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Revolutionising Clinical Trials
Harnessing data and real-time action for better healthcare

Unveiling the Evolution
A thought leader's insights into the pharmacovigilance industry



DIGITALISATION AN ALL-PURPOSE TOOL

Win the race against time

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Revolutionising Clinical Trials with Real-time Data

Clinical trials have long been the cornerstone of medical progress, providing the practical base upon which new treatments and therapies are built. Today, this journey from laboratory discovery to patient treatment is undergoing a profound evolution.

The convergence of cutting-edge technologies, data-driven insights, and patient-centric approaches is ushering in an era of unprecedented change, fostering a more efficient, inclusive, and dynamic clinical trial ecosystem.

The integration of consumer-facing digital health technologies, from wearable devices to mobile health apps, is fostering a new era of patient engagement and data collection. Real-time, objective information is enabling researchers to gain deeper insights into patient behaviours and treatment responses.

The advent of sophisticated technologies and the exponential growth of data have empowered us with tools to collect, analyse, and interpret information at an unprecedented scale. This data-driven approach has the potential to unlock insights paving the way for more efficient and effective clinical trials. No longer bound by the constraints of the past, we can now envision a future where the pace of discovery matches the urgency of patient needs.

This surge in data has meant that pharma companies are able to take action in real-time to address persistent challenges in clinical trials. Researchers are able to address recruitment obstacles faster and identify and address adverse events swiftly. This capability allows for adaptive strategies in real-time, optimising protocols and ensuring each patient significantly contributes to the advancement of medical knowledge.

Furthermore, the incorporation of artificial intelligence and machine learning into the fabric of clinical trial processes unveils hitherto uncharted possibilities. Predictive analytics play a crucial role in discerning potential risks and opportunities, steering researchers toward decisions grounded in comprehensive insights. The realisation of personalised medicine, once considered a distant aspiration, is now materialising as we harness the ability to customise treatments according to individual patient characteristics and responses.

In this issue, the article on *'Revolutionising Clinical Trials-Harnessing data and real-time action for better healthcare'* by *Preetha Vasanji, President-Emerging Markets, Doceree* explores the impact of real-time data on clinical trials in the Asia-Pacific region and how it is revolutionising the way healthcare is delivered and research is conducted, accelerating the drug development process, enhancing patient outcomes, and reshaping the future of healthcare.



Prasanthi Sadhu

Editor

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FROM DISCOVERY TO DELIVERY

Neuronal exosomes and the evolution of neurodegenerative disease treatment

Neuronal exosomes are revolutionising neurodegenerative disease management. They are unlocking new treatment avenues in diagnostics, drug development, and clinical trial management. This work explores innovative, personalised approaches, transforming traditional challenges into opportunities for enhanced neurological care.

Manda Venkata Sasidhar
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The rising challenge of Neurodegenerative diseases (NDDs), including Alzheimer's, Parkinson's, Huntington's disease, multiple sclerosis and others, is mirrored in the growing neurodegenerative drugs market, valued at US$ 36,277.20 million in 2021 and projected to reach US$ 74,809.38 million by 2031. This market, expanding at a CAGR of 7.5 per cent from 2022 to



2031, focuses on conditions that cause progressive neuron damage. Amid this landscape, neuronal exosomes emerge as a significant innovation. These nanoparticles, released by neuronal cells, offer promising cellular communication and drug discovery, development and delivery solutions. By advancing targeted treatments and patient care, neuronal exosomes could play a key role in revolutionising the management of NDDs, aligning with the evolving market trends and medical needs (Huo *et al.*, 2021). The surge in NDDs can be attributed to several interconnected factors:

1. Ageing Population:
NDDs are primarily age-related disorders. As life expectancy continues to increase globally, a more significant proportion of the population is reaching the age where they are more susceptible to these diseases. By 2050, the number of people aged 60 and older will reach 2 billion, nearly double the number in 2020 (Stambler et al., 2018).

2. Genetics and Familial Factors:
Some NDDs have a vital genetic component. The increased understanding and diagnosis of these genetic factors have led to the identification of more cases.

3. Environmental Factors:
Exposure to certain environmental toxins and lifestyle choices, such as poor diet and lack of physical exercise, are increasingly recognised as contributing factors to NDDs. For example, pesticide exposure has been linked to a higher risk of developing Parkinson's disease (Lahiri et al.,2009).

4. Chronic Diseases and Co-Morbidities:
The rise in other chronic conditions, such as obesity, diabetes, and cardiovascular diseases, has a compounding effect on neurodegenerative diseases. These conditions often share common pathways or risk factors that can contribute to the onset or progression of neurodegeneration.

5. Improved Diagnosis and Awareness:
Enhanced awareness and better diagnostic tools have led to more people being diagnosed with neurodegenerative conditions. Previously, many cases may have gone unrecognised or been misdiagnosed, especially in low- and middle-income countries (Lewczul et al.,2018).

> Neuronal exosomes are emerging as a significant innovation, offering promising solutions in diagnostics, drug discovery, and delivery vehicles, and are increasingly recognised as cell-free therapeutics for NDDs.

6. Globalisation and Urbanisation:
Rapid urbanisation and lifestyle changes are leading to shifts in diet, physical activity, and stress levels, all of which may contribute to the rise in NDDs. Urban areas may also expose individuals to new environmental toxins.

Demographic shifts, genetics, and environmental factors contribute to the rise in NDDS. Thus, improved diagnostics are crucial as they improve disease detection, foster better understanding, and necessitate innovative treatment approaches.

Traditional Challenges in Drug Discovery, Delivery, and Clinical Trials Management

A. DRUG DISCOVERY:

Current Challenges:

- **Labour-Intensive Processes:** Traditional drug discovery methods rely on high-throughput screening, iterative testing, and manual analysis. The identification of viable targets and subsequent validation consumes significant time and resources (Steinmetz, K. L., & Spack, E. G. 2009).
- **Lack of Specificity:** Many conventional techniques need more precision to isolate specific biological targets related to NDDs, leading to potential misdirection in research (O'Malley *et al.*,2019).
- **High Costs:** The extensive man-hours, specialised equipment, and consumable resources contribute to soaring expenses in the discovery phase.
- **Failure Rates:** The disconnect between *in vitro* models and human biology contributes to a high attrition rate, with many compounds failing to progress beyond the early stages (Mullane et al.,2014).

Impact:

- **Extended Development Timelines:** These challenges result in protracted timelines, slowing the progress of potentially life-saving treatments to the market.
- **Frequent Failures:** A lack of effective discovery methods contributes to a high failure rate with significant financial implications.

B. DRUG DELIVERY:

Current Challenges:

- **Blood-Brain Barrier (BBB):** The BBB's function to protect the brain also acts as a formidable obstacle in delivering therapeutic agents to target sites, hindering the treatment of neurological conditions.
- **Limited Targeting Capability:** Traditional delivery systems often fail to ensure that the drugs reach the specific neurons or regions the disease affects, leading to reduced efficacy.
- **Invasive Methods:** In some cases, direct injections into the brain or other invasive techniques bypass the BBB, posing significant risks.

Impact:

- **Ineffective Therapeutics:** Many drugs are rendered unusable for brain-related conditions due to their inability to penetrate the BBB. ▶

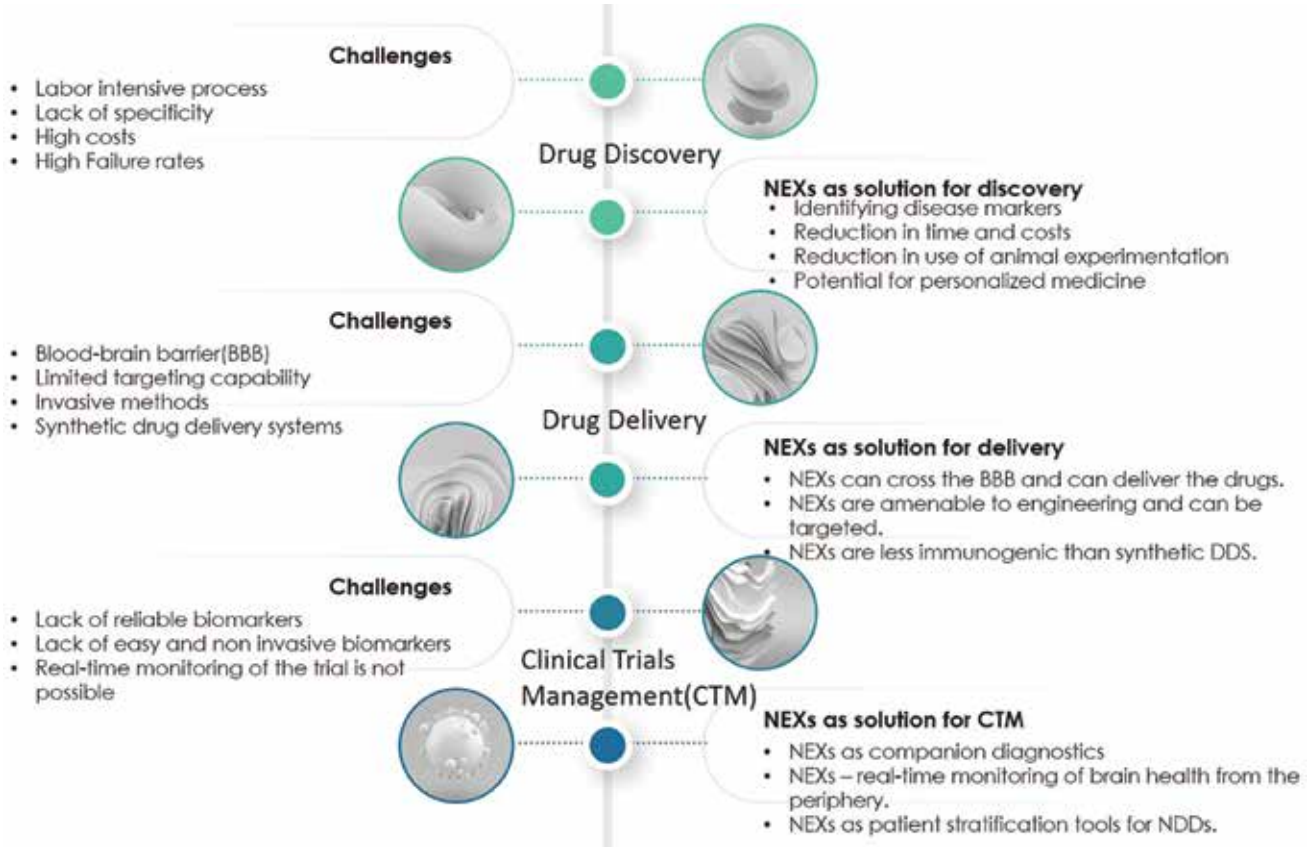

Figure1: Challenges in Traditional Drug Discovery, delivery and Solution:A Schematic representing the current challenges in drug discovery, delivery, and clinical trials, and how neuronal exosome (NEXs) platform would solve the current challenges.

