik V maintained a consistent efficacy at 91.8% even among the group of 2,144 volunteers over 60 years old.

G V Prasad, Co-chairman and Managing Director, Dr. Reddy's Laboratories said, "The efficacy of Sputnik V was reported to be 91.6 % by the Lancet, which is an impressive development in the fight against COVID-19. The initiation of the EUA process will be a critical step forward for us in ensuring speedy access to the Sputnik V vaccine in India."

Sputnik V developed by the Gamaleya National Research Institute of Epidemiology and Microbiology was registered by the Ministry of Health of Russia on 11th August 2020 and became the World's first registered vaccine against COVID-19 based on the human adenoviral vector platform. More than 250 clinical studies over two decades have proven the safety, efficacy, and lack of negative long-term effects of adenoviral vaccines. Sputnik V is one of only three vaccines in the world with an efficacy of 91.6% and has most authorizations granted with 26 countries globally. The vaccine has already been administered to more than 2 million people worldwide.

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Lincoln Pharmaceuticals Ltd reports 31 % rise in the Standalone Net Profit at Rs. 13.37 crore in Q3 FY21

Mahendra Patel, MD, Lincoln Pharmaceuticals Ltd

Ahmedabad, Gujarat: Lincoln Pharmaceuticals Limited, one of India's leading healthcare companies has reported net profit of Rs. 13.37 crore for the Q3 FY21 ended December 2020 as against net profit of Rs. 10.18 crore in the corresponding period last year, growth of 31.35%. Net revenue for the Q3 FY21 was reported at Rs. 113.26 crore, higher by 15.56% over previous fiscal's same period net revenue of Rs. 98.01 crore. Company reported EBITDA of Rs. 19.94 crore in Q3FY21, rise of 43.25% as compared to Rs. 13.92 crore in the corresponding period last year. EPS for Q3FY21 was at Rs. 6.68 per share for as compared to Rs. 5.09 in the corresponding period last year.

Commenting on the results and performance, Mahendra Patel, Managing Director, Lincoln Pharmaceuticals Limited, said, "On back of strong domestic and international business, company posted 15.56 % sales growth, 4.00 % rise in exports and 31.35 % rise in the PAT for the quarter ended Q3FY21. Exports sales in nine months ended December 2020 was reported at Rs. 212.47 crore, growth of 17.56 % Y-o-Y. Geographical and product expansion coupled with operational efficiency contributing to the growth. Company is in the process of expanding presence in Africa, South East Asian countries and exploring entry in EU. Expanding the product basket, company will be introducing 6-7 new products in the domestic markets and expects 20-25 new dossiers approval for the exports market."

As a result of expansion in geographical reach in domestic markets, relentless focus on exports and sustained marketing, the Net sales for the nine months ended December 2020 was reported at Rs.339.77 crore, higher by 10.44% over previous fiscal's same period net sales of Rs. 307.65 crore. Company reported Net profit of Rs. 48.56 crore for the nine months ended December 2020 as against net profit of Rs. 40.33 crore in the corresponding period last year, growth of 20.74 %. EPS for the 9MFY21 was reported at Rs. 24.28 per share. Exports for the 9MFY21 stood at Rs. 212.47 crore, up 17.56 % as against exports of Rs. 180.74 crore in 9MFY20. To complement the company's strong presence in the acute segment, the company is also building a portfolio in lifestyle and chronic segment especially dermatology, gastro and pain management and plans to introduce them in the EU markets. Company has received EU approval and plans to enter the region soon. Company currently exports to 60 plus countries and plans to expand to 90 plus countries in next 1-2 years.

Lincoln Pharma has a state-of-the-art manufacturing facility unit at Khatraj in Ahmedabad, Gujarat, complying with stringent international quality and compliance norms and certified by EUGMP, WHO-GMP and ISO-9001: 2015. Company has developed 600 plus formulations in 15 therapeutic areas and has a strong product/brand portfolio in anti-infective, respiratory system, gynaecology, cardio & CNS, anti-bacterial, ant-diabetic, anti-malaria among others. Company has filled 25 plus patent applications and is awarded with seven patents. Company has a strong presence in the domestic market with good strength of own field force and also exports to more than 60 countries.

Kaisha Group announces further increase in vial production capacity by 2022

Rishad Dadachanji, Director, Kaisha Group of Companies

"Announcement by Indian Finance Minister, Nirmala Sitharaman to commit a 137% budget increase for healthcare and nearly 200% boost for developing the pharma sector instils a high level of optimism in the industry. The allocation of INR 35,000 crores for COVID-19 vaccine development and immunization was a much-needed impetus for Atmanirbhar Bharat, as it continues to maintain its global lead in tackling the pandemic. Kaisha Group of Companies, has been a crucial contributor in India's drive against novel Coronavirus by providing medicinal supplies and more importantly, storage of Covid vaccines and other life-saving medication. Schott Kaisha, an Indo-German joint venture leads the Indian market in supplying Type 1 tubular glass vials for vaccine manufacturers in India and abroad. Its sister company, Sovereign Pharma supplies the anti-viral Remdesivir medicine to Cipla under a licensing agreement in India. This year's unprecedented increase in the budget allocation is further assuring for the pharma industry as it is working to provide for the mammoth task of immunizing 1.3 billion Indians. As the first phase of the vaccine drive continues, Schott Kaisha has announced a fresh investment to further increase vial production capacity by another 100 million pieces from its manufacturing sites based in Gujarat and Daman. This is in addition to the announced an immediate investment of INR 122 crores to increase its vial production capacity by 300 million pieces in a record time period of one year. The company is supplying to 8 active customers and 10 vaccine candidates currents, which includes key players in India and abroad. We are currently producing 1.2 billion vials per annum, which will be increased to 1.5 billion vials by

December 2021 and to 1.6 billion vials by mid- 2022.

The Indian healthcare and pharma industries have emerged as a shining example of rising up to the challenge in order to support the country as well as the world during the pandemic. While Kaisha Group has collectively supported the pharma supply chain which saw soaring demands, the government's backing with quick decision-making, boosting the supply chain and addressing existing loopholes in the ecosystem has shown great results for its vision to make India a global pharmaceutical hub."

ENPICOM introduces an end-to-end solution for fast and efficient antibody discovery

Jos Lunenberg, Co-founder & CEO, ENPICOM

's-Hertogenbosch, The Netherlands: ENPICOM BV, an innovative bioinformatics software engineering company, announces a major release of its ImmunoGenomiX (IGX) Platform featuring the new Antibody Discovery Module (ADM). This solution will allow scientists in biopharmaceutical companies and academia, as well as service providers working in the antibody discovery field, to make the most of their Sanger and NGS data and independently perform complex analyses.

Nicola Bonzanni, Co-founder & CPO, ENPICOM

In recent years, antibody discovery workflows have started relying more on sequencing data and in-silico analysis to identify the best candidates. However data integration, analysis, and visualization can be challenging and require diverse expertise, including immunology, protein biology, and bioinformatics. In close collaboration with over 50 industry leaders, ENPICOM has pinpointed the bottlenecks and challenges in

the antibody discovery process and validated the new product designed to solve these. ENPICOM introduces a set of specialized IGX Platform Apps engineered to rapidly identify a diverse set of promising antibody candidates from integrated sequencing data. "By conducting thorough interviews with a large group of industry leaders, we gained a deep understanding of the specific pain points and needs in the market." explained Jos Lunenberg, co-founder and Chief Executive Officer at ENPICOM. "We learned exactly what researchers need, and as a result, can offer something truly unique: a validated solution, tailored to the specific needs of antibody developers. This allows researchers without extensive bioinformatics expertise to independently perform their discovery analysis and stay focused on what matters the most – their research."

"Extensive product discovery efforts have led to the identification of several new analyses and data management features that are key to the workflow of antibody developers." commented Nicola Bonzanni, co-founder and Chief Product Officer at ENPICOM. "With our new module built on top of the powerful IGX Platform core, we empower scientists to discover and perform in-depth analysis on drug candidate sequences in the context of therapeutic antibody development."

The two new Apps developed for the ADM release are IGX-Cluster and IGX-Branch. IGX-Cluster groups sequences based on user-defined parameters such as CDR3 similarity, gene usage, and CDR3 length. It effortlessly performs large clustering tasks in the cloud and supports a wide variety of workflows for both paired and unpaired receptor chains. Subsequently, IGX-Branch creates interactive visualizations to prioritize clusters and pick antibody candidates for follow-up analysis through information-rich phylogenetic trees.

