PHARMA FOCUS AMERICA

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Challenges in GMP, GCP & REGULATORY AFFAIRS

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Welcome & Introduction

We are thrilled to announce the release of the second edition of **Pharma Focus America** magazine for 2023! This achievement fills us with both pride and a sense of responsibility. I take this opportunity to acknowledge the exceptional dedication, expertise, and collaborative efforts of our proficient team, advisory board panel, and esteemed authors. Together, they have created high-quality industry literature that caters effectively to our readers and seekers.

In this edition, we present a diverse knowledge base from industry experts, spanning topics such as Regulatory Affairs, **Outsourcing in Clinical Trials, Targeted Therapeutics in Precision Oncology, Digital Biomarkers,** and more. Additionally, our second edition marks the launch of two new sections – **"Industry Sense"** and **"Through the Hourglass."** These sections aim to bridge the gap between industry experts and our readers by offering their perspectives and insights.

Below, we present a thoughtfully curated selection of noteworthy topics, designed to provide you with a quick reference and an engaging introduction.

The pharmaceutical world's march forward is accompanied by the imperative to uphold the highest standards in GMP, GCP, and Regulatory Affairs. Join us as **Josipa Ljubicic, QA Director and Principal Auditor at Proqlea Ltd,** delves into the intricacies of GMP& GCP vital areas, highlighting the challenges and solutions that drive excellence.

Evolution is a constant companion on the journey to enhanced pharmaceuticals. **Sumana Sundaramurthy, Technical Account Manager at Sino Biological,** takes us through the Evolution of Antibody Humanization and Affinity Maturation. Witness the transformative progress that has reshaped antibody research, ushering in groundbreaking treatments.

Packaging transcends mere formality – it embodies technology itself. **James Bury, Head of Technology at Tjoapack,** unravels the dynamic world of Pharma Packaging Innovations. Explore how cutting-edge advancements in packaging enhance drug delivery, patient safety, and environmental sustainability.

Collaboration between pharmaceutical companies and outsourced partners is pivotal for success. **Joab Williamson from Faron Pharmaceuticals and Tegen Winstanley from Catalent** provide insights into optimizing Outsourcing Relationships in Clinical Trials. Learn how seamless collaboration achieves mutual success.

In the realm of precision medicine, the future unfolds intricately. **Ravi Dashnamoorthy, Principal Scientist at Genosco Inc,** uncovers the potential of Metabolism-targeted Therapeutics in Precision Oncology. Witness the convergence of genomics, metabolomics, and oncology, shaping personalized treatments.

Safety remains paramount in drug development. **Maciej Czerwinski, Director of XenoTech Scientific Consulting at BioIVT,** delves into Safety Considerations for Antibody Drug Conjugates. Discover the delicate equilibrium between innovation and safety in this cutting-edge field.

Success in pharmaceutical research often emerges from unpredictability. **J. Mark Treherne, Director and Chairman of Talisman Therapeutics Ltd,** invites reflection on research's dynamic journey. Embrace the uncertainty that leads to breakthroughs.

N D Vijaya Lakshmi
Editor

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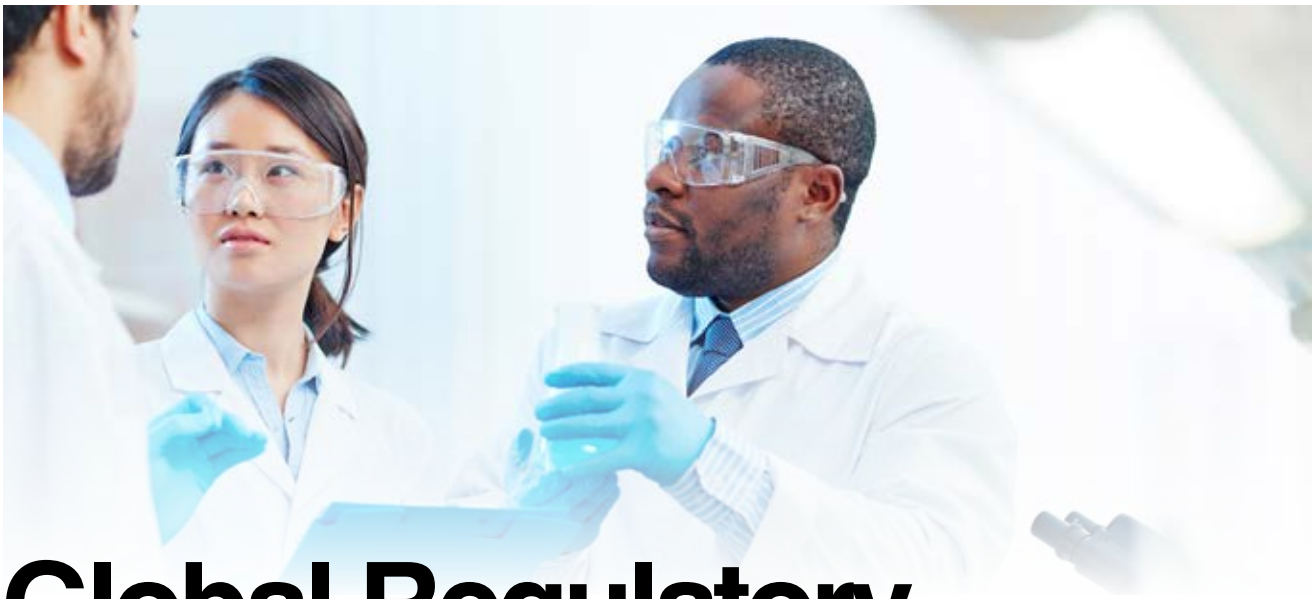

Global Regulatory Landscape for Cell and Gene Therapies

In the last decade, the number of approved gene therapies for the treatment of genetic disorders has increased rapidly. Currently there is a trend to adopt technologies that maintain safety and efficacy while reducing production costs during manufacture.

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Vice President, Nucleic Acid & Viral Vector Technology, ReciBioPharm

Traversing the dynamic gene therapy regulatory landscape

Navigating the complex and dynamic gene therapy regulatory landscape has been a persistent challenge for developers and manufacturers. Ensuring these life-changing therapies successfully pass critical regulatory milestones on the journey to market requires gene therapy producers and their partners to demonstrate both flexibility and agility.

With gene therapy being a fast-paced yet relatively new therapeutic area, regulatory bodies have struggled

to keep up with continuous technological advancements and our expanding knowledge of genetics, virology and molecular biology. With no blueprint to follow, a practical approach has been necessary to ensure regulations and guidance can safeguard the quality, efficacy and safety of new therapies entering the market.

In this article, Kai Lipinski, Ph.D., Chief Scientific Officer; Xiaojun Liu, Director of AAV Process Development; and Jing Zhu, VP of Nucleic Acid & Virus Technology at ReciBioPharm, explore the current gene therapy regulatory landscape and provide their expert insights into the tactics developers and manufacturers must employ to overcome regulatory challenges.

The evolution of gene therapies

For many years, researchers and developers have endeavored to realize the potential of therapeutics that introduce specific cells or genetic material to patients for disease treatment and prevention. Owing to breakthroughs and advancements in technology and genetic engineering in the last two decades, we are now at the dawn of a new cell and gene therapy (CGT) era.

There are currently 15 approved gene therapies and 12 cell-based immunotherapy products. Although the gene therapy space has come a long way since the first approved therapy in 1990, which utilized a retroviral vector to deliver functional adenosine deaminase genes, most gene therapies approved today still harness the delivery capabilities of viral vectors.

Viral vectors have proved to be efficient tools for gene delivery to specific target cells or tissues. Commonly used gene therapy viral vectors, including adenoviruses (AV), adeno-associated viruses (AAV), retroviruses (RV), lentiviruses (LV) and herpes simplex viruses (HSV), have unique characteristics that provide distinct advantages for gene delivery. For example, AAVs are ideal for *in vivo* gene therapies due to their mild immunogenicity. Integrating viruses such as LVs are useful for ex vivo treatments like CAR-T therapies, where genes must be stably integrated into the host cell genome to enable long-term expression.

As our understanding of genetic engineering has grown, the safety and efficacy of gene therapies have advanced, in part owing to improvements in viral vector construction and the creative use of pseudotyping to increase cell or tissue specificity.

Advancements have enhanced not only the safety and efficacy of viral vector-based gene therapies, but also their manufacturability. The application of single-use technologies (SUTs), the development of stable packaging and/or production cell lines and the progression of analytical equipment have all played an important role in furthering manufacturability. These improvements have helped to broaden access to gene therapies.

A complex and changing market

Although the first FDA gene therapy approval was only in 2017, CGTs have garnered a significant amount of investment in this short time. In part, this has been driven by the increasing recognition of the potential of gene therapies. The number of these revolutionary drugs entering the development pipeline targeting various indications, from rare diseases to cancer and metabolic disorders, is continuously growing.

Propelled by a desire to broaden patient access by reducing manufacturing costs and technical limitations of viral vectors, gene therapy developers are also increasingly looking towards non-viral options, including nucleic acid delivery platforms. As a result, there is a growing desire to use innovative technologies such as engineered lipid or protein nanoparticles, DNA-based nanocarriers and novel physicochemical methods in gene therapies.

Reflecting the expanding potential of gene therapies, the global gene therapy market is predicted to continue to grow rapidly. Valued at USD $5.6 billion in 2022, the market is expected to reach USD $49.3 billion by 2032, registering a CAGR of 25%.

Increasing gene therapy approvals

Despite this promising outlook and continued improvements in safety, efficacy and manufacturability, the number of gene therapy product approvals has been slow to rise, with only four such therapies gaining FDA approval in the five years prior to 2022. Factors that have contributed to this include:

- Communication issues between sponsors and regulatory agencies
- A shortage of qualified specialist staff owing to the gene therapy space being relatively new
- Economic headwinds and investors being selective in their capital allocations
- High manufacturing costs and small patient populations
- Manufacturing bottlenecks

In spite of these challenges, 2022 marked a turning point for gene therapy FDA approvals, with five achieved by the end of the year,

including therapeutics targeting rare diseases and cancer indications. Looking ahead, close to 20 CGTs are now set for a regulatory decision in 2023. As a result, we could be within reach of the FDA's 2019 prediction of approving 10-20 new CGTs a year by 2025.

However, there are still several difficulties gene therapy developers and manufacturers face when navigating the complex regulatory landscape. These challenges must be carefully addressed to enable potentially life-changing therapies to reach patients.

Obstacles hindering gene therapy approvals

There are currently 2,022 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) in development, 284 of which are at phase 2, phase 3, or pre-registration. The approximate success rate for CGTs from phase 2 through to approval is only 14%. This is less than half of the expected success rate of small molecule drugs from phase 2 (43%), highlighting the difficulties CGTs face on the journey to market.

Meeting the FDA's 10-20 new CGT approval target will require developers and manufacturers to understand, navigate and overcome various challenges. The most pressing of these include:

1) Compliance difficulties, with regulatory agencies "building the plane as it flies"

A recent survey revealed that dealing with confusing regulatory guidelines was considered one of the top obstacles developers face when bringing a CGT to clinic.

As CGT is a relatively new therapeutic space, the understanding surrounding it has quickly expanded. Regulatory bodies have had to react quickly to this new information and provide guidance on best practices to ensure safety and quality. This has been compounded by the fact that CGTs are an order of magnitude more complex than small molecule therapeutics and traditional biologics, such as monoclonal antibodies.

2) Caution in the approval process leading to stringent requirements

As gene therapies have advanced, the regulatory requirements surrounding their production have become increasingly rigorous. The fact

> Meeting gene therapy regulations requires adaptable strategies from developers.

that gene therapies typically involve genetic manipulation and have long-lasting effects has driven regulators to be more cautious in their review of these drugs to safeguard against unpredictable effects on patient health. This wary approach to reviewing gene therapies may slow down the approval process.

Regulatory body caution also stems from the limited available clinical trial data surrounding long-term safety and efficacy. The resulting difficulty in assessing the risks and benefits of a new gene therapy can lead to further delays in the approval process.

> Navigating gene therapy regulations demands awareness and open communication for compliance.

3) Unique analytical conditions adding complexity in meeting regulatory requirements

For both clinical trials and commercial gene therapy use, developers and manufacturers must provide extensive analytical data and evidence to regulatory bodies to demonstrate compliance. Meeting the analytical needs of gene therapies is often more difficult compared with traditional biologics because:

- The analytical tests required for traditional biologics like monoclonal antibodies (mAbs) have been around for years and are well understood and established
- Guidance surrounding gene therapy analytical testing is limited
- Gene therapy analysis often requires the adapted use of equipment techniques originally designed for traditional biologic analysis purposes, including potency assays to full/empty particle ratio analysis and genome DNA heterogeneity analysis
- The need for cell based-assays, particularly for assessing potency and infectious titer show high variability, are challenging to validate and product specificastions must be set carefully to avoid out-of-specificaiton and therefor batch-failure.

4) Manufacturing issues impeding dose needs as projects scale

As gene therapies are typically complex, they require specialized manufacturing processes, including introduction of viral vector and helper genes/plasmids to the production cell line (typically HEK293 cells) through transfection. In addition to creating unique challenges, these processes can be difficult to scale up. This can lead to difficulties in manufacturing enough

doses to meet the demand at various stages as the project progresses, potentially slowing the timeline to critical milestones and regulatory approval.

Addressing internal FDA issues

Despite the difficulties gene therapy developers may face ensuring regulatory compliance, it is important to remember the FDA's goal is to increase the number of gene therapy approvals, but not to the detriment of patient safety. Although maintaining diligence in ensuring therapeutics are safe and of high quality, the FDA is making changes to enable a greater number of approvals in the future, including:

Establishment of specialized "super offices"

A fundamental challenge the FDA has faced in meeting its goal to approve 10-20 CGTs a year by 2025 is understaffing. This lack of personnel has made it difficult to progress therapies swiftly through the review process. In March 2023, the Office of Therapeutic Products (OTP) was established as the first "super office" at the FDA's Center for Biologics Evaluation and Research following reorganization. By centralizing departments involved in the review, inspection and research of CGT drugs, the OTP could streamline workflow processes while creating flexibility and capacity to increase employee numbers.

New initiative launches to strengthen communication

In the past few years, the FDA has launched a number of programs to help grow the gene therapy pipeline and provide opportunities for developers and regulators to communicate more frequently.

Serving as a traffic light system for the progression of small-batch gene therapy programs, the Bespoke Gene Therapy Consortium (BGTC) is an effort to remove barriers and streamline processes for these projects. The BGTC will achieve this by providing details on basic and clinical research, manufacturing, production and regulatory needs to gene therapy producers.

Additionally, the FDA's INitial Targeted Engagement for Regulatory Advice on

CBER/CDER ProducTs (INTERACT) meeting program aims to facilitate IND-enabling efforts where the sponsor is facing a novel, challenging issue that could delay product progress towards clinic entry. The INTERACT meeting program could help to address issues early in development programs and prevent delays in initiating or progressing IND-enabling studies.

The recently launched Gene Therapy Pilot Program will also provide gene therapy developers with real-time FDA input throughout the clinical development process. This could enable shorter development cycles and submission review timelines.

Although these changes provide promise in achieving the FDA's approval goal by 2025, the FDA cannot meet the need for new gene therapies alone. Drug developers and manufacturers must know how to navigate ▶

the regulatory requirements set to demonstrate gene therapy safety, efficacy and quality to ensure successful approval and delivery to patients.

Navigation tactics for gene therapy developers

Gene therapy developers and manufacturers should employ a number of tactics to ensure regulatory compliance while accelerating timelines to approval.

Communication is key

Ensuring compliance with often confusing and complex gene therapy regulatory guidelines can only be achieved if drug developers and manufacturers are aware of and understand them. Prioritizing open communication with regulatory bodies will ensure clarity and prevent possible mistakes caused by misunderstandings.

Proactively communicating with the FDA is particularly important before IND submission. By arranging pre-IND meetings with the FDA, developers can reach an agreement on the proposed animal safety and toxicology testing needed to support the phase 1 clinical trial design. This is particularly helpful to those with little or no prior IND submission experience.

Keep up with analytical advancements

Cutting-edge analytical capabilities are often needed to overcome the difficulties involved in gene therapy analytical characterization. Regulatory bodies can also be expected to continue requiring developers to meet stringent analytical demands surrounding the demonstration of gene therapy safety, potency and efficacy.

To meet these analytical needs, it will become increasingly important for gene therapy developers to employ novel options and sophisticated techniques in their analytical development. These include digital PCR, flow virometry (e.g., Sartorius, ApogeeFlow, NanoFCM), virus mass photometry, interferometric microscopy or multi-angle dynamic light scattering.

Be flexible

In the coming years, we can expect new insights — including those around the cause of possible side effects and lack/loss of stable efficacy — to continue to influence regulatory guidelines. Gene therapy developers and manufacturers must stay abreast of guideline changes and predict the changes to come, as much as possible. To respond quickly to changes in regulatory requirements and rising demand for gene therapies, their producers will need to continue to adopt new technologies. These technologies will include SUTs, continuous processing and perfusion-based cell culture for process intensifications.

Looking ahead

With increasing innovation in virology and genetic engineering, the future of gene therapies looks bright. As these revolutionary

therapeutics venture into new therapy areas and address the needs of wider patient populations, regulatory bodies must continue to respond to advancements. By producing guidance reflecting these changes, the safety, efficacy and quality of gene therapies achieving approval can be assured.

Meeting the FDA's ambitious future approval goals will require changes not only on the part of regulatory bodies — to reduce delays — but also on the part of drug developers and manufacturers — to adapt their processes with these changes in mind. With so many moving parts, strong communication between gene therapy producers and regulatory bodies is expected to be increasingly important. ■

References are available at www.pharmafocusamerica.com

AUTHOR BIO

Kai Lipinski initially joined Vibalogics. He was a Head of Cell Culture and Virus Production and was most recently promoted to Chief Scientific Officer at ReciBioPharm. With a wealth of experience in viral vector manufacturing from a variety of previous roles, Kai is central to the establishment of virus Process Development and Manufacturing capabilities, and technical developments.

Xiaojun leads a committed team in viral vector process development. He has dedicated expertise in molecular biotechnology and viruses, specifically AAV for gene therapy. Before joining ReciBioPharm, Xiaojun was Associate Director at EdiGene Biotech USA Inc.

Jing Zhu is responsible for overseeing process development activities and technology platform establishment at ReciBioPharm. Previously, Jing was Director, Process and Analytical Development at a number of biotech startups, leading the development of new technology platforms for gene therapy applications. He also led the Phase I clinical trial of an mRNA COVID-19 vaccine.

Evolution of Antibody Humanization and Affinity Maturation

Antibody humanization and affinity maturation have revolutionized the biotech industry by enabling the development of highly effective therapeutic antibodies, vaccines, and other treatments. The use of AI in antibody humanization and affinity maturation has accelerated their development, making them more accessible to biotech companies and researchers.

Sumana Sundaramurthy
Technical Account Manager
Sino Biological

Antibodies play a vital role in the immune system by providing protection against foreign invaders, such as bacteria and viruses. Produced by B cells, antibodies are protein molecules that can be harnessed to treat cancers, autoimmune disorders, and various infectious diseases. However, the human immune system may recognize modified therapeutic antibodies as foreign substances, reducing their efficacy. To overcome this challenge, the following two processes have been developed: antibody humanization and affinity maturation.

Antibody humanization and affinity maturation have revolutionized the biotech industry in the past 10–20 years, enabling the development of highly effective therapeutic antibodies that can be used to treat a wide range of diseases. Prior to antibody humanization and affinity maturation, therapeutic antibody development was a slow and challenging process, often reliant upon less effective nonhuman sources that lead to elicitation of unwanted immune responses and low binding affinities. Antibody humanization and affinity maturation have changed this paradigm by enabling the development of therapeutic antibodies that are more effective at treating diseases. By enhancing binding to the target molecule, increasing half-lives in the body, and improving immune cell recruitment, these processes have improved therapeutic antibody effectiveness while avoiding elicitation of an immune response in humans. Therefore, the advancement of antibody humanization and affinity maturation

technology holds immense potential in facilitating the development and enhancing the quality of therapeutic antibodies.

Antibody Humanization

Antibody humanization is a crucial process in the development of therapeutic antibodies, which involves modifying nonhuman antibody molecules to make them more compatible with the human immune system. Although nonhuman antibodies, such as those of mice and rabbits, are commonly used in research to develop therapeutic antibodies, they can elicit an immune response when used as therapeutic agents in humans, reducing their efficacy.

To achieve humanization, the amino acid sequence of a nonhuman antibody molecule is modified to match that of a human antibody molecule. X-ray crystallography and nuclear magnetic resonance spectroscopy are used to identify the antigen-binding site, and then bioinformatics and computational modeling allow the prediction of the structural consequences of framework and complementarity-determining region (CDR) modifications. This process enables the creation of a molecule that can be used as an effective therapeutic agent in humans without causing an immune response. Overall, antibody humanization is critical in developing therapeutic antibodies, as it enables them to be used in humans with reduced immunogenicity, improving their efficacy in treating diseases (Fig. 1).

Sino Biological offers an antibody humanization service through its CDR grafting technology, providing a success rate of 100% and >95% sequence homology compared to human antibody frameworks. Our humanized antibody packages guarantee equal or higher affinity than any parental or chimeric antibody (Fig. 2).

Affinity Maturation

Affinity maturation is another integral process in the development of highly effective

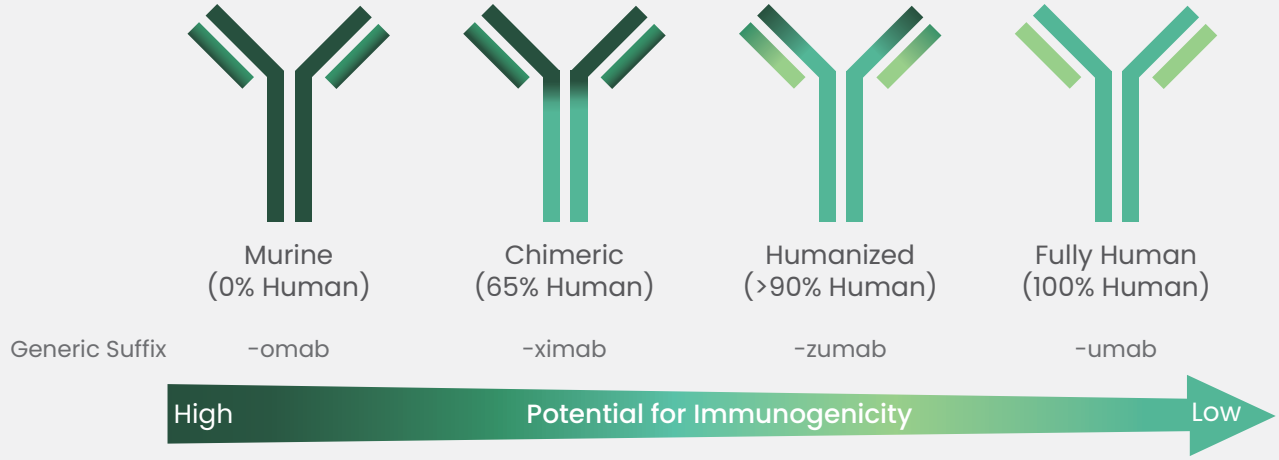

Figure 1. Humanization of therapeutic antibodies has reduced their immunogenicity.