- **Side Effects and Risks:** The necessity to utilise higher doses or invasive techniques can lead to adverse side effects and potential complications.

C. CLINICAL TRIALS MANAGEMENT:

Current Challenges:

- **Lack of Reliable Biomarkers:** Traditional biomarkers often fail to provide an accurate and early assessment of disease progression and response to treatment.
- **Invasive Monitoring Techniques:** Frequent lumbar punctures or biopsies can be required to monitor treatment, causing patient discomfort and risk.
- **Regulatory and Ethical Complexities:** The sensitive nature of neurodegenerative conditions introduces additional layers of regulatory and ethical considerations, further complicating trial management.

Impact:

- **Prolonged Trials:** The challenges above extend trial durations, contributing to the delayed availability of potentially effective treatments.
- **Increased Costs:** Inefficiencies and imprecisions in trial management inflate costs, burdening research institutions and the healthcare system.
- **Uncertainty in Evaluation:** A lack of robust monitoring techniques creates uncertainty in evaluating the true efficacy of treatments, potentially leading to erroneous conclusions.

The traditional challenges in drug discovery, delivery, and clinical trial management present substantial obstacles to advancing therapies for NDDs. These problems hinder scientific and medical progress and have profound socio-economic implications. As the burden of NDDs continues to rise, innovative approaches such as neuronal exosomes offer a promising avenue to overcome these barriers, paving the way for a new era in NDDs research and treatment (Kanojia *et al.,* 2022).

Neuronal Exosome Platform: A Transformative Solution

A. DRUG DISCOVERY:

Neuronal Exosomes as Tools:

- **Identifying Disease Markers:** Neuronal exosomes encapsulate specific proteins, lipids, and nucleic acids reflective of their cell of origin (brain cells). Analysing these contents allows identifying disease-specific markers and creating targeted drug development opportunities (Schneider, A., & Simons, M. 2013).
- **Reduction in Time and Costs:** The precise targeting made possible by exosomes ▶



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can streamline the drug discovery process, reducing the time, labour, and costs associated with traditional methods.

- **Potential for Personalised Medicine:** Exosome analysis may enable a more personalised approach to drug development, tailoring treatments to an individual's unique genetic and molecular profile.

Neurodex uses exosomes to identify synucleinopathies in dementia using blood-based biomarkers. These vesicles provide minimally invasive, stable diagnostic tools for disease monitoring and progression. Positive data for Alzheimer's diagnosis was shared. Neurodex's innovation promises improved neurodegenerative disease management and therapeutic development.

B. DRUG DELIVERY:

Targeted Delivery:

- **Crossing the BBB:** Neuronal exosomes can naturally traverse the BBB, offering a targeted and non-invasive method for delivering therapeutic agents to the brain(Younas *et al.*, 2022).
- **Enhanced Efficacy and Safety:** Encapsulating drugs within exosomes can be directed to specific cellular targets, enhancing treatment efficacy while minimising systemic side effects.
- **Versatility in Treatment:** Exosome-based delivery systems can be engineered to carry a variety of therapeutic agents, including small molecules, proteins, and RNA-based drugs, expanding the scope of treatable conditions.

Aruna Bio's proprietary neural exosome platform, highlighted by AB126, overcomes the BBB. AB126 (Neural exosome), which are derived from proprietary non-transformed neural stem cells, has a wide range of effects including anti-inflammation, neuroprotection, and regeneration stimulation. This discovery has the potential to revolutionise the treatment of acute neurological conditions and chronic NDDs, with global implications.

C. CLINICAL TRIALS MANAGEMENT:

Real-time Monitoring:

- **Non-Invasive Biomarkers:** Neuronal exosomes can be isolated from bodily fluids like blood, offering a non-invasive way to monitor disease progression and response to therapy .
- **Dynamic Insights:** The continuous monitoring made possible by exosomal markers allows for adaptive trial designs, adjusting treatment protocols in real time based on patient response.
- **Improved Precision and Reliability:** Exosome-based assessments can provide more precise and reliable data, reducing trial duration and costs (Jan *et al.*,2017).

Multiple sclerosis (MS) is a complex autoimmune disease that affects the central nervous system (CNS) and immune cells. Exosomes, which are essential for cell communication, may shed light on its enigmatic molecular processes. These small vesicles found in bodily fluids carry a variety of contents and have the potential to be used for exosome-based diagnostics in neurologic disorders such as MS.

Neuronal exosomes offer a transformative approach to neurodegenerative disease treatment, addressing challenges in drug discovery, delivery, and clinical trials. This evolving technology paves the way for more efficient and patient-centric methodologies. Collaboration among academia, pharmaceuticals, and biotech firms will be pivotal in leveraging the potential of neuronal exosomes, changing the treatment landscape (Sun et al.,2022). (Figure 1)

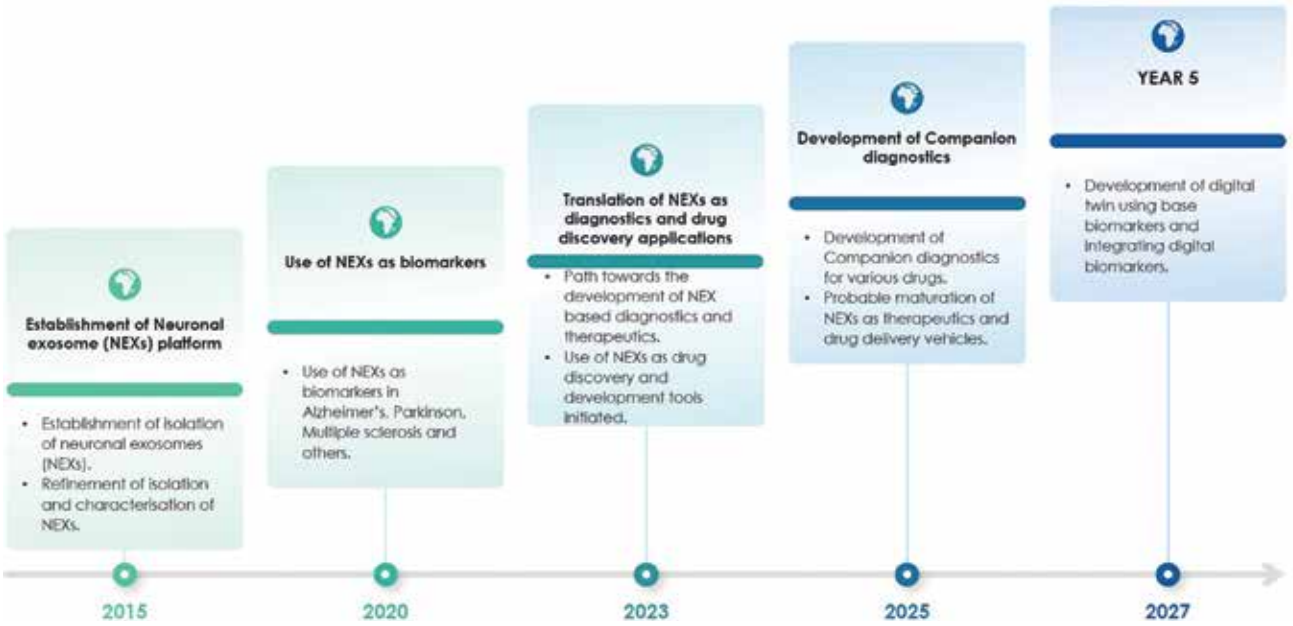


Figure 2: A roadmap representing the integration of neuronal exosomes (NEXs) with AI and big data, highlighting the transformative potential in healthcare and illustrative timelines



> The pharmaceutical and biotech industries are transforming by integrating the neuronal exosome platform. This integration is enhancing patient outcomes, lowering clinical trial costs, and promoting a more ethical approach to healthcare

Future Prospects

Integrating neuronal exosomes into drug processes is a promising frontier in personalised medicine, with applications extending beyond NDDs to fields like psychiatry, ageing, and neuroimmunology. Combining exosome research with advanced AI (Figure 2) and big data analytics could enable more refined applications, transforming microscopic insights into actionable knowledge. This burgeoning area represents a potential transformation in understanding, monitoring, and treating diseases, necessitating collaboration and innovation across the scientific community. The future of exosome research holds immense potential, redefining approaches to healthcare and marking a commitment to medical advancement.

Impact of Adoption of Neuronal Exosomes in the Pharma and Biotech Industry

Integrating the neuronal exosome platform offers a transformative approach to the pharmaceutical and biotech industries. By enhancing real-time insights in clinical trials, enabling personalised diagnostics, and streamlining drug discovery, the platform contributes to improved patient outcomes and reduced costs. It also fosters a more ethical approach through non-invasive diagnostics, potentially reducing reliance on animal testing. The overall increase in efficiency accelerates responses to health challenges, positioning the neuronal exosome platform as a critical driver in redefining medical research and intervention, fostering a more effective and compassionate industry.