ENPICOM's IGX Platform is a professional tool to manage, analyze, integrate, and visualize immune repertoire sequencing data in a single environment. Technology-agnostic and code-free, it enables scientists to securely and effortlessly analyze immune repertoires. Together with the two new Apps introduced today, it provides an ideal setup for crucial tasks like candidate selection and hit expansion, thus creating a versatile system to discover promising antibody candidates. Other prominent new features released today include revamped receptor profiling workflows and vastly improved metadata importing. The earlier announced collaboration with MiLaboratories has resulted in a new MiXCR App, fully embedded in the platform. ■

Maximizing the Efficiency of Clinical Trial Supply Chain

Clinical trials are an essential part of the product development process for both pharmaceutical and biotech companies and if run efficiently can provide the company with a competitive advantage. This article discusses various key factors pertaining to an efficient and effective clinical trial supply management.

Sujay Salvi
Head - Clinical Trial Supplies Management, SIRO Clinpharm

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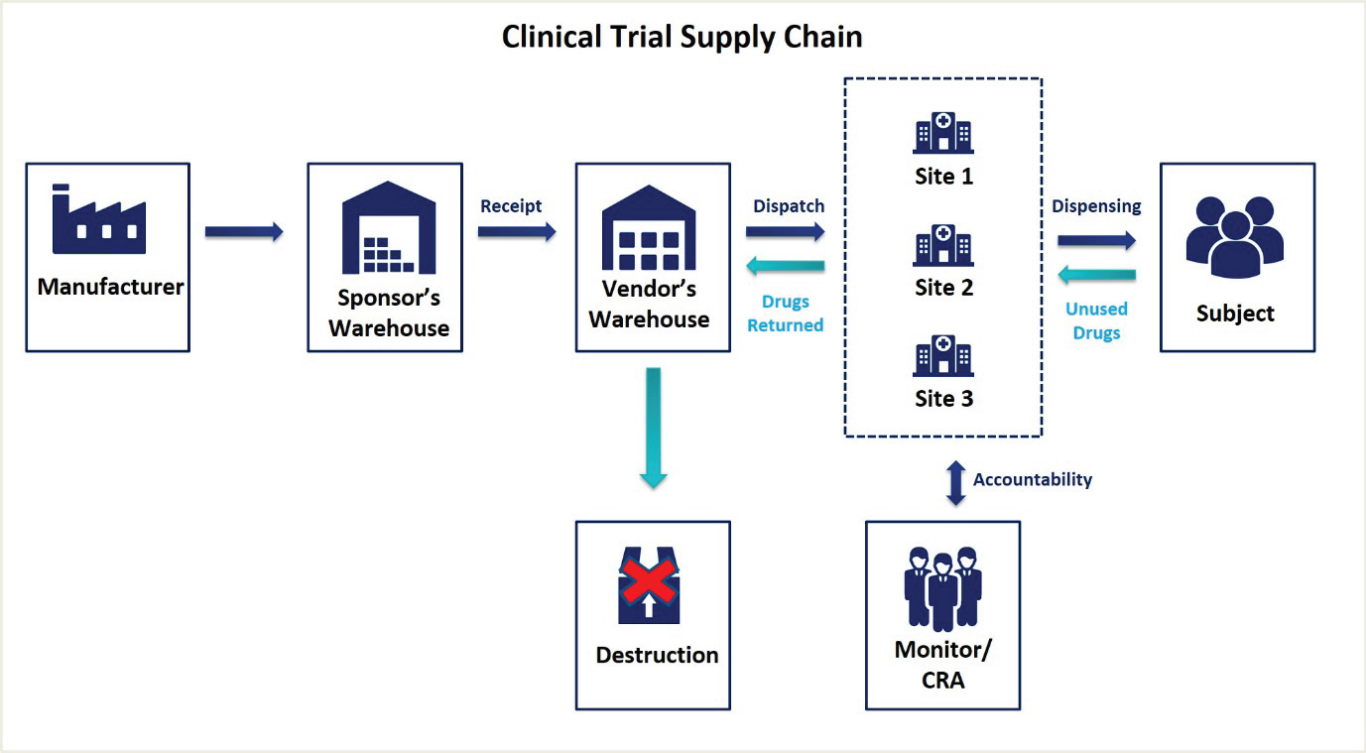
For a new drug to reach the market it has to undergo a robust clinical trial process which requires considerable amount of investment and can continue in excess of 10 years. The process involves global multi-center trials and recruiting a large number of patients to achieve the trial objectives e.g. safety and efficacy. Different types of clinical trial supplies, from investigational products to ancillary supplies are required to conduct clinical trials. The clinical trial supply chain is an integral part of any clinical trial; it constitutes packaging, labeling, storage, distribution to patients located in different geographic locations, and accountability and destruction of clinical trial supplies.

Below are the examples of Clinical Trial Supplies:

- Clinical Trial Drug Supplies:

  Investigational Product & Comparators, Background / Rescue Medication



- Clinical Trial Non Drug Supplies:

  Equipment & Lab Kits, CRFs, Blinding / Randomization Envelopes

The primary goal of clinical trial supply process is to deliver

The RIGHT SUPPLIES at the RIGHT TIME to the RIGHT INVESTIGATIONAL SITE for the RIGHT PATIENT

Although the basic principles of logistics apply to Clinical trial supply chain, it is different from Pharmaceutical commercial supply chain due to the following aspects:

- Investigational Products are still under testing hence many aspects of the investigational product are still under 'investigation' or in other words the product needs to be administered to a selective group of patients who has consented for the clinical trial. It is, therefore, extremely critical to have a controlled use of such products right from the lab where it is being produced, till the time it is consumed by the patient, while all the extra supplies are accounted for and destroyed.
- Investigational Products are exclusively manufactured and packaged depending on the trial design so they are not available off-the-shelf.
- Some investigational products eg Oncology products are very expensive and available in limited quantity, hence any wastage could affect the fate of the clinical trial.
- Each kit used at the investigational site is accounted for down to the unit

level eg tablet, capsule and it needs to be returned to the sponsor for destruction.

- The trial data is submitted to the regulatory authorities for registration hence clinical trial supply chain is prone to regulatory audits and inspections.
- The compliance level of the investigational product during the trial has a direct co-relation with the final outcome of the trial. If it is not as per the desired level, the entire trial data would be of no use. Hence, one needs to have built-in quality checks in a study design and monitor closely so that the final outcome is achieved.

Therefore, it is imperative to optimize the clinical trial supply chain process with respect to time, quality, safety & integrity, and at the same time, bring in cost efficiencies.

In order to maximize the efficiency of clinical trial supply chain, it's important to know the various challenges associated with the process and the approaches/ techniques to address them.

Geography - Multicenter/ Multinational Trials

One of the biggest challenges is the geographical location of the source and sites.

With the rapid growth in the number and spread of clinical trials, there are many multinational & multi-center trials, where multiple countries across the globe and various hospitals in those countries are involved. The clinical trial supplies need to be delivered at these sites from the source e.g. central depot. This could result in longer transit time, for example the central depot could be in USA and the sites in South East Asia.

In most of the countries, the drugs cannot be shipped to sites unless necessary approvals from Regulatory and Ethics committee are in place. Hence the clinical trial supplies cannot be sent in advance.

Global Regulatory Requirements

Regulatory requirements could differ from one country another and inadequate knowledge about it could lead to delays in customs clearance. In many countries, import license is required to import drugs and the invoice should match the import license. The labels on investigational product kits should be as per country regulatory requirements which could be country specific. For example, expiry date on the kits is not mandatory in USA but it is mandatory in India.

These situations could result in longer transit time. In case of delays in clearance, there are chances of improper handling of supplies at the custom warehouse which could ultimately compromise the cold chain and affect the quality of the product.

There is also a risk of shipments being misplaced resulting in product wastage.

Product wastage can also be caused due to inaccurate forecasting, eg supplying excess investigational product to sites with low or no recruitment, or supplying products with short expiry date. Such incidences will have an adverse impact on the outcome of the clinical trial.

Poor subject compliance can occur if the investigational product is not available as the subject will not be able to adhere to the protocol specified time regime. This will adversely affect the company's reputation as it is the social and ethical obligation of the sponsor to make the investigational product available to the patients at all times during the trial period; this is also a GCP requirement.

Substandard products resulting from improper handling may jeopardize the clinical trial outcome and there could be chances of data being rejected by the regulatory authorities.

Such issues will also delay the completion of the clinical trial and, in the worst case scenario, could lead to cancellation of the trial all together. The sponsor ultimately could incur heavy losses because of all these issues.

- Based on years of industry experience, here's a checklist which could help in developing the right clinical trial supply chain strategy. Use of a service provider (local depot)

The sponsor can appoint local depots in the countries which are participating in the clinical trial. As Clinical Trial Supplies Management is a niche area, many sponsors prefer to outsource it to the experienced partners rather than managing it by themselves. These depots are GxP compliant and provide end-to-end service from receipt till destruction of the investigational product. These depots can be audited and approved by the sponsor's Quality Assurance department. This partnership has many advantages, shorter transit time to sites being the most important advantage. The local depot can receive the drugs from the central depot after DCGI approval is received for the trial & import license is in place. Once the ethics committee approval is in place, the local depot can distribute the supplies to various sites.