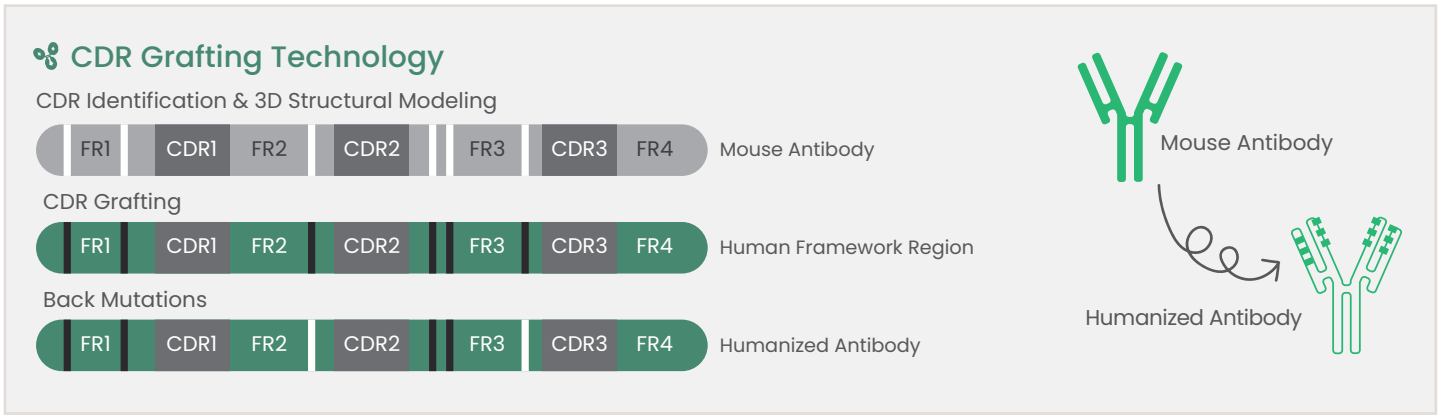

Figure 2. Complementarity-determining region (CDR) grafting technology developed by Sino Biological.

therapeutic antibodies. It involves creating mutations in the CDRs of an antibody, which results in structural changes that can facilitate optimal interactions with the antigen, thereby increasing its binding affinity, i.e., the strength of the interaction between the antibody and its target. The higher the affinity, the more effective the antibody is at binding to its target and eliciting a response. Traditionally, affinity maturation has involved multiple rounds of testing and modification to identify an amino acid sequence that will maximize the antibody's affinity to the target.

Application of Artificial Intelligence

The use of artificial intelligence (AI) has revolutionized antibody humanization and affinity maturation in the biotech industry. By analyzing large datasets of antibody molecules, AI can identify specific amino acid sequences that are most likely to increase the binding affinity of the antibody to its target and be compatible with the human immune system. This has greatly reduced the time and cost involved in developing therapeutic antibodies, making the process more accessible to researchers and biotech companies. Consequently, there has been an increase in the number of therapeutic antibodies in development and a decrease in the time it takes for these antibodies to reach the market.

Sino Biological has partnered with Ainnocence to offer cutting edge AI-based antibody affinity maturation and denovo antibody design. Powered by Ainnocence's SentinusAI™ self-evolving AI search engine, this new platform effectively rank up to 10^{10} antibody sequences based on their predicted affinity toward one or more antigens. Then, Sino Biological's high-throughput recombinant antibody development service can produce >1000 high-purity recombinant antibodies per project, with SentinusAI™ validating the affinities of these antibodies. (Fig. 3)

Real-world Applications of Antibody Humanization and Affinity Maturation

Antibody humanization and affinity maturation have had a significant impact on the biotech

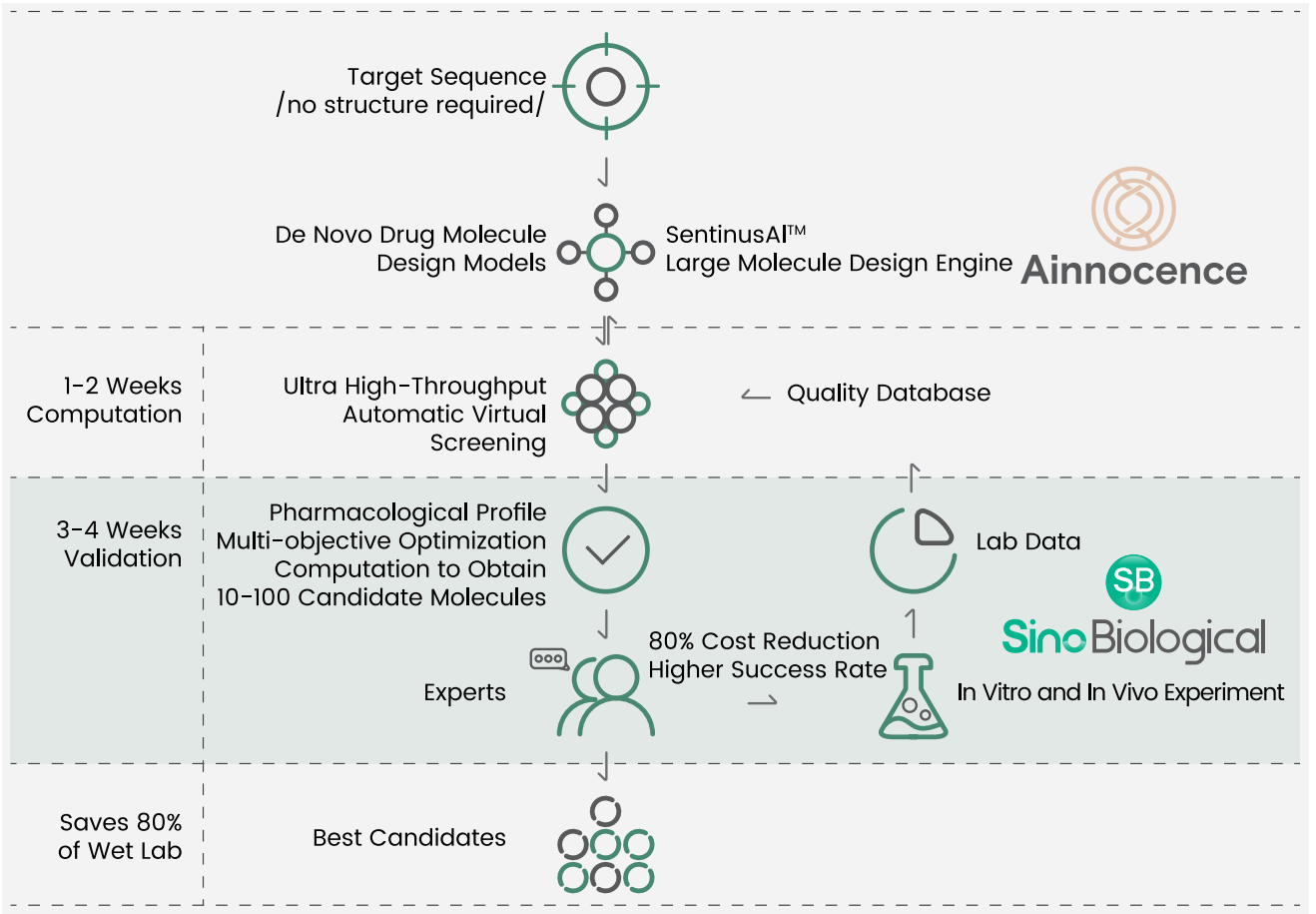

Figure 3. AI-Powered Affinity Maturation Service by Sion Biological

industry, particularly in the development of monoclonal antibodies (mAbs) for cancer treatment. mAbs are designed to bind to specific molecules on cancer cells, triggering an immune response that leads to the destruction of the cells. Through humanization and affinity maturation, the development of mAbs with low immunogenicity, high specificity, and therapeutic activity has been facilitated, resulting in effective targeting of cancer cells. Another area influenced by antibody humanization and maturation has been the development of therapeutic antibodies to treat autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, which are caused by the immune system attacking the body's own tissues. Humanized and affinity-matured antibodies have enabled the development of highly effective therapies that can block the immune response responsible for causing these diseases.

The humanization and affinity maturation of antibodies has also played a critical role in the development of highly effective vaccines that protect against a wide range of infectious diseases including viral infections like HIV, hepatitis C, and respiratory syncytial virus (RSV). In addition to their application in the development of therapies and vaccines, antibody humanization and affinity maturation ▶

have opened up new opportunities for biotech companies and researchers. By reducing immunogenicity and increasing specificity, these processes have made the development of new therapies and treatments possible.

Conclusion

Overall, antibody humanization and affinity maturation have revolutionized the biotech industry in the past two decades by enabling the development of highly effective therapeutic antibodies, vaccines, and other treatments. The use of AI in these processes has accelerated their development, making them more accessible to biotech companies and researchers. As these technologies continue to evolve, they are likely to have an even greater impact on the biotech industry, leading to the development of new and innovative therapies for a wide range of diseases.

Both antibody humanization and affinity maturation are critical steps in the development of therapeutic antibodies. However, traditional methods associated with these processes can be time-consuming and expensive. AI has revolutionized these processes by reducing the time and costs involved, as AI algorithms can analyze massive datasets of antibody molecules to identify the optimal amino acid sequences for humanization and affinity maturation. This information can be used to modify the antibody molecule, resulting in a more effective therapeutic agent.

Although the use of AI in antibody humanization and affinity maturation is still in its early stages, the potential benefits of this technology are clear. As AI algorithms become more sophisticated, they will be able to analyze even larger datasets and provide more accurate predictions, further reducing the time and costs involved in the antibody humanization and affinity maturation processes. AI is on course to become an essential tool in the development of therapeutic antibodies because of its ability to optimize antibody sequences and structures, identify novel targets, aid in repurposing of existing drugs and antibodies, and perform high throughput screening. ■

AUTHOR BIO

Sumana Sundaramurthy is a Technical Account Manager at Sino Biological, where she supports R&D projects for industry and academic clients. Prior to joining Sino Biological, Sumana completed her doctoral studies at SUNY Upstate Medical University. In addition to her academic pursuits, Sumana held various leadership positions supporting student life at Upstate and other professional organizations. She has also worked for a preclinical CRO and a few notable research groups at Loyola University, the University of Chicago, and Sanofi Pasteur.

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Safety Considerations for Antibody Drug Conjugates

Maciej Czerwinski
PhD, Director of XenoTech Scientific Consulting, BioIVT

Antibody Drug Conjugates (ADCs) are an innovative and evolving modality targeting cancer cell populations with highly toxic chemotherapeutics. An overview of the state of the field from the perspective of drug safety is followed by a discussion of FDA-approved ADCs for oncology patients, and *in vitro* evaluation of ADC drug-drug interaction (DDI) potential. Cases of DDI involving ADC are presented. Best practices for an *in vitro* safety evaluation of the ADC, which are based on the FDA guidance document, are discussed.

Current state

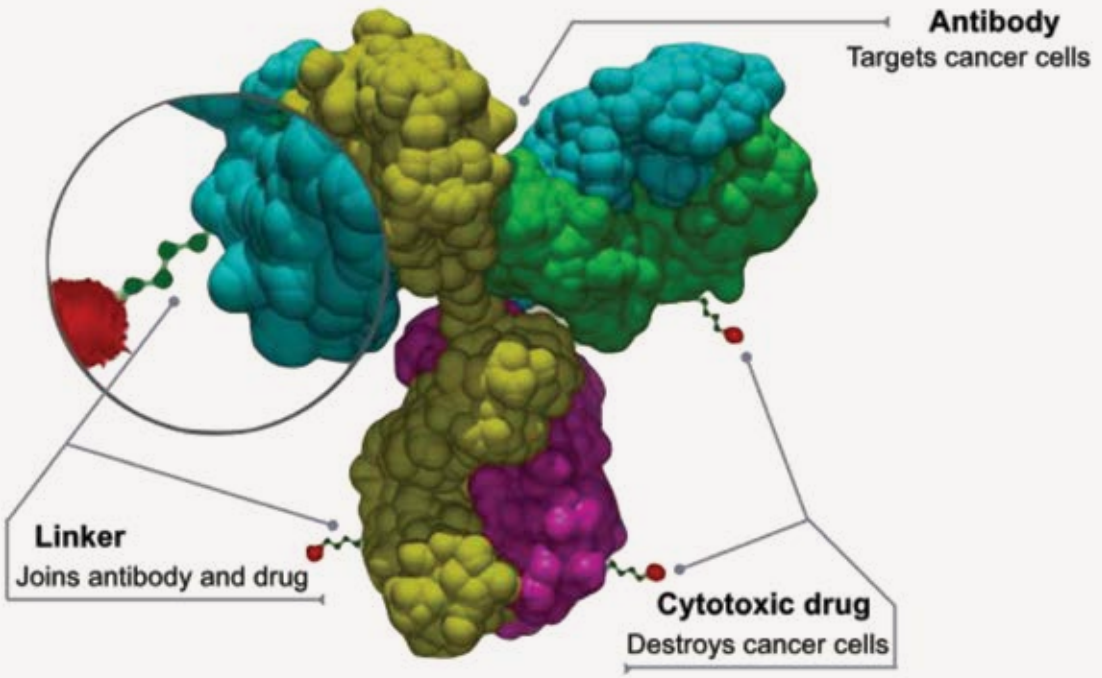
Antibody drug conjugates (ADCs) are innovative modalities to deliver chemotherapeutics to specifically targeted populations of cancer cells. The first ADC approved by the United States Food and Drug Administration (FDA) in 2000 was gemtuzumab ozogamicin developed by Celltech and Wyeth for treatment of patients with Acute Myeloid Leukemia (AML). Currently, there are 12 FDA-approved ADCs on the US market for treatment of hematologic and solid tumors (Table 1). The basic purpose of this novel modality is to increase efficacy of anti-neoplastic therapies and to reduce their toxic side effects. Toxicity of chemotherapy often prevents dosing drug to an effective level or leads to a reduction in drug dose

or cessation of a treatment. ADCs aim to deliver chemotherapeutics at an effective level combined with elimination or reduction of dose-limiting toxicity.

Typically, ADCs comprise a monoclonal antibody (mAb), a payload molecule e.g., "a small molecule" chemotherapeutic and a linker between the two (Figure 1). The mAb guides the drug to the population of tumor cells expressing a unique, targeted epitope absent on the surface of healthy cells. This combination of specificity of the mAb and the tumor marker provides a mechanism for reduction of off-target toxic effects of the chemotherapy and allows an increase of the drug efficacy. The linker stably attaches the payload to the mAb without affecting the mAb's ability to bind to its target and allows the payload to be released from the ADC upon reaching the intended cancerous cell. Mechanisms by which payload molecules can kill tumor cells include DNA cleavage and cross-linking (calicheamicin, pyrrolobenzodiazepine dimer), microtubule inhibition (auristatin, maleimidocaproyl monomethyl F, maytansine, maytansinoid DM4), topoisomerase inhibition (Deruxtecan, SN-38) and induction of apoptosis (Pseudomonas exotoxin A). Table 1 lists malignancies targeted by ADCs currently in the clinic. Patient populations presenting with advanced or metastatic tumors that were not responsive to one or more of the conventional chemotherapies often receive ADC therapies.

The potential toxicity of the ADC therapies is a recognized concern. Nine out of 12 ADCs

Figure 1: Schematic Representation of an Antibody Drug Conjugate



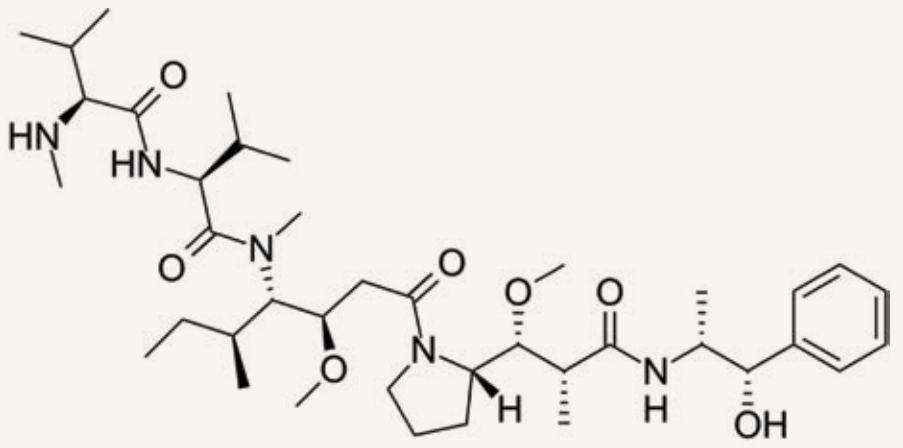
(Source of the image - https://commons.wikimedia.org/wiki/File:Antibody-drug_conjugate_structure.svg)

Table 1: FDA-Approved Antibody Drug Conjugates for the Treatment of Cancer (as of August 2023)

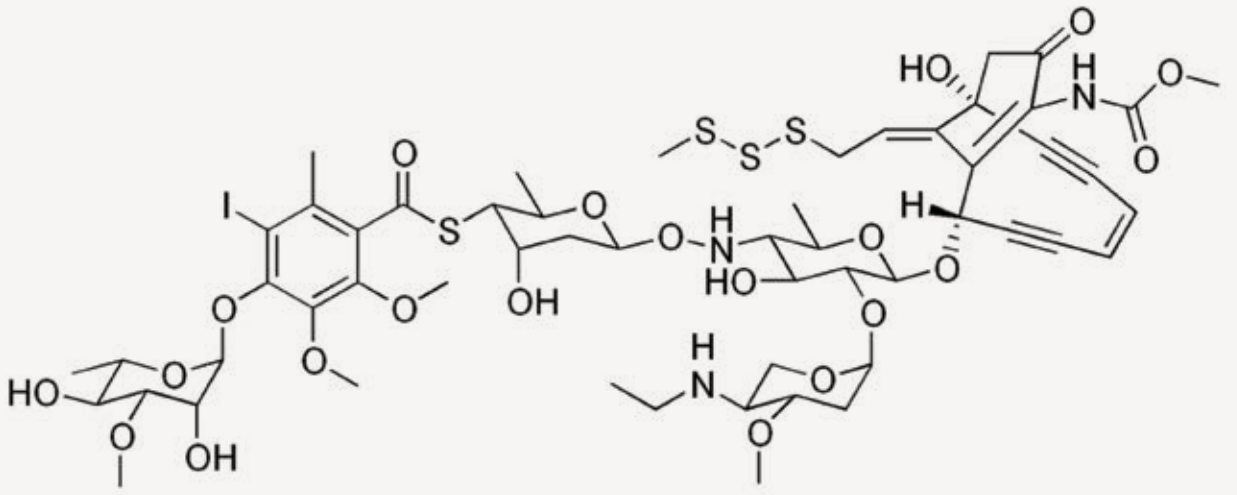
ADC year approved	Indication	Target Payload (mechanism)	Boxed warning
Gemtuzumab ozogamicin 2000, 2017	Acute myeloid leukemia	CD33 Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Brentuximab vedotin 2011	Hodgkin lymphoma, anaplastic large cell lymphoma	CD30 Auristatin (microtubule inhibitor)	Progressive multifocal leukoencephalopathy (PML)
Trastuzumab emtansine 2013	HER2-positive breast cancer (after prior anti-HER2 therapy)	HER-2 Maytansine (microtubule inhibitor)	Hepatotoxicity, cardiac toxicity, embryo-fetal toxicity
Inotuzumab ozogamicin 2013	B-cell precursor acute lymphoblastic leukemia	CD22 Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Moxetumomab pasudotox 2018	Hairy cell leukemia	CD22 Pseudomonas exotoxin A (induction of apoptosis)	Capillary leak syndrome, hemolytic ureic syndrome
Polatuzumab vedotin* 2019	Diffuse large B-cell lymphoma	CD79b Auristatin (microtubule inhibitor)	NA
Enfortumab vedotin* 2019	Urothelial cancer	Ncetin-4 Auristatin (microtubule inhibitor)	NA
Trastuzumab deruxtecan* 2019	HER2-positive breast cancer, unresectable or metastatic non-small cell lung cancer,	HER-2 Deruxtecan (topoisomerase inhibitor)	Interstitial lung disease, embryo-fetal toxicity
Sacituzumab govitecan 2020	Metastatic triple-negative breast cancer	Trop-2 SN-38 (a topoisomerase inhibitor)	Neutropenia, diarrhea
Tisotumab vedotin 2021	Metastatic cervical cancer	FT Auristatin (microtubule inhibitor)	Ocular toxicity
Loncastuximab tesirine 2021	Large B-cell lymphoma	CD19 pyrrolobenzodiazepine (PBD) dimer (DNA crosslinking)	NA
Mirvetuximab soravtansine* 2022	Platinum-resistant ovarian cancer	Fra maytansinoid DM4 (microtubule inhibitor)	Ocular toxicity

*- accelerated approval
NA – not applicable
Not listed above is belantamab mafodotin approved in 2020 for treatment of adult patients with relapsed or refractory multiple myeloma but withdrawn in 2022 due to the lack of efficacy.

Figure 2: Cytotoxic payloads microtubule inhibitor auristatin E (718 Da) and DNA breaking agent calicheamicin (1368 Da).
All currently utilized cytotoxic ADC payloads are derivatives of natural products discovered in bacteria, fungi, mollusks and plants. They often exceed molecular mass associated with 'small molecule drugs.'



Auristatin E



Calicheamicin

on the market carry a boxed warning. Boxed warnings, formerly known as Black Box Warnings, are the highest safety warnings that the FDA assigns to medications. The toxicities observed in clinical trials can vary among ADCs carrying the same payload. Four ADCs utilize auristatin E as a chemotherapeutic agent: brentuximab vedotin, tisotumab vedotin, polatuzumab vedotin and enfortumab vedotin (Figure 2, Table 1). Only the former two ▶

required boxed warnings; brentuximab vedotin for progressive multifocal leukoencephalopathy in Hodgkin's lymphoma, systemic anaplastic large cell lymphoma and HER2-positive, metastatic breast cancer patients; and tisotumab vedotin for changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration in patients with recurrent or metastatic cervical cancer.

The diversity of toxicities between brentuximab vedotin and tisotumab vedotin suggests that the individual components of an ADC as well as disease and genetic characteristics of the patient population are jointly responsible for the findings. Intrinsic factors such as renal or liver impairment, pharmacogenomics, body weight, age, gender, and race have potential to influence clinical pharmacology of an ADC (Clinical Pharmacology Considerations for Antibody-Drug Conjugates, Guidance for Industry, FDA, 2022, draft). ADC immunogenicity and drug-drug interactions (DDI) can have similar potential to influence the exposure of the medication.

In addition to the two ADCs containing auristatin E, gemtuzumab ozogamicin and inotuzumab ozogamicin that utilize calicheamicin as their payload, also carry boxed warning for the same toxicity, namely hepatotoxicity (Figure 2, Table 1). Gemtuzumab ozogamicin is approved for treatment of newly diagnosed CD33-positive AML and for treatment of relapsed or refractory CD33-positive AML, and inotuzumab ozogamicin is approved for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), caused hepatotoxicity. The toxicity includes severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS). These severe adverse reactions result in dose reduction and can lead to discontinuation of treatment and therefore deprive the patients of the modality's promise of delivering a precisely targeted and effective dose of chemotherapeutic agent.