Conclusion

Neuronal exosomes are revolutionising neurological disorder treatment by enabling innovative drug discovery, targeted delivery, and efficient clinical trials. This technology, validated in practice, heralds a future of patient-centred care with profound industry impact. Investment in neuronal exosomes represents a commitment to more than symptom treatment; it's a stride towards understanding, preventing, and healing at the core of health. This promising step signifies an investment in a future where medicine transcends mere symptom management to embrace holistic healing and prevention. ■

References are available at www.pharmafocusasia.com

AUTHOR BIO

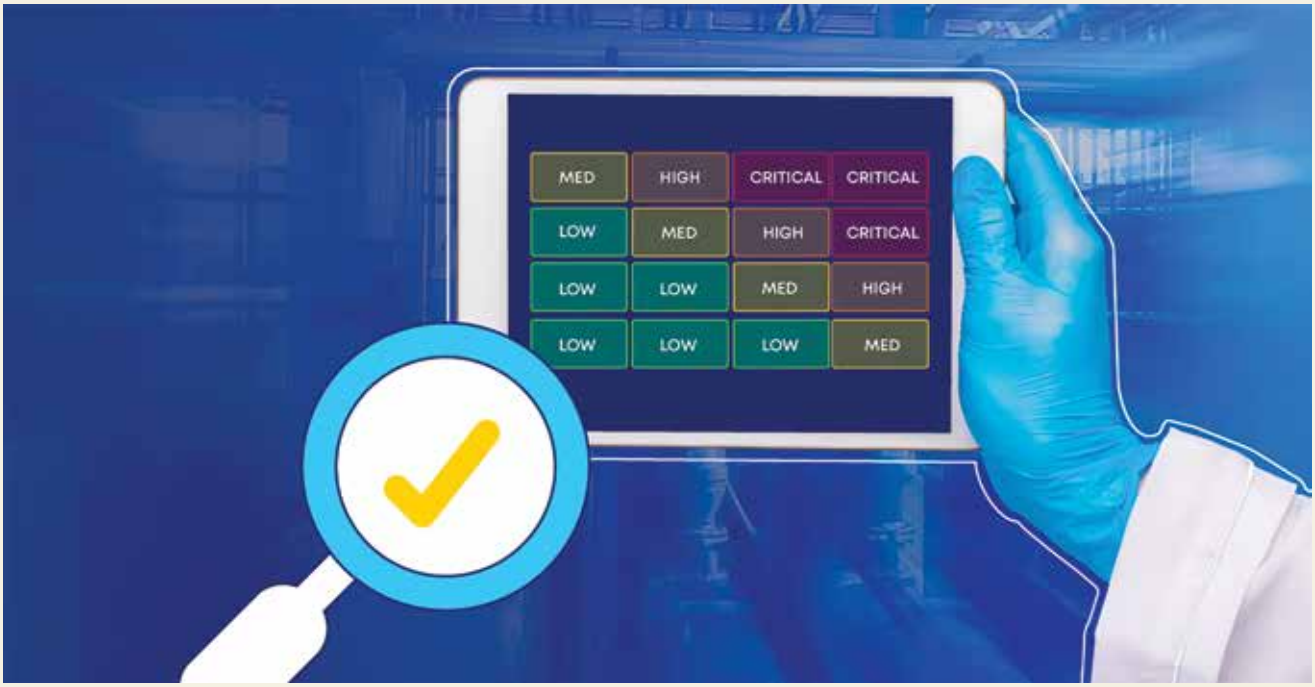


Dr. Manda Venkata Sasidhar, a prominent immunologist with a PhD in neuroimmunology from Heinrich Heine University, Germany, and postdoctoral-studies at UCLA, is the CSO of AHERF and Founder of Urvogelbio. He has contributed to diagnostics, drug delivery systems, and vaccine breakthroughs and has held key roles in the biotechnology industry.



Dr. Ganji Praveena, a PhD in Biological Sciences from CSIR-IICT, Hyderabad, specialises in nanotechnology and exosome biology. As a Scientist at Urvogelbio Pvt Ltd, she explores neuronal exosome platforms, particularly their applications in diagnosing and treating neurodegenerative disorders such as Parkinson's and Alzheimer's, thereby influencing future medical diagnostics and therapeutics.

IT'S TIME TO IMPLEMENT ICH Q9(R1)



The ICH Q9(R1) guideline on Quality Risk Management (QRM) is on its way[1] to reaching Step 5 of the ICH process around the globe. As you can see, a large part of the world has already implemented it, while the rest plans to do so within the next few months:

- ANVISA, Brazil- Implemented; Date: July 9, 2023
- EC, Europe- Implemented; Date: July 26, 2023
- FDA[2], United States-Implemented; Date: May 4, 2023
- Health Canada, Canada-In the process of implementation
- MFDS, Republic of Korea-Not yet implemented; Date: December 1, 2023
- MHRA, UK-Implemented
- Swissmedic, Switzerland-Implemented; Date: January 18, 2023.

In this article, we'll explore what steps you need to take to comply with the new revision.

What is this revision all about?

The ICH Q9 guideline provides guidance on the principles and examples of tools for quality risk management that can be applied to various aspects of pharmaceutical quality.

Initially implemented in 2006, ICH Q9 has been due for a revision that would tackle aspects left out of the original document.

Thus, the revision addresses[3] four fundamental areas:

- Lack of understanding as to what constitutes

1 https://ich.org/page/quality-guidelines

2 https://www.fda.gov/media/167721/download

3 https://database.ich.org/sites/default/files/Q9-R1_Concept%20Paper_2020_1113.pdf

Characteristics	Lower levels of formality	Higher levels of formality
QRM process	One or more parts of the process are not performed as stand-alone activities but are addressed within other elements of the quality system.	All parts are explicitly performed.
QRM tools	QRM tools might not be used in some or all parts of the process.	QRM tools are used in some or all parts of the process.
Team involved	A cross-functional team might not be necessary.	A cross-functional team is assembled for the QRM activity.
Facilitator	---	Use of a facilitator with experience and knowledge of the quality risk management process may be integral to a higher formality process.
Reporting	Stand-alone quality risk management reports might not be generated. The outcome of the quality risk management process is usually documented in the relevant parts of the quality system.	Stand-alone quality risk management reports or related documents which address all aspects of the process may be generated and documented (e.g., within the quality system).

Table: 1

formality in QRM work
- Reducing the high levels of subjectivity in risk assessments and QRM outputs
- Management of end-product availability risks
- Lack of clarity on risk-based decision-making.

Clarifying formality in QRM

Quality risk management activities will have different degrees of formality depending on certain factors, such as:

- **Uncertainty** - lack of knowledge about hazards, harms, and, consequently, their associated risks.
- **Importance** - risk-based decision importance in relation to product quality.
- **Complexity** - the degree of complexity associated with the process or subject area.

Higher levels of uncertainty, importance, or complexity may require more formal quality risk management approaches to manage potential risks and support effective risk-based decision-making. (Table: 1)

Additionally, while importance and complexity are relatively straightforward to identify, uncertainty can be managed, up to a point, with a systematic approach for acquiring, analysing, storing, and disseminating scientific information, which, in turn, will inform all QRM activities.

Therefore, at ValGenesis, we recommend setting up a system to perform this knowledge management to guarantee a better assessment of proper formality.

Minimising subjectivity in risk assessments

Connected to the previous point, there's the aspect of subjectivity in risk assessments.

Subjectivity can impact every stage of a quality risk management process, especially the identification of hazards and the estimation of the probability of occurrence and severity of harm. It can also impact the estimation of risk reduction and the effectiveness of decisions made from quality risk management activities. Subjectivity cannot be eliminated entirely, but it can be minimised by addressing bias and assumptions.

At ValGenesis, we recommend the following:

1. Using software that can make risk management activities systematic. And more than systematic, it needs to streamline the risk operations of the entire organisation.
2. Installing a system that aggregates all the manufacturing data, processes it, and informs your QRM system of the real impact of your QRM activities.

	High importance		Low importance	
	Low complexity	High complexity	Low complexity	High complexity
Low uncertainty	Less structured	Highly structured	Less structured	Highly structured
High uncertainty	Highly structured	Highly structured	Highly structured	Highly structured

Table: 2

By enabling this virtuous circle, you can make QRM decisions that are both science- and knowledge-based, thus less subjective.

Managing product availability risks

Quality and manufacturing issues can lead to product availability issues (e.g., product shortages).

ICH Q9(R1) identifies that, in order to proactively identify and implement preventive measures that support product availability, QRM activities should include the following factors:

- Manufacturing process variability and state of control
- Manufacturing facilities and equipment
- Oversight of outsourced activities and suppliers

Clarifying risk-based decision-making

Risk-based decision-making is implied in all quality risk management activities. In the case of QRM activities, they include decisions related to:

- What hazards exist
- The risks associated with those hazards
- The risk controls required
- The acceptability of the residual risk after risk controls
- The communication and review of quality risk management activities and outputs.

ICH Q9(R1) predicts three approaches to risk-based decision-making. The approaches are:

1. **Highly structured:** involves a formal analysis of the available options before making a decision and an in-depth consideration of relevant factors associated with the available options.
2. **Less structured:** simpler approaches are used to arrive at decisions, and they primarily use existing knowledge to support an assessment of hazards, risks, and any required risk controls.
3. **Rule-based:** standardised approaches, which do not require a new risk assessment to make such decisions, are typically based on previous risk assessments, which usually lead to predetermined actions and expected outcomes.

These approaches are adopted based on different levels of formality, which, in turn, are based on their levels of importance, complexity, and uncertainty of each decision. (Table: 2)

ValGenesis can ensure your ICH Q9(R1) compliance

The ValGenesis consulting services team comprises industry experts who thoroughly understand the global regulations that impact life sciences businesses.

Whether you have completed implementing the revision or are starting now, we are ready to assess and guarantee your processes' ICH Q9(R1) compliance. You can learn more by reaching out to our experts.



AUTHOR BIO

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Quality Risk Management Tech Lead

Margarida is currently the Quality Risk Management Tech Lead at ValGenesis. Working in the Risk Management field for the past 4 years, Margarida has been managing the implementation of QRM approaches on several pharmaceutical and biopharmaceutical companies around the globe. In addition, she supports the development and validation of the digital solutions provided by ValGenesis to its clients.