Shorter transit time also ensures lower courier costs. The drugs can be shipped by the central depot /sponsor to the local depot as a bulk supply instead of supplying in bits and pieces, thus there will be fewer shipments imported for a trial resulting in less frequent customs clearance.

Appointing a local depot will give an added advantage of excellent awareness of local regulatory requirements. The supplies will be always available at the depot and can be dispatched to sites

on a short notice. The local depot can provide dedicated resources/ project team handling a particular client ensuring a customer-focused approach and prompt action.

Many clinical trials like Oncology trials require comparators, background or rescue medication. Local depot can also provide support in sourcing the comparators from the local market; this can ease the burden on the sponsor as the sponsor won't have to make arrangements for procuring it centrally and then distributing across the globe. Local sourcing will save time and ensure availability of supplies. By delegating this responsibility to the service provider, the sponsor can increase focus on the investigational product.

> Selection of the right courier partner

A courier agency with the right experience and expertise is essential for the Clinical Trial Supply Chain to succeed. Sponsor can directly or through the depot partner appoint a courier agency which is focused on the life sciences and has a proven track record in cold chain management. This will ensure on-time and safe delivery of supplies without any transit issues, e.g. excursions, off-loading. Such issues may result in product wastage and add to the overall cost as the product will have to be resupplied to the sites. The courier agency can be audited by Sponsor/ Depot partner.

The courier agency should have processes in place for conditioning / preconditioning of gel packs, preparation of insulated shippers. They should always use validated shippers and calibrated data-loggers for the shipments.

The courier agency should track the shipment till delivery and provide the POD and data logger readings to the sponsor/ depot partner upon delivery. They should ensure that the supplies are delivered to the right person. In case of any issue, the courier agency must proactively and promptly inform the client.

> Technology and Innovation

Technology and innovation play an important role in the optimization of clinical trial supply chain. Multilingual labels or booklet labels are used for multinational clinical trials. Their main advantage is the flexibility of drug supplies. The supplies can be used in more than one country or redistributed between countries. This minimizes the drug wastage and reduces the overall medication cost. This hugely helps in trials where drugs are in short supply or expensive, e.g. Oncology trials. Booklet labels also complement the use of IXRS technology and pooled supplies.

IXRS (IWR /IVR) - Interactive Web / Voice Response System is used for forecasting, randomization, drug distribution, Inventory Management etc. This system also tracks

the expiry date. As this system is linked to randomization, the drug orders are generated as per the patient recruitment and visit schedule. This minimizes product wastage and ensures the availability of supplies at sites. It also underlines the importance of using a local depot in order to manage the JIT (Just in time) delivery to the site.

Case Study

Here's a case study to help demonstrate the how a sponsor can save much of their precious time and co-ordination exercise with an experienced clinical trial supplies vendor.

In a multicentre, randomized, blinded trial number of shipments containing investigational products were sent to the sites. After using these drugs on patients at the sites, these supplies were returned to the depot on an ongoing basis by the sites. The study had a long duration of about three years. After the recruitment target and all the patient visits were over the sponsor asked the depot to provide the drug reconciliation records. As the depot had not done the reconciliation of investigational product at the time of receipt of the returned supplies they faced lot of issues in the accountability. The depot staff spent no. of days in conducting the drug accountability and found that the documentation received from sites was not adequate, mismatch between the quantities mentioned on the returned documents and the physical returned stock received at the depot. Even after spending considerable time in this activity all the kits dispatched to the sites could not be accounted for and finally sponsor had to report them as missing with a great risk of potential audit and inspection finding. This situation could have been easily avoided if the drug accountability was done on a real time basis and all the discrepancies were promptly reported and resolved.

Conclusion:

The number of global multi-center clinical trials is increasing by day. Trial design and dosage regimes are becoming complex, and so are the challenges in clinical trial supply chain. The clinical trial supply chain has evolved over the past few years. The testing phase is over; sponsors nowadays are actively looking to reduce the cost of clinical trial supply chain without compromising the quality and integrity of the trials. The sponsors can achieve this by collaborating with the service providers who are experts in their domain and can provide a customized solution to their clinical trial supply chain requirements. ■

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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.

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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.

“IoT extends visibility into every area of the business from development through manufacturing, transport, distribution, dispensing, and consumption.”

- 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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Biosimilars: Advancements, Future and the Role of Indian Pharma Market

Biosimilars is a fairly new area in pharma as the guidelines and procedures are yet to be set by FDA. Since, they are prepared with the help of living cells, just like biologics, it becomes important to understand the composition and if it is suited for the stated ailment.

Biologics are drugs regulated by the Food and Drug Administration (FDA) used to treat chronic diseases. These are large molecule drugs and made up of living cells which make them unique and more complex than a chemically synthesized drug that is made up of small molecules. Due to the complexity of large molecules, characterization of biologics becomes difficult. Slight differences in these products are normal and are accepted by the FDA within certain limits however, it becomes important to maintain and control within-product variations so as to maintain the right amount of active ingredients in the drug.

In order to reach a larger base of patients that need biologics, their identical copies are manufactured with similar bioactivity and structure. These drugs are called biosimilars. These are drugs that are highly similar to biologics in function and structure in addition to being inter-changeable with a FDA- approved biological product. High-end technological

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support is needed to compare characteristics of a reference product and a biosimilar that includes chemical identity, bioactivity and structure.

The existence of an alternative pathway paves way for providing more treatment options, extended access to important lifesaving medicines and fundamentally lower costs as a result of increased possibilities in front of pharmaceutical companies. Biosimilars are at a nascent stage today with an estimated market size of $2.2 billion out of the total $32 billion Indian pharma market.

It is a fairly new area in pharma as the guidelines and procedures are not set by the FDA for biosimilars. Since, they are prepared with the help of living cells, just like biologics, it becomes important to understand the composition and if it is suited for the stated ailment. A biological product might be different than a biosimilar in terms of application as the suitability matters for the patients. Hence, biosimilars when developed are clinically tested to test the suitability for a particular patient in question.

Role of Biosimilars

Biological products are very complex in nature as they are produced in a living environment that could be yeast, bacteria or a cell. These products have transformed treatment methods for various serious diseases including cancer, dermatological conditions, rheumatoid arthritis, etc. In developing a biological product, vast amount of research and innovation is essential for the end-product. To solve this, biosimilar can play an important role. Generic drugs are copies of small molecule drugs whereas biosimilars can be similar to or sometimes interchangeable with an FDA approved biological product.

They provide the following advantages in the long run:

- More treatment options
- Increased access to medication to save lives
- Economies of scale
- FDA's Abbreviated Pathway

Biosimilars are safe and effective, approved by the FDA and cost-competitive. Biosimilars could provide enormous savings to consumers through more product competition. Inherent variability in case of biosimilars can exist because of their biological nature. The molecules are bigger than that of a chemically synthesized product. Biological products did not have an abbreviated approval pathway that made it difficult for them to be manufactured at low costs as the requirement was of a full data package. This gets reflected in the cost of these products in the marketplace. Data packages between a biosimilar product and the originator product are different and that is where abbreviated approval pathway comes into picture.

Steps to ensure usefulness of a Biosimilar

A biosimilar has to be highly similar with no clinically meaningful differences as compared to a reference product in terms of structure and functions. Following are the two steps that a biosimilar goes through in the tests against reference or originator drug.

1st Step: Analytical comparison for structural and functional usages-The biosimilar should have the same primary sequence and quaternary and tertiary structure that assists the functions

2nd Step: To see for no clinically meaningful differences – Pharmacokinetics - Exposure in the body, release of drug in the body, its circulation in the body, if the transit is similar to that of the reference drug

Safety profile of the drug also needs to be monitored to ensure it has the same profile between the products. Hence, conclusively it is determined if the product is safe and effective and it will work the same way in the body whether it's a biosimilar or a reference product. It also needs to be ensured that the same clinical result is achieved in any given patient; the application needs to include data or information that supports this. Also, medication given more than once and the impact of switching back and forth between the interchangeable products is evaluated with the switching study.

Indian Pharma market

Indian pharma market holds a prominent position in the global market scenario dominating branded generics and making up around 80% of the retail market, according to a report by Mckinsey. Due to the intense competition present in this industry, the price levels tend to be low making it further favorable to the patients. The pharmaceutical industry in India ranks 3rd in the world in terms of volume and 10th in terms of value. The industry has given rise to numerous innovations in products, infrastructure and processes. India's indigenous manufacturing methods have paved way for the development of another set of generics, this time biogenerics or biosimilars.

According to an Assocham report in 2017, the domestic biosimilars market is expected to reach $40 billion by 2030. With a CAGR of approximately 30%, biosimilars are slated to become popular very soon, as the more affordable version of biologics. Development of a biosimilar might take approximately 5-9 years to be fully developed with a cost that is only 1/26th the cost of developing a biologic. Hence, it has the potential of providing treatment options at a significantly lower cost.