ADCs are large molecules, typically >150,000 molecular weight mass, which may present multiple safety issues. Safety considerations presented by ADCs include DDI potential of the payload molecule. Specifically, the ADC may act as a DDI precipitant through the effects of the payload molecule on the mRNA expression or enzymatic activity of drug metabolizing enzymes and on drug transporters. These effects of payload molecules are a major concern to be addressed during the drug development process and are the focus of our discussion. The mAb portion of the ADC is proteolytically degraded to small peptides and individual amino acids in lysosomes, and therefore generally it's not considered to be a risk factor for the DDI. It's noteworthy that the trastuzumab deruxtecan antibody portion itself may contribute to interstitial lung disease observed in patients treated with the ADC (SOT 2023 Annual Meeting, abstract

Table 2: *In Vitro* Studies to Establish Drug-Drug Interaction Potential of ADCs

Metabolism-mediated interactions

Study type	Test system
a. Is the payload a substrate of drug metabolizing enzymes? Conduct metabolic stability study and reaction phenotyping studies	hepatocytes, microsomes, hepatocytes, microsomes, recombinant enzymes
b. Is the payload an inhibitor of drug metabolizing enzymes? Conduct evaluation of direct and metabolism-dependent inhibition of CYP and potentially UGT enzymes	microsomes, hepatocytes
c. Is the payload an inducer of drug metabolizing enzymes? Conduct CYP induction study in hepatocytes from three donors	cultured hepatocytes

Transporter-mediated interactions

Study type	Test system
d. Is the payload a substrate of drug transporters? Conduct drug transporters substrate potential study	cell lines, membrane vesicles
e. Is the payload an inhibitor of drug transporters? Conduct drug transporters substrate potential study	cell lines, membrane vesicles

Metabolites-mediated interactions

Study type	Test system
f. Questions analogous to the payload molecule may need to be answered for the metabolites of the payload	multiple systems

Table 2.

5057). A fragment of the linker that finds its way to plasma may have the potential to contribute to DDI. An unwanted degradation of an ADC in plasma rather than inside of the target cell could lead to systemic exposure to the toxic payload. Metabolic stability of the ADC payload in plasma, in the lysosomes and the cytosol is of concern from the perspective of toxicity and efficacy. The payload, typically an extremely potent toxin, needs to retain its potency while transitioning through the lysosomal compartment and should not be freely present in the plasma, as it may enter healthy cells. But the payloads selected for stability in these environments present an additional challenge as they may still be active when the content of the killed cancer cells is released. Other safety considerations for the payload molecules include long half-life, bystander killing activity, systemic accumulation, and potential for development of tumor resistance. ▶

Our review of the package inserts found no indication of ADC being a perpetrator of DDI *in vivo*. *In vitro* studies addressing DDI perpetrator potential of the ADC are presented below (Table 2). These studies were conducted on a case-by-case basis, as they may not be necessary for repeated use of payloads or the payload chemistry, e.g., Pseudomonas exotoxin A, a peptide, is not expected to be a CYP enzyme inhibitor or an inducer. An ADC can be a victim of DDI, also referred to as an object of DDI, when metabolism of its payload is changed by co-administered drugs, e.g., inhibitors or inducers of drug metabolizing enzymes. *In vitro* metabolism of the payloads, followed by reaction phenotyping studies, elucidate victim potential of ADCs (Table 2).

Drug-drug interactions involving ADC

Auristatin E. Various ADC currently in pre-clinical and clinical development and in the clinic (brentuximab vedotin, polatuzumab vedotin, enfortumab vedotin and tisotumab vedotin), are designed to treat several forms of cancer utilizing auristatin E as their payload. *In vitro* data indicate that monomethyl auristatin E (monomethyl auristatin E, MMAE) is a substrate and an inhibitor of CYP3A4/5. *In vitro* data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp). These *in vitro* data indicated a perpetrator and a victim potential for the auristatin E-containing ADC. A victim potential was considered due to the molecule being extensively metabolized by CYP3A4. The *in vitro* studies were followed up with clinical studies. For brentuximab vedotin it was demonstrated that the ADC did not affect exposures of sensitive CYP3A4 substrate midazolam. ADC exposures were unaffected by concomitant rifampin or ketoconazole; however, the auristatin E exposures were lower with rifampin and higher with ketoconazole consistent with the molecule being metabolized by CYP3A4. The study demonstrated the low magnitude of the interaction such that dose adjustments were not required (J Clin Pharmacol. 2013 August; 53(8): 866–877). Similar interactions can be expected for other ADC delivering auristatin E.

Sacituzumab govitecan. An SN-38, an active metabolite of anticancer drug irinotecan, is a payload of Sacituzumab govitecan. The SN-38 is inactivated by UDP-glucuronosyl transferase UGT1A1, therefore the ADC can be a DDI victim when co-administered with UGT1A1 inhibitors which would lead to a toxic level of the payload molecule. Concomitant administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. The package insert recommends avoiding administration of sacituzumab govitecan with UGT1A1 inhibitors or inducers

(sacituzumab govitecan package insert). Use of sacituzumab govitecan presents an analogous risk of toxicity in patients who are genetically deficient in the activity of UGT1A1, e.g., homozygote UGT1A1*28. Interactions of sacituzumab govitecan with UGT inducers have not been identified, presumably due to a relatively low level of inducibility of this family of enzymes as compared to cytochrome P450 enzymes (CYP).

Inotuzumab ozogamicin. A potential for non-pharmacokinetic DDI has been identified in the ADC label. Concomitant use of inotuzumab ozogamicin with drugs known to prolong the QT interval or induce Torsade de Pointes may increase the risk of a clinically significant QTc interval prolongation. Discontinuation or use of alternative concomitant drugs that do not prolong QT/QTc interval while the patient is using inotuzumab ozogamicin was recommended (inotuzumab ozogamicin package insert).

In vitro DDI evaluation considerations

To assure safety of the ADC, regulatory agencies recommend certain *in vitro* studies of their potential DDI. The studies can be based on the FDA Guidance "*In vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" (2020) and the draft "Drug Interaction Studies M12" guidance issued in 2022 by the International Council for Harmonization (ICH). The ICH guidance is expected to be finalized in 2024. The two regulatory documents focus on small molecule drugs and therefore apply to evaluating payloads of the ADC. Two important points presented in the draft ICH M12 guidance regarding potential DDI of the ADCs are –

- For ADCs, the small molecule drug component conjugated to the antibody component can be released in unconjugated form. Therefore, the DDI potential of both the antibody and the small molecule drug component should be considered. In general, for the small molecule component, the potential to inhibit or induce enzymes and transporters should be addressed in line with what is described elsewhere in this guideline. In many cases, however, the systemic concentration of free drug might be too low to act as a perpetrator *in vivo*.
- It is important to understand the formation, distribution, and elimination kinetics of the small molecule and to assess the systemic exposure of the small molecule drug component of the ADC. It might be necessary to evaluate the small molecule component (administered as an ADC) as a victim drug, in particular if increased levels of free drug may be associated with safety concerns. Understanding the exposure-response relationship of the various moieties is important in determining whether to conduct DDI studies and their significance.

Mechanisms of DDI include metabolism- and transporter-dependent processes that ▶

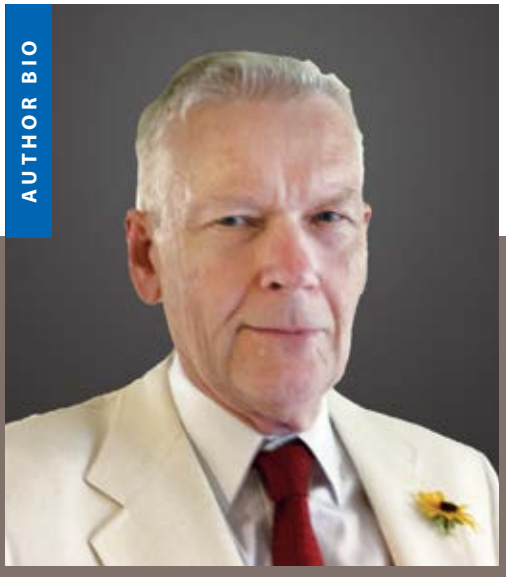
may involve the parent compound and its metabolites. Table 2 presents types of studies and their respective appropriate test system used for addressing questions of DDI potential of chemotherapeutic payloads of the ADC. Design details of the studies are provided by the regulatory documents issued by the FDA and the ICH.

Growth of the ADC field will bring new antibodies, conjugation technologies, and payloads. While the *in vitro* studies to evaluate DDI potential of the payloads are well delineated by the regulatory agencies, the impact of novel linking mechanisms on safety and efficacy of the ADC remains to be investigated. In addition to oncology, ADCs are being developed for autoimmune disorders and infectious diseases. ADCs being developed for rheumatoid arthritis carry payloads such as alendronate (anti-IL-6 ADC), siRNA (anti-C5aR1 ADC), Pseudomonas exotoxin A (anti-FRβ ADC) and glucocorticoid (anti-TNFα, ABBV-3373). Dexamethasone is a payload for two ADCs for inflammatory disorders (Vaccines 2021, 9, 1111). Some of these novel payloads, e.g., siRNA or bacterial exotoxin may not attract scrutiny regarding their effects of drug metabolizing enzymes and drug transporters. A follow-up therapeutic modality of peptide drug conjugates, represented by two FDA-approved cancer chemotherapeutics, will benefit from the experience gained in evaluating safety and DDI potential of the ADC (Molecules 2022, 27, 7232).

Conclusions

Vigilance and application of the best practices for safety evaluation of the ADC will continue to deliver life-saving therapies to critically ill cancer patients. Current DDI evaluations of the ADC are based on *in vitro* studies of the payload molecules. These efforts are successful, as DDI interactions in which ADC would play a role of a victim or a perpetrator did not cause withdrawal of the drugs from the market. Future ADC safety guidance developed by the regulatory agencies may contain recommendations for novel studies that are uniquely suited for this modality. ■

AUTHOR BIO



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Challenges in GMP, GCP & REGULATORY AFFAIRS

Josipa Ljubicic
QA Director, Principal GCP and GVP auditor, Proqlea Ltd

In the rapidly evolving world of pharmaceuticals and biotechnology, ensuring the safety, efficacy, and quality of drugs and medical products is crucial. The responsibility lies with professionals dedicated to upholding Good Manufacturing Practices (GMP), Good Clinical Practices (GCP), and Regulatory Affairs. While these guidelines are designed to safeguard public health, their implementation is fraught with challenges. In this article, we delve into the key obstacles faced by these professionals as they navigate the complex and ever-changing regulatory landscape.

The Regulatory Rollercoaster

The pharmaceutical industry operates in a constantly shifting regulatory environment. Health authorities worldwide are continually updating and revising regulations to adapt to scientific advancements and the global healthcare landscape. Keeping up with these changes and ensuring compliance can be a daunting task for industry stakeholders. Professionals in GMP, GCP, and Regulatory

Affairs must remain vigilant, continuously educating themselves, and collaborating with regulatory bodies to stay ahead of the curve.

Navigating the complexities of Good Manufacturing Practices (GMP), Good Clinical Practices (GCP), and Regulatory Affairs is a daunting task for professionals in the pharmaceutical and biotechnology industries. These guidelines are essential to ensure the safety, efficacy, and quality of drugs and medical products. However, their implementation comes with a myriad of challenges. In this article, we explore some of the key obstacles faced by professionals in these critical areas.

The Ever-changing Regulatory Landscape

One of the most significant challenges faced by professionals in GMP, GCP, and Regulatory Affairs is the ever-evolving regulatory landscape. Health authorities worldwide are continually updating and revising regulations to keep pace with advancements in science, technology, and the global healthcare environment. This constant flux creates a dynamic and challenging environment for industry stakeholders who must stay informed about the latest changes, adapt their practices, and ensure compliance.

The pharmaceutical and biotechnology industries operate within a regulatory landscape that is in a constant state of flux. Health authorities around the world frequently update and revise regulations to keep pace with scientific advancements, changes in technology, and the evolving global healthcare landscape. For professionals in GMP, GCP, and Regulatory Affairs, keeping track of these regulatory changes and ensuring compliance is a monumental task. The ability to adapt quickly and effectively to these changes is critical to maintaining a competitive edge and ensuring patient safety.

Stringent Quality Control and Assurance

GMP principles demand rigorous adherence to quality control and assurance processes throughout the entire manufacturing process. Maintaining consistent product quality is not only a complex endeavor but also necessitates substantial investment in equipment, training, and process improvement. Any deviation from quality standards can result in costly consequences, including product recalls, regulatory penalties, and damage to a company's reputation.

Maintaining stringent quality control and assurance processes is paramount in the world of GMP. Ensuring consistent product quality requires substantial investment in equipment, training, and process improvement. Any deviation from quality standards can lead to severe consequences, such as product recalls, regulatory penalties, and irreparable damage to a company's reputation. Professionals must be vigilant in adhering to best practices and ▸

harnessing advanced technologies to enhance product quality.

Ensuring Clinical Trial Integrity

For professionals involved in GCP, ensuring the integrity of clinical trials is a paramount challenge. Clinical trials are the cornerstone of drug development, and any mishandling or mismanagement can lead to biased results, jeopardizing the safety of participants and compromising the credibility of the data. Maintaining trial integrity requires meticulous planning, adherence to strict protocols, and effective communication among stakeholders.

Clinical trials play a crucial role in drug development, and their integrity is essential for ensuring patient safety and the efficacy of new treatments. Professionals involved in GCP must meticulously plan and execute these trials, adhering to strict protocols and ensuring that the rights and welfare of trial participants are protected. Any mishandling or mismanagement of clinical trials can lead to biased or unreliable data, potentially jeopardizing the approval and market access of new medications.

Data Integrity and Security

Both GMP and GCP environments heavily rely on accurate data to ensure product quality and patient safety. As technology advances, the volume and complexity of data generated in the life sciences industry are increasing exponentially. Ensuring data integrity, security, and compliance with data protection regulations

poses a considerable challenge. Professionals in these areas must implement robust data management systems, cybersecurity measures, and comprehensive training programs to safeguard sensitive information.

Data integrity and security are critical in both GMP and GCP environments. As technology continues to advance, the amount of data generated in the life sciences industry is growing exponentially. Ensuring data accuracy, privacy, and compliance with data protection regulations is a significant challenge for professionals in these areas. Robust data management systems and cybersecurity measures are essential to protect sensitive information and maintain the trust of patients, regulators, and stakeholders.

Global Harmonization

In today's globalized pharmaceutical market, companies often operate across multiple countries, each with its regulatory requirements.

Achieving global harmonization in GMP, GCP, and Regulatory Affairs practices can be a formidable task. Professionals must reconcile conflicting regulations, streamline documentation, and develop strategies to comply with various regional requirements while maintaining consistency in quality and safety standards.

Global harmonization is essential for pharmaceutical companies operating in multiple countries. Achieving consistent compliance with different regulatory requirements can be challenging, as each region may have its unique standards and expectations. Professionals must navigate these complexities and find ways to maintain product quality and patient safety across diverse markets.

> Pharma navigates dynamic regulations, demanding vigilant compliance efforts.

Resource Constraints

For many organizations, particularly small and medium-sized enterprises, allocating adequate resources to meet the demands of GMP, GCP, and Regulatory Affairs can be a challenge. Compliance with regulatory guidelines requires substantial financial investment, skilled personnel, and time-consuming processes. Smaller companies may struggle to match the capabilities of larger, well-established pharmaceutical corporations, potentially hindering their market access and growth opportunities.

Resource constraints are a common challenge faced by organizations, especially smaller ones, operating in the pharmaceutical and biotechnology industries. Compliance with GMP, GCP, and Regulatory Affairs requires significant financial investments, skilled personnel, and time-consuming processes. Smaller companies may find it challenging to allocate sufficient resources, limiting their ability to compete and innovate in the market.

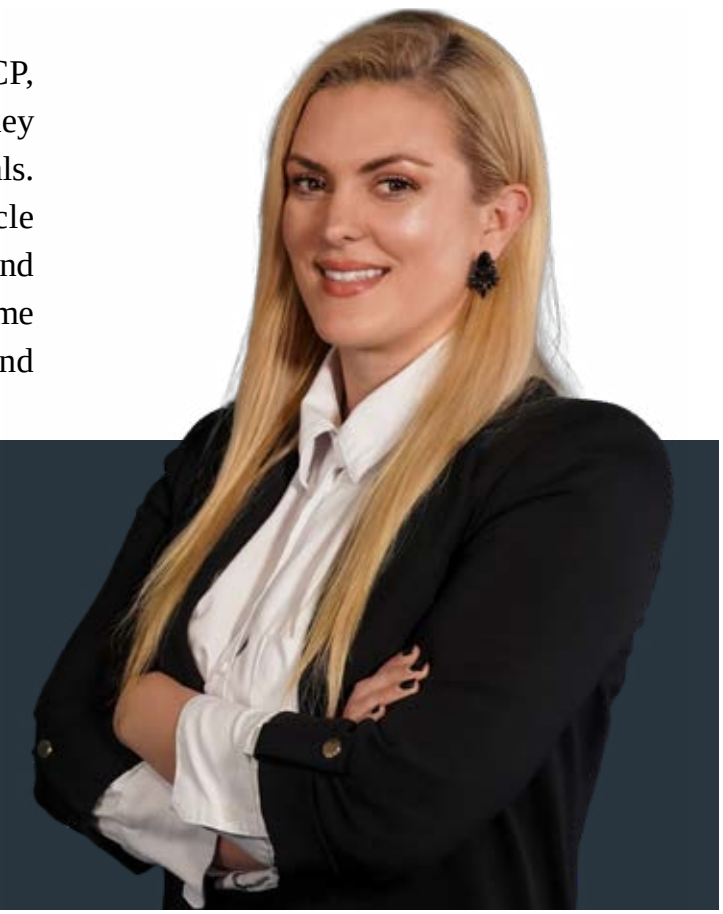
Rapid Technological Advancements

While technological advancements offer numerous benefits, they also present challenges in GMP, GCP, and Regulatory Affairs. The incorporation of cutting-edge technologies such as artificial intelligence, blockchain, and virtual reality in the pharmaceutical and clinical trial sectors requires professionals to adapt their practices continuously. Additionally, health authorities must assess the regulatory implications of these emerging technologies to ensure patient safety while promoting innovation. ▸

Rapid technological advancements have the potential to transform the pharmaceutical and clinical trial sectors. The integration of cutting-edge technologies such as artificial intelligence, blockchain, and virtual reality can enhance efficiency, accuracy, and patient engagement. However, the adoption of these technologies comes with challenges, as professionals must continually update their skills and knowledge to harness their full potential. Additionally, health authorities must stay abreast of these advancements to establish appropriate regulations that ensure patient safety and maintain the integrity of clinical data.

Conclusion

Navigating the complexities of GMP, GCP, and Regulatory Affairs is an ongoing journey for pharmaceutical and biotech professionals. The challenges discussed in this article represent a mere glimpse into the intricate and demanding nature of these fields. To overcome these obstacles successfully, companies and professionals must embrace a proactive approach, prioritize continuous learning, foster collaboration, and invest in robust systems to maintain compliance and uphold the highest standards of patient safety and product quality. By doing so, they can navigate the regulatory rollercoaster with confidence and usher in a new era of pharmaceutical excellence. As science and technology continue to advance, the landscape of GMP, GCP, and Regulatory Affairs will undoubtedly evolve. Embracing these challenges and staying ahead of the curve will be essential for the continued success of the pharmaceutical and biotechnology industries in delivering safe and effective treatments to patients worldwide. ■



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Success in Pharmaceutical Research Can Be Highly Unpredictable

Success in pharmaceutical research can be highly unpredictable. However, more predictive pre-clinical screens can now be implemented to score therapeutic candidates in a way that better correlates with their potential clinical utility. This article explains the influence of predictive validity in analysing such pre-clinical screens to increase productivity in drug discovery.

J. Mark Treherne

Director and the Chairman, Talisman Therapeutics Ltd

The drug discovery productivity problem

The macroeconomic fundamentals of the pharmaceutical industry remain strong. High demand for innovative pharmaceutical products is driven by a growing and ageing global human population with significant unmet medical needs. However, discovering new drugs is a costly, lengthy and, still, a largely unpredictable endeavour. The pharmaceutical industry has consistently experienced high rates of compound attrition throughout the drug discovery process over many decades now. Consequently, the biotechnology and pharmaceutical industries are continuing to

develop new strategies to improve their overall productivity and reduce the high attrition rates in their development pipelines. Nonetheless, the successful products that do make it on to the market are still having to compensate for too many compounds that are discontinued, as often a lack of compelling efficacy data is uncovered too late during subsequent development. Overall, the number of new drugs approved per billion US dollars spent on research and development has roughly halved about every nine years from 1950 to 2010 with no obvious signs of any substantial improvements over the subsequent decade. So, how can success in pharmaceutical research now become less unpredictable in the future?

Improving the predictivity of pre-clinical screens

Previous analyses have uncovered how assay validity and reproducibility can be correlated across a wide range of simulated screening assays and disease models, such as described in the publication by Scannell and Bosley in 2016 (PLoS ONE 11, 1-21). These authors proposed that increasing the implementation of more relevant and predictive screens should be incorporated pre-clinically into the drug discovery process. A more rigorous understanding of efficacy and toxicity at multiple biological levels would then offer a potential solution to this systemic productivity problem. ▶

Initiating a new drug discovery programme typically requires a chemical starting point for small molecule drugs to initiate the optimisation of that compound's biological properties, which can also be guided by constantly improving computational chemistry methods. The optimised development candidate needs to possess an adequate balance of efficacy, pharmacokinetics and safety pharmacology to then be progressed into the clinic. Although the discovery process differs somewhat for antibodies and other biological drugs, they are still required to meet adequate biological criteria to be progressed into clinical development. Biological selection criteria need to be driven by assays with a higher probability of predicting clinical efficacy in comparison with the current more established workflows. It has been argued that such pivotal decision-making assays need to be introduced much earlier into the discovery process to enable disruptive changes in drug discovery to make a real difference to productivity. For more details on the rationale underlying this conclusion, see the publication by Treherne and Langley in 2021 (Drug Discovery Today 26, 2489-2495).

> Demand-driven pharmaceutical industry thrives despite unpredictable drug discovery.