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Recent Advances in Small-molecule Broad-spectrum Inhibitors of Bacterial Metallo-β-lactamases

Antibiotic resistance is a major threat posed by pathogenic bacteria to human health globally. It occurs through the destructive catalytic hydrolysis of β-lactam antibiotics by metallo-β-lactamases (MBLs) produced by the organisms. Some small-molecules are herein presented as potent broad-spectrum inhibitors of clinically relevant MBLs with ideal safety profiles for further studies.

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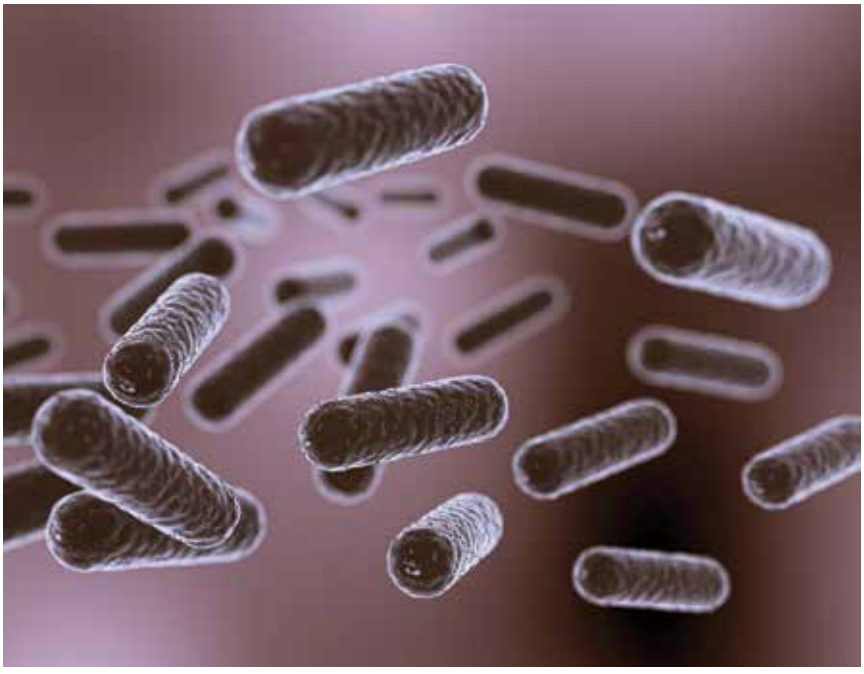

Incessant resistance of pathogenic bacteria to almost all forms of antibiotics continues to pose a major threat to human well-being worldwide. Consequently, antibiotic resistance (AR) has become renowned and constitutes an unimaginable burden on the global healthcare and economic systems. For instance, an international collaborative analysis on the global burden of AR by Murray and co-workers provided an alarming rate of occurrence, epidemiology, morbidity and mortality associated with AR across the human populations in their pedigrees. Accordingly, in 2019, about 4.95 million deaths were estimated to have resulted from antimicrobial resistance-related events generally, out of which 1.27 million were attributable to AR. Six bacteria strains, mostly belonging to the *Enterobacteriaceae* (otherwise referred ▶

to as superbugs) are implicated in most cases. They are *Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus pneumonia,* contributing to their enlistment among the pathogens list of Priority 1 by the World Health Organization. Worrisomely, a forecast of 10 million annual deaths by 2050 has been documented on the menace and more resistant strains with higher lethality could emerge if left unchecked. Thus, concerted scientific efforts are critically required to unveil the pathogenesis of the superbug-inclined AR expansively and strategise effective approaches for overcoming it.

Notably, the production of defensive enzymes such as the metallo-β-lactamases (MBLs) understandably constitutes a major pathogenesis AR among other factors. The New Delhi MBL (NDM), Imipenemase (IMP) and Verona-integron MBL (VIM) are among the most relevant MBLs produced by superbugs for inducing AR. The producer organisms evade the actions of almost all labelled antibiotic medications, including the β-lactam/carbapenem groups (even in combined forms) that are commonly prescribed in chronic AR-related clinical conditions. They execute this minacious mechanism by releasing the destructive enzymes, MBLs which in turn damage the integrity of the drugs through a hydrolytic cleavage of their pharmacophoric β-lactam rings, facilitated by the coordination chemistry at their Zn sites (Figure 1A). Once deactivated, the molecule is released from the active site of the enzymes and the targeted organism remains drug-free and debilitating in the host. (Figure 1)

Several efforts are being deployed to mitigate the AR challenge by inhibiting the destructive catalytic activities of the relevant MBLs. Among the effective approaches, targeting the Zn ions cofactor of the MBL sites has proved relevant since their enzymatic activities are Zn-dependent. Thus, the strategic chelation of the active site Zn ions through coordination chemistry with small molecules (acting as ligands) (Figure 1B) has attracted an array of scientific interests. Through the fascinating technique, coordinating small molecules reactively sequestrate the Zn ions from the MBL active sites, making the metal less available and distorting the enzymatic activities. Some of the small molecules are potent antibiotics as well, supporting their multi-target-directed actions while acting as adjuvants to conventional antibiotics. Either way, the integrity of antibiotics is protected/restored and the MBLs become inhibited, resulting in an effective mitigation of AR-related cases. More interestingly, some of the reported small molecules have demonstrated excellent inhibitory potencies against multiple strains of the MBL. Such molecules are regarded as broad-spectrum inhibitors and the potent ones with minimal toxicity reported in recent literature are herein overviewed.

Potent broad-spectrum inhibitors of bacterial metallo-β-lactamases

The development of effective MBL inhibitors (MBIs) that combine selectivity and low toxicity is a formidable challenge due to shallow grooves and structural diversity characterising MBLs. Researchers' collective efforts have led to the discovery of some promising small-molecule inhibitors with a broad spectrum of action against various MBL subtypes. The progress made in identifying these diverse MBIs offers new hope in combating AR. Few notable ones from both *in vitro* and pre-clinical *in vivo* studies are identified below for further translational studies.

Two synthetic molecules, 2,5-dimethyl-4-sulfamoylfuran-3-carboxylic acid (**MBI01**) and 2,5-diethyl-1-methyl-4-sulfamoylpyrrole-3-carboxylic acid (**MBI02**), possessing a sulfamoyl heteroarylcarboxylic acid skeleton, exhibited nM-μM range of inhibitory activities on clinically relevant MBL types, including IMP, NDM, and VIM. Additionally, their potencies extend to other types such as the Sao Paulo MBL, Seoul imipenemase, Dutch imipenemase, Tripoli MBL, and Kyorin hospital MBL. These inhibitors bind competitively, weakening the MBL potential for antibiotic deactivation by sequestering the metal cofactors from their active sites. Interestingly, in combination with meropenem, they synergistically reduce the minimum inhibitory ▶

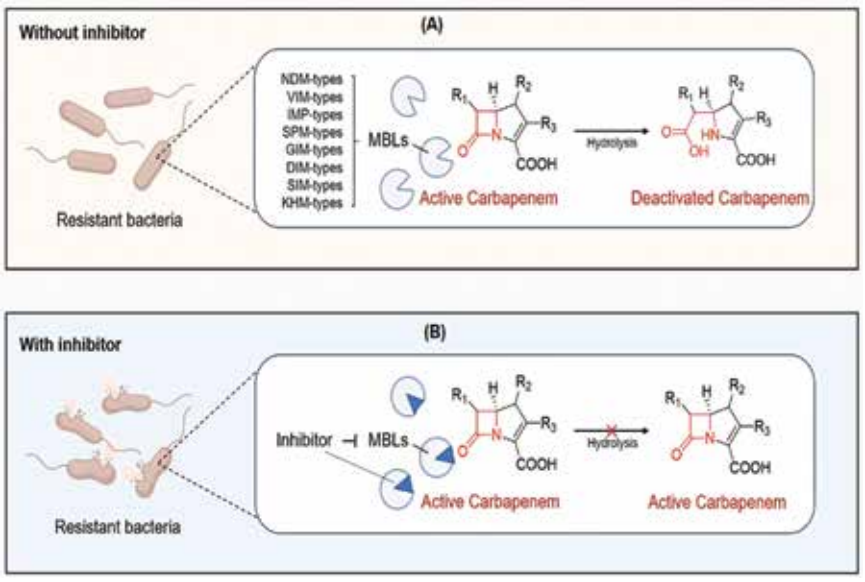

Figure 1. Mechanism of antibiotic resistance through MBLs (A) Catalytic hydrolysis of β-lactam antibiotic (B) Inhibition of MBL to preserve β-lactam antibiotic

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concentration (MIC) on various clinical isolates of some MBLs-carrying *Enterobacteriaceae* up to a hundred-fold. Particularly, **MBI02** achieved a feat by raising the survival rate of murine model infected with NDM-1/VIM-1-carrying *K. pneumonia* clinical strain to an astounding 100 per cent. These findings highlight their potential to be developed for clinical application, especially due to their minimal toxicity.

Another promising candidate, 3-(6-aminopyridin-3-yl)-1-sulfamoyl-1H-pyrrole-2-carboxylic acid (**MBI03**), synthesized with a pyrrole-carboxylic acid analogue, performed selectively against IMP-1, NDM-1, and VIM-2. When tested in combination with meropenem, it effectively suppressed MBL-producing clinical isolates. Remarkably, the synergism was actively apparent in murine models with resistant bacterial infections. Despite its potent MBL inhibitory action, MBI03 exhibited a remarkable safety profile. It displayed minimal off-target toxicity effects, even beyond the pre-clinical therapeutic doses. This compelling safety profile lays the groundwork for exploring its therapeutic potential with confidence.