Open Market Sourcing for clinical trials

Biosimilars face stringent clinical timelines and it becomes important for companies

to fast-track the development process of a biosimilar for a release that is well before the market gets crowded. Open market sourcing is considered as an effective strategy to support the growth of the biosimilars market. Open market strategy proves beneficial to the biosimilar makers as the clinical trial data can be kept discreet. In addition to this, the biologics are made available at shorter lead times due to the availability of stock with the wholesaler or at a known manufacturing site.

Further, to support these clinical trials, a greater emphasis needs to be given in choosing the appropriate Comparator Sourcing Organization (CSO). The requirements range from the ability to source and transport products worldwide to validated storage/shipping systems. GNH India is an organization with industry experience of over 12 years in comparator sourcing with exports to close to 180 countries around the world. Their validated shipping and storage shipments account for more than 135,000 products in their portfolio that present a great opportunity domestically in front of the market.

Future of Biosimilars in the Indian pharma market

With the rising acceptance of this biogeneric, it is fast gaining popularity among pharmaceutical companies in India and abroad. The guidelines and procedures are moving towards providing biosimilars with the status that the industry has been waiting to attain. Adding to the catalysts is the recent USFDA approvals to various pharmaceutical organizations like Pfizer, Biocon, etc. With these progressions, the industry is fast striding forward. Biosimilars are drugs aimed at the treatment of serious and life-threatening diseases.

The Indian pharma companies are focusing all their efforts in developing their portfolio in this segment with the country's large pharma players investing in huge numbers for the Research and Development of Biosimilars. As patents of many biologics are expiring in the next few years, this aspect presents a great opportunity for the companies in India to focus their resources on the development of biosimilars.

India has a robust pipeline for biosimilar drugs that is in line with the Indian government's plans to offer grants to Indian biosimilar manufacturers. According to Decision Resources Group's analysis, more than 40 biosimilars are in the clinical development phase in India; a number higher than that in the US and almost similar to those in development in the European Economic Area (EEA). Another trick of the trade lies in strategic partnerships with companies outside of the Indian market to uplift their profiles in the world markets. Differential pricing strategies present another set of opportunity in market expansion. This could work by targeting different economical sections of consumers with differentiated pricing strategies. ■

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Novel Approaches in Preclinical Research, Pharmacogenomics, Drug Design and Drug Delivery

Novel approaches in drug discovery are required as they may reduce cost of R&D, improve safety and efficiency. This article highlights novel approaches in drug discovery with particular emphasis on preclinical research, pharmacogenomics, drug design and drug delivery.

Drug discovery is the process by which new chemical entities are discovered. Historically, drugs were discovered by studying and identifying the active component from traditional remedies. Some have been discovered by serendipity. Later in the classical pharmacology methodology chemical libraries of synthetic small molecules, natural products or extracts were screened in vitro or in vivo to identify substances that have a desirable therapeutic effect. Since the recent past pharmacogenomics has gained lot of significance wherein human genome sequencing is the basis and collated with the pharmacology.

In the modern drug design process High throughput screening is carried out on large compounds libraries against isolated biological targets which are hypothesized to be disease modifying. Hits are then tested in cells and then in animals for

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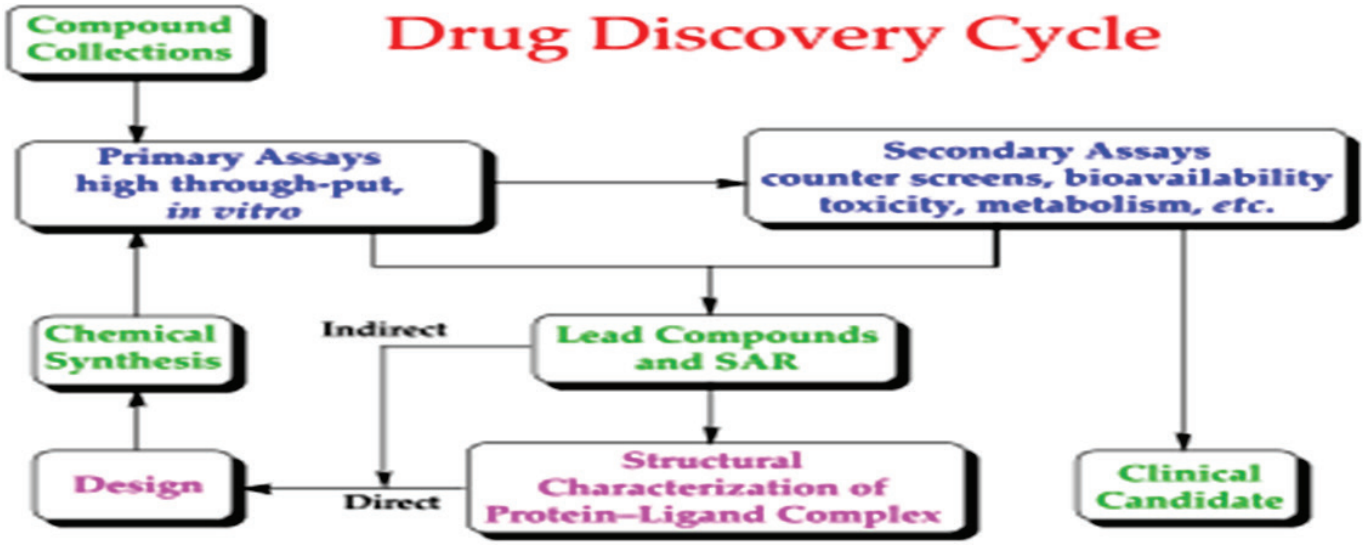

efficacy. In the drug development cycle, preclinical development, also named preclinical studies and nonclinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected. The main goals of pre-clinical studies are to determine the safe dose for first-in-man study and assess a product's safety profile. On average, only one in every 5,000 compounds that enters drug discovery to the stage of preclinical development becomes an approved drug. Drug delivery studies have come a long way and have reached very advanced levels of research in drug administration such as thin film, magnetic, self micro-emulsifying , acoustic, neural.

The Drug Discovery Cycle

Modern drug discovery involves the identification of screening hits, and optimization of those hits to increase the affinity, selectivity, efficacy/potency, metabolic stability, and oral bioavailability. The identified compound then undergoes the process of drug development prior to clinical trials. Some steps may involve computer-aided drug design.

Modern drug discovery is a capital-intensive process. However despite advances in technology and understanding of biological systems, drug discovery is still a cumbersome process with low chances of new therapeutic discovery. A single new molecular entity (NME) cost was approximately USD 2.0 Billion. Drug discovery is done by pharmaceutical companies, with research assistance from universities. The drug requires very expensive Phase I, II and III clinical trials, and most of them fail. Small companies have a critical role, often then

selling the rights to larger companies that have the resources to run the clinical trials.

Discovering drugs that may be a commercial success, or a public health success, involves a complex interaction between investors, industry, academia, patent laws, regulatory exclusivity, marketing and the need to balance secrecy with communication. A drug discovery process ends up in a patent on the potential drug.

The Drug Discovery Techniques

The modern era in pharmacology began with the idea that the effect of a drug in the human body is mediated by specific interactions of the drug molecule with biological macromolecules, (proteins or nucleic acids in most cases) led scientists to the conclusion that individual chemicals are required for the biological activity of the drug. Thus pure chemicals, instead of crude extracts, became the standard drugs. Morphine, the active agent in opium, and digoxin, a heart stimulant originating from Digitalis lanata are Examples of drug compounds isolated from crude preparations. Organic chemistry also led to the synthesis of many of the natural products isolated from biological sources.

In Classical pharmacology, forward pharmacology or phenotypic drug discovery. historically substances, whether crude extracts or purified chemicals were screened for biological activity without knowledge of the biological target. Only after an active substance was identified was an effort made to identify the target. Small molecules were synthesized to specifically target a known physiological/ pathological pathway, rather than adopt the mass screening of banks of stored compounds. This led to great success, such as the work of Gertrude Elion and George H. Hitchings on purine metabolism, the work of James Black on beta blockers and cimetidine, and the discovery of statins by Akira Endo.

Another champion of the approach of developing chemical analogues of known active substances was Sir David Jack at Allen and Hanbury's, later Glaxo, who pioneered the first inhaled selective beta2-adrenergic agonist for asthma, the first inhaled steroid for asthma, ranitidine as a successor to cimetidine, and supported the development of the triptans. Gertrude Elion, working mostly with a group of fewer than 50 people on purine analogues, contributed to the discovery of the first anti-viral; the first immunosuppressant (azathioprine) that allowed human organ transplantation; the first drug to induce remission of childhood leukaemia; pivotal anti-cancer treatments; an anti-malarial; an anti-bacterial; and a treatment for gout.