How to increase future productivity across drug discovery

There have been huge advances in our understanding of the underpinning science of human disease, as well as the introduction of new technologies that should, at least in theoretical principle, have improved the overall productivity of drug discovery. However, success rates still remain stubbornly low. Analytical methods based on decision theory have demonstrated that small changes in the "predictive validity" of an assay have a remarkably significant impact on downstream success rates. In this context, predictive validity refers to the ability of a test or other measurement to predict future outcomes in a human clinical trial. The mathematical basis underlying this approach was described by Scannell et al. in 2022 (Nature Reviews Drug Discovery 21, 915-931), who exemplify the relevance of predictive validity in drug discovery to demonstrate why it matters and then set out how it could be improved. There are many long-standing and unmet medical needs that would benefit from more advanced *in vitro* assay systems. Historically, drug discovery has

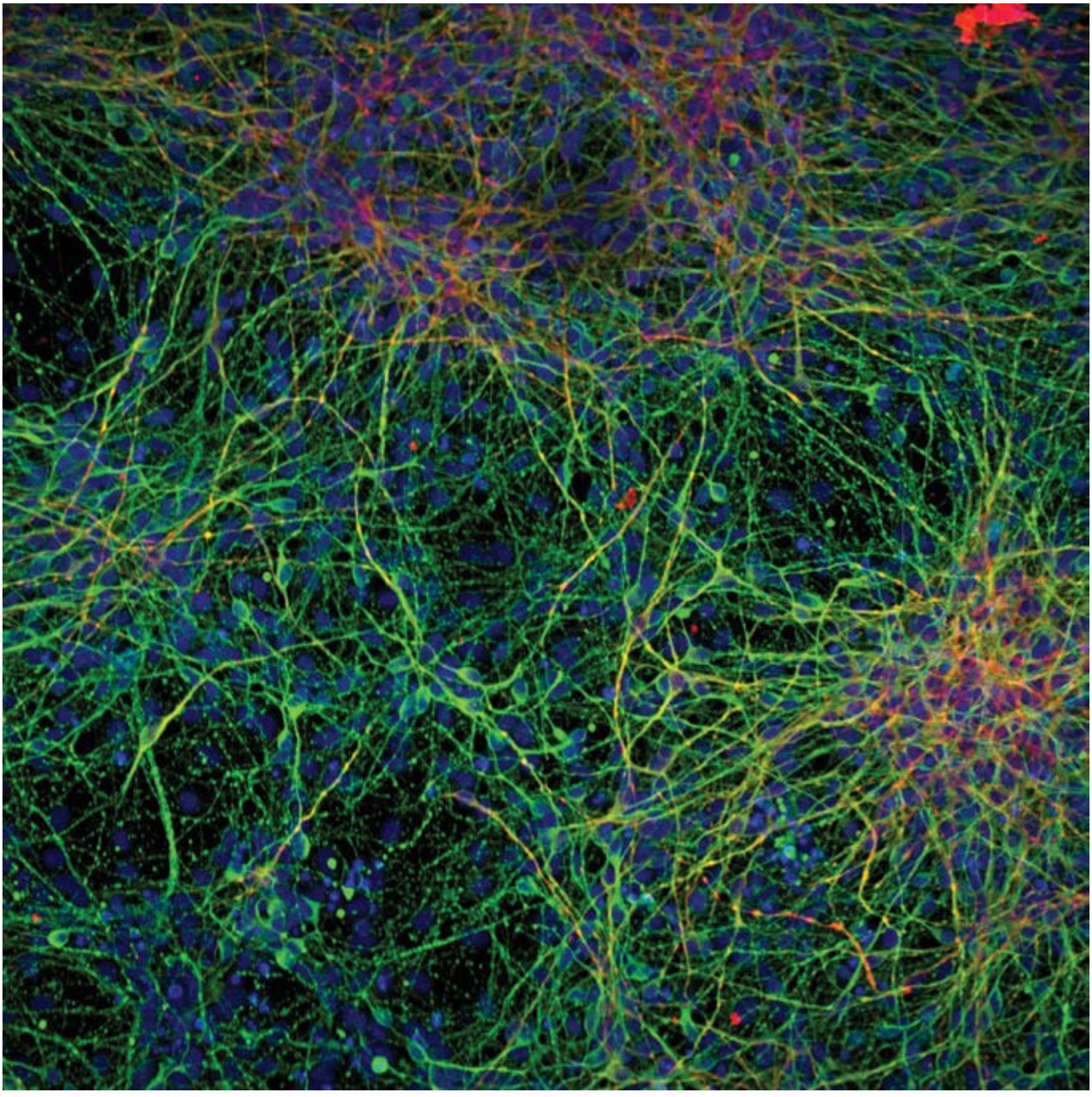
been overly dependent on animal models that can be poorly predictive of human pathology, even when human diseased-associated genes are engineered into transgenic mice. Increasingly, more advanced human-specific cellular models are now becoming available. The US Food and Drug Administration (FDA), the US National Institutes of Health and the Environmental Protection Agency have provided long-term support for the incorporation of human cellular models. In fact, animal testing of drugs is no longer required by the FDA following the introduction of a new law that was passed in December 2022. Consequently, the FDA can now approve drugs that have only undergone non-animal testing, such as testing with laboratory-based human tissue models, before proceeding into human clinical trials. The practical implementation of this way of thinking will now be discussed below, particularly in relation to the use of human cellular assays and their more effective exploitation in drug discovery.

More predictive assays can enable the discovery of better drugs

In vitro human cellular assays have been well established in drug discovery workflows for the last five decades or more. Explant cultures, for example, are a type of *ex vivo* tissue culture technique that involves culturing live fragments of human tissues that retain some of the original *in vivo* characteristics of the source tissue when maintained in culture. Explants can be used in drug discovery to test the efficacy and safety of potential drugs on patient-derived samples and can also be used to study the molecular mechanisms and biomarkers of many diseases. Some advantages of explant cultures are that they can better reflect human biology than most animal models do, as they can preserve the heterogeneity and surrounding microenvironment of the relevant tissue. Some challenges of using explant cultures are that they require a regular supply of fresh, viable tissue samples and they often have limited viability and long-term stability in culture. Cell lines, on the other hand, have been developed to become immortal to provide a reliable and inexhaustible source of human cells. Cell lines were originally used as monolayer or as suspension cultures. However, explant cultures, human tissues and organs are more 3-dimensional (3D). Consequently, spheroid-like cultures have been developed that are typically derived from cell lines that have previously been grown in monolayers or suspensions and then clumped together into 3D-compatible culture systems. Spheroids allow cells to communicate with each other in a similar manner to an *in vivo* 3D environment, although the lack of vascular flow can still be a limitation. Organoids, on the other hand, are typically referred to as 3D cultures derived from stem cells, which can self-organise in culture owing to their self-renewal and differentiation capacities. Organoids are, typically, seeded and maintained in 3D for the entirety of their life in tissue culture.

Human induced pluripotent stem cells (iPSCs) can self-renew indefinitely in culture

and differentiate into all specialised cell types. Although iPSCs do not exist naturally, they can be "induced" or reprogrammed in culture from any non-reproductive cell. Since they can be generated from any patient with a disease, iPSCs are considered as a valuable technology platform to better model human diseases *in vitro*. They can then be used to discover new drugs in a variety of screening formats, including the 3D formats described above. For example, iPSCs have been used to develop new screening strategies to treat



Alzheimer's disease by developing assay systems that recapitulate both amyloid and tau pathologies. Such *in vitro* translational models are now enabling pivotal decisions on compound progression to be made earlier in discovery and can be established in most conventional tissue culture laboratories. The figure below illustrates how IPSCs sourced from an individual patient donor can form mature-looking neurons that develop complex morphologies. The image of the neurons shows that Microtubule-Associated Protein 2 (MAP2), which is shown in green, is located predominantly in the neuronal cell bodies and dendrites, whereas β3-tubulin in red is located in the neuronal processes. The neuronal nuclei are shown in blue by staining with DAPI, a fluorescent stain that binds strongly to adenine–thymine-rich regions in DNA. Such complex *in vitro* cultures are now helping identify drug candidates and new targets for clinical intervention in Alzheimer's research and other related neurological disorders.

Significant research efforts are also aimed at recapitulating disease models and early-stage efficacy and toxicity screening at the organ level, using *in vitro* physiological flow systems or "organs-on-chips". These platforms offer controlled, reproducible and sensitive systems with dynamic flow and tissue-tissue interfaces that support 3D cellular constructs with extended viability. They are amenable to high-content analysis, as they can accommodate electrical, chemical, mechanical and optical sensors and can re-create some aspects of complex human physiology and pathology. Disease modelling in these systems can use human primary cells, conventional cell lines and/or iPSCs. Cells may also be gene edited or subjected to environmental triggers to generate relevant disease pathologies. Unlike simpler cultures, organs-on-chips and fluidically coupled human body-on-chip platforms can give more detailed mechanistic insights into disease processes and the pharmacological effects of compounds. Awareness is needed to understand the limitations of each technology, for example, neuronal cells derived from iPSCs can be relatively immature in some cultures and do not always spontaneously express disease phenotypes. No single platform in isolation is likely to solve the productivity problem in drug development on its own but it is entirely plausible that carefully selected and validated panels of new methodologies could do so.

Developments in organ-on-chip and related cell-based assays continue to support the development of *in vitro* disease modelling and improved predictions of drug efficacy and toxicity early in drug discovery, leading to the replacement of some animal models. Meta-analyses, comparing *in vivo* animal toxicity studies with *in vitro* human-cell high-throughput screening assays, revealed that animal studies did not perform significantly better in predicting adverse drug effects in humans. Both kinds of tests performed only moderately well. However, adding a small ▶

set of drug targets to the human-specific *in vitro* data resulted in models that outperformed those built with the existing animal models.

Why predictive validity matters

The costs of introducing new drugs into a practical clinical setting often impedes their extensive use in the patients who most need them. These high costs often arise from the need to compensate for the high attrition rates of potentially promising therapeutics throughout the drug discovery process and into clinical development. Many apparently attractive new drugs fail to deliver meaningful endpoints in clinical trials. This article has analysed the challenges and proposed some novel solutions required to allow the widespread implementation of improved screening strategies into drug discovery. Analytical methods based on decision theory have demonstrated that small changes in the predictive validity of an assay can have a remarkably significant impact on downstream success rates. Predictive validity measurements can then be used to score and rank therapeutic candidates in a way that better correlates with their potential clinical utility. Therefore, improving the predictive validity of pre-clinical assays *in vitro* can be used to better predict future outcomes in a human clinical trial. If the productivity problems of the pharmaceutical industry can be overcome by the introduction of these novel screening strategies, then the medical benefits to patients in an ever growing and ageing global population are clear. ■

References are available at www.pharmafocusamerica.com

AUTHOR BIO

Mark Treherne is currently working as a Director and the Chairman of Talisman Therapeutics Ltd. He has over 30 years' experience in the discovery of novel treatments for diseases with unmet medical needs. He has served on the boards of multiple therapeutics, research services and diagnostics companies. Mark has a particular interest in the predictive validity of pre-clinical disease models to better predict more efficacious treatments.

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Using Existing Data to Create and Validate Digital Biomarkers

Digital health measures have the potential to transform medicine from reactively treating acute illness to proactively managing disease. This discussion will explore how existing real-world and digital health data can be reused to develop and validate digital biomarkers. It will also highlight regulatory and clinical considerations, and patient privacy issues.

Geoffrey Gill
MS, Founder and CEO, Verisense Health

Daniel R. Karlin
MD, MA, Chief Medical Officer, MindMed

James Connolly
PhD, Lecturer in Computing at Atlantic Technical University, Co. Donegal

William Crown
PhD, MA, Distinguished Scientist at Brandeis' Heller School for Social Policy, and Management

Geoff: The first challenge when implementing digital health technologies is achieving the adoption and acceptance of digital biomarkers, which can determine whether someone is getting better or worse and if medical intervention is required. A significant part of the problem is that researchers lack some of the data needed to develop and validate those biomarkers. We believe this gap can be addressed by reusing clinical data that is being generated already and by connecting it to real-world evidence.

The Challenge

Daniel: For digital biomarker development and validation to progress, three core tensions need to be addressed.

1. Reality Versus Models of Reality

Reality is too complex for human brains to understand, so we employ heuristics and comprehensible models as tools to help us interact with reality in meaningful ways. Our understanding of human biology is necessarily based on reductive models.

2. Richness Versus Reusability

Arguably the richness of human experience, and therefore the underlying basis for the field of psychology and psychiatry is partially contained in all the novels in human history. While one could get an incredibly deep and rich understanding of people by reading novels that level of richness does not make for useful diagnostic ontologies.

On the opposite end of the taxonomic spectrum are things like the Diagnostic and Statistical Manual of Mental Disorders (DSM), a highly specified and therefore reusable ontological system but without much in the way of descriptive richness. We must consider a similar balance with data collection strategies and remember that excessive focus on reusability sacrifices richness. ▶

3. Validated Against What?

Clinical measures always need to be validated against something established to be clinically meaningful.

Concurrent criterion validation is the easiest to achieve because it essentially states you have an accepted meaningful measure of disease, and the new measure comes to the same conclusion when assessing the same person simultaneously.

But there is a much more critical type of validation – predictive clinical validation – which takes much longer to achieve. With predictive clinical validation, there is an established clinical state, and the new measure provides data about the likelihood of that clinical state occurring. Essentially it pushes state identification backward in time, ultimately defining a novel clinical state that is predictive of a known clinical state.

For example, by measuring blood pressure repeatedly in a standardized way in clinical settings in many people many times, and subsequently watching what happened to them clinically, researchers could recognize and define the clinical state of hypertension. Then by reducing a person's blood pressure—treating their hypertension—it was possible to reduce the likelihood of negative clinical outcomes, now newly known to be consequences of hypertension, predominantly damage to end organs: the heart, the brain, the kidneys, etc.

However, with the more recent introduction of high-quality at-home blood pressure monitoring equipment, it became apparent that episodic, in-office sphygmomanometry was not as reliable or valid a measure of real-world blood pressure as initially thought. That episodic approach had inadvertently introduced a measuring error or measuring bias. As a result, it is likely that hypertension was both under and over-diagnosed. In essence, some people who didn't need treatment were treated, and some who did weren't.

> Digital health data transforms medicine, shifting from reactive to proactive care.

For digital health data to be predictively clinically validated, researchers must determine how to take the same measurement in the same way in many people and then share that data between them in a pre-competitive or non-competitive environment.

Standardizing Measurement

Geoff: Can you use raw or minimally processed sensor data?

James: We cannot directly access totally raw sensor data. Software that controls sensors typically filters the data to improve its stability or to remove outliers. This can happen at the firmware level, or sometimes the sensor data goes through a summative process before it is transmitted to the host computer.

That said, the ideal scenario with any type of measurement is for the data not to have a filter applied to it, because filtering reduces the granularity of the data. Sometimes the filtering process creates summary information, reduces outliers, and tries to improve the data, to make our lives as consumers a bit easier, and to make the sensor data easier to work with.

In doing that, it reduces its usefulness. The sensors become functionally standalone units. We cannot compare the data from one sensor against another because we do not know what type of algorithms have been applied to them. Future data comparisons of research studies are no longer possible.

We want to get as close to the raw information as possible. We do not want anything to be applied to the sensor data, and for it to be transmitted as cleanly as possible.

We employ Euclidian Norm Minus One (ENMO), which is a typical measurement of physical activity, and uses the open-source GGIR algorithm. But we also use the six-minute walk test, and are beginning to look at maximum six-minute activity.

Measuring the maximum amount of movement that happens within a specific time, whether that is an hour, a day, or a week, is shaping up to be a better way of detecting light and sedentary movement.

One of the advantages of using an open-source algorithm, such as GGIR, is that everyone can use the same algorithm to process data and it can be independently measured no matter what sensor or device is being used.

Being able to reuse data is very helpful. Whenever we use any type of hardware, we need to validate its accuracy and reliability. If we could gain access to a global repository of raw data that could save us a lot of time and effort in validation.

As it is, we must spend months applying for ethical approval, comparing our device with the state-of-the-art device, then validating the data, and measuring what is an acceptable level of error before we can begin our tests.

Why could we not use existing inertial measurement unit data from a repository, whether it be from a chronic obstructive pulmonary disease study or from patients who have had a stroke and are being tested for rehab?

Using Real-world Data

William: While I was Chief Scientific Officer at OptumLabs, we built a massive real-world database containing more than 100 million covered lives of claims data and 85 million lives of electronic medical record data. These data were also linked to patient mortality, social

demographics, and county-level data from the Area Health Resource File from the Agency for Healthcare Research and Quality (AHRQ).

Academics around the country were keen to analyze that data to generate evidence. Real-world datasets can generate evidence much faster than randomized clinical trials (RCTs).

RCTs are valuable but observational data can generate very credible, useful information when appropriate methods are used to analyze it.

There is also a lot of interest from regulators, especially since the passage of the 21st Century Cures Act which requires the FDA to develop a framework for incorporating real-world evidence into regulatory decision-making about new indications for previously approved treatments, as well as safety surveillance. The FDA has been involved in safety surveillance for a long time with the Sentinel Network, which is a massive national claims database that it uses to evaluate the safety of existing products on the market. But using real-world data to assess new indications for previously approved products is new.

The FDA has shifted its mindset from focusing solely on evidence from randomized trials to considering what role real-world data can play in regulatory decision making about new indications and safety surveillance for previously approved products. The Agency is now considering whether it is possible to generate causal inference like it would have with a randomized trial from observational data.

There is a very large national study out of Harvard called RCT Duplicate, which is emulating 37 randomized trials; 30 of which have been completed. This study is using claims data to emulate the inclusion/exclusion criteria, endpoints, and follow-up periods for those trials.

Randomized trials are also conducted of products that are on the market to test their real clinical effectiveness. Observational studies are being run to predict what the results will be from those trials. It has been remarkable to look at the evidence and the degree of agreement between those observational studies and randomized trials.

Regulatory Perspective

William: With FDA approved products, such as glucose monitors, there is a time lag from when the regulatory approval occurs, and an approved Centers for Medicare & Medicaid Services (CMS) code is entered into the databases.

Without that code, researchers cannot identify what device was used to treat the patient. That initial coding issue places a major limitation on the analysis of digital device data by academic researchers.

Geoff: How do we improve the system? Without access to raw or minimally processed sensor data, we do not have digital biomarkers, hence the product cannot be used as a medical device, so it is not going to get a CMS code, which means we can't use the data.

William: There are two sides to that issue. The FDA is a strong proponent of accessing data as close to the source and in as original a form as possible. The FDA wants to know the source and providence of data before it is included in commercially available databases.

But in cases where a device is not going to be used as a treatment but as a source of data on patient outcomes, we need to link the device data to other data to put the results into context.

Researchers face challenges with linking datasets due to HIPAA regulations, which are designed to minimize the reidentification risk to patients. The more granular the data gets and the rarer the condition the patient has, the more information researchers must relinquish to continue to mask that patient's identity.

Precompetitive Collaboration

Daniel: Pharmaceutical companies are involved in several collaborative, pre-competitive projects, including WATCH-PD, a Parkinson's disease study, and TransCelerate's digital biomarker effort. CTTI is also developing policy papers and research best practices to make data more interoperable and integrated. The Digital Medical Society (DiME) is working on a large number of collaborative measure development projects, including a nighttime itch-and-scratch quantification project using wrist-wearing accelerometry to analyze scratching behavior. DiME is also involved in direct risk factor research and establishing best practices across several domains in digital medicine.

William: Life sciences companies have been conducting secondary analyses of claims data for a long time to understand the burden of an illness better and support the commercialization of their products. Pharmaceutical companies analyze large claims datasets to determine the comparative effectiveness of their products and support their value propositions around pricing.

Closing Advice for Researchers

Geoff: Researchers should use minimally processed data, which is as close to the sensor as ▶

they can get, and can be independently verified. They should also identify a mechanism upfront that will allow them to share that data.

What advice would you give researchers who want to reuse real-world data?

James: They need to understand how the data was collected. For example, if they are going to do a 40-meter walk test, then they need to define the parameters they will use to collect that data. If we do not all use the same protocol, the data collected is going to be different, even though the test that was examined is the same. For example, the 40-meter walk test could be 1 x 40 meters, or 8 x 5 meters, and that is going to change the shape of and underlying patterns in the data.

William: The 21st Century Cures Act has really changed the game in terms of the FDA's interest in real-world data. Regulatory authorities around the world are interested in this now, as are health technology assessment groups that make decisions about drug coverage, pricing, and reimbursement decisions.

There is a lot of existing data infrastructure on general patient populations in the United States and elsewhere. But we need sensor and device data to be brought together in one place where we can link it to those existing databases and bring in information about the patients, their diseases, and comorbidities to provide context.

From a technical standpoint, it is an easy problem to solve. If we have identifiers in this data that are required in the other datasets, we can link it without having to exchange names and addresses and social security numbers. We can just hash the identifiers in both places and link the hashed IDs together. Then we have a deidentified dataset that we can use that has the sensor and the device data in it.

The first big challenge is to centralize the device and the sensor data so that we can link it to other datasets.

James: We also need a reliable software system to control the connection between them. That can be a nightmare when it comes to trying to amalgamate data from several sensors. We need to ensure that all the amalgamations are happening accurately.

Daniel: Be proactive regarding informed consent in research, and get permission to share data, even at an identifiable level. Go as far as your IRB will let you because I have not yet met a research participant who says "no" when asked, "Can we share your data to advance science as much as possible from your participation?"

Pressure test your assumptions about the boundaries which you consider to be the edges of a research question. Stop doing recurrent criterion validation against crappy legacy standard measures. If you find yourself replacing something low burden, quick to complete, not very useful, and free, such as the Patient Health Questionnaire-9 (PHQ-9), with something expensive, proprietary, and time-consuming, you are probably making a mistake.

AUTHOR BIO

Geoffrey Gill, MS, is Founder and CEO of Verisense Health, a digital health software and data company, and Co-founder of the Open Wearables Initiative (OWEAR). Geoff's goal is to accelerate the adoption of digital health technologies industry wide by standardizing digital biomarkers and making them useable for providers. He joined Verisense Health from Shimmer Research, the global wearable technology provider, where he served as President of Shimmer Americas. He received his MS in Management of Technology from the MIT Sloan School of Management.

Daniel R. Karlin, MD, MA, is Chief Medical Officer of MindMed. Dan joined MindMed in February 2021 when it acquired HealthMode, the company he co-founded and led as CEO. Prior to HealthMode, Dan built and led clinical, informatics and regulatory strategy for Pfizer's Digital Medicine and Innovation Research Lab. He also served as Global Clinical Lead for psychiatry clinical compounds at Pfizer. He is a strategic advisor to several pharmaceutical, biotech and health technology companies. Dan is board-certified in psychiatry, addiction medicine, and clinical informatics. He is also an Assistant Professor of Psychiatry at Tufts University School of Medicine.

James Connolly, PhD, is a lecturer and researcher in computing at Atlantic Technical University in County Donegal, Ireland. James' areas of expertise include digital healthcare and connected health, big data analytics, and artificial intelligence. James has a PhD focused on wearable technology and computing from Ulster University.

William Crown, PhD, MA, is a Distinguished Scientist at Brandeis' Heller School for Social Policy, and Management and an internationally recognized expert in real-world data analysis. He specializes in research designs and statistical methods for drawing causal inferences from transactional health care datasets such as medical claims and electronic health records. Bill began his career at the Heller School in the early 1980s focusing on the demography and health economics of aging and he taught a series of statistics courses in the Heller PhD program. He left Brandeis to lead health economics consultancies at Truven and Optum. He received his PhD in regional economic modeling from MIT, and an MA in Economics from Boston University.

Clinical trials form the backbone of pharmaceutical development, acting as the proving ground where the safety and efficacy of novel medical interventions are thoroughly evaluated. These trials often present complex challenges in their design, implementation, and evaluation, leading to the development of a multidimensional ecosystem comprising various entities. Each entity brings unique expertise to the table, contributing to the intricate tapestry of the trial process. Within this web of interdependencies, outsourcing emerges as an influential strategy, allowing clinical trial sponsors to engage with CDMOs, Contract Research Organizations (CROs), and other service providers.

Outsourcing in Clinical Trials

Optimizing Outsourcing Relationships for Mutual Success

This article explores potential strategies for cultivating effective outsourcing relationships in clinical trials, blending insights from a CDMO project manager, and a trial sponsor. It places emphasis on the power of collaboration, transparency, and mutual respect in driving success and accelerating pharmaceutical innovation.

Joab Williamson
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Project Manager, Catalent

The choice to outsource services in a clinical trial setting is not merely a financial or logistical decision but rather a strategic consideration. It enables sponsors to tap into external expertise and state-of-the-art technology, enhancing their operational efficiency and focusing their internal resources on core competencies. At the same time, outsourcing providers enhance their relationships with sponsors, and have the opportunity to significantly expand their service capabilities.

However, to fully unlock the potential of outsourcing and optimize the value it brings, it is crucial to go beyond the transactional nature of the process and cultivate relationships based on mutual trust, transparency, and a shared sense of mission. This article, crafted by two authors from distinct vantage points – one as a representative of a Contract Development and Manufacturing Organisation (CDMO) and another from the perspective of a trial sponsor – delves into strategies for building, maintaining, and reaping the benefits of successful outsourcing partnerships in clinical trials. By bridging these two perspectives, the article aims to provide a comprehensive view of the collaborative dynamics that drive success in the complex world of clinical trials.

Understanding the Importance of Outsourcing in Clinical Trials: A Perspective from a CDMO:

As a CDMO, providing outsourcing solutions to clinical trials is how we learn of the latest pharmaceutical advances. As part of the outsourcing dynamic, we offer our extensive expertise and experience to sponsors who leverage that expertise to give themselves the best chance of successfully supplying their clinical trial. From the beginning of every ▶

relationship, a mutual commitment is to put the patient first. While this commitment is a common thread binding all collaborations, there are many aspects of service delivery which can be adapted to the size, requirements, and strategic focus of the individual trial sponsor.