In the pursuit of a broad MBL inhibition, di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (**MBI04**), a synthesised dipyridyl-substituted thiosemicarbazone-based molecule has shown promising results. Its potency remains consistent across the clinically relevant MBLs including IMP-1, NDM-1, and VIM-2, in the range of nM-μM via the formation of Zn-inhibitor complex, indicating a metal-chelating mechanism. When combined with meropenem against IMP-1-, NDM-1-, and VIM-2-producing *E.* coli at a concentration of just 8 μg mL-1, it exhibited remarkable restorative effects on carbapenem activity, reducing the MIC by up to 256-fold (especially on NDM-1). Encouragingly, in further testing using a carbapenem-resistant *K. pneumoniae* infected murine model, the combination therapy of this inhibitor with the antibiotic significantly reduces the bacterial load. Cell-based assays also validate the safety profile, indicating low cytotoxic even at concentration several times higher than the effective dose. This notable efficacy hints at the potential of this molecule as a valuable addition to the antibiotic arsenal in combating resistant bacterial infections.

In addition, (S)-2-(bis((1H-imidazol-4-yl)methyl)amino)-5-(3-phenyl-5-thioxo-1,5-dihydro-4H-1,2,4- triazol-4-yl) pentanoic acid (**MBI05**) demonstrated robust targeting actions on NDM- and VIM-type variants. Its mechanism involves a selective interference with the zinc coordination in the MBL active site, resulting in significant inactivation of the enzymes. While it exhibits moderate activity towards IMP-type, its limited zinc accessibility confers greater resilience. Notably, its co-administration alongside meropenem yielded an interesting synergistic effect. They substantially reduced the MIC values by 500 to 1000-fold against NDM-1, VIM-1, and VIM-4 carrying ultra-resistant clinical isolates. The compound stands as a promising candidate due to its minimal off-target toxicity risk, metabolic stability, and reduced cytotoxic potential.

Likewise, 1-(4-(thiophene-2-yl) phenethyl)-1H-imidazole-2-carboxylic acid (**MBI06**) displayed a broad-spectrum activity against various MBLs. Its most pronounced efficacy, however, is discerned in its ability to selectively target VIM-type MBLs, encompassing VIM-1, -2, and -5 variants. At a minimal concentration (10 μg mL^{-1}), a synergistic interaction with meropenem proved evident. The observed effect can be attributed to its compact molecular size, facilitating facile permeation through bacterial membranes and thereby establishing effective interaction with the Zn active site within MBL enzymes.

The compounds, (R)-6,6'-(((1-carboxyethyl)azanediyl)bis(methylene)) dipicolinic acid (**MBI07**) and (S)-6,6'-(((1-carboxyethyl)azanediyl) bis(methylene))dipicolinic acid (MBI08) merit attention for their distinctive inhibitory properties. Acting through a non-competitive metal-chelating mechanism, these compounds exhibited a micromolar-level inhibitory effects across a broad spectrum of MBLs, IMP-, NDM-, and VIM-types. In time-kill kinetic assays, co-administration of either of these compounds with meropenem significantly reduced an MBL-inclined bacterial load. Qunatitatively a 10,000-fold reduction in bacterial load carrying IMP-1, a >10,000-fold reduction against NDM-1, and a decrease to <2 CFU mL-1 in the case of VIM-1. Importantly, these

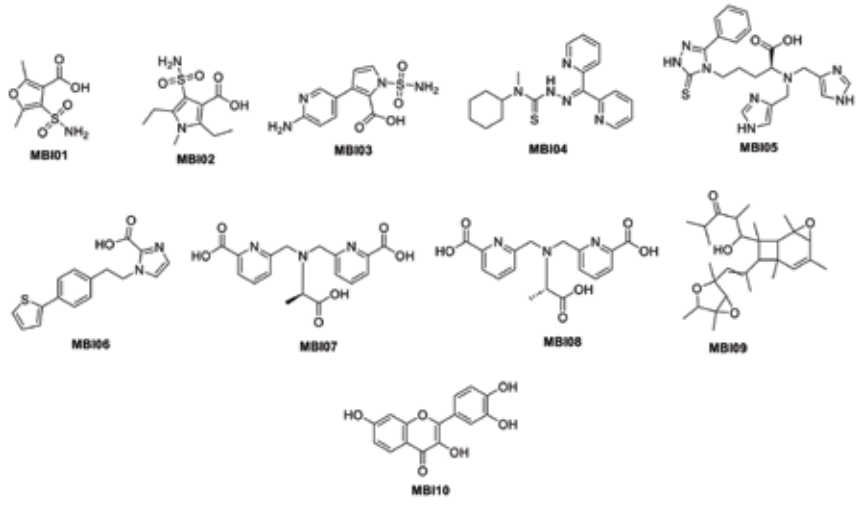

Figure 2. Chemical structures of some broad-spectrum inhibitors of metallo-β-lactamases

compounds displayed a favourable safety profile, worthy of further assessment as future antibiotics.

Beyond the synthetic compounds, nature offers potent alternatives in the form of secondary metabolites or phytochemicals that effectively suppress the MBLs. Noteworthy, emerione A (**MBI09**), from *Aspergillus nidulans,* and fisetin (**MBI10**), found in various vegetables and fruits, stand out as promising candidates. Acting as metal chelators, either through direct interaction with Zn at the MBL enzymatic site or by forming a ternary complex, they inhibit MBLs within the μM range and exhibit independent antibacterial actions against NDM-1-producing *Enterobacteriaceae.* Co-administration of **MBI09** or **MBI10** with carbapenem significantly reduced the susceptibility of NDM-1-expressing bacterial strains, and effectively revived the potency of meropenem. *In vivo* experimentation, the restoration ability of **MBI10** is validated in a murine model infected with resistant bacterial strains. Impressively, the two compounds feature ideal systemic safety profiles. Even at acute and chronic high doses, they showed no apparent adverse effects and only insignificant haemolytic effects, positioning them as potential therapeutic agents for addressing MBL-mediated AR.

The chemical structures of the ten highlighted MBL inhibitors are presented in Figure 2. Their structural scaffolds support further modification upon structure-activity relationships (SAR), quantitative SAR (QSAR) and other molecular modelling for synthetic derivatization. (Figure 2)

Conclusion

Antibiotic resistance continues to dominate the causes of epidemiology, morbidity and mortality associated with microbial infections. The production of MBL enzymes by the pathogenic bacteria has been implicated in the pathogenesis of AR, affecting the efficiency of almost all antibiotics including the supposedly highly active β-lactam types. Thus, the quests for effective MBIs are essentially significant to relevant science fields. From the concerted efforts, researchers have identified some small-molecules with promising inhibitory effects on the devastating MBLs. Ten of them, **MBI01-MBI10** with strong inhibitory activities against various MBL strains have been surveyed from some recently documented *in vitro* and *in vivo* experimental validations. These molecules have demonstrated potential for mitigating the Zn-dependent destructive MBL activities inclusively via the mechanistic sequestration of the Zn ions from the MBL active sites. They also displayed a synergistic restoration of antibiotic effects of labelled medications on MBL-carrying organisms and possess ideal safety profiles. Thus, the compounds (eight from synthetic route and two natural products) represent potential broad-spectrum small-molecule inhibitors of MBL amenable for future antibiotics upon further analysis. Although, by targeting and chelating metal ions, concerns have been raised on their potential for off-target inhibition of beneficial metalloenzymes. However, future efforts could be directed at their appropriate delivery to sites of actions suggestively with the aid of nanotechnology. The overview models a template for designing efficacious therapeutics for curbing AR trends upon further translational investigations. ■

References are available at www.pharmafocusasia.com

AUTHOR BIO



Yusuf Oloruntoyin Ayipo recently completed his PhD in Medicinal Chemistry at the Centre for Drug Research, Universiti Sains Malaysia (USM), with interests in antibacterial, anticancer and neurological drug development. He won several awards/scholarships including a PhD Scholarship by TETFUND, Nigeria (2019), ACS Sci-Mix Presenter, Atlanta (2021) and Sanggar Sanjung Award, USM (2021).



Chong Chien Fung is an emerging scholar with a strong foundation in bacteriology and biochemistry, leveraging interests in studying clinically isolated resistant strains and natural product-based antibiotic alternatives. Currently, his pioneering research is in the field of clinical immunology, where he explores novel biomarkers for advancing medical diagnostics and treatments.



Mohd Nizam Mordi received his PhD in Medicinal Chemistry from the University of Manchester in 2001. He began his professional career at the Centre for Drug Research, USM in 2001 and became a professor in Medicinal Chemistry in 2016. His research entails design and synthesis of analgesia, antidepressant, anticancer and addiction treatment agents.

Digitalisation An All-purpose Tool

Win the race against time

New diseases call for new medications, and growing competition calls for faster, leaner processes in all areas of business. Rebecca Vangenechten, 38, describes the potential offered by automation and digitalisation for the pharmaceutical industry. She heads the pharmaceutical segment at Siemens and knows what makes the industry tick.

Rebecca Vangenechten
Head of pharma business, Siemens



Rebecca Vangenechten, the recent years dominated by the pandemic have given the pharmaceutical industry even greater prominence: We've all experienced how long it can seem to take until a vaccine or medication reaches the market. What role does the time factor play in this sector?

A massive one! The reality is that the faster drugs or vaccines can be made market-ready, or manufactured in large volumes, the faster people can be protected from diseases, and the faster people who are already ill can be helped. That's a huge incentive. And at the same time, it's also true that early market-readiness keeps the costs as low as possible. And what's more, speed also means being faster than your competitors. The time factor is therefore of major importance.

In your view, what other urgent challenges is the industry facing?

There's a range of challenges for the pharmaceutical industry. What affects patients drives market growth for the pharmaceutical industry, especially in regions and countries that aren't financially strong. And that impacts on the products, because they have to be affordable. Another major question is how patient data will be used in the future. What influence will it have on treatment: will patients only be willing to pay for successful treatments?

The product range is also in transition. There are many innovations in the areas of pharmaceuticals and treatments. Innovations like customised medicine – in other words, the production of individual batches for a single person – create major challenges for production. Today's factories aren't designed for that, and a different infrastructure and supply chain will be needed. This also comes with uncertainty: How quickly can new technologies be incorporated in existing processes? What does that mean for workflow validation? And, of course, cost pressure plays a huge role. In this regard, companies have to consider where their core business lies and think about outsourcing, as appropriate.

How can we take a positive approach to these future-oriented trends?