Cloning of human proteins made possible the screening of large libraries of compounds against specific targets thought to be linked to specific diseases.

This approach is known as reverse pharmacology and is the most frequently used approach today. Thus a paradigm shift has occurred in the drug design methodology.

The drug target is usually the naturally existing cellular or molecular structure involved in the pathology of interest that the drug-in-development is meant to act on. There are two types of drug targets, established and new. "Established targets" are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and how it is involved in human pathology. target is fully understood. Rather, "established" relates directly to the amount of background information available on a target, in particular functional information. The process of gathering such functional information is called target validation in pharmaceutical industry parlance.

Established targets also include those that the pharmaceutical industry has had experience mounting drug discovery campaigns against in the past; such a history provides information on the chemical feasibility of developing a small molecular therapeutic against the target and can provide licensing opportunities and freedom-to-operate indicators with respect to small-molecule therapeutic candidates.

"New targets" are all those targets that are not "established targets" but which have been or are the subject of drug discovery campaigns. These typically include newly discovered proteins, or proteins whose function has now become clear as a result of basic scientific research.

The majority of targets currently selected for drug discovery efforts are proteins. Two classes predominate: G-protein-coupled receptors (or GPCRs) and protein kinases.

In this decade to date an estimated 435 human genome products were identified as therapeutic drug targets of FDA-approved drugs.

1) High Throughput Screening

The process of finding a new drug against a chosen target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target. For example, if the target is a novel GPCR, compounds will be screened for their ability to inhibit or stimulate that receptor (see antagonist and agonist): if the target is a protein kinase, the chemicals will be tested for their ability to inhibit that kinase.

Another important function of HTS is selectivity ie to show how selective the compounds are for the chosen target. To this end, other screening runs will be made to see whether the "hits" against the chosen target will interfere with other related targets - this is the process

of cross-screening. Cross-screening is important, because the more unrelated targets a compound hits, the more likely that off-target toxicity will occur with that compound once it reaches the clinic.

It is more often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can then be developed. At this point, medicinal chemists will attempt to use structure-activity relationships (SAR) to improve certain features of the lead compound:

- increase activity against the chosen target
- reduce activity against unrelated targets
- improve the drug likeness or ADME properties of the molecule.

This process will require several iterative screening runs, during which, it is hoped, the properties of the new molecular entities will improve, and allow the favored compounds to go forward to in vitro and in vivo testing for activity in the disease model of choice.

While HTS is a commonly used method for novel drug discovery, it is not the only method. It is often possible to start from a molecule which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market which could be improved upon (so-called "me too" drugs). Other methods, such as virtual high throughput screening, where screening is done using computer-generated models and attempting to "dock" virtual libraries to a target, are also often used.

2) Drug Design

Another important method for drug discovery is drug design, whereby the biological and physical properties of the target are studied, and a prediction is made of the sorts of chemicals that might (e.g.) fit into an active site. One example is fragment-based lead discovery. Novel pharmacophores can emerge very rapidly from these exercises. In general, computer-aided drug design is often but not always used to try to improve the potency and properties of new drug leads.

Once a lead compound series has been established with sufficient target potency and selectivity and favorable drug-like properties, one or two compounds will then be proposed for drug development. The best of these is generally called the lead compound, while the other will be designated as the "backup".

3) Combinatorial Chemistry

Combinatorial chemistry was a key technology enabling the efficient generation of large screening libraries for the needs of high-throughput screening.

However, now, after two decades of combinatorial chemistry, it has been pointed out that despite the increased efficiency in chemical synthesis, no increase in lead or drug candidates has been reached. This has led to analysis of chemical characteristics of combinatorial chemistry products, compared to existing drugs or natural products.

The chemo-informatics concept chemical diversity, depicted as distribution of compounds in the chemical space based on their physicochemical characteristics, is often used to describe the difference between the combinatorial chemistry libraries and natural products. The synthetic, combinatorial library compounds seem to cover only a limited and quite uniform chemical space, whereas existing drugs and particularly natural products, exhibit much greater chemical diversity, distributing more evenly to the chemical space.

The most prominent differences between natural products and compounds in combinatorial chemistry libraries are the number of chiral centers (much higher in natural compounds), structure rigidity (higher in natural compounds) and number of aromatic moieties (higher in combinatorial chemistry libraries). Other chemical differences between these two groups include the nature of heteroatoms (O and N enriched in natural products, and S and halogen atoms more often present in synthetic compounds), as well as level of non-aromatic unsaturation (higher in natural products). As both structure rigidity and chirality are both well-established factors in medicinal chemistry known to enhance compounds specificity and efficacy as a drug, it has been suggested that natural products compare favorable to today's combinatorial chemistry libraries as potential lead molecules.

4) Structural Elucidation

The elucidation of the chemical structure is critical to avoid the re-discovery of a chemical agent that is already known for its structure and chemical activity. Mass spectrometry is a method in which individual compounds are identified based on their mass/charge ratio, after ionization.

Chemical compounds exist in nature as mixtures, so the combination of liquid chromatography and mass spectrometry (LC-MS) is often used to separate the individual chemicals. Databases of mass spectras for known compounds are available, and can be used to assign a structure to an unknown mass spectrum. Nuclear magnetic resonance spectroscopy is the primary technique for determining chemical structures of natural products. NMR yields information about individual hydrogen and carbon atoms in the structure, allowing detailed reconstruction of the molecule's architecture.

Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States.

With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

Preclinical Research

Each class of product may undergo different types of preclinical research. For instance, drugs may undergo;

- pharmacodynamics (what the drug does to the body) (PD),
- Pharmacokinetics (what the body does to the drug) (PK),
- Absorption, distribution, metabolism, and excretion, (ADME),
- Toxicology testing.

This data allows researchers to estimate a safe starting dose of the drug for clinical trials in humans.

Most preclinical studies must adhere to GLPs in ICH Guidelines to be acceptable for submission to regulatory agencies such as the Food & Drug Administration in the United States.

Typically, both in vitro and in vivo tests will be performed. Studies of a drug's toxicity include which organs are targeted by that drug, as well as if there are any long-term carcinogenic effects or toxic effects on mammalian reproduction.

Animal Testing

The information collected from these studies is vital so that safe human testing can begin. Typically, in drug development studies animal testing involves two species. The most commonly used models are murine and canine, although primate and porcine are also used.

Choice of Species

The choice of species is based on which will give the best correlation to human trials. Differences in the gut, enzyme activity, circulatory system, or other considerations make certain models more appropriate based on the dosage form, site of activity, or noxious metabolites. Depending on a drug's functional groups, it may be metabolized in similar or different ways between species, which will affect both efficacy and toxicology.

Importantly, the regulatory guidelines of FDA, EMA, and other similar international and regional authorities usually require safety testing in at least two mammalian species, including one non-rodent species, prior to human trials authorization.

NOAEL

Based on preclinical trials, No Observable Adverse Effect Levels (NOAEL) on drugs are established, which are used to determine initial phase 1 clinical trial dosage levels on a mass API per mass patient basis. Generally a 1/100 uncertainty factor or "safety margin" is included to account for interspecies (1/10) and inter-individual (1/10) differences.

Drug Delivery

This refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body to safely achieve its desired therapeutic effect safely as needed . Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. The concept of drug delivery is in synchronization with dosage form and route of administration

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release is from: diffusion, degradation, swelling, and affinity-based mechanisms.

Most common routes of administration include the preferred non-invasive peroral (through the mouth), topical (skin), transmucosal, (nasal, buccal / sublingual, vaginal , ocular and rectal)and inhalation routes. Many medications such as peptide and protein, antibody, vaccine and gene based drugs, in general may not be delivered using these routes because they might be susceptible to enzymatic degradation or can not be absorbed into the systemic circulation efficiently due to molecular size
and charge issues to be therapeutically effective. Many protein and peptide drugs have to be delivered by
injection or a nano needle array precisely for this reason

Current efforts in the area of drug delivery include the development of targeted

delivery in which the drug is only active in the target area of the body (for example, in cancerous tissues), sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation, and methods to increase survival of peroral agents which must pass through the stomach's acidic environment. In order to achieve efficient targeted delivery, the designed system must avoid the host's defense mechanisms and circulate to its intended site of action. Types of sustained release formulations include liposomes, drug loaded biodegradable microspheres and drug polymer conjugates. Survival of agents as they pass through the stomach typically is an issue for agents which cannot be encased in a solid tablet. ■

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A Practical Approach to Successfully Navigate the Safety and Regulatory Continuum for Mature Products

Mature pharmaceutical products are those that are long past their marketing exclusivity period but are still sold in substantial volumes because of their well-established effectiveness and safety in certain medical conditions. Mature products have a significant role in the healthcare for many patients both in the developed and developing world. The majority of the large pharma companies have a sizeable portfolio of mature products, which are in the final stages of their lifecycle; although they may be marketed or sold for many years to come. These products can still play a crucial role in the company's strategy, more so in emerging markets than in innovation-focused, developed markets.