The contrast between small pharmaceutical firms and larger corporations is noticeable smaller companies, given their limited resources, often rely on CDMOs, to contribute significantly to their clinical trial. By relying on our technical know-how, years of industry experience, regulatory expertise and global network, sponsors can focus their internal resources elsewhere. Often approaching us with less clinical trial experience and fewer resources, we work hand-in-hand with sponsors of smaller size to help understand and establish their clinical trial outsourcing requirements. CDMOs often find themselves fulfilling multiple roles because of their variety of service offerings.

The role of a CDMO tends to be more specific, but by no means less significant, when performing outsourcing services for larger pharmaceutical companies, as these collaborations are much focused. With considerable clinical trial experience, these sponsors often approach CDMOs with defined requirements in mind, knowing exactly what they seek from the relationship. Collaborations with large pharma often demand a high level of integration with systems, workflows and procedures, but can provide an opportunity for both parties to benefit from sharing best practices and continuous improvement.

Each collaboration has diverse needs and CDMOs need to be agile and adaptable in their approach, tailoring offerings to meet each sponsor's requirements. Understanding the unique needs and challenges sponsors face CDMOs can often adopt a flexible model, ready to provide solutions, either comprehensive or modular, depending on the company size. To effectively execute these services and fulfil sponsors' outsourcing needs, the establishment and nurturing of strong working relationships is key.

At the heart of each partnership is project management. Whether it's a complete project for a small company or a specific service for a large firm, CDMOs can employ a relationship-centric approach to project management with project managers acting as relationship builders. In my experience, this means forging a connection with the sponsor's team from the get-go to understand their goals and concerns, aligning our efforts to their strategic vision. Once an initial relationship is established, transparency is crucial to achieving a successful collaboration. The project manager works to foster open and frequent communication with sponsors, providing regular progress updates and highlighting risks. Ensuring complications are tackled as a team and taking opportunities for lessons learnt are some of the ways project managers can encourage trust and mutual respect.

> Clinical trials drive drug development, fostering intricate collaborations.

The outsourcing relationships we as project managers build, be it with small start-ups or multinational giants, are fuelled by transparency and respect with a shared purpose at the core - to bring safe therapies to patients. This shared purpose reinforces the importance of the works CDMOs do, fuelling commitment to uphold the highest quality standards, continually innovate to enhance offerings and ultimately provide effective outsourcing solutions that enable clinical trial sponsors to bring life-changing therapies to patients.

Effective Collaboration with Outsourcing Partners: Insights from a Clinical Trial Sponsor:

From the perspective of a clinical trial sponsor, partnerships with outsourcing entities such as CDMOs and CROs are a crucial component of their strategic outlook. These relationships are more than mere contractual agreements. They are the bedrock upon which we lay the foundation for our trials, and hence, they deserve careful cultivation, guided by the principles of mutual respect, transparency, and shared commitment.

One vital aspect that shapes these partnerships is the size and scale of the pharmaceutical company in question. For smaller pharmaceutical companies or biotech's, these outsourcing partnerships often hold the key to their trial execution. With a typically limited internal capacity, they lean heavily on the expertise and infrastructure of their partners. In such cases, the outsourcing entities might handle multiple tasks, ranging from trial design and patient recruitment to data management and statistical analysis. The collaborative relationship, therefore, needs to be robust, resilient, and flexible, to accommodate the diverse needs and inherent uncertainties of smaller-scale operations.

On the other hand, larger pharmaceutical companies often leverage outsourcing to supplement their in-house capabilities. They may outsource specific tasks to multiple specialized entities, capitalizing on each partner's unique strengths. Given the larger scale and complexity, these collaborations require precise coordination, seamless communication, and diligent oversight to ensure harmonious integration with the in-house operations. Irrespective of the size, mutual understanding and aligned objectives remain pivotal, creating a partnership that is not just transactional but transformative.

Creating such a collaborative atmosphere with outsourcing partner's calls for transparency in communication and operations. It means creating spaces for open dialogue, acknowledging, and addressing concerns, and

appreciating the expertise that our partners bring. We have found that regular check-ins and performance evaluations help keep the partnership aligned and dynamic, allowing us to quickly address issues and adapt to new circumstances.

A cornerstone of these successful collaborations is the establishment and rigorous monitoring of Key Performance Indicators (KPIs). These quantifiable metrics serve as the North Star, guiding the course of the collaboration and providing unbiased, tangible feedback on its effectiveness. Be it timelines, budgets, patient recruitment rates, data quality, or regulatory compliance, KPIs span across all critical domains. For these KPIs to serve their purpose effectively, they should be mutually agreed upon, directly relevant to the trial's objectives, and consistently tracked. Regular evaluations against these benchmarks not only provide an objective gauge of the collaboration's health but also act as early warning systems for potential issues. In the grand scheme of things, the insights gleaned from these metrics and the improvements they drive form an invaluable part of the partnership, contributing significantly to the shared mission of advancing clinical trials.

An essential element of this collaboration is the recognition of shared goals. We are, after all, united in our pursuit of advancing medical science and improving patient outcomes. Encouraging a sense of shared mission and celebrating the milestones together fosters a relationship that extends beyond the business confines. It is this deeply rooted sense of shared purpose that ultimately makes these collaborations successful and paves the way for future endeavours in clinical trial advancements.

The Synergy of Collaboration: Creating a Success Story:

In the narrative of clinical trials, the collaboration between trial sponsors and outsourcing partners often stands as a pivotal force, driving the breakthroughs that shape medical advancement. This intertwined relationship, rooted in shared dedication and synergistic expertise, facilitates a collective pursuit of pharmaceutical breakthroughs. It's the essence of such collaborations that weaves the success stories of innovative therapies reaching patients across the globe.

From the perspective of the manufacturing partner, the journey commences with absolute transparency. By providing a detailed insight into manufacturing processes, rigorous quality control measures, and possible risk landscapes, the partner effectively lays a foundation of trust. In response, trial sponsors should reciprocate with open communication regarding their expectations and concerns, fostering a dynamic communication channel conducive to early problem identification and resolution.

This collaborative journey is not confined to the realm of problem-solving; it extends to encompass shared learnings and ongoing process improvement. In an industry where

innovation reigns, each interaction, success, or setback provides invaluable learning opportunities. Any unforeseen event in the manufacturing process transforms from being a roadblock into a valuable lesson that fortifies systems, refines protocols, and strengthens the partnership.

Alignment of goals and objectives stands at the core of a successful collaboration. When a manufacturing partner shares in the mission of the trial sponsor, it infuses an unparalleled sense of commitment and engagement. This mutual investment transcends transactional relationships, forging a bond that encourages exceeding contractual obligations and fosters a sense of genuine partnership.

Shifting the lens to the trial sponsor, collaborations with outsourcing partners mean acknowledging and appreciating their unique value. Each clinical trial brings its distinct challenges, demanding novel solutions that a team of diverse expertise can effectively create. By cultivating an environment of mutual respect, trial sponsors can empower their partners to contribute their unique insights, thereby amplifying the trial's problem-solving capacity.

The nurturing of these partnerships must be a continuous process. Routine evaluations, open discussions about challenges, and acknowledgments of success are crucial to maintaining a robust relationship. These evaluations serve more than administrative purposes; they act as drivers for positive change, enhancing efficiency and solidifying the bond of mutual trust and respect.

Collaboration in the realm of clinical trials is inherently dynamic. It calls for adaptability, a thirst for learning, and an unwavering commitment to shared objectives. As the landscape of clinical trials evolves, the relationships underpinning their success must evolve in tandem. While challenges may be inevitable, they transform into opportunities for growth with the right collaborative approach, strengthening the partnership and ensuring the smooth progression of clinical trials.

True success transcends the boundaries of delivering a product on time and within budget. It encapsulates leveraging collective expertise to drive innovation, safeguard patient safety, and contribute to the shared mission of improving global health outcomes. This comprehensive view of success stands as a testament to the transformative power of collaboration. It demonstrates how, through shared commitment and expertise, trial sponsors and outsourcing partners can form partnerships that not only meet but

also exceed the multifaceted objectives of clinical trials.

In essence, the story of collaboration is indeed a success story. It illuminates the potential of collective expertise and underlines the premise that individual capabilities, while important, are magnified exponentially when synergistically combined. It underscores the idea that the innovative theories of today can, through effective collaboration, transform into the life-changing therapies of tomorrow.

Conclusion:

The outsourcing landscape in clinical trials is dynamic, presenting numerous opportunities for growth and innovation. However, the key to unlocking these opportunities lies in the ability to build and nurture effective partnerships. As the pharmaceutical landscape evolves, the relationships between trial sponsors and their outsourcing partners must also evolve, adapting to new challenges and capitalizing on emerging opportunities. The success of clinical trials and the subsequent delivery of ground-breaking therapies to patients hinge on the strength of these partnerships, making them a cornerstone of modern pharmaceutical development.

By intertwining the perspectives of a manufacturing partner and a trial sponsor, this article provides a nuanced understanding of how best to build and maintain these essential relationships. The common thread tying these perspectives together is the belief that fostering successful outsourcing relationships is not a mere business transaction; it is a journey of collaboration, learning, and shared success. Together, we can unlock the full potential of outsourcing in clinical trials, accelerating the pace of innovation and bringing life-changing therapies to patients more efficiently and effectively. ■

AUTHOR BIO

Joab Williamson is the Director, Program Management at Faron Pharmaceuticals, a clinical stage biopharmaceutical company developing novel treatments for medical conditions with significant unmet needs caused by dysfunction of our immune system. Joab has a range of experience in pharmaceutical project management, holds an MBA and is a certified lean six sigma black belt.

Tegen Winstanley is an experienced Project Manager at Catalent, a leading global CDMO. Tegen has significant experience developing and building relationships with industry peers. The opinions and views expressed in this article are my own and do not reflect the opinions of my employer, Catalent. The following article is based upon my experience as an individual in the pharmaceutical industry and Catalent does not warrant its completeness or accuracy.

Perspectives on the Future of Metabolism-targeted Therapeutics in Precision Oncology

Every living cell, including cancer, depends on metabolism. The metabolic dysfunction associated with cancer was recognized nearly 100 years ago by Otto Warburg and is now recognized as an important hallmark of the disease. In addition, metabolic alterations have been reported as an important event during early stages of cancer progression. In precision medicine, drugs designed to block altered metabolic functions are integrated, but their clinical effectiveness remains uncertain. Metabolic targeted therapeutic paradigms are still evolving, and this opinion discusses the challenges of developing and implementing these drugs.

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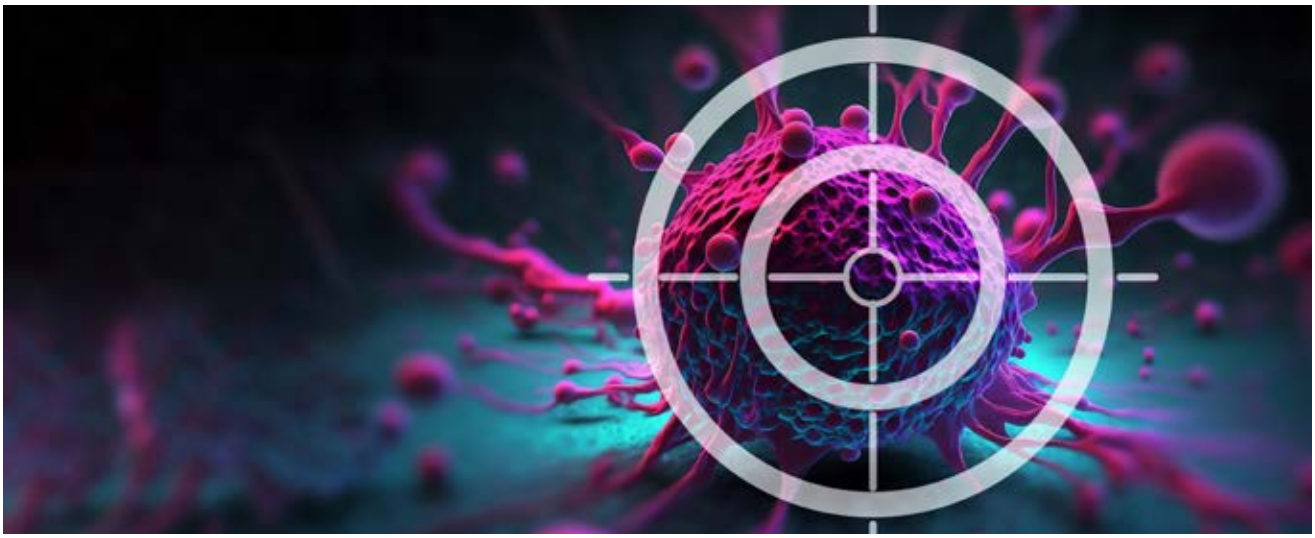
Although genes encode cellular functions and fates, with DNA acting as an inert cookbook, metabolism is the lifeblood of every living cell. Every living cell is governed by metabolic processes that consist of thousands of biochemical reactions that serve as architects, supply chains, energy sources, chefs, signaling and timekeepers, etc. Consequently, healthy living is characterized by a physiologically well-regulated metabolic state, and pathological diseases are characterized by metabolic imbalances. Disease symptoms are primarily manifestations of metabolic disturbances occurring within sick or affected cells. As a result, clinical biochemistry is an essential part of modern medicine for diagnosing and treating most diseases, such as diabetes, metabolic disorders, oncology, cardiology, neurology, organ failures, allergies, infectious diseases, and various genetic conditions. The fact that metabolic changes are closely related to diseased states makes it vital that drugs used for disease treatment do not disrupt normal metabolism. It is therefore essential that metabolic investigations focused on mechanism of action, safety assessments, and pharmacokinetics and pharmacodynamic properties are conducted in pharmacological drug discovery and development so that FDA approval can be gained for every new drug to be introduced to the clinical setting. ▶



Metabolic dysregulation is a hallmark of cancer. It is important to recognize that cancer is a disease characterized by uncontrolled proliferation. It is impossible for any living cell, including malignant, to survive or proliferate without metabolic support. When it comes to pharmacological interventions that target cancer metabolism, a better understanding of the differences between physiological metabolisms and (cancer) pathological metabolic imbalances is necessary, as well as the interplay between them. The development of metabolic targeted therapy for cancer depends on establishing these fundamental concepts, and this perspective discusses some of these fundamental concepts as well as progress and challenges facing the clinical development of cancer therapies that disrupt dysregulated metabolism.

All living creatures of this nature rely on metabolism for survival. From our understanding about the biological relationships between plant and animal cells, it becomes clear that carbon dioxide, water, oxygen, and glucose are essential for respiration, energy transduction, as well as are the fundamental metabolites necessary for cell division and growth. Pentose sugars, derived from glucose, serve as the backbone upon which genetic codes are imprinted, preserved, and propagated. Consequently, glucose metabolism is the most vulnerable function that can be altered to initiate and spread cancerous growth. Accordingly, Otto Warburg's first and foremost fascinating discovery, which laid the foundation for cancer biology in 1923, revealed that cancer cells require glucose and oxygen (aerobic glycolysis), but he also observed strange lactate production, which is only expected to occur when glucose is metabolized without oxygen. Despite this long-standing recognition, therapeutics targeting metabolic functions in cancer only began to emerge in the past few decades. A major reason for the slow progress in discovery and development of cancer metabolism-targeting

drugs is that the biochemical principles behind the "Warburg effect" remain obscure. In addition, enzymes that participate in metabolic pathways use complex biochemical principles, so changing the metabolic activity by mutation or overexpression alone is not sufficient. As metabolic activity is influenced by feedforward activation, feedback inhibition, post-translational modifications, concentrations of substrates, products, and cofactors, it is hard to understand these dynamics. Although metabolic imbalances are directly known to contribute to cancerous growth, recent research has shown that these imbalances also become important barriers through which cancer cells escape natural antitumor immune activity and enable developing resistance to standard treatments and immunotherapy. When it became apparent that altered metabolism interfered with the effectiveness of standard treatments (chemo/radiotherapy), targeted therapies (small molecules or immunotherapy),

Drug	Target	Trial; Cancer types	Combination
Telaglenastat (CB-839)	Glutaminase (GLS1)	Leukemia Colorectal cancer Metstatic renal cell cancer Recurrent multiple myeloma Platinum-resistant BRCA-wild-type ovarian cancer Solid tumors Advanced Non Small Cell Lung Cancer Astrocytomas EGFR-mutated stage IV NSCLC KEAP1/NRF2–mutated NSCLC	 Panitumumab and irinotecan Cabozantinib Carfilzomib and dexamethasone Niraparib or talazoparib [PARP inhibitors] Palbociclib (cyclin-dependent kinase inhibitor) Sapanisertib (mTOR inhibitor) Radiotherapy and temozolomide Osimertinib (kinase inhibitor) Embrolizumab/chemotherapy
Sirpiglenastat (DRP-104)	Glutamine-utilizing enzymes	Advanced solid tumors Advanced solid tumors	Single agent Atezolizumab
AZD3965	(Lactate efflux) monocarboxylate transporter 1 (MCT1)	Advanced solid cancers and diffuse large B-cell lymphoma	
Devimistat (CPI-613)	Ketoglutarate dehydrogenase (KGDH) and pyruvate dehydrogenase (PDH)	Relapsed/refractory AML Pancreatic cancer Burkitt's lymphoma Cutaneous T-cell lymphoma	cytarabine/mitoxantrone modfied FOLFIRINOX
IACS-010759	Mitochondrial complex I inhibitor		
INCB001158 (CB-1158)	Arginase I		
TVB-2640	Fatty acid synthase (FAS)	High-grade astrocytoma HER2-positive metastatic breast cancer KRAS-mutant NSCLC	Bevacizumab Paclitaxel and trastuzumab Rastuzumab and taxane
Ivosidenib (AG-120) Enasidenib (AG-221) LY3410738 DS-1001b Olutasidenib (FT-2102 Vorasidenib (AG-881)	Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2)	AML AML Glioma Glioma Glioma Glioma	 Nivolumab (anti-PDL1)
aminopterin methotrexate trimetrexate pemetrexed	Folate metabolism Folate metabolism Folate metabolism Folate metabolism		
5-FU	Thymidylate synthase		
6-mercaptopurine (6-MP) 6-thioguanine (6-TG) Cytarabine and gemcitabine	*de novo* purine biosynthesis *de novo* purine biosynthesis incorporates into the DNA		
2-deoxy- D -glucose PI3K inhibitors Metformin Dibenclamide PFK158	Gycolysis Gycolysis Gycolysis Gycolysis Gycolysis	Leukemia Advanced solid tumors	
AT-101	Gycolysis	non-small and small cell lung cancer refractory solid tumors head and neck squamous cell carcinoma glioblastoma multiforme	Paclitaxel and carboplatin Docetaxel

Table 1. Pharmacological drugs designed to target cancer metabolism.

drug development strategies changed. As a result, several novel agents targeting glucose and metabolic functions were developed and tested either as single agent or in combination. A review of clinical evidence on such drugs aimed at targeting metabolism from the past few decades indicates that drugs that directly inhibit nucleic acid synthesis (methotrexate, 5-FU, pemetrexed, cytarabine, gemcitabine, etc.,) showed greater efficacy than drugs that targeted glucose/glutamine metabolism enzymes (see Table 1). So far, direct targeting of glycolytic, citric acid cycle and glutamine metabolic enzymes has yielded mixed results, but some promising results are being seen as drug combinations are being investigated in clinics (see Table 1). On the biological level, cancerous growth is indeed influenced by metabolic modifications, but so far, therapeutic interventions targeting these mechanisms have not yielded dramatic results. Although disappointing, it is crucial to understand that our incomplete biological knowledge is the greatest challenge, rather than pointing fingers at rationale for targeting metabolic functions in cancer treatment. (Table 1)

For a better understanding of why targeting metabolic pathways in the clinic is not yielding the therapeutic benefits expected and what needs to be done to improve on these, one must be able to take a holistic view of metabolic networks as they relate to signaling and functional pathways. It would be unfair to compare metabolic inhibitors that induce DNA damage to inhibitors designed to interrupt metabolic pathways. As unrepaired DNA damage is lethal for cell survival and interrupted metabolic pathways and/or energy deprivation would simply stop cells from dividing, these differences are explained partly by their mechanisms of action. Additionally, metabolic inhibitions could be overcome through anaplerosis (backfilling metabolic reactions), exchange of metabolites between nearby or distant cells, metabolic compensation, or pathway rewiring, which are all dynamically adaptable processes. Therefore, in drug discovery, it is crucial to identify the Achilles' heels of metabolism and develop appropriate targeting and or co-targeting strategies to ensure that compensatory metabolic and signaling responses are mitigated. Therefore, prior to even planning the path for target discovery, it is necessary to have comprehensive knowledge or conduct appropriate research to bridge gaps with existing knowledge. Once the drug has been developed, in addition to assessments of its targeted mechanism and cancer, further rigorous investigations must be conducted to identify the effects on global metabolic and signaling pathways, and this knowledge must be gathered before clinical trials can begin.

Although our knowledge of cancer biology is incomplete, a compendium of molecular and metabolic basis of disease progression in cancer does not exist either. In spite of rocket science being very complex, its success is largely due to the establishment and availability of blueprints from design to

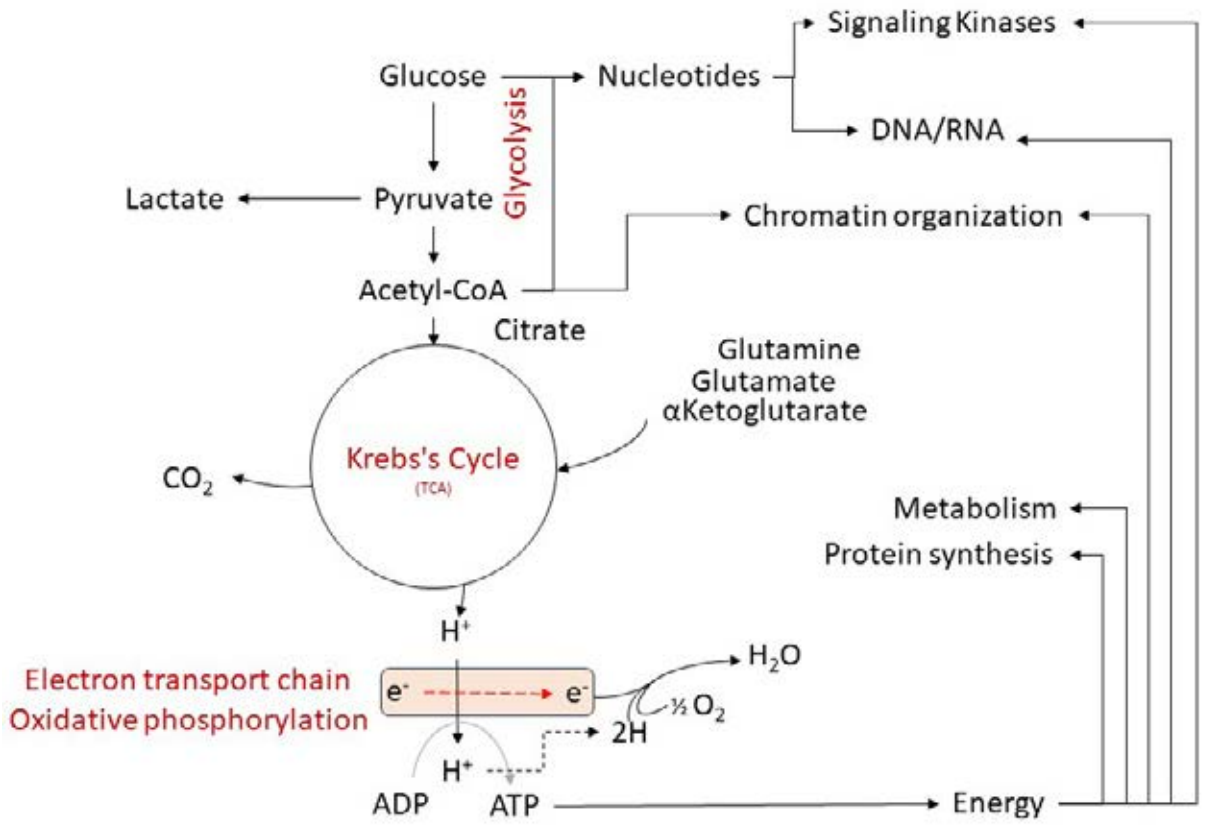


Figure 1. Metabolic wiring and cellular functions.

launch, collective responsibility shouldered by exhaustive collaborative efforts from diverse disciplines. It is unfortunate that disorganized research and the loss of unrecognized meaningful discoveries prevent millions of lives each year from being saved from cancer. While life-saving cancer research is progressing and better treatments such as precision medicine are becoming available, death rates may seem to be declining, but the sad truth is that the total number of deaths continues to rise. Precision medicine is therefore crucially dependent on improving our understanding of cancer progression at both molecular and biological levels. Cancer is generally considered to be a heterogeneous disease, but recent studies have shown that many different cancer types have linear biological patterns throughout their progression. Among these discoveries, genes associated with metabolism (Citric acid cycle, oxidative phosphorylation and electron transport chain) are found to increase at very early stages of cancer progression. Further genes associated with glucose, nucleotide and lipid metabolism were also found to be highly elevated in progressed cancers. As metabolism is deeply interconnected with virtually every cell function, simply accelerating that function has a profound impact on the ability of ▶

cancer cells to proliferate, resist treatment and immune responses, and spread rapidly. This makes metabolism a powerful force to be reckoned with when it comes to drug discovery. An overview of the impact of metabolism on major cellular functions is provided in Figure 1.