At Siemens, we've derived five main industry drivers from these challenges: flexibility, speed, quality, sustainability, and efficiency. Entities that are well positioned in these areas will be equal to these challenges and will achieve a very strong market position. The direction is clear: We need more digitalisation! It's the most valuable all-purpose tool.

> At Siemens, we firmly believe that when the real and digital worlds work together, the result is faster and safer production. That's why we've developed an end-to-end portfolio of software and automation solutions in the form of the Digital Enterprise to help us digitalize the entire value chain.

In our personal lives, we're now accustomed to the fact that digital services make our day-to-day lives easier. A navigation app on your smartphone, for example, that takes us safely to our destination and helps us avoid current traffic congestion. Or messenger apps that enable us to stay in constant contact with our friends and family. And there are many other examples. Day-to-day business in the pharmaceutical industry is still much less digitalised, whereas other industries have certainly made more progress in this area. But there's huge potential for digitalisation!

What does that mean, in concrete terms?

At Siemens, we firmly believe that when the real and digital worlds work together, the result is faster and safer production. That's why we've developed an end-to-end portfolio of software and automation solutions called the Digital Enterprise to help us digitalise the entire value chain. The important thing is to understand and use the vast amount of data supplied by the industrial Internet of Things (IIoT). And that's exactly what the Digital Enterprise does! It combines the real and digital worlds so we can utilise our limited resources to make efficient use of the limitless volume of data and make our industry more sustainable. Specifically, we've developed eight portfolio modules that cover the entire value chain.

That includes digital twins and simulation. What opportunities do these technologies offer?

Depending on what's important to our customers, they can be used to create digital twins of prod-ucts, product lines, processes, or buildings. A digital twin links the real and digital worlds – and by recording real-time data, the virtual counter-part can document the current condition and simulate the future condition, which lays the groundwork for optimisation. It enables early recognition of problems, it can be used as the basis for in-silico tests, it and offers the opportunity to improve checking processes. With our customer GlaxoSmithKline (GSK), for example, we've developed a digital process twin for vaccine manufacture (p. 9). The digital twin not only makes it possible to check complex processes, it also predicts how changes would impact on those processes. This means that process engineers can perform simulations in just a few hours instead of having to construct trial facilities. This ultimately made the production process at GSK much more robust while improving the company's product quality and increasing its speed. ▶

Can you name other examples of ways that automation and digitalisation optimise production?

When facilities are designed or built, we provide support with Integrated Engineering. It's important in these cases to maintain an overview of the entire process lifecycle: Where is there potential for improvement? Where can we make improvements in speed? Where can processes be simplified? Siemens aims to create complete solutions that are in the customer's best interests. For Bayer AG in Bitterfeld, for example, we integrated a new type/instance concept incorporating both MES and DCS functions

> The added value of paperless production is much more than what a purely digital version of paper documents would offer.

We can also assist many pharmaceutical manufacturers with the transition to continuous production. This production method is used to manufacture active ingredients in compact, closed units with a high level of automation and less manual intervention.

The production stages that make up the sequential workflow in a traditional batch process are integrated into a comprehensive process, with quality measured in real time. Pfizer applies this method to its production in Freiburg, for example, and has just expanded its plant to include a high-containment facility – a facility where it can produce up to seven billion tablets every year. Along with several partner companies, Siemens played a role in making this production plant one of the most modern and sustainable facilities in the world

Many manufacturers would like to switch to paperless production. What does this involve, and how can Siemens help them?

I'd like to make one point clear to begin with, to deal with a false impression that still persists in some cases: The added value of paperless production is much more than what a purely digital version of paper documents would offer. The major advantage is that workflows become trans-parent! In paperless production, the process data, conditions, and results are recorded in detail, saved, and displayed. The processes are made more error-resistant – in other words, more robust and less susceptible to deviations – and the cost and effort of data input and documentation are reduced. Siemens can realise this using its MES solution Opcenter Execution Pharma, which fully complies with GMP (Good Manufacturing Practice) requirements and is pre-validated for its observance of all current standards for pharmaceutical production. When BioNTech converted a new plant in Marburg to produce its very popular vaccine during the COVID-19 pandemic, it was essential to begin production as quickly as possible. Part of the solution therefore involved paperless manufacturing.

What is Siemens doing to drive digitalisation in the pharmaceutical industry?

We know from studies that more than half of the digitalisation projects that are initiated fail, that brownfield facilities are rarely touched, and that expertise in digitalisation is often lacking. That's something we want to change! Siemens wants to speed up the digital transformation. That's possible with Siemens Xcelerator, a new, open, digital business platform that provides a curated portfolio of IoT-capable hardware and software, a marketplace for them, and a powerful ecosystem of partners. Siemens makes three promises with Siemens Xcelerator: First, to turn super- complicated into super-simple. Second, to make Siemens Xcelerator products flexible by making them fully modular and interoperable in stages so that customers can select exactly what they want. And third, to focus on openness and ensure that Siemens software works well with other systems. In all these ways, Siemens will continue to be a powerful partner in the advancement of digitalisation. ■

AUTHOR BIO

Rebecca Vangenechten is heading the pharma business at Siemens since April 2020. She began her career at Siemens in July 2009 as a Business Development Consultant at Siemens in Belgium, working with end customers in the pharmaceuticals industry. She then spent five years working as Global Account Manager for a large company in the chemicals and pharmaceuticals industry at the Siemens locations in Frankfurt and Karlsruhe. Before taking on her current position as head of the Pharma Vertical, Vangenechten was responsible for Process Automation in the Middle East Region.



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Powering Decentralised Drug Development

Enabling downstream disruptive technologies to generate high fidelity output

Decentralised clinical trials are the latest and rapidly growing trend in conducting clinical trials through leveraging improved disruptive digital technologies and remote data collection methods. Blockchain oracle is the keystone technology, upstream from disruptive technologies, such as machine learning (ML) and artificial intelligence (AI) that can significantly enable and enhance decentralised clinical trials' efficiency, transparency, and security.

Frank Leu, Founder and Managing Member, BioPharMatrix LLC



The Decentralised Drug Development (DDD) process involves coordinating various vendors and pulling together contract research organisations (CRO) to operate seamlessly to achieve developmental milestones from conception to market. Currently, there are inefficient legacy technologies and non-digital methods used together during pre-clinical drug development to meet the Investigational New Drug application requirements set by the Federal Drug Administration (FDA). However, the scrutiny of drug candidates' toxicity and efficacy in humans during its clinical trial is becoming more intensive as data fidelity, security, and data/information immunity are critical attributes required for the FDA's final approval. Recently, during human clinical trials, the evolution of moving away from centralised to decentralised developments are means to eliminate bottleneck restraints and delays as the decentralised method allows flexibility in patient recruitment and could reflect a much better geographical representation

of a diverse patient background. For instance, for rare disease drug development, this could facilitate the trial's ability to collect as many patients in the shortest amount of time possible as there is no geographical barrier. In this article, I will focus on the discussion of Decentralised Clinical Trials (DCT) and how these most expensive and often the least efficient phases of drug development could get a turbo boost from implementing disruptive technologies. This discussion will further focus on the requirements of the Blockchain Oracle (BO) and how it could power the rest of the blockchain architecture and provide high fidelity and immutable data collection for ML and AI training.

Running a DCT involves conducting a clinical trial with the use of digital technology, remote devices, and customised approaches for data gathering, participant monitoring, and trial process management. DCTs offer several advantages, such as increased patient participation and reduced logistical burdens as opposed to centralised trials. Here is an outline of key steps for running a decentralised clinical trial:

1 Define your trial's questions and objectives. It is also very important to develop a detailed clinical trial protocol that outlines the study design, inclusion/exclusion criteria, endpoints, and data collection methods;

2 Upon submission of an Investigational New Drug (IND) application or Investigational Device Exemption (IDE), continue to establish close communication with the regulatory agency (i.e. FDA in the United States) to make sure your proposed DCT execution complies with local regulatory requirements;

3 Pick and choose and adopt technology that can digital tools for data collection, information transfer, patient recruitment, and monitoring. Automating and integrating electronic informed consent (eConsent), wearable devices, mobile apps, and telehealth platforms;

> Running a decentralised clinical trial requires careful planning, technology integration, and adherence to regulatory guidelines.

4 Recruit and screen participants remotely via digital communications/advertising and online platforms to recruit patients that accurately meet the study criteria;

5 To facilitate and make a decentralised trial workable, eConsent procedures needed to be put in place to validate participants' consents were informed. Most importantly, participants need to be aware that throughout the study, their consent can be given electronically;

6 Use a real-time monitoring system to track patient progress and safety remotely. Data can be detected and collected remotely using digital tools, wearables, and patient self-reported outcomes;

7 In addition, maintain regular and informed communications with participants to keep them engaged and prevent participant dropout;

8 In the event of an adverse event, establish a procedure and system that participants can immediately notify relevant authorities;

9 In site-less trial management, coordinate trial activities, data collection, and patient interactions remotely. Define various decentralised trial platforms or clinical trial management systems (CTMS) for centralised control;

10 Timely and accurate distributions of investigational products and supplies to participants' locations. Construct and put in place an effective remote system monitoring and management of the supply chain;

11 Implement a robust data transfer among stakeholders, however, the integrity of participants' data and sensitive information have to be protected with security and privacy safeguards in place to be in compliance with local data privacy regulations (e.g., GDPR, HIPAA);

12 Analysing collected data and prepare interim and final study reports for local regulatory submissions;

13 Once submitted, engage the regulatory authorities in a transparent manner, maintain open and free communication throughout the trial. Promptly submit required documentation and updates as required;

14 Ensure trial results are completed with quality assurances that are ready for regulatory inspections and audits; Enabling the trial to come to a closure in accordance with the predefined criteria, submitting final reports to local regulatory agencies for approval;

15 Publish and share clinical trial results via journals, conferences, or clinical trial registries and continue to monitor participants for any long-term safety or efficacy concerns as post-trial follow-up.