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While development of promising new products is an obvious area of focus for biopharmaceutical companies, maintenance of already established marketed products is a critical activity that cannot be ignored. Ensuring regulatory compliance and reducing product risk whilst still working within the cost constraints presents unique challenges to companies in managing established products and requires innovative and cost-effective approaches that can help ensure patient safety and compliance while continuing to meet ever-increasing and complex regulatory demands. Rather than handling

all products in the same way, marketing authorization holders (MAHs) have an opportunity to look at managing the more stable mature products differently and more efficiently, allowing them to consider the benefits of an integrated safety, regulatory and benefit-risk model.

The Importance of Mature Products

Mature products, those that are still sold substantially but are long past their marketing exclusivity, have a significant role in the healthcare industry in both the developed and developing world. Mature products make up a large portion of many pharmaceutical organizations portfolios; these are likely to be sold well into the future despite being in the final stages of their lifecycle.

Established products have proven effectiveness and safety profiles making them even more important in emerging markets compared to newer products. However, since the cost of maintaining mature products is usually significantly lower than launching newer ones, pharma companies can focus on tailoring them for individual market needs, innovating the formula, dosage forms or packaging for optimal results, or expanding geographically.

Yet, due to increasingly stringent drug regulations in emerging markets, the documentation needed to remain compliant for mature product maintenance has risen dramatically in the last decade. Pharmacovigilance (PV) activities must be continued, while maintaining regulatory dossiers and managing labels is all required to uphold licenses. Non-compliance can result in critical regulatory penalties, with significant financial implications. The most significant financial impact for any manufacturer is when blockbuster drugs pass their patent exclusivity, requiring most companies to look carefully at minimizing costs to sustain their profitability.

A Pragmatic Approach to Managing Mature Products

Organizations have the opportunity to manage their mature products differently from others in their portfolio by focusing on efficiency to free up resources. Mature products, by nature, are typically more stable with a predictable revenue stream, thus, the reduced amount spent on managing the product can increase profitability. A more pragmatic approach can be taken to streamline processes making it less resource intensive. In some aspects, such as the frequency of Periodic Safety Update Reports (PSUR) production, the regulations also support a more streamlined approach and although aspects such as signal detection activities need to be maintained, there are opportunities to take a more pragmatic approach by reducing the frequency of many routine activities.

There are three main areas to traverse

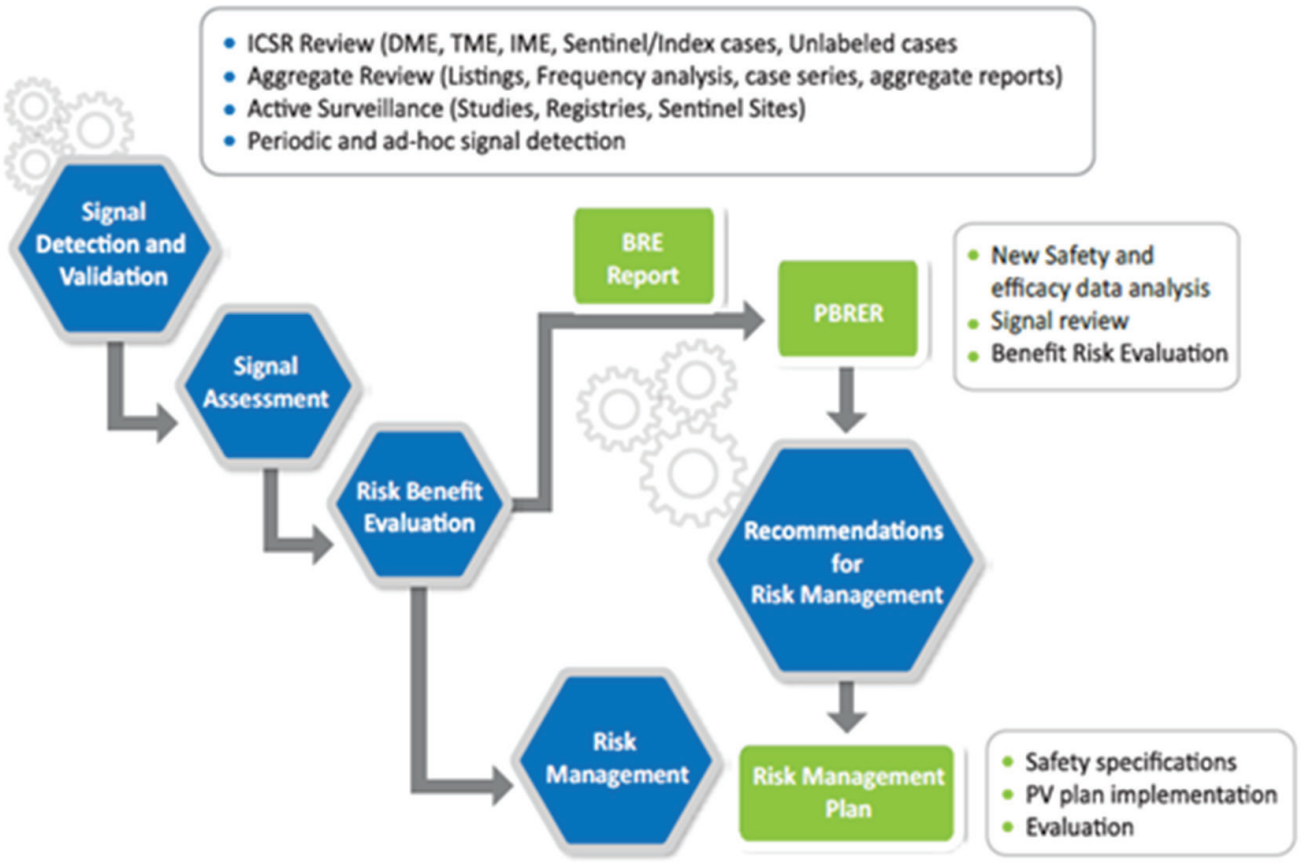

Figure 1. The Safety Continuum

when managing mature products, namely, safety and risk management, labeling and regulatory. Taking an integrated approach for these three areas is vital to efficient management. Yet, often these functions can act independently within organizations which can result in overlapping and duplicative work or in worse case scenarios some elements being missed completely, due to fragmented processes and oversight. Furthermore, with the evolution of Good Pharmacovigilance Practices (GVP) in Europe and many other regions following suit, more rigorous standards need to be upheld. This requires a substantially skilled manpower pool who are knowledgeable of each region's regulations, which often means stretching the same resources between mature product portfolios and new products.

The Safety Continuum

Whilst mature products are often much more stable and well defined than new ones, safety activities are still required, although usually under less scrutiny. These are done to ensure the product remains safe and effective for patients.

PV is a central function to supporting the safety of a product and ensuring the benefits out-weigh the risks of using the drug. It is acknowledged that some