The increased glucose metabolism associated with cancer is a fundamental biological property, which led to the establishment of fluorodeoxyglucose (FDG) positron emission tomography (PET) as the most reliable tool in cancer diagnostics. While oxidation of glucose is the primary source of energy, cancer cells use amino acids such as glutamine/glutamic acid as alternate energy fuels, reducing the burning of glucose, which causes lactate production as observed by Otto Warburg. According to recent studies, these metabolic changes are merely meant to facilitate the redirection of glucose's carbon backbone into nucleotide synthesis. In malignancy, the synthesis of nucleotides may appear intuitively as a catalyst for facilitating DNA and RNA synthesis and promoting cell proliferation. However, nucleotides are more versatile molecules, carrying high energy transfers and facilitating thousands of reactions within the cells.

Nucleotides exert enormous biological influence through their participation in 3494 metabolic reactions, their roles as cofactors in proteins (996) and protein complexes (1007), and their roles as reactants/messengers in signaling pathways that activate or inhibit 668 pathways (Figure 2). In addition, breakup analyses of major nucleotides show that ATP, a component of 636 metabolic reactions and 300 protein complexes, is essential to a variety of cellular functions, including DNA/RNA synthesis, repair, organ function, cell death, metabolic function, signaling function, and transport function (Figure 2). In addition, GTP, UTP, and CTP play an important role in macromolecular synthesis, transport, signaling, as well as metabolism (Figure 2).

In conclusion, the magnitude of biological influences impacted by nucleotides, which themselves come from a very modest carbon source, namely glucose, indicates why cancer cells attach such importance to the efficient ▸

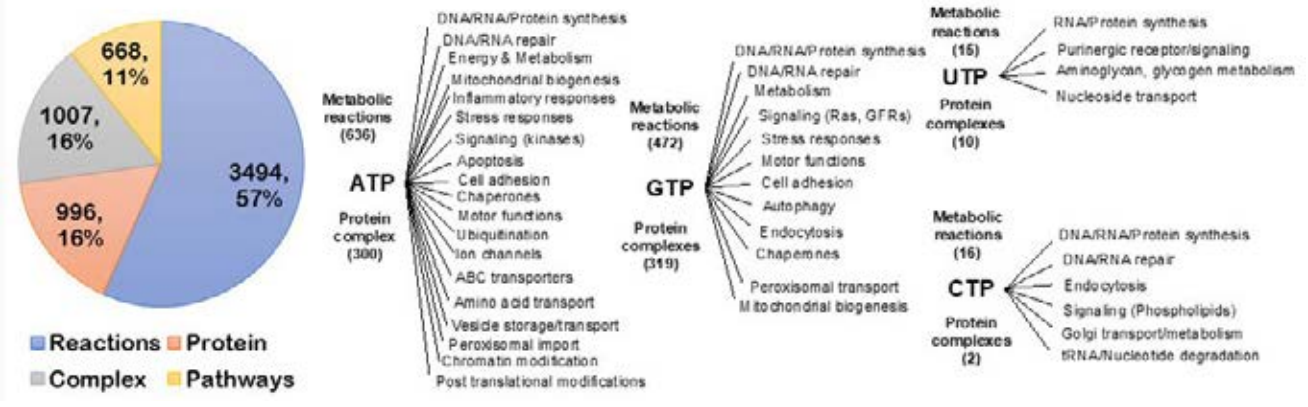


Figure 2. Cellular functions regulated by nucleotides.

handling of glucose. Blocking glucose (or dependent) metabolism, which is necessary both for cell survival and death, puts cancer cells in double jeopardy and therefore spares them the killing effects induced by metabolism-targeted therapies. As a result, most metabolic blockades simply prevent cells from dividing, causing them to remain suspended for prolonged periods of time, until conditions are reversed, when the cells can begin dividing again. There has been evidence that such effects can be observed in animal tumor models treated with glibenclamide (antidiabetic drug) (unpublished data), and as reported in several studies involving metformin, etc., In designing rationale drug combinations, such important lessons can help us apply metabolic principles to create effective therapies. As an example, we showed that depleting nucleotides through inhibiting a vital lipid metabolism improved 5-fluorouracil's (chemotherapeutic) cell killing activity in lymphoma, which otherwise would not be active. To summarize the current status of metabolic targeted cancer treatments, the development and design of drugs has been phenomenally successful, but the clinical outcomes of implementing these therapeutics as cancer treatments are surprisingly less impressive. Several roadblocks exist, including gaps in knowledge accumulated so far on understanding the wholistic nature of metabolism, its ramification with cellular pathways, how these are dynamically rewired, etc., as cancer progresses, has not been clearly established. As metabolic or signaling systems use complex networks of pathways, if blocked, they can take alternative routes. That makes it extremely challenging to develop appropriate therapeutic strategies. The challenges associated with understanding and navigating biological dynamics can be overcome by possibly integrating artificial intelligence in a way that enhances accuracy and provides benefits in clinical care in the future.

References are available at www.pharmafocusamerica.com

AUTHOR BIO

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Big Data Analytics - A Revolution in the Pharmaceutical Industry.

"A Pharma Focus America's initiative fostering exclusive and open discussion on industry trends"

Welcome to our panel discussion on "Big Data Analytics - A Revolution in the Pharmaceutical Industry." Our esteemed panelists are leading experts driving transformative change in pharmaceuticals through data analytics:

Michael N. Liebman: Managing Director, Co-Founder at IPQ Analytics, LLC
Catherine Hall: Head of GXP Quality at Egnyte
Christopher Bouton: Ph.D.: Head of AI, SVP at Certara

The Discussion Ahead:

In this panel discussion, our panelists will explore how big data analytics is reshaping drug discovery, clinical trials, patient care, and regulatory decisions. Join us as we uncover the challenges, opportunities, and ethical dimensions of leveraging data to advance healthcare.

Let's begin the conversation!

With the abundance of real-world patient data, how can big data analytics drive the identification and validation of new therapeutic indications for existing drugs, leading to faster and more cost-effective drug development?

Michael N. Liebman: I would actually rephrase this question and put the goal first…to achieve faster and more cost-effective drug development, how can we best use real-world patient data and big data analytics. When we do this, we are better able to focus on the current challenges and then see where these approaches can be applied to reduce them. Faster and smaller trials could be achieved by recognizing that most diseases as defined in clinical trials inclusion/exclusion criteria and, even earlier, as used for initial target selection are really complex disorders under an umbrella diagnosis and code which contribute to their high rate of failure for lack of efficacy. Real-world patient data, i.e. EMR data not claims data, should be used to stratify the disease to enhance target selection and establish the potential patient population size to evaluate commercial potential much earlier and more accurately. Furthermore, clinicians recognize the differences between real-world patients and clinical trial patients and addressing greater alignment of patient recruitment in trials with real-world patients could enhance the commercial opportunity beyond development cost-savings.

Personalized medicine heavily relies on patient data. How can the pharmaceutical industry strike a balance between utilizing patient data to tailor treatments while respecting patient privacy and complying with evolving data protection regulations?

Catherine Hall: I think to answer this question you have to first consider that some things have not changed when it comes to data security and privacy. When patients volunteer to participate in a clinical trial they heavily rely on the trial investigator, sponsor, and sub processors to ensure their personal information is treated with confidentiality and do all things possible to protect it from harm. Personalized medicine, decentralized trials, and electronic capture of patient outcomes now make complete de-identification insufficient for protecting trial data. However, today's technology is able to isolate and obscure data based on multiple parameters, so it is not a matter of needing to strike a balance but rather a need to have thoughtful intent and planning focused on the data itself. With careful mapping of data across the various e-clinical systems utilized in the trial, appropriate technical and operational measures can be put in place to effectively protect the data not only from any potential threat but also restrict its access to only those that must know the information from the point of data collection to data archive. The industry is thus best positioned to ensure at the foundation of any trial that there is a cross-functional risk assessment that works to ▶

identify what data is truly required to be collected and ensure that there are appropriate and tested measures in place to secure that data from end to end across the e-clinical network of computerized systems.

Christopher Bouton: I believe that there are a number of ways in which the pharma industry is already attempting to strike this balance. That said there is going to be continually more and more data generated and that data can help to develop better, more specific and efficacious medicines on a personalized level if done correctly. As a result, the pharma industry will need to continue to work with patient communities and individuals in order to properly protect patient -level data and adhere to evolving regulations.

The integration of real-world evidence (RWE) is gaining traction in regulatory decision-making. How can big data analytics enhance the reliability and acceptance of RWE as a complement to traditional clinical trials in drug approval processes?

Michael N. Liebman: We have to understand that RWE is typically comprised of real-world clinical data, e.g. EMR's, lab results, and real-world business data, e.g. claims data and pharmacy records. The latter commonly reflects the clinician's need to address reimbursements and minimize denials of claims, and frequently (more than just frequently) does not reflect the true clinical picture of the patient that is more comprehensively captured in the EMR and clinician notes. This does not invalidate either data source, only differentiates how their analysis should be interpreted and presented. Current coding, e.g. ICD-10 codes, are an attempt to bridge this gap but are not adequate to reflect the true complexity of the patient and the disease and frequently present challenges to the physician by requiring them to place the patient and their evaluation/diagnosis into a "box" in which they do not really fit.

Catherine Hall: I think the key to accepting any data is to understand not only the data itself from origin to report, but also the context in which the data was collected, transformed and stored. For example, utilizing the average blood pressure of an adult female easily becomes muddled when one data set was taken during from patients participating in an early pregnancy trial, and another data set is from a diabetes trial for geriatric patients. Good data analytics platforms at their core help to retain the contextual metadata in sync with the data itself to help assure that the final data is well understood. In this way, data previously collected from other sources, can be effectively utilized given the assurances to accurately represent a data set that would be otherwise collected within the parameters of the trial it will be compared to.

Advanced analytics can optimize clinical trial design, recruitment, and monitoring. How are data-driven approaches

reshaping the design of adaptive trials and enabling the industry to make quicker go/no-go decisions?

Christopher Bouton: We're actually just at the very beginning of a wide range of novel advanced analytics approaches that can be applied to clinical trial design, recruitment and monitoring. Fundamentally these approaches have to do with better pattern detection at multiple levels. For example, we can now use GPT / large language model (LLM) driven AI approaches to do a better job of clinical trial outcomes aggregation and associated model based meta-analysis. There are also faster and more efficient ways to apply generative AI to all of the documentation necessary for trials and regulatory filings. These approaches of course need to be overseen by experts in these fields in order to make sure that the technologies are generating the correct outputs. This is the very beginning of a decade's worth of these types of advancements in trial design and implementation which will hopefully yield better outcomes and more efficacious medicines for patient populations.

> Incorporating SDOH into patient care must consider patient culture, trust, and perspectives, going beyond guidelines

Big data has the potential to empower patients in their healthcare journeys. How can the pharmaceutical industry leverage data analytics to enhance patient engagement, improve treatment adherence, and ensure equitable access to therapies?

Michael N. Liebman: There is increasing recognition of the importance for considering and incorporating social determinants of health (SDOH) into patient management, from engagement and diagnosis to treatment adherence. It is also being applied to understand how to make access to care more equitable. While this is a critical step towards incorporating patient-centricity, to a certain extent it is missing some critical perspectives, namely patient culture and trust. SDOH tends to establish criteria and guidelines and makes efforts to close gaps that may exist but does not adequately address the reality that an individual, and population group, may possess significant cultural differences in prioritization, etc. that can limit such SDOH approaches. An additional level of complexity comes from the patient's perspective of trust, trust in what the physician says, what the drug "promises", and largely what has been the "historical" experience. It is critical to recognize this in efforts around "DEI" which need to focus more on the patient perspective and not solely "checking the box". We needs to do much more listening to the patient and to their trusted physicians to understand how to achieve these goals. ▸

Christopher Bouton: We first need to refer back to the first question and state that of course the use of big data in this context must be conducted with the utmost focus on patient data privacy and protection. That said, the "voice of the patient" is much louder and more prevalent now. Multiple forums including social media, telehealth, and doctor/patient secure messaging, and other means allow for the healthcare system to learn much more about what is important to patients and what their challenges are. In a similar manner to the last question, the core additional activity that we can apply now to these forms of data is better, AI-powered pattern recognition. Instead of having to build ontologies or heuristics to find particular patterns in the data, we can now take all of that messy data and use GPT / LLM models to sift through the content to find important patterns and unexpected discoveries. In order to do so, novel architectures for running these technologies on data in a secure, behind-firewall manner are going to become critical. These systems also need to be specialized to these areas so that they can find the most salient patterns in the data.

AI-powered algorithms are becoming essential in pharmacovigilance for adverse event detection. How can the industry ensure transparency and accountability in these algorithms while addressing concerns about bias and algorithmic decision-making?

Catherine Hall: I am going to separate bias from algorithmic decision making and address the latter first. Whether information is human generated or computer-generated I think what we all want to know is how the decision was arrived at as being able to reconstruct the way the decision was made is a core principle of good Clinical Practices. I feel the issue is not in the idea that an algorithm made the decision in as much as that many times it is not obvious how the AI came to its decision. For example, if you ask an AI to group trials into groups, you may be expecting to see the trials arranged by Phase of Development or therapeutic area or patient population, but instead you might find the AI grouped the studies in a way that makes no sense to you at all. Does this result imply AI is not yet reliable, or does it mean there is yet another way to organize the data that you have not thought about? Reality is if you cannot understand how AI arrived at the result, you are more likely than not to discount it. This applies to bias as well. Bias is based on the experiences we have had, and a developed preference for outcomes based on those experiences. If an AI is trained to learn on a particular set of data, it is going to apply its experiences to arrive at similar outcomes. Just as we value diversity and having a difference in opinion to debate the problem, AI, to be more trusted, will need to be exposed to a diversity of data to ensure that the problem has been analyzed from a variety of experiences. It is only through a variety of experiences treated equally can bias truly be eliminated. The question is, if humans choose to expose the AI to data, it will be biased toward the data being adopted. Most likely it will and just as we

parse our trust toward others based on our knowledge of their experience, AI too will be judged on the diversity it has been exposed to.

The pharmaceutical industry generates diverse data across research, clinical, and commercial domains. How can companies effectively integrate and analyze data from disparate sources to gain holistic insights for informed decision-making?

Catherine Hall: If we are to make bigger strides toward wholistic data sets we must come together as an industry on the adoption of true data standards. More often than not the issue with data integration and compilation of large data sets is that the data must be transformed to one standard or another. When working with highly precise data, these transformations can introduce inconsistencies depending on the data mapping or other processes employed. Even something as simple as time can be difficult to align considering all of the various time zone rules, not to mention the precision of the tools used to collect it. While CDISC has gone a long way to begin the process of standardization in the Industry, there are plenty of exceptions to the rules that still exist. The standards also cannot just apply to the data points themselves but also to metadata associated with the data. As stated before, to reliably trust in the data, one must have assurances of the context around the data. If that context is not clearly associated, it cannot be well understood and may not be considered reliable.

Christopher Bouton: What we're seeing is a move away from traditional data integration strategies that have to do with centralized storage of data from across an organization (e.g., data warehouses and/or data lakes). Instead, more flexible, modern architectures such as data fabrics allow for an organization's data to be distributed and instead of trying to bring the data to the architecture, we can bring the architecture to the data. We've seen significant benefits of these kinds of approaches both for data integration as well as for the application of advanced AI analytics against the data stored in those systems. Furthermore, AI analytics approaches can help with the derivation of insights from messy data as well as helping to clean and organize data even when entity naming, and other attributes of the content aren't controlled. This is because these novel analytics approaches are far more robust to variants than traditional data cleaning and harmonization / normalization approaches.

As data becomes a valuable asset, collaborations between pharmaceutical companies and data-driven tech firms are increasing. How can these collaborations ensure a win-win scenario for data providers and pharmaceutical innovators while maintaining data security?

Michael N. Liebman: These collaborations are potentially invaluable…but! There is an absolute need for data security and there are increasing use of federated ▶

data and learning models that can help maintain and comply with both privacy and provenance issues. A greater concern is that these efforts focus on "more is better" whereas Mies van der rohe stated that "less is more". In an effort to collect more data, i.e. to apply AI/ML, etc, there is a. tendency to minimize the need to emphasize interoperability (among databases) over potential quality issues. Most, if not all, databases inadequately annotate the data within a data field especially in clinical data where the testing/laboratory modality and/or specific algorithm used to measure or compute is not included in the annotation. The example I use is the Glomerular Filtration Rate which is estimated, not measured, as eGFR. There are 5 different equations to generate eGFR, each developed for a different reason and with different populations, and two incorporate a "race adjustment factor" which is incorrect. Incorporation of eGFR into typical data analytics without recognizing these differences can only contribute to increasing the noise, i.e. inaccuracy, of the results.

Catherine Hall: Data being an asset is the key mentality to focus on here. So often data is taken for granted as a necessary item sought after for other means, but data is not as often treated as a true asset in itself. For many pharmaceutical companies, the value of data is that it extends beyond one single use. Did this trial succeed or not?

The technology industry however understands the value of data as a reusable asset. Through partnership and collaboration, the technology sector can help the pharmaceutical industry refocus their vision of data and structure it in such a way that can maximize its value. By moving more and more toward data standards and cross network data management practices, the measures needed to protect and secure data can also be more reliably applied. The relationship between people, process and technology is one that is often referred to, but as the data has grown in complexity from the growing volume, variety and velocity, gaps between these three factors have grown as well. It is only through true partnership that expertise can be better shared, processes can better align and technology can better support to ensure the quality controls are in place that allow data to be verified and trusted to hold its value.

How can predictive analytics enhance post-market surveillance, assist in forecasting demand, and inform strategic decisions in drug lifecycle management, ultimately leading to optimized resource allocation and patient safety?

Michael N. Liebman: Predictive analytics, if based on enhanced disease and patient stratification as noted earlier in this discussion, can be much more successfully applied in post-market surveillance because a more accurately "labelled" patient/market will have been identified for the product. Also, as noted, earlier stratification of the disease and application in target selection, will lead to better defining the potential patient population in terms of size and specific characteristics. These could naturally lead to better

resource allocation to patient groups in these target populations and the physicians who treat these patients. This approach could dramatically reduce the preponderance of mis- and missed diagnoses, inappropriate testing and inappropriate prescribing that currently exists.

Christopher Bouton: As noted in the responses to other questions on the panel, most of this comes down to the data being analyzed, how one is bringing that data together, what sorts of patterns one is looking for and what kinds of analytics approaches you're using to identify those patterns. This is no different in the post-market space where a better understanding of how a therapeutic is performing in the market can help to inform areas such as adverse event reporting for safety all the way to therapeutic product demand for supply chains and resource allocation. We see the advent of both data fabrics as a novel more flexible and modular form of data integration along with AI analytics for robust pattern detection as two critical advances in helping to extract signal from noise for better decision making in these spaces.

> Improved patient stratification enhances post-market surveillance, leading to better resource allocation and reducing misdiagnoses and inappropriate prescribing

Given the rapid evolution of big data analytics in the pharmaceutical industry, where do you foresee the most impactful and exciting developments occurring in the next five years? How do you believe these advancements will shape the future of healthcare and pharmaceutical innovation?

Michael N. Liebman: I believe that the increasing cost and inefficiency in drug development and its impact on the cost of drugs to patients presents a significant opportunity to apply new approaches and technologies to the benefit of all…the patients, the physicians, pharma/biotech and payers. This will require greater collaboration among these groups and an emphasis on understanding both their "surface needs" and carrying out root cause analysis to identify the real core issues. I believe that many efforts accept what we have and know today to be the "gold standard" rather than simply the "standard of care" and as a result typically drive the use of new technologies to facilitate reproducing these standards rather than questioning them. An example of this is to use evolving digital technologies. Not simply monitor alerts against existing standards but rather enable new ways to stratify disease as a process, ▶

not a state. There is a need to incorporate true "critical thinking" and "systems thinking" into identifying these root cause issues in medicine and then applying the appropriate technology to address the question (or modify existing or create new methods) rather than look to apply the next shiny object. More cost-effective and disease/patient-specific drug development will follow on improving the accuracy of medicine.

Catherine Hall: I am not sure we are as of yet within 5 years of this, but I have often thought a great advancement in our industry would be the development of smart contracts within a life sciences blockchain. The ability for companies to share select data sets that help to advance our industry and stimulate innovation would be priceless. If supply chains exchanged temperature data across international shipment lanes, transport companies might readily adapt to climate changes or innovate new shipping containers that, in turn, help the supply chain reduce product losses. If hospitals exchanged more real-time data regarding the demand for saline, the suppliers could readily adapt to the changes in demand and help hospitals avoid shortages. There are mountains of data that have been collected for such limited purposes that, if shared, could universally help make a difference in how we operate as an industry. To get to that point, however, we need to handle the basics of data exchange and step up our practices in how we collect and store data so that it could be one day more readily shared for these kinds of advances to our industry. Acceptance of real-world data in clinical trials by the regulators is a good first step that will help motivate the industry to think of data on a new playfield of being a true reusable asset.

Christopher Bouton: I would point to the development of the Covid vaccines as a seminal moment in the pharma industry. We saw the entire industry come together to apply novel technologies, modalities and business approaches to accomplish something that was practically unimaginable not many years earlier. Between novel AI analytics, more flexible data integration architectures and greater volumes of data available, I believe that we're hitting a tipping point in technological progress that will help to fuel paradigm shifting advances in the speed and effectiveness with which we can address our most pressing therapeutic and healthcare challenges. At Certara we are focused on applying these types of approaches across the entire pharma pipeline from early basic research to regulatory filings and post-market access. It's a very exciting time to be working in the industry and I'm personally very excited to see what the next 5 to 10 years bring.

As we bring this insightful discussion to a close, we extend our sincere gratitude to our esteemed panelists, Michael N. Liebman, Catherine Hall, and Dr. Christopher Bouton. Your expertise has shed light on the transformative power of big data analytics in the pharmaceutical realm.