Blockchain technology can be adopted to improve the efficiency, transparency, and security of the entire decentralised clinical trial process mentioned above. There are thousands of blockchain projects under development, creating some of the most exciting and innovative technologies to enable Web 3.0, which is an online universe that allows the internet to be as decentralised as possible and places control of information/data back to users' control. Running a decentralised clinical trial requires careful planning, technology integration, and adherence to ▶

regulatory guidelines. Collaboration with experienced clinical trial experts, data scientists, and regulatory professionals is essential for success in this rapidly expanding field.

A blockchain could only be used properly in a decentralised clinical trial if the methods and devices used to track and collect data have been properly designed with a chosen blockchain oracle platform. A blockchain oracle is a trusted source of external data that feeds information into a blockchain smart contract. The chosen blockchain oracle would then be integrated with the wearable devices placed on the clinical trial participants to collect patient data and store it on the drug development blockchain. The oracle would also monitor the patient data for certain events, such as when a participant reaches a certain milestone or when a safety event occurs. In a decentralised clinical trial, this can be crucial for verifying off-chain data such as patient electronic health records (EHRs), lab results, and other relevant information.

The blockchain oracle can also be used to manage clinical trial data, such as participant eligibility, randomisation assignment, and data collection schedules. This can help to ensure that clinical trials are conducted efficiently and ethically. Oracles can be used to trigger smart contracts embedded in the blockchain to automatically advance to the next phase and/or distribute incentives to participants who have reached certain milestones in the trial. The blockchain oracle ensures the integrity and reliability of data in a DCT via feeding accurate and immutable information/data for downstream disruptive technologies, such as ML and AI training.

The first step in constructing a functional blockchain to power DCT is to choose a blockchain platform that supports smart contracts and oracles of choice. Ethereum is a popular choice, but other platforms like Binance Smart Chain, Polkadot, or Tezos may also be suitable. Next, define and develop smart contracts that will be used in your decentralised clinical trial. These contracts should outline the rules and conditions of the trial, including data verification and storage. Selecting a reliable oracle provider, such as Chainlink is a widely used oracle service in the blockchain ecosystem. You'll need to integrate their services into your blockchain platform. Once integrated, identify the external data sources that the oracle will need to access for your clinical trial. These could include medical records systems, laboratory databases, or other sources of relevant clinical data. Integrate these clinical data into selected oracle and convert them into your smart contract code. The oracle will then fetch data from external sources and provide it to your smart contract when needed. A data verification mechanism will then need to be implemented within the smart contract. The data from the oracle should be cross-checked for accuracy and reliability, methods such as cryptographic hashing, digital signatures, or other methods to ensure the integrity of the data. Once the data verification method is set in place, set-up triggers in the smart contract initiate the oracle to fetch and feed data into the blockchain when specific conditions are met. For example, when a new clinical trial participant submits their health data, the oracle can be triggered to verify and store this data on the blockchain. Once data is stored on the blockchain, it is imperative to ensure that sensitive patient data is handled securely and with utmost strict privacy measures. Compliance with data protection regulations such as HIPAA (in the United States) or GDPR (in the European Union) is critical. Before deploying a decentralised clinical trial solution on the chosen blockchain platform, first thoroughly test your smart contract and oracle integration. Conduct security audits to identify vulnerabilities and address them before deploying the solution. Once deployed, one needs to continuously monitor the data feeds from the oracle to ensure accuracy and reliability throughout the trial. Stakeholder's data accessibility will need to be set up considering how participants researchers, and other stakeholders can access and interact with data stored on the blockchain. A user-friendly interface or applications will be extremely crucial for this purpose. In the end, it is extremely crucial to ensure your decentralised clinical trials comply with all relevant regulations and ethical standards, especially in the healthcare sector.

In conclusion, by integrating a blockchain oracle into a decentralised clinical trial, you can enhance the trustworthiness and transparency of your trial's data, potentially improving the overall integrity and efficiency of the trial while maintaining the security and privacy of data/patient information. ■

AUTHOR BIO



FRANK LEU is the founding managing member of BioPharMatrix LLC, providing intelligence in the areas of innovative processes and platforms for biotech, pharmaceutical, and life sciences. Frank has over two decades of experience in drug discovery and development. Frank has over a hundred speaking presentations and publications on the discovery, bio-ventures, and disruptive technologies for drug discovery and development processes.

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Breathing New Life into Poorly Soluble Drugs Through Lipid Nanoparticles

Oral drug delivery remains indispensable although it presents challenges to poorly soluble drugs. Paradoxically, nanoparticles, especially lipid carriers, provide opportunities for these drugs to achieve maximal therapeutic efficacy as they have the potential to traverse gastrointestinal barriers and deploy in the lymphatic pathway, which aptly, bypasses the first pass effect.

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What are poorly soluble drugs?

The oral route of delivery remains the most popular and convenient way to get medicines into the body. More than 60 per cent of the drugs are administered orally, representing a global share of 90 per cent of all dosage forms. Based on the Biopharmaceutical Classification System (BCS), oral absorption is mainly governed by two factors: water solubility and permeability (Figure 1) (Khan et al., 2022). However, 70-90 per cent of the newly discovered drugs are poorly soluble (BCS Class II and IV), which greatly challenges oral delivery due to the low absorption and therapeutic effect. For instance, anticancer drugs such as docetaxel, paclitaxel, and antimicrobial agents like colistin and amphotericin B have poor solubility and permeability. Due to their poor solubility, these drugs are eliminated in the gastrointestinal tract (GI) prior to absorption, leading to low bioavailability and therapeutic effects (Tan and Billa, 2021).

Lipid nanoparticles

With the advent of nanotechnology, it is now possible to formulate drugs into lipid nanoparticles. These lipid nanoparticles hold the key to revolutionising drug delivery systems, offering a safe and targeted approach to the delivery of poorly soluble drugs. Researchers have been captivated by the immense potential of lipid nanoparticles due to their biocompatibility, biodegradability, and wide biomedical applications (Magalhães et al., 2019). From cyclosporine A to lipid-soluble vitamins and protease inhibitors, these lipid nanoparticles have already demonstrated remarkable commercial, pharmaceutical, and therapeutic benefits (Essaghraoui et al., 2019).

What sets lipid nanoparticles apart from other nanoparticulate formulations is their nano-sized dimension and lipidic nature. They exhibit better tolerability in vivo and they can mimic the natural digestive process of dietary fat. Unlike polymer-based nanoparticles, lipid nanoparticles offer safer toxicology profiles, as they eliminate the need for organic solvents during formulation, making them a more desirable choice (Lu et al., 2021). Additionally, the absorption of poorly soluble drugs is enhanced by virtue of stimulation of biliary and pancreatic secretions by the particles, as evidenced by improved bioavailability of lipophilic vitamins (vitamin A, D, E and K), testosterone and halofantrine co-administered with fat-rich diet (Tan and Billa, 2021). The simultaneous absorption of the drug along with the lipids is also known as the "Trojan Horse effect".

Lipids offer protection to susceptible drugs that degrade via chemical, oxidation, and enzymatic reactions. Moreover, lipid-based nanoparticles can alter the pharmacokinetic profiles of drugs through the manifestation of slow-release behaviour from the delivery system. This, in turn, will minimise an abrupt exposure of high drug concentration in vulnerable organs (Montoto et al., 2020). In this context, the pharmacokinetic profile of the drug is now governed by the particle size, charge, type, and concentration of the lipids rather than the intrinsic physicochemical properties of the drug (Magalhães et al., 2019).

> With the emergence of nanotechnology, drugs can now be formulated into lipid nanoparticles, revolutionising drug delivery - offering advantages in terms of safety, specificity and therapeutic applications.

Two notable lipid-based nanoparticles are solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLNs, the first-generation lipid-based nanoparticles, are colloidal suspensions with particle size range in the order of 40–1000 nm. They remain solid at both room and body temperatures (Montoto et al., 2020). NLCs formulations were developed in 2000 and within five years, two NLCs products were approved for the market (Nanorepair Q10 cream and Nanorepair Q10 serum, Dr. Rimpler, Wedemark, Germany) (Tan and Billa, 2021). NLCs formulations consist of a blend of solid lipids with liquid oil. Despite the presence of liquid oil, the NLCs retain the solid matrix at normal temperature. This unique combination disrupts the crystallinity of the solid lipid matrix and thus, creates imperfections that allow the incorporation of high loads of drugs (Essaghraoui et al., 2019). As a result, NLCs offer significantly increased drug load compared to SLNs, up to five-fold increase observed in retinoids NLCs, opening new possibilities for efficient drug delivery (Jenning and Gohla, 2001).

GI uptake of lipid-based nanoparticle formulation

In the quest for effective drug delivery, lipid nanoparticles have emerged as a promising solution. However, their successful systemic delivery relies on navigating various barriers within the GI tract. One of the obstacles is the protective mucosal layer that lines the GI tract, acting as a shield for the underlying epithelia. To counteract the dislodging forces exerted by GI motility, lipid nanoparticles possess a unique ability to adhere to the mucosal layer. Smaller particle sizes exhibit increased mucoadhesion, allowing them to remain attached for longer periods, effectively overcoming the challenge of GI shear stress (Liu et al., 2021).

Additionally, due to the lipidic nature, the lipid-based nanoparticles permit the absorption of drugs through the lymphatic pathway. The lymphatic system serves as an additional pathway for the absorption of lipid nanoparticles or other lipophilic compounds (e.g., long-chain fatty acids, cholesterol esters and fat-soluble vitamins) (Montoto et al., 2020). This is in contrast to most orally administered drugs, which are transported mostly via the portal blood vein before reaching the systemic circulation. The lymphatic system consists of lymph, capable of maintaining homeostasis through the regulation of extracellular fluid and helps in the body's defence system by transporting immune cells to injury sites.

Lipid nanoparticles that are absorbed by the intestinal lymphatics are transported through the mesenteric lymph duct that enters the thoracic duct and empty in the systemic circulation via left jugular and subclavian veins. The lymphatic system is a formidable absorption pathway for drug delivery because it (i) bypasses the first-pass metabolism that increases drug bioavailability, (ii) has prolonged drug delivery due to the longer duration of drug transport and (iii) offers the possibility of targeting drugs to lymph, potential application ▶

in lymphatic cancers and relevant infections such as leishmaniasis, malaria and AIDS (Tan and Billa, 2021).