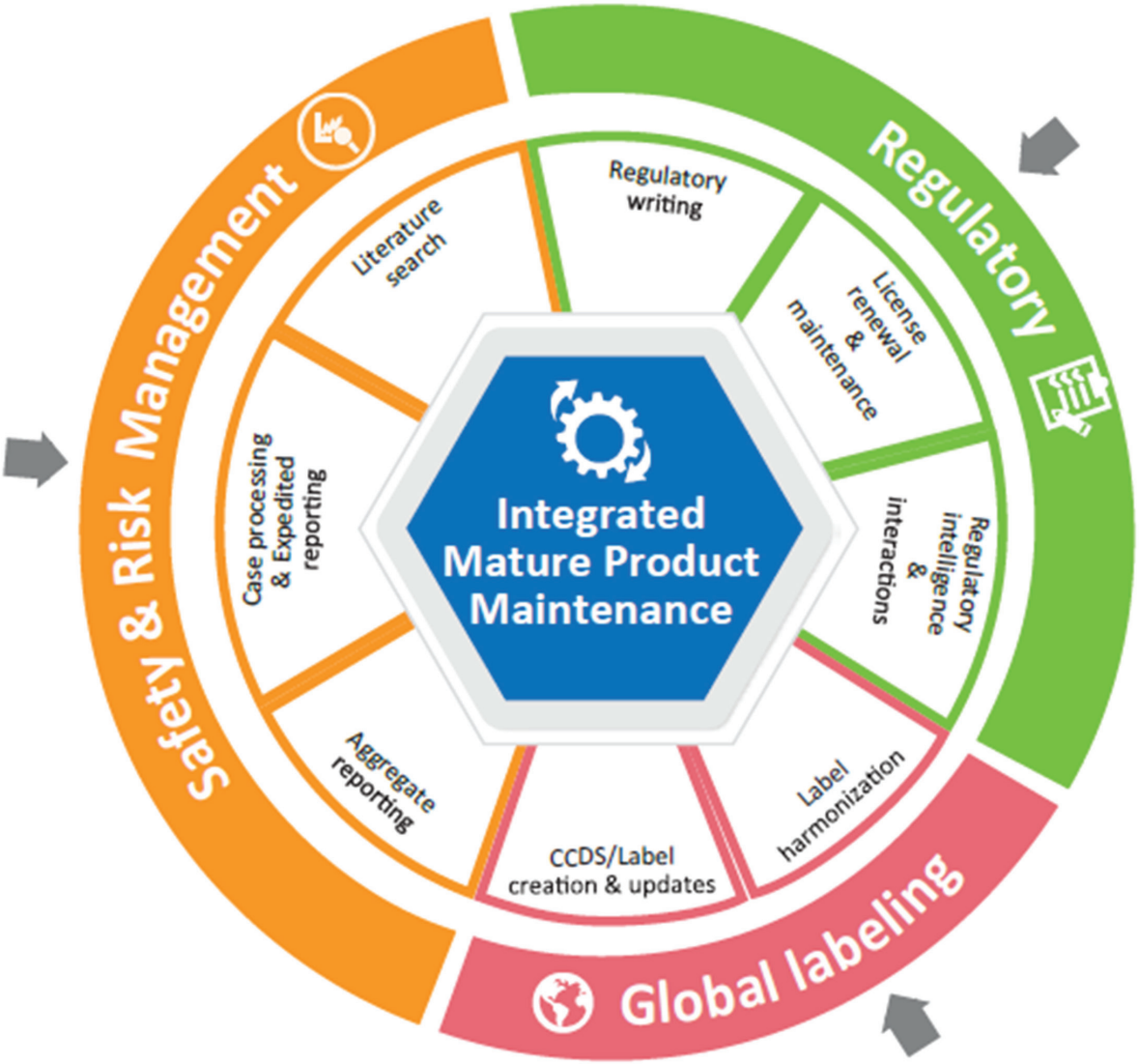

Figure 2. The integrated safety, regulatory and labeling contin uum.

products, across multiple classes that have been on the market for a long time, still require extensive support from a PV perspective. These include clozapine, thalidomide, isotretinoin, and leaner approaches to managing these products are not applicable. However, even the majority of the stable mature products can still go through many changes due to increasing exposure, differences in physician practices, new or untested drug interactions and pharmacogenetic variations as they are introduced to new patient populations. A variety of activities are therefore still required, along with risk management plans that may go beyond routine PV. These activities from single adverse event processing to signal identification and risk management are part of the safety continuum, which is illustrated in the figure below.

Signal Management

Signal management can be defined as the activities performed to identify new risks or changes in character or severity of a known risk. It remains an essential component in assuring the safe use of a drug throughout its lifecycle. Avoiding and minimizing risks can be done through alerting patients and healthcare providers to the identification of a new risk or change in a known risk. This requires discussion with regulators, changes to labels and occasionally direct communications. This can often include a spectrum of teams in an organization from PV, to clinical development, to regulatory affairs and medical information, especially if the communications become urgent. Even for mature products, signal management remains an essential part of the safety continuum and product lifecycle.

Signal Detection to Implementation of the Label

A label change is an example of a truly collaborative and cross-functional process which has a high degree of operational complexity and is often an outcome from signal management, subsequent to the validation of a safety signal. The label change communicates formally important and, at times, essential information to regulators, patients and HCPs, regarding the safe use of a product. Label changes are also a complex procedure involving cross-functional processes, requiring written safety practices and high level expertise. For mature products there is normally a large amount of safety data that needs to be managed efficiently. In order to complete a safety driven label change, an organization must have written practices in place to organize the different functional groups with the required expertise.

The Regulatory Continuum

Regulatory submissions are often time intensive and require multiple teams and stakeholders to fulfil, but for mature products the strategy for filing is often managed regionally or locally, requiring an understanding of the local environment. However, in order to manage the regulatory activities, the local regulatory resources still require documentation and support from central regulatory experts who are often unable to dedicate time to supporting mature products as the focus is on the new product portfolio. With this and the increasing pressure to be cost and time efficient, new operating models and adapted standard operating practices (SOPs) need to be considered. Typically these allow local or regional regulatory professionals to manage activities themselves by re-purposing documents that have been created centrally.

Dossier Repurposing

When maintaining mature products, some key strategies allow for expedited safety

labeling and regulatory procedures. The first of these is dossier repurposing, which consists of reusing and reformatting the existing dossier submitted in highly-regulated countries to then meet region-specific requirements. Obtaining regulatory approval of new uses for existing drugs is an important part of innovating mature products. Sections of existing dossiers can be repurposed, along with the creation of any additional content needed to meet the specific requirements in order to file applications for mature products with well-established safety and efficacy profiles. This includes changes from prescription to over the counter drugs.

License Maintenance and Renewals

MAHs of pharmaceutical products are responsible for validating the effects of any manufacturing or product quality (generally CMC) related changes to the identity, strength, quality, purity, and potency of the drug as these factors can affect the safety or efficacy of the drug. CMC changes are a significant source of license maintenance activity and are inevitable due to many reasons including continuous process improvement in manufacturing and quality of the product, changing business needs, or implementation of regulatory authority stipulations. Deviations or violations from filing such documentation can result in regulatory actions such as warning letters and import alerts. License renewals are also required periodically to continue marketing a drug. In order to keep a continuous supply of product these activities must be managed ahead of drug license expiration dates and site registrations.

An Integrated Safety, Regulatory and Labeling Continuum for Mature Product Maintenance

Organizations should consider the merits of an integrated safety, regulatory and labeling service model for mature product maintenance with a flexible structure that promotes continuous improvement, whilst lowering the costs and maximizing product value. The figure below illustrates an example matrix of the different activities that need to be managed within an integrated framework.

Mature Product Lifecycle Management

A meaningful way to address the challenges in today's complex regulatory environment is to focus on an integrated team approach to product lifecycle management. Most pharmaceutical companies suffer from building virtual walls between functional silos, along with data and processes being separated, thus, making it difficult for cross-functional information to flow quickly and securely.

Outsourcing regulatory and safety activities for mature products is a viable

option and can streamline the process while minimizing costs. A partner can employ a centralized approach and is able to communicate with multiple teams globally and efficiently manage data to fully coordinate operations. Ideally a partner should manage the end-to-end safety and regulatory deliverables to support mature products, however, a flexible model can be employed if required. A dedicated and integrated team is able to proactively manage risks, including generating risk management plans and risk mitigation strategies. They are also able to track regulatory commitments, such as US FDA annual reports and PSURs, and ensure all deliverables are submitted on time.

Furthermore, for generic products the regulatory intelligence capabilities of an outsourced vendor can be leveraged to track and implement updates to the reference label.

As with any outsourced model, internal resources would still be required to manage relationships with the vendor and provide access to necessary data, over time this will diminish and the provider will be able to manage the safety and regulatory activities to support the entire mature product portfolio in a much more independent manner.

An integrated regulatory, safety, risk management, and product labeling model was implemented at a large generics company to manage their product portfolio. With the client's products being manufactured at various locations worldwide, and teams located in different geographies, the main challenge was to manage the data generated across the different locations and coordinate regulatory submissions. A dedicated cross-functional team with in-depth knowledge of the product portfolio, various regulatory information management systems, and publishing tools was assigned to the project. Data was collated into a single repository that allowed for early identification of potential risks, the ability to quickly address emerging problems, improved efficiency, and reduced the need for regulatory oversight from the client. The reliance on input from the client has reduced over time and they are being successfully supported through this integrated model.

Conclusion

Whether product lifecycle activities are managed internally or by a service provider, creating a structure in which all elements (people, process and technology) are integrated is critical to being able to successfully manage mature products efficiently. This allows all stakeholders to be aligned and companies can streamline tasks and free up resources to focus on other activities. ■

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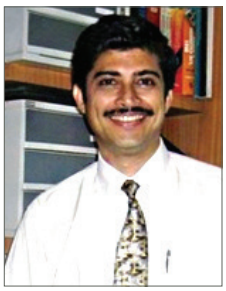
Pharmacovigilance in India: An Overview

The origin of pharmacovigilance in India goes back to 1986, when a formal ADR monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India. This article provides a brief overview about the current situation and the future prospects of pharmacovigilance in India and analyses importance of implementing proper pharmacovigilance in the Indian context.



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Pharmacovigilance in India has come a long way. A formal system for adverse drug reaction monitoring started in 1986. There were 6 regional centers then, viz., Mumbai, New Delhi, Kolkata, Lucknow, Puducherry and Chandigarh. Three institutes are linked to the Uppsala Monitoring Center of WHO, viz., KEM, AIIMS and AMU. In 2004 CDSCO or the Central Drug Standards Control Organization established the National Pharmacovigilance Program with sponsorship from WHO and the World Bank. There were 2 zonal, 5 regional centers and 24 peripheral centers. Due to lack of funding it folded up in 2008.