Looking ahead, the fusion of data and pharmaceuticals promises an exciting era of innovation. ■

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What Innovations Are Shaping the Future of Pharma Packaging?

Artificial intelligence (AI), blockchain and automation have the potential to streamline the pharmaceutical packaging process and optimise traceability of finished units. The use of new packaging materials can minimise the industry's carbon footprint. However, as James Bury explains, integrating them into packaging operations poses challenges companies must overcome to harness them effectively.

James Bury
Head of Technology,
Tjoapack

James Bury, head of Technology at Tjoapack explores the barriers that need to be overcome if the pharmaceutical packaging industry is to benefit from the potential productivity gains offered by artificial intelligence (AI), blockchain and automation.

A number of exciting innovations have begun to gain the attention of companies within the pharmaceutical sector. Artificial intelligence (AI), blockchain and automation all have the potential to streamline the pharmaceutical packaging process and optimise traceability of finished units.

AI, for instance, is now being explored as a means of speeding up drug discovery and development, and minimising the risk of delays or project failures. In addition, it is being harnessed in the drug manufacturing and packaging process alongside other automation solutions to optimise efficiency. Blockchain, meanwhile, shows considerable promise as a means of enhancing traceability of individual drug doses to minimise the risk of counterfeit products entering the supply chain.

On top of this, a renewed industry focus on sustainability is shaking up the sector, with new packaging and filling processes being explored to minimise the segment's environmental impact.

However, integrating all these advances into packaging operations poses challenges companies must overcome to harness them effectively.

What's driving the need to innovate and harness new solutions?

A number of trends are leading the pharmaceutical industry to innovate and introduce new technologies into the manufacturing and packaging process.

Some of the key trends include:

- **Personalised medicines and cell and gene therapies (CGTs) are driving demand for smaller batch sizes and more flexible capacity:** Due to their nature, personalised medicines and CGTs pose manufacturing efficiency challenges that will need to be addressed. Production lines will have to adapt to smaller, more niche production runs.

This means there will be a need for intelligent packaging processes, with multiple packaging formats. Single-use vials or pre-filled syringes that can accommodate smaller volumes of medication and a wider range of dosages and formulations may become more popular. Due to the higher production costs of personalised therapeutics and CGTs compared with traditional treatments, it is even more important to protect and preserve the medication with solutions such as tamper-evident or specialised temperature-controlled

packaging (like RFID chips). As personalised treatments could be delivered directly to the patient — bypassing the clinic or hospital setting — packaging will have to protect them from being negatively affected by various environmental factors.

Personalised medicines will also significantly impact labelling and patient education materials, requiring dosage and formulation information tailored for the specific patient. Ageing patient populations will also need complex information to be delivered in a more accessible manner. Materials will require multilingual delivery via a variety of media, harnessing smart barcode technologies or digitally generated hard-copy booklets describing the patient's unique treatment regime.

- **The drive to optimise efficiency and increase productivity:** With the costs of energy, raw materials and manufacturing components on the rise, pharmaceutical companies are having to explore innovative solutions to optimise efficiency and reduce manufacturing expense. This doesn't just mean exploring alternative sources of vital suppliers, but also rethinking operations and maintenance processes to find more efficient ways of manufacturing their end products.
- **Compliance with increasingly stringent serialisation legislation:** The updated U.S. Drug Supply Chain Security Act (DSCSA) is due to come into force in November 2023 and it will have enormous implications for packaging and labelling logistics. The new regulation will

place more stringent serialisation requirements on pharma companies seeking to ship drug products to the US.

Companies and their contract packaging organisation (CPO) partners will be required to provide interoperable and electronic tracing for products at the package, case and pallet level from this year onwards. To achieve this while minimising the risk of errors or inefficiencies, innovative new technologies will be required.

- **Sustainability is rising up the pharmaceutical agenda:** Stringent new legislation is being introduced by governments around the world to counteract the climate emergency by requiring companies to minimise their carbon emissions and reduce waste.

This has traditionally presented a challenge to the pharma industry, particularly within the packaging space. It is still difficult to implement new packaging solutions that are workable as well as recyclable or biodegradable. All new formats and materials must be tested for compatibility with drug products and receive regulatory approval.

Despite all this, it will be necessary for pharma companies to revise their approach over the coming years, moving to more environmentally responsible sources of packaging to reduce their carbon footprint.

Innovations shaping the future

With these drivers in mind, it is clear that the pharmaceutical industry and its packaging partners must find new solutions to keep pace with the changing market landscape and thrive into the future. A number of advanced technologies have the potential to enable companies to achieve this goal, but also present challenges that need to be overcome if they are to be successfully harnessed:

- **Automation can transform line flexibility for the better:** With the smaller, more complex batch requirements of personalised treatments and similar new therapies, automation offers the potential to enhance flexibility, ensure process reliability and boost traceability.

Keeping manual interaction with products and packaging to a minimum can prevent human error and reduce waste. Increased automation can also help ensure optimum sterile integrity for products, such as parenterals and ophthalmics, where sterility is a vital requirement.

Automated systems offer an exciting means to streamline supply chain management for package drug products, by enhancing track-and-trace capabilities. They can track and monitor inventory in storage and during transport, helping to reduce waste, improve efficiency and even prevent the risk of counterfeit medicines entering the supply chain.

However, implementing new automation technology requires significant financial investment, which can present a barrier for some companies. This is particularly the case if they cannot find equipment that offers the flexibility they need to manufacture smaller batches. In addition, some packaging

processes may be harder to automate. Kitting for injectable drug products is one such example as it can be difficult to ensure the right information is included when manufacturing for multiple markets.

Integration of new automation technologies into existing packaging lines can be an issue, and line operatives must be retrained to operate and maintain new equipment.

● **AI can optimise manufacturing and packaging efficiency:** AI is already being used in the drug discovery stage on development projects to analyse reams of data to identify potential drug targets, but it offers plenty of scope to transform manufacturing and packaging, too. On production lines, it has the potential to enable effective predictive maintenance — where companies can implement preventative measures to replace or repair components before equipment begins to fail. This can minimise downtime and increase productivity.

Inventory management of finished drug products is another area where AI can more effectively identify potential improvements and ensure that necessary stock levels can be forecast. AI can also be used on packaging lines to detect packaging defects (for example due to product leakage and contamination) that lead to waste and potentially put patients at risk. Deep-learning AI models can offer a more robust inspection compared with traditional image processing techniques. They can learn and adapt to changing environmental conditions, such as different lighting intensities. All in all, AI can help increase packaging line speed, improve quality control and ensure more accurate product count.

● **Blockchain can make serialisation more effective:** A method of recording information that reduces the chance that a system is altered, hacked or otherwise manipulated, blockchain can optimise efficiency when implementing serialisation. Although not currently required by U.S. law or regulations in other markets, it can be harnessed to make product tracking more secure, with fewer errors.

Blockchain also has the potential to fix global supply chain vulnerabilities, accelerate collaboration among companies, reduce fraud and assure product authenticity.

An Internet of things (IoT)-based supply chain guided by blockchain, for instance, could allow the temperature and location of individual drug packs to be recorded in real time, harnessing wireless sensors and GPS devices attached to the packages. Serial numbers unique to the manufacturer added to the label can then be scanned by the consumer when purchasing the medicine to gain access to all relevant information. The product manufacturer, pharmacy warehouse and the individual pharmacy could also have access to complete, reliable and secure information about the origin and quality of the drugs registered on the blockchain.

Nevertheless, to benefit from blockchain, companies must invest in the software, hardware and connectivity solutions to properly track their products throughout their journey to the consumer.

> AI, blockchain, and automation enhance pharmaceutical packaging, tackling challenges.

- **New product packages can make the dream of a circular pharmaceutical economy a reality:** Although sustainability may be a daunting subject in today's pharmaceutical space, there are developments that have the potential to bring the concept of a circular economy, where some pharma materials are reused and recycled, closer to reality. For example, drug packaging and containers could be designed for reuse or recycling and waste from drug production could be repurposed or recycled. It's important to explore options to enable this for secondary packaging and other appropriate drug device components.

However, sustainability is about more than increasing recyclability. It covers a much broader remit, including reducing energy consumption in the manufacturing and packaging process, minimising waste and changing the industry's mindset. Pharma companies need to explore all of these areas, looking at how the supply chain behind the drug product and its packaging can be reworked to minimise its environmental footprint.

The need for expert support

Although new technologies offer exciting scope to enhance efficiency and flexibility for companies in the future, their implementation does pose challenges that can hinder takeup. Failure to address these challenges could mean that companies are unable to stay ahead of the competition.

To overcome these issues, particularly those related to integrating new technology into packaging processes, it is important to reach out to specialist CPOs for support.

CPOs are well placed to support the industry in harnessing the power of new technology to enhance packaging efficiency. In addition to already having specialist packaging infrastructure installed and ready to go, they also have experts exploring ways to incorporate new technologies into their processes efficiently. They also have the resources already available to invest in innovations such as AI or blockchain early, if they believe their clients can benefit from them. As a result, they are able to provide pharmaceutical companies with the technologies of the future the minute they begin working together. ▶

In addition, CPOs have comprehensive knowledge of the packaging needs of a range of dosage forms, as well as the regulatory environment in a number of key markets. Due to the nature of their role in the supply chain, they can offer the flexibility and capacity to develop customised services that can add real value to pharmaceutical companies.

In recent years, CPOs have grown as an integral component in the pharmaceutical ecosystem, supporting drug developers and their contract manufacturing partners to meet patients' needs while optimising production efficiency. They offer much more than a simple transactional service; they are an integral strategic partner that can help pharma companies harness new technologies to keep up with trends and thrive in a fast-changing market.

Looking ahead

The pharmaceutical landscape is undergoing a rapid evolution. Changing market demands, rising costs and increasingly stringent regulation are all creating new challenges that pharmaceutical companies must overcome if they want to succeed.

Cutting-edge technologies offer potential solutions to address these issues, particularly at the packaging stage, but they will only work if companies are able to access them and incorporate them effectively into their operations. Collaboration with expert packaging partners can help companies achieve this goal, providing them with the knowledge, the infrastructure and resources to stay one step ahead, enabling them to continue providing vital therapies to patients. ■

AUTHOR BIO

James Bury is Head of Technology at Tjoapack. He joined the company in 2016. James holds a bachelor's degree in business, economics & law (MER) and master's in organization studies. Prior to Tjoapack, he worked as an ERP consultant. James's journey within the company started with the Supply Chain team followed by transferring to the IT department where he successfully implemented multiple projects such as ERP and serialization implementation and integrations between systems. Currently James is responsible for Tjoapack's IT network and infrastructure and all digital systems. Together with his team, James is focused on utilizing digital technology to create the most value for both internal users and Tjoapack's customers.

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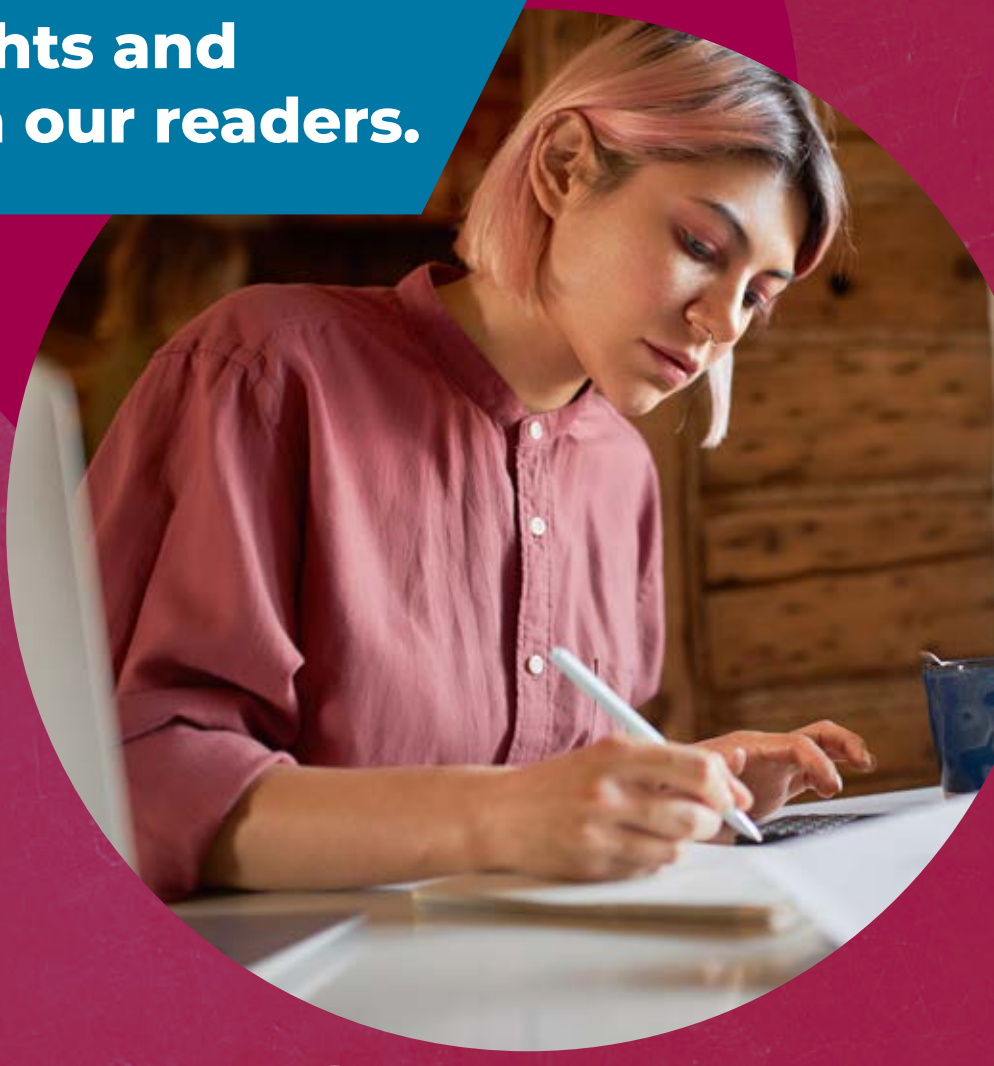

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eBR for Paperless Manufacturing in the Pharma Industry

Gustavo Samojeden
CEO of Eriochem S.A

1. The pharmaceutical industry operates under stringent regulatory requirements. How does the adoption of eBR systems assist pharmaceutical manufacturers in achieving and maintaining compliance with regulations like FDA 21 CFR Part 11 and EU Annex 11? What specific features of eBR systems contribute to compliance efforts?

eBR systems are more reliable and compliance than traditional paper documents, log in measures, electronic signature, e-traceability, are only a few of the key advantages of digital records over paper-based ones. Regulators and inspectors prefer by far these new technologies when they perform regular audit visits to our companies.

2. The transition to paperless manufacturing through eBR implementation requires robust data security measures. How can pharmaceutical companies ensure the confidentiality, integrity, and availability of electronic batch records? What strategies are employed to protect against potential cyber threats and data breaches?

The support of a strong IT group in our pharma companies is essential. This group must make proper cyber risk assessments to ensure the security and integrity of the e-systems protecting them from internal and external attacks. At the end it as not different from the safety of e-banking systems as an example of a few.

3. In the context of the pharmaceutical supply chain, how does the integration of eBR systems with Enterprise Resource Planning (ERP) and Manufacturing Execution Systems (MES) facilitate real-time data exchange and decision-making? How does this integration optimize overall supply chain efficiency?

In the current hard supply chain environment that we have in our pharmaceutical

industry in these post-pandemic years, the integration of all our systems is critical to achieve success in all our production sites. Sales forecasting, stocks, lead times of the suppliers, etc. must be fully available, and with online time refresh, to give the right inputs to supply chain professionals so they can make the right and accurate decisions to assure WW pharma supply chain, essential to ensure also the right treatment to all patients that needed.

4. The pharmaceutical industry often deals with complex and highly regulated manufacturing processes. How do eBR systems assist in automating and standardizing workflows to improve operational efficiency and reduce errors during batch execution?

The electronic systems have a lot of right features to decrease errors in manufacturing execution, for example, auto-corrections, auto dating and timing, a list of choices so you avoid mistyping, etc. All these systems assure data integrity and avoid mistakes. Of course, the more efficiency of the process is assured through them, as we can see in different KPIs we monitor across our production sites.

5. Continuous improvement is vital in pharmaceutical manufacturing to enhance product quality and ensure patient safety. How can eBR systems aid in monitoring and analyzing manufacturing data to identify trends and potential areas for improvement? Share examples of how this data-driven approach has led to process optimizations.

You can use different continuous improvement systems, like Kaizen, Six Sigma, etc. but all of them can take profit from eBR systems. We are also nowadays performing a big Quality Culture program in the company, that takes some inputs in a direct way from our e-systems, including eBR of course also.

6. In a global pharmaceutical manufacturing setting, companies may have production facilities across different countries. How does the use of eBR systems enable seamless collaboration, data sharing, and standardized processes among geographically dispersed sites while adhering to regional regulations?

Today the full harmonization between your different production sites, in the same or different countries, is critical. Regulators like the FDA expect Quality Oversight between all your production sites, you only need to see some of the last Warning Letters on their WEB. In our case we have production sites in two different countries and electronic systems, like document management systems for deviations, change control, CAPA follow-up, etc., and eBR for online data sharing are pillars of this objective.

7. Data integrity is a critical concern in the pharmaceutical industry. How can an eBR system provide an audit trail for all data and actions, ensuring transparency and traceability throughout the manufacturing process? How does this audit trail support regulatory inspections and internal quality audits?

A reliable audit trail system that assures log-on follow up, electronic signature, date and time monitoring is essential to assure the correct performance of all electronic programs in our company. They are also a key factor for inspections and audits success, as inspectors focus in these points most of the data integrity findings.

8. With the increasing adoption of advanced technologies like Artificial Intelligence (AI) and Machine Learning (ML) in manufacturing, how can eBR systems leverage these technologies to enhance process efficiency, predict potential deviations, and support real-time decision-making?

We think so, but honestly, we do not have so much experience yet in AI or ML to give a solid feedback to our colleagues.

9. As the pharmaceutical industry moves toward personalized medicine and smaller batch sizes, how can eBR systems adapt to these changing manufacturing needs? Discuss the flexibility and scalability of eBR systems in meeting the demands of modern pharmaceutical production.

Absolutely, electronic systems are much more flexible and adaptable ones, that traditional paper based. Time to change an scale up as example that is very common in our industry could be cutted 2 or 3 times manging the change electronically, this

advantages apply also to other common changes in our industry like new line validation, variable processes changes, etc.

10. Validation is a crucial aspect of eBR implementation. How can pharmaceutical companies ensure the validation and qualification of eBR systems meet regulatory requirements? What challenges might arise during the validation process, and how can they be effectively addressed?

IT groups in our companies must be fully trained and qualified in quality systems validation requirements, GAMP rules and FDA (EU expectations. Then they must roll out in the organization a correct IT control change sytem to assure full compliance during all the time of operation of the site. The new role of the IT compliance officer is key in the success of this task, find a right person in this position is crucial.

11. As pharmaceutical manufacturers implement eBR systems, employee training and adoption become essential. How do companies ensure that the workforce is adequately trained to use eBR systems effectively? What strategies are employed to overcome resistance to change and promote user acceptance?

We have now the advantage that the digital have become familiar in day-to-day life, e-banking, mobile phone apps, auto parking cars, etc, are present all days in our lives, crossing our normal activities. So workers and employees are now not so reluctant to e-sytems, as like to be in the past some years ago. But we still need to use some strategies to close our people to new tech-

nologies, the support of a good HR department is very important for that, we make some special programs that sometimes are not more than like “funny games”, but very effective to close the e gap, and make the induction process to the electronic world much softer.

12. The pharmaceutical industry is moving toward a more data-driven approach to quality management. How does the integration of quality control and quality assurance processes with eBR systems facilitate real-time monitoring of critical quality attributes and enable early deviation detection?

Electronic systems, not only in production like eBR, but also in quality control labs like LIMS systems, allow online monitoring of all process variables, and of course, alarms associated, that never sleep or lunch, and could prevent mistakes or implement quick early corrections, avoiding a lot of future problems and costs. Traditional paper based-systems never could make this happen in this efficient way.

13. Continuous auditing is gaining traction as an alternative to traditional periodic audits. How can eBR systems support the concept of continuous auditing in pharmaceutical manufacturing, providing real-time insights into compliance and quality performance?

We do not have yet real experience in continuous auditing, but of course, seems something possible in view of all we have discussed in the last questions. As we have made possible virtual inspections during the pandemic, and now are normal stuff for all of us, I imagine that this continuous auditing concept will be standard in the short future in our industry, improving compliance and q performance by sure.

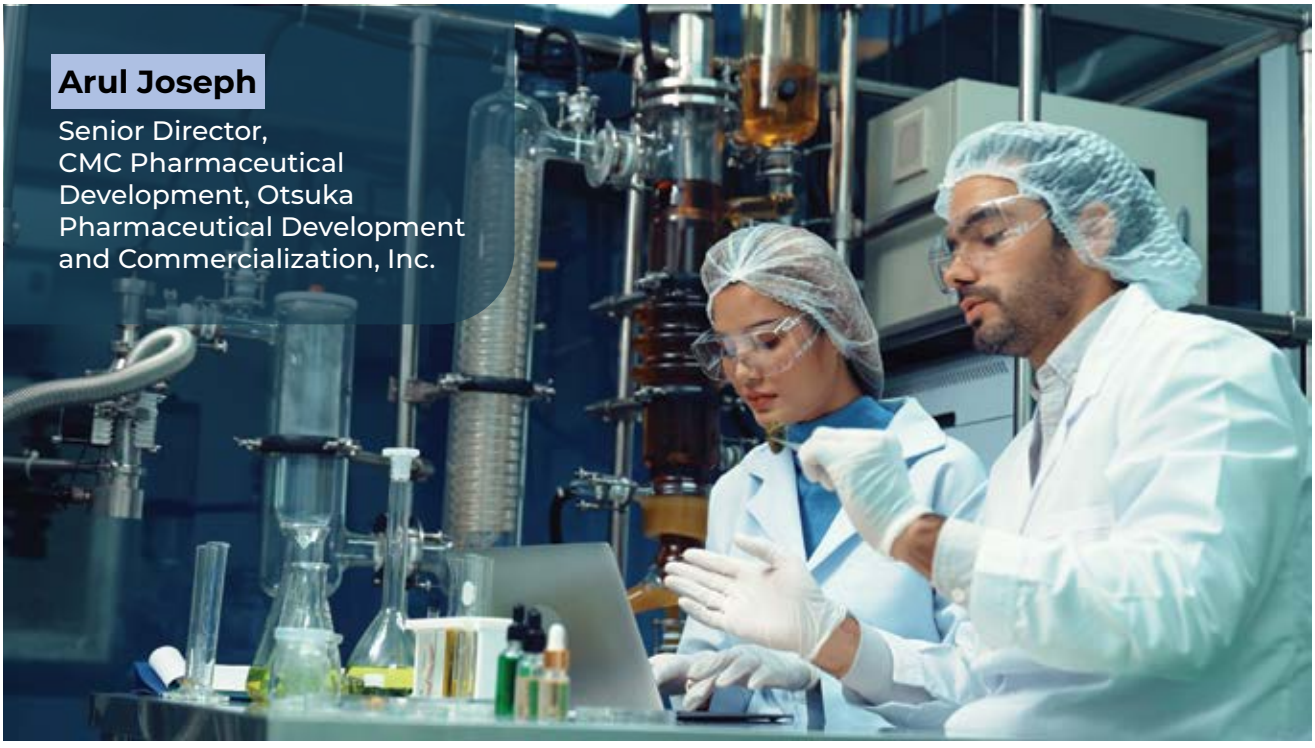
14. Lastly, what are the future trends and innovations in eBR systems for the pharmaceutical industry? How do you envision eBR systems evolving to meet the dynamic needs of the industry in the coming years?