In July 2010, the PvPI or Pharmacovigilance

Program of India began in AIIMS which was the National Coordination Center for reporting adverse drug reactions. Later it was shifted to the building of the Indian Pharmacopoeia Commission (IPC), Ghaziabad. Doctors in India get SMSes from PvPI from time to time alerting them to some clinically relevant adverse events reported with some drugs.

CDSCO expects companies to report to PvPI adverse events that occur, both during clinical trials, and during clinical practice (spontaneous adverse events). This practice helps in further characterizing a drug's safety profile. PV is a discipline which starts from the time a drug is discovered or invented, continues through its clinical development till it gets marketing authorization approval, and lasts for as long as the drug is in the market. In other words, PV is with you when you cross the road and even when you reach the other side (there could be potholes in the footpath).

So what exactly is meant by Pharmacovigilance? It is the science of being vigilant about a drug's safety profile. It is not enough to preach pharmacovigilance. One should practise what one preaches too. Over the years drugs have been made safer for patients. It is time to make patients safer for drugs. Pharmaceutical companies need to inform doctors about the benefits and risks of

their products so that the doctor knows how to select the right patient for the right drug. In effect, they need to tell doctors where not to prescribe the drug too.

The locally approved prescribing information of a drug is available as a pack insert inside the pack of the product as a leaflet. However, this pack insert is with patients who buy the drug. The information in the pack insert is actually meant for the prescribing doctor looking at the way the language is so medically intensive. It is therefore imperative that the pharmaceutical company medical representative leaves behind the label of the drug with the prescribing doctor, as an LBL (Leave Behind Label). Ideally the medical representative should 'detail' salient features of the label (eg, dosage form/strengths, indications, contraindications, warnings and precautions, undesirable events and dosing recommendation) to the doctor and then leave it behind.

The doctor can sign and rate the medical representative on his/her detailing of the label on a tear-off that the medical representative can then send back to his/her company. This can also protect the company just in case the doctor uses the product in an off-label indication which has undesirable consequences for the patient. It is important that a company should never promote its products in off-label indications. A doctor may prescribe a product in an off-label indication, only when there is no other alternative, there is a credible medical body of evidence that justifies its use, and
the doctor conducts informed consent as a process.

There is nothing adverse about reporting an adverse event. Not reporting an event can have adverse consequences, especially for the pharmaceutical company as and when they are intimated about the event. Doctors can and should report in confidence and with confidence. The PvPI website has an adverse event reporting form, in different languages, separate for physicians and patients, that can be downloaded by anyone and used to report the event to PvPI.

The Oxford Textbook of Clinical Pharmacology, in its chapter on adverse events, starts with the maxim that, "unless a drug is capable of causing some harm, it is unlikely that it will have much of an effect." In other words, there is no drug which does not have a single adverse event. One can have adverse events even to a placebo, when it is sometimes called a nocebo. Let us all understand that when a doctor decides to prescribe a drug to a patient s/he has evaluated the benefit to risk ratio of the drug and found it to be positive.

What is an adverse event and how is it

different from an adverse drug reaction? In the case of the former there is a temporal association of the event with the drug but it need not have a causal relationship. In the case of the latter, the causal relationship has been determined by a process which includes drug de-challenge when the event abates and drug re-challenge when the event recurs. For obvious reasons drug re-challenge is not always attempted.

A serious adverse event is one that results in death, or is life-threatening, or results in hospitalisation or prolongation of existing hospitalisation, or which leads to significant or persistent incapacity or disability or which results in a congenital anomaly. In addition, any important medical event may also be considered a serious adverse event if one has to take urgent medical or surgical measures to prevent one of the above five outcomes. In an investigator's opinion if the event is adjudicated to be a serious adverse event then it is also considered a serious adverse event.

In a clinical trial, the investigator is asked to decide whether the event is related or not related to the trial or drug used in the trial. There is a third box which the investigator can tick if s/he is not sure whether the event is related or not related to the drug. This is taken to mean that the event might be related to the drug and is clubbed with those events marked as related to the drug; only to be on the safer side.

Also, if any adverse event happens in the 28-30 day period after the last dose of the study drug, it is still taken to mean that the event could be related to the drug as it takes about five half-lives of a drug to fully exit a patient's body, and sometimes the effect of a drug may outlast its physical presence in the body (hit and run drugs, eg, aspirin irreversibly acetylates platelet cyclo-oxygenase, and even if aspirin is no longer in the patient's body, the platelet cyclo-oxygenase enzyme is irreversibly inhibited so the effect of aspirin lasts much longer, viz., about 2 weeks, till new platelets are synthesized; platelet life span is 8-11 days).

In short, during clinical trials, conscientious companies take a lot of pains to ensure safety of the study participants. When translated to the less standardised world of clinical practice the safety profile may change and hence it is important that one continues this safety surveillance for as long as a drug is on the market. No matter how well a drug is studied in the controlled environment of a pre-marketing randomized clinical trial, post-marketing surveillance (observational, non-interventional, naturalistic setting) will always be needed to unearth rare adverse events.

When a doctor asks a pharmaceutical

company how many adverse events have been reported on the company's product, the answer is always accompanied by a disclaimer that one cannot use this information to estimate the incidence of the adverse event because at any point in time one does not know whether all adverse events of that nature have been reported, at any point in time one does not know how many patients have received the drug, and one is not always able to assess the causal relationship of the drug with the event. Though, in the case of spontaneous adverse events on marketed drugs in the real world, causality is taken to be implied.

It is not always that an adverse event is harmful. Sometimes it could just be a side effect, eg, dryness of mouth and nose with anti-histaminic drugs that also have anti-cholinergic properties. At times the side effect can be developed into an indication as happened with Viagra (sildenafil citrate) which was developed as an anti-anginal and then when patients in the trial experienced an erection as a side effect, it was developed as a treatment for erectile dysfunction. Sometimes as with some targeted therapy in cancer, development of a side effect may indicate that the drug will be more effective in that patient, eg, skin rash and cetuximab or hypertension and sunitinib.

All this is fine but do patients, doctors and pharmaceutical companies in India report all adverse events? There is certainly scope for improvement. Doctors sometimes believe that if they report an adverse event they might get into trouble. Especially, if they use the product, not per its prescribing information. Or they feel that the event is only to be expected, eg, diarrhea with anti-microbials, as it is listed in the product's locally approved prescribing information. But all events need to be reported so that one can fully characterize the safety profile of a product. It might lead to changes in the prescribing information and can even lead to withdrawal of a product. It was an astute doctor who first observed the gray baby syndrome with chloramphenicol. And then he traveled the length and breadth of his country and tracked many more such events to make all aware of this adverse event.

Pharmaceutical company medical representatives are sometimes scared to report events thinking it might lead to loss of sales. However, they should realize that not reporting events can have this end result. The doctor may stop writing the product, stop writing other products of the company or even tell his/her other colleagues about it, telling them not to write the company's products.

Reporting the event shows the doctor that the company is serious about its commitment to doctors and patients. The PV professional and medical affairs

colleagues, based in head office and in the field, get in touch with the doctor, provide him with information on similar adverse events, and with this wealth of safety data, from both RCTs and in the real world, the doctor is reassured about the safety profile, and continues prescribing the product.

The pharmaceutical company can come out with patient profiles where the drug should not be used. Or an eligibility score which can then be validated in the real world. Even within a drug's label, there could be patients who respond to a drug optimally, in terms of safety, efficacy or both. And there could be some patients within the label who do not respond optimally. The pharmaceutical company can delve into its clinical trials database and try and correlate response of patients to clinical characteristics. Ideally the company should communicate this information to doctors so that they in turn can use this information to ensure the best patient is selected who can get optimal benefit from the drug. This enhances credibility.

The PV team can use this market intelligence to feedback to the brand teams at regular core committee on safety monitoring meetings, where risk management is also discussed. The PV team can facilitate drug utilization evaluation studies in the real world. Sometimes a risk management plan may need to be in place as demanded by the regulator. At times the regulator may ask for a risk minimization action plan (MAP), for products that are extremely critical but have serious adverse events associated with their use. Basically, a risk MAP ensures that the benefit to risk ratio is always positive.

The PV team must do field work which will help gain customer insight (eg, a drug safety poster can be a useful item to grace the wall of a doctor's clinic) and bring the doctor closer to the company as PV is also a core competence. It is in effect the seat belt of a company, not coming in the way of fast paced growth, but protecting the company from accidents.

PV is not just about reporting an adverse event on time and with due quality and completeness (initial and follow up). It is more than this. The PV professional must interact with her/his medical affairs and medical information colleagues and provide the reporting doctor with the requisite information that helps the doctor choose the right patient for the right drug. ■

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