Systems in general are evolving to pure friendly user interfaces, and in some cases, you are not even aware that you are interacting digitally, instead of analogically. This is the trend, the use of AI tools like chatbots, and the penetration of digital systems in our industry will be unstoppable. ■

AUTHOR BIO

Gustavo Samojeden is currently working as the CEO of Eriochem S.A. He is a Pharma executive with more than 35 years of experience in both technical and business aspects of the industry. Has managed C-level organizations in 5 countries on 3 continents with a focus on emerging markets like South East Asia Pacific and Latin America.

Integration of Emerging Technologies in Drug Substance and Drug Product Development and Manufacturing



Arul Joseph
Senior Director, CMC Pharmaceutical Development, Otsuka Pharmaceutical Development and Commercialization, Inc.

1. Can you provide an overview of your understanding of the term "emerging technologies" in the context of drug substance and drug product development and manufacturing?

Emerging technologies are technologies that are in the early stages of adoption in drug substance and drug product development and manufacturing in the biopharmaceutical industry. In some cases, the technology may have been known for several decades;

however, its adoption in drug substance and drug product development and manufacturing may still be in the nascent stage. I would include these technologies under the term "emerging technologies" in the context of drug substance and drug product development and manufacturing.

2. What are some specific emerging technologies that you believe hold significant promise for advancing the pharmaceutical industry in terms of efficiency, quality, and innovation?

I think machine learning, robotics, continuous manufacturing, additive manufacturing, new catalysts (novel organic catalysts, photocatalysts, and enzyme catalysts), click and flow chemistry, drug bioavailability enhancement, drug delivery technologies, and blockchain are emerging technologies that hold a lot of promise in the next 5-10 years.

3. When integrating emerging technologies into drug development and manufacturing, what challenges do you foresee in terms of regulatory compliance and validation? How do you plan to address these challenges?

The typical challenge with regulatory compliance and validation and adoption of emerging technologies is the uncertainty of regulatory acceptance. This lack of guidance can hinder the integration of emerging technologies in the highly regulated environment of the biopharmaceutical industry, as any questions with the emerging technology can extend the timeline for regulatory review and approval of a marketing application. There are several ways to address such challenges: The firms that promote the technology can form a consortium and engage directly with the regulatory agencies with proposed standards and seek guidance for a process/pathway for implementing their technology in the biopharmaceutical industry in a compliant manner as part of drug development and manufacturing.
From the perspective of someone leading drug development in the biopharmaceutical industry, early engagement with the regulatory agencies through meetings to propose a plan and seek agreement on implementing the new technologies can help avoid surprises. For some new technologies, there may not be an official position or guidance from the agency, and the lack of guidance can delay the implementation of those technologies.

In recent years, regulatory agencies have supported innovation and adoption of emerging technologies. through contact points such as the FDA Emerging Technology Program, and the EMA Innovation Task Force to help support the implementation of emerging technologies in drug substance and drug product development and manufacturing. Companies can use these contact points to help with the adoption of emerging technologies Examples of this support are the new FDA discussion paper and request for feedback on Artificial Intelligence/Machine Learning titled "Proposed Regulatory Framework for Modifications to Artificial Intelligence/ Machine Learning (AI/ML) - Based Software as a Medical Device". The draft guidance "Marketing Submission Recommendations for a Predetermined Change Control Plan for

Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions."

4. Could you discuss potential hurdles in terms of workforce readiness and skill development that might arise with the adoption of complex emerging technologies? How do you plan to bridge these skill gaps?

Workforce readiness and skill development are critical issues for complex emerging technologies and some solutions include:

1) Training programs
2) Partnering or collaborating with academic or research institutions,
3) Partnering or contracting with technology or solution providers, and
4) Targeted hiring of skilled talent

5. How do you approach the process of selecting emerging technologies for integration? What criteria do you consider to ensure that the chosen technologies align with your business goals?

Some questions to consider when selecting an emerging technology include:

1. Does the technology support current and future drug development and business goals?
2. Does it provide a sustainable competitive advantage?
3. In which stage of the hype cycle is the technology? It is preferable to and to avoid technologies that are still at the peak of inflated expectations,
4. How long would it take to implement the technology, and what is the time needed for it to make a significant difference in an R&D or manufacturing environment?
5. What are the upfront and ongoing resource commitments required to implement the new technology, and what is the return on investment?

6. Maintaining product quality is paramount in pharmaceuticals. How do you plan to implement quality control measures for newly integrated technologies, and what strategies will you employ to minimize associated risks?

The quality impact depends on the technology, the area, and the stage of drug development in which the technology is adopted. For instance, the quality impact in the early stages of drug development is lesser than in later stages. To manage and mitigate risk, a change control process phased implementation feasibility testing, use testing, protocol-driven qualification and validation, and comparison of release and stability data for impacted drug substance and drug product batches before and after the change are used. ▶

7. How do you stay updated on the evolving regulatory landscape and guidelines related to the integration of emerging technologies in drug development and manufacturing?

There are various regulatory information sources that one can use to stay updated, including Health authority websites (FDA, EMA, etc.), societies such as Regulatory Affairs Professionals Society RAPS, regulatory news publishers, blogs, software vendors, and newsletters such as Dickinson's FDA review and FDA Aware. The above description is not an endorsement of any of the vendors or services; it is shared as an example of external sources of regulatory information that are available to keep oneself updated on the evolving regulatory guidelines.

8. Collaboration is often crucial in technology integration. How do you identify potential collaborators, such as technology providers or research institutions, and what factors do you consider when forming these partnerships?

It's very important to choose the right technology partners and collaborators. Some factors that can help in choosing the right partner/collaborator research institution or technology provider are

1. Does the research institution or technology provider have the level and depth of expertise in the given technology domain?
2. Can they support your department/company's specific needs and objectives?
3. Are they going to be around 5 to 10 years from now to support the implemented technology at your organization through its lifecycle?
4. Size, scope, capacity and capability of the team - scientists, engineers, and project managers who will support your project after business development has moved on
5. Culture fit - transparency, flexibility, etc.
6. Budget is also a factor so knowing the total cost/expense associated with the implementation of the technology through its lifecycle at your organization - including implementation, troubleshooting, upgrades, training, etc.

9. In your opinion, how do you envision the pharmaceutical landscape evolving over the next 5 to 10 years due to the integration of emerging technologies?

In the next 5 to 10 years, I expect the pharmaceutical landscape to evolve to become more automated, with more environment-friendly processes and more patient-friendly products,

Greater access to large volumes of more reliable curated data sets, the exponentially increasing computing power to process the data, and the sophistication of the machine learning algorithms will drive the increased use of machine learning in drug development and manufacturing. Advances in hardware and software will increasingly drive automation and robotics in manufacturing.

Greater adoption of flow chemistry, click chemistry, novel organic catalysts, photochemical catalysts, and enzyme catalysts will drive more environmentally friendly processes for drug substance manufacture. Increasing adoption of continuous

manufacturing can lead to more environmentally friendly drug product manufacture closer to the markets where those drugs are needed and the adoption of additive manufacturing can lead to more custom drugs for patient-stratified medicines with distinct release profiles.

Novel drug bioavailability enhancement technologies will allow for the development of more chemical space in drug development, and novel drug delivery technologies will allow for the development of unique delivery of drugs allowing for patient comfort with extended release over a period of time supporting patient medication adherence, Greater adoption of blockchain can allow for more robust drug product supply chains and near real time update to patient drug labels.

10. Reflecting on your experiences, could you provide insights into where the integration of an emerging technology did not go as planned? What were the key takeaways and adjustments made from that experience?

Three important lessons learned on the integration of an emerging technology include,

1) It's important to choose the right technology partner who can support your department/company's specific needs, and match the organization's culture.
2) Don't overestimate your own capabilities or your organization's capabilities in the area of an emerging technology i.e., be aware of the risk of the Dunning-Krueger effect and try to be objective about your capabilities and that of your team, your organization, and partners when implementing an emerging technology.
3) Implementing an emerging technology at the local US R&D site is a challenge, but when the same emerging technology is being transferred to other R&D or manufacturing sites globally then even small differences can compound and lead to greater roadblocks. Having the same technology team available to manage the integration of the emerging technology at the site and to trains SMEs capable of troubleshooting any issues on an ongoing basis is critical. ■

AUTHOR BIO

Arul Joseph is a Senior Director of Pharmaceutical Development and Clinical Supply Chain and leads drug substance and drug product development at Otsuka Pharmaceuticals. He has 18-plus years of experience and has held roles of increasing responsibility at Gilead Sciences, Merck, and other pharmaceutical companies. He conducted postdoctoral research at the Scripps Research Institute in La Jolla, CA. Arul earned his Ph.D. in Organic Chemistry from the University of Maryland in College Park, MD, and an MBA in Strategy and Finance from New York University's Stern School of Business in New York, NY.

TEMPERATURE CONTROL & LOGISTICS

NORTH AMERICAN SUMMIT

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BUILD A RESILLIENT & EFFECTIVE END-TO-END TEMPERATURE CONTROLLED SUPPLY CHAIN

Temperature Control & Logistics - North American Summit

Join us at the Temperature Control & Logistics North American Summit, taking place 19 - 21 September in Falls Church, VA, as we cut through the complexity to identify which approaches will work for you, bringing genuine value to your supply chain, your business, and your patients. Key Speakers Include:

Bill Mcgillian
Associate Director, Supply Chain Management, **Merck**

Victoria Wilmore
Global Temperature Control Support Director, **Johnson & Johnson**

Tonino Antonetti
Executive Director, Regulatory, Affairs & Quality, **Roche Diagnostics**

What to Expect

The temperature-controlled supply chain is a hotbed of innovation, with pharmaceutical and biotechnology companies continuously finding new ways to mitigate the threat posed by potential temperature excursions and supply chain disruption. New visibility tools, packaging technologies and logistics services are redefining what is possible, allowing the industry to confidently protect and transport life-saving products.

It is crucial we discover how to demonstrate both reliability and true business value of any given technology and/or approach. That is why we have built a program built around the unique needs of medium-to-large pharmaceutical manufacturing and small-to-medium biotechnology companies, with bespoke learning outcomes and opportunities for cross-industry collaboration and exchange.

Medium-Large Enterprise Stream

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- Enhance your logistics network design & forecasting to bolster resilience, security & ensure success
- Partner across the network to confront an increasingly complex operating & regulatory environment
- Discover the implications for your logistics network of disruptive technologies & new therapies
- Small-Medium Size Enterprise Stream
- Discover the logistics strategies that will allow you to navigate the path from clinical to commercial
- Identify & partner with the vendors capable of delivering the service your products require
- Implement best GDP practice to achieve & demonstrate long-term regulatory compliance
- Scale the size of your operations to put supply chain & logistics at the heart of your growth strategy
- Build your supply chain & logistics strategy around the unique requirements of your products

Temperature Control & Logistics

Date: September 19 - 21, 2023
Location: Falls Church, Virginia, USA
Website: https://www.pharma-iq.com/events-temperature-control-and-logistics/agenda-mc
Email: enquire@iqpc.co.uk

Pharmaconex

September 03-05, 2023

Cairo, Egypt

https://www.pharmaconex-exhibition.com/en/home.html

About the Event: Pharmaconex is Africa's pharmaceutical manufacturing hub, connecting the entire supply chain in Egypt, the largest producer of the pharmaceutical market in the MENA region. Offering a comprehensive experience for the pharma community to network and build knowledge around the latest industry trends.

Listed Under: Manufacturing

4th Annual Gene Therapy Immunogenicity

September 05-07, 2023

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https://genetherapy-immunogenicity.com/

About the Event: 4th Annual Gene Therapy Immunogenicity Summit is the industry-focused meeting to get into the detail on selecting the most appropriate antibody assays to assess relative risk in different patients, dive deep into the latest understanding and mitigation strategies of the innate immune response, and analyze the best ways to predict and measure short and long-term immune responses to generate accurate safety profiles.

Listed Under: Research & Development

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https://www.sept23.pharmamarketingsummit.com/

About the Event: The PharmaMarketing Summit is an invitation-only, premium Summit bringing leading pharmaceutical marketing executives and innovative suppliers and service providers together. The Summit's content is aligned with key pharmamarketing challenges and interests, relevant market developments, and practical and progressive ideas and strategies adopted by successful pioneers

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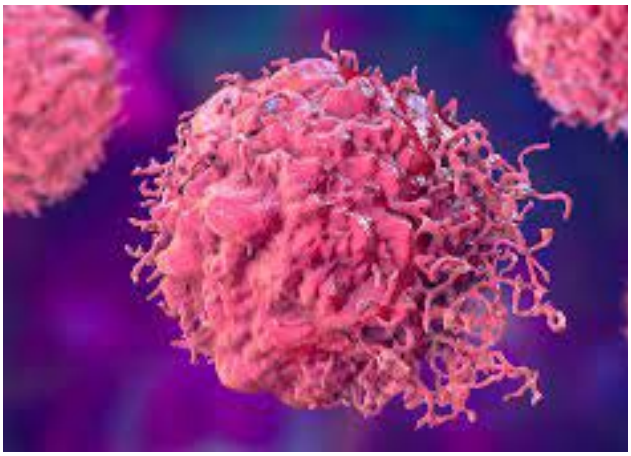
September 19 - 21, 2023

Virginia, USA

https://www.pharma-iq.com/events-temperature-control-and-logistics

About the Event: The temperature-controlled supply chain is a hotbed of innovation, with pharmaceutical and biotechnology companies continuously finding new ways to mitigate the threat posed by potential temperature excursions and supply chain disruption. New visibility tools, packaging technologies and logistics services are redefining what is possible, allowing the industry to confidently protect and transport life-saving products.

Listed Under: Manufacturing



World Cancer Series Europe

September 20 -21, 2023

Brussels, Belgium

https://events.economist.com/world-cancer-series/

About the Event: 9th Annual World Cancer Series is a two-day summit features over 90 speakers and welcomes an audience representing policymakers, healthcare providers, industry leaders, academics, patient groups and investors.

Listed Under: Research & Development

CPHI Barcelona

October 24 – 26, 2023

Barcelona, Spain

https://europe.cphi.com/europe/en/agenda/programme.html

About the Event: CPHI creates connections and inspires partnerships across the global pharma community.

Listed Under: Manufacturing

Pharmacovigilance World 2023

November 01 - 02, 2023

London, UK

https://corvusglobalevents.com/conference/pharmacovigilance-world-2023

About the Event: Pharmacovigilance World 2023 will serve as a knowledge-sharing and networking platform, providing a unique opportunity for researchers, pharmacists, healthcare professionals, industry representatives, and regulatory authorities to come together and discuss the latest trends, challenges, and advancements in pharmacovigilance. By sharing experiences and best practices, we aim to enhance global drug safety and improve patient outcomes.

Listed Under: Research & Development

2nd Pharma Summit: Drug Discovery & Community Trial

December 04 – 05, 2023

Dubai, UAE

https://assopharm.com/pharma-summit/

About the Event: Pharma Summit: Drug Discovery & Community Trial aims to bring together leading academic scientists, researchers and scholars to exchange and share their works and research results on all aspects of Pharmacology, Pharmaceutical Biotechnology, Pharmacogenomics, Drug Delivery, Bio-drugs, Pharmacovigilance and Drug Safety, Pharmaceutical Microbiology, Pharmaceutical Research and Development, Pharmaceutical Analysis and Quality Curatives, Bio-therapeutics, Radiopharmaceuticals, Vaccine Design, Formulation Technologies, Clinical Pharmacy, Industrial Pharmacy, Pharmaceutical Chemistry and Pharmaceutics

Listed Under: Clinical Trials

FDA Approves Puma's Alisertib IND for Small Cell Lung Cancer

Puma Biotechnology has received U.S. notification allowing the advancement of alisertib monotherapy for extensive-stage cancer (SCLC).

The Phase II trial, named Study PUMA-ALI-4201, is set to enroll 60 patients who progressed after initial platinum-based chemotherapy and immunotherapy.

Patients will undergo tissue-based biopsies for biomarker analysis. Alisertib will be administered at 50 mg BID on days 1-7 of a 21-day cycle, with the trial expected to begin in H2 2023.

The main focus is on the objective response rate, with additional attention to response duration, disease control rate, progression-free survival, and overall survival. Enhanced efficacy will be explored within biomarker subgroups.

Concurrently, biomarker analysis will be conducted during the trial, incorporating an initial interim assessment for both biomarker evaluation and effectiveness appraisal.

Puma's objective is to engage the FDA in conversations about expedited approval, drawing from the study's results.

Read the complete post

FDA Grants Orphan Status to Actuate's Elraglusib for Pancreatic Cancer

Actuate Therapeutics, Inc. (Actuate) has revealed that the U.S. Food and Drug Administration (FDA) granted Orphan Drug Designation to elraglusib for treating pancreatic cancer patients.

Elraglusib (9-ING-41), Actuate's proprietary small molecule inhibitor of glycogen synthase kinase-3 beta (GSK-3□), is in development for refractory cancers in adults and children.

Incorporated into the phase 1/2 1801 trial (NCT03678883, EudraCT#:2018-003739-32) as an extra arm, Actuate initially enrolled advanced pancreatic cancer patients for a phase 2 study of 9-ING-41 combined with gemcitabine/nab-paclitaxel.

Orphan Drug Designation from the FDA is granted to investigational therapies targeting rare medical conditions affecting under 200,000 people in the U.S. It provides developers with advantages, including developmental assistance, clinical cost tax credits, certain FDA fee exemptions, and seven years of exclusivity in post-approval marketing.

Read the complete post

Ginkgo Bioworks Teams Up with Merck to Enhance Biologic Manufacturing

Ginkgo Bioworks has unveiled a fresh partnership with Merck, also known as MSD beyond the United States and Canada, with a primary focus on enhancing biologic manufacturing processes.

Leveraging its proficiency in cell engineering, ultra-high-throughput multiplexed screening, protein characterization, and process optimization, Ginkgo aims to boost production efficiency and yield.

The collaboration terms outline a potential aggregate payout of up to US $490 million to Ginkgo in upfront research fees, research milestone fees, option license payments, and commercial milestone payments.

This marks the second collaboration between Ginkgo and Merck.

In October 2022, the companies joined forces for a biocatalysis project aimed at refining Merck's active pharmaceutical ingredient (API) manufacturing.

Read the complete post

Aspen Neuroscience Gets FDA Nod for Parkinson's Cell Therapy Trial

Aspen Neuroscience has received FDA clearance for its Investigational New Drug (IND) application, a significant step toward clinical trials for ANPD001.

This innovative cell therapy, designed to address Parkinson's Disease, employs the patient's own induced pluripotent stem cells (iPSCs) to create dopamine neuronal precursor cells (DANPCs).

The company is set to initiate a Phase 1/2a clinical trial for individuals with moderate to severe Parkinson's Disease, following a successful 2022 Trial-Ready Screening Cohort Study that identified potential candidates.

This upcoming trial is groundbreaking, marking the first multicenter Phase 1/2a trial of an autologous iPSC-derived therapy in the U.S.

The pioneering approach behind ANPD001 can be attributed to Aspen's co-founders, Dr. Jeanne Loring and Dr. Andres Bratt-Leal.

Aspen NEUROSCIENCE

Read the complete post

FDA Approves Georgiamune's GIM-122 and Secures US$75 million Funding

Georgiamune Inc. marks a significant milestone with FDA approval for its groundbreaking dual-function monoclonal antibody, GIM-122, via the Investigational New Drug (IND) application process.

Simultaneously, the company successfully concludes a Series A financing round, securing an impressive $75 million in funding.

This IND clearance propels Georgiamune Inc. into its debut clinical trial, focused on oncology. Spearheaded by Dr. Samir Khleif, Founder and CEO, GIM-122 tackles immunotherapy resistance through an innovative strategy.

Preparations are underway for an innovative phase 1/2 clinical trial, pioneering human participation.

The trial assesses GIM-122's safety, pharmacokinetics/pharmacodynamics, tolerability, and anti-tumor potential.

Slated for the latter half of 2023, the trial targets adults with advanced solid malignancies, previously unsuccessful with checkpoint inhibitors.

This pivotal study underscores Georgiamune's commitment to addressing unmet medical needs in cancer and autoimmune diseases.

Concurrently, Georgiamune announces the successful conclusion of an oversubscribed Series A financing round.

This round secured a substantial $75 million from influential biotech investors and venture capital firms. General Catalyst and the Parker Institute for Cancer Immunotherapy (PICI) co-led the round, with participation from prominent entities like Mubadala Capital, Alexandria Venture Investments, Catalio Capital Management, CJNV BioVenture, and Verition Fund Management.

This substantial financial support amplifies Georgiamune's emergence as a promising player in the biotech arena, dedicated to propelling medical innovation in oncology and autoimmune diseases.

Georgiamune

Read the complete post

First Over-the-Counter Naloxone Nasal Spray Launched by Padagis

Padagis LLC has introduced the first non-prescription Naloxone HCl Nasal Spray in the United States.

This nasal spray contains Naloxone, a medication designed to swiftly counter the effects of opioid overdose.

This product, which was previously only available through a prescription, is a critical lifesaving measure.

The PADAGIS® Naloxone HCl Nasal Spray, with a 4 mg dose, is now accessible for purchase without a prescription both in physical stores and online.

It has the same active ingredient and dosage as the prescription-based NARCAN® Naloxone HCl Nasal Spray.

It's important to note that NARCAN® is a registered trademark of Emergent Operations Ireland Limited.

Both PADAGIS® Naloxone HCl Nasal Spray and NARCAN® HCl Nasal Spray serve as opioid antagonists, indicated for the immediate response to known or suspected opioid overdose, characterized by respiratory and/or central nervous system depression.

While PADAGIS® Naloxone HCl Nasal Spray is a valuable option, it should not be considered a substitute for emergency medical treatment, and in some cases, and repeated dosing might be required.

Usage should strictly adhere to the provided instructions.

Based on IQVIA data, NARCAN® Naloxone HCl Nasal Spray 4mg recorded approximately US$257 million in sales during the one-year period ending May 2023.

Read the complete post

Astellas' CRESEMBA® Pediatric Use NDA Accepted by FDA

Astellas Pharma US, Inc. has revealed that the U.S. Food and Drug Administration (FDA) has acknowledged the company's supplemental New Drug Application (sNDA) for CRESEMBA® (isavuconazonium sulfate).

CRESEMBA®, a prodrug of isavuconazole, is an azole antifungal drug, with the sNDA seeking approval for treating invasive aspergillosis (IA) or invasive mucormycosis (IM) in pediatric patients aged one to 17.

The FDA aims to provide a decision by December 9, 2023, under the Prescription Drug User Fee Act (PDUFA).

While CRESEMBA® is already authorized for IA and IM treatment in adults, its potential approval for pediatric use might bring significant progress or address treatment gaps where suitable therapies are lacking. IA and IM are major concerns for immunocompromised and hospitalized pediatric patients, causing notable morbidity and mortality.

The sNDA builds on outcomes from a Phase 2 multicenter study (NCT03816176), which assessed CRESEMBA's safety, efficacy, and pharmacokinetics for IA or IM treatment in pediatric patients aged one to 17.

Read the complete post

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STRATEGY

To achieve its goals, the pharmaceutical industry needs a winning strategy.

MANUFACTURING

Production methods include pharmaceutical production strategies that are necessary to develop pharmaceutical services.

INFORMATION TECHNOLOGY

With Information Technology, organizations can operate more efficiently and productively.

RESEARCH DEVELOPMENT

Biopharmaceutical companies conduct R & Dto achieve a variety of goals, including saving lives and enhancing patients' quality of life.

CLINICAL TRIALS

Clinical trials are a constantly evolving field, and more and more relevant scientific research is being published.

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