Lymphatic absorption of lipid nanoparticles has been extensively explored as a viable means for delivering poorly soluble drugs. Shackleford et al. (2003) demonstrated that the lymphatic pathway played a significant role in the absorption of testosterone dissolved in oleic acid (Andriol®), accounting for the majority (91.5 per cent) of its overall absorption. Additionally, the incorporation of methotrexate into SLNs resulted in a 10-fold increase in bioavailability, hypothesised to be predominantly attributed to enhanced lymphatic absorption. (Paliwal et al., 2009). Furthermore, that vincopecetine-loaded NLCs also observed a twofold increase in the maximum concentration obtained compared to pure vinpocetine solution (Khan et al., 2013). The lymphatic pathway was hypothesised to be the main transportation route for the NLCs as opposed to the solution, which suffered a significant first pass effect in the liver.

Future perspectives of lipid nanoparticles

Lipid nanoparticulate carriers provide a means for deploying drug cargoes systemically, when delivered orally, by virtue of lymphatic uptake of the particles. In this regard, the bioavailability of several class III or IV drugs has been improved when formulated as orally administered lipid-based nanoparticles. Additionally, the systemic bioavailability of those drugs can be further attained through the incorporation of mucoadhesive polymers, coating the lipid-based nanoparticles.

As a result, the mucoadhesive lipid-based nanoparticles can adhere to the mucous layer of the GI epithelia, and thus, effectively prolonging the residence time of the formulation at the absorption site as depicted in Figure 2 (Tan and Billa, 2021). This intimate contact with the epithelium confers a higher permeation propensity which subsequently increases the systemic bioavailability of the drugs. Although lipid-based nanoparticulate delivery systems are inherently muco-adhesive, this property may be enhanced further by coating the particles with appropriate polymers. Such coated particles also protect labile drugs from the GI milieu so that unaltered form of the drugs traverses across the epithelia.

> A key strategy for enhancing drug delivery is through the lymphatic pathway, which provides an alternative absorption route for lipid nanoparticles. Not only does this method bypass first-pass metabolism, but it also greatly improves bioavailability.

Conclusion

The utilisation of lipid-based nanoparticles introduces a groundbreaking avenue for enhancing the systemic bioavailability of poorly soluble drugs, revolutionising their delivery following oral administration and GI absorption. By overcoming the barriers faced by poorly soluble drugs, these nanoparticles provide a game-changing solution, unlocking the full potential of therapeutic agents that were previously hindered by their low bioavailability. As the field of pharmaceutical science continues to advance, the utilisation of lipid-based nanoparticles promises to reshape the landscape of drug development and patient care, ushering in a new era of enhanced drug efficacy and improved treatment options.

Citation

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Competing Interest

The authors declare no conflict of interest. ■

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Getting The Most Out of Your Clinical Trial

Collecting human factors data to improve commercial device design

You can integrate human factors engineering (HFE) research into clinical trials to assess whether patients can use your device safely and effectively. This article describes key considerations when preparing, collecting and analysing HFE data collected during a clinical trial with the goal of improving commercial device design.



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Human factors engineering (HFE) is crucial in developing an effective device and is critical to meeting global regulatory expectations. HFE is a multidisciplinary field involving engineering, psychology and design, and it focuses on ensuring that a device's design is well-matched to its intended users. Specifically, drug–device combination products should be safe, usable and satisfying while accounting for intended users' skills, knowledge, abilities and limitations.

HFE activities can occur throughout the device development process, with the ultimate end goal of demonstrating that intended users can use the device safely and effectively. At the same time, clinical trials play a well-known and crucial part in the drug development process, where each trial exposes the drug's potential efficacy. Clinical trials require such a significant time and monetary investment that you might wonder whether there is an opportunity to integrate HFE data collection within clinical trials.

A clinical trial provides an excellent opportunity to collect HFE data, such that you can gain valuable insights about the device's use alongside data about the drug's efficacy. Sample HFE-oriented research questions that you can embed in clinical trials include: will intended users know the proper injection angle for injecting the drug within your prefilled syringe such that the drug is injected into the proper tissue? Will the intended user know the appropriate way to disinfect their nebulizer to avoid infection? Can intended users understand how to properly reconstitute the drug so they receive the intended benefit?

This article explores how HFE activities can play a critical role throughout the drug-device development process — particularly during clinical trials — by describing how to prepare for HFE activities and collect and analyse HFE data.

Key considerations during preparation

While HFE research is often a standalone activity, collecting HFE data during a clinical trial can prove advantageous. Because intended users of a device are already participating in the clinical trial, collecting HFE data alongside clinical trial data allows you to maximise participant engagement and your monetary investment. When collecting HFE data during clinical trials, consider the following key points during preparation to optimise the quality of data and, ultimately, the positive impact on your device.

Clinical trial data collection methods

The data collection method for your clinical trial will impact the methods for collecting HFE data. For example, ▶

if the clinical trial participants are undergoing treatment at a clinical trial site, as is traditionally the case, you could observe and interview the involved users, including healthcare professionals (HCPs) or lay people in the case of supervised self-administration, regarding their experience preparing and administering the drug. However, if the clinical trial is fully or partially decentralised, participants might administer medication at home. In that case, it would not be practical to observe them directly, and you would need to use other data collection methods, such as remote interviews or questionnaires.

HFE data collection methods

Within the HFE field, a wide array of data collection methods are aimed at refining a device's design and labelling, including contextual inquiry, individual and group interviews, surveys, expert reviews and usability tests. Certain HFE data collection methods are more or less suitable based on the clinical trial approach. Direct observation of device use is often the most powerful method because you observe interactions firsthand rather than relying on self-reported experiences. Observations are often paired with interviews to gather participants' perspectives and maximise the value of the exercise, but interviews about device interactions could also be used as a stand-alone activity if direct observations are not practical. While surveys typically do not yield data with as much richness or depth as interviews and observations, they can still be a valuable tool to rapidly collect participants' perceptions of using a device from relatively large sample sizes. Manufacturers can also pair their clinical trials with a diary study, a form of survey in which participants record their responses to questions or prompts over multiple days or weeks to gain in-depth data over a sustained period.

You can use the aforementioned data collection methods individually, but combining different approaches within a clinical trial provides the opportunity to dig deeper into the data. For example, combining a diary study with telephone or in-person interviews enables you to follow up on data collected in the diary study to gain a greater understanding of the intended users' needs and preferences. Furthermore, consider implementing multiple rounds of HFE research at different clinical research stages and throughout your device's development process to work toward the strongest possible design.

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HFE research goals

The stage of device development often influences the goal of HFE research, considering the device itself as well as instructional materials, packaging and training.

If the manufacturer has more flexibility to refine the device design earlier in the device development process, they can appropriately scope HFE research to collect and analyse feedback on the device itself. For example, observations and interviews regarding the use of a pen injector might reveal that participants struggled to read the dose counter when dialling up a dose because the numbers were too small. Consequently, the manufacturer could opt to increase the size of the numerals on the dose counter.

Later in the development process, manufacturers tend to be more limited in their flexibility for design refinements. HFE research might focus on improving the instructions for use or device labelling in such a case. For example, interviews might reveal that participants found the steps related to priming a syringe confusing. To improve clarity, the manufacturer could refine the text and enhance the images for those steps.

The data yielded from HFE research described thus far would be considered "formative" in that they are data collected during the device's development. Contrasting this is an HF validation test. From an HFE perspective, manufacturers must conduct an HF validation test for any medical device posing potential harm to users to validate that the intended users can safely use the device design in the intended use environments. HF validation tests require a high level of rigour and control related to participant user groups and the test environment. Because of this, formative data lends itself to collection alongside a clinical trial. However, manufacturers can focus formative data collection on interactions that could lead to harm — which are typically the focus of an HF validation test — with the goal of improving the overall safety of the device for any subsequent HF validation testing.

Sample size

Though the scope of formative research is up to manufacturers, a common practice for formative usability testing (including observations and interviews) is that five to eight participants per type of user (e.g., patient, HCP) will yield the majority of potential interaction challenges. If the research involves only interviews and no observations, consider skewing higher (e.g., eight to 10, depending on the user group's homogeneity) than this recommendation, as you likely will not uncover as many interaction challenges. Along those lines, a survey could include even more participants, noting the data is not as rich and the time associated with distributing a survey to a larger group is minimal.

Data collection

Researchers should prepare for data collection after planning the HFE research parameters. Below are some key points to keep in mind when collecting data.

Notably, each point requires significant skill and practice to get the most out of your HFE activities. When staffing HFE research projects, consider the experience researchers bring to bear to help ensure that you collect meaningful and relevant data.

Data collectors

While there is no specific requirement for who can collect HFE data, choose someone who has a deep enough understanding of the device, the research goals and at least a minimal level of training on how to best collect HFE data to yield robust and unbiased results. This person could be a representative from the manufacturer, particularly if the study takes place at a clinical site, or they could be an HCP overseeing patient self-administration. Manufacturers with limited internal resources to support HFE research can also choose to engage HFE consultants to leverage the consultant's expertise.

Observing device use

The most important thing to keep in mind when conducting an observation of device use is to be a neutral observer. The observer likely has a deep knowledge of the device but should avoid intervening and keep a neutral demeanour. Encourage the participant to think independently as if they were working on their own. For example, if the participant asks, "What do I do now?," you can ask, "What do you think you should do?"

Moderating interviews

When conducting an interview, either as a standalone activity or after observing device use, the moderator's ultimate goal is to understand what aspects of the interaction participants struggle with and why. If the moderator observes or the participant reports a difficult or incorrect interaction, the moderator should ask questions to understand the root cause of the challenge. When doing this, avoid leading questions, such as "That small needle made the medication difficult to draw up from the vial, right?," and ask open-ended questions, such as "Why do you think that happened?" or "Is there something about the device or the instructions that led to that mistake?"

Designing surveys

Surveys can yield valuable insights if you have limited access to participants during device use. For example, participants could be using the device at home without the presence of an HCP. Begin your survey with an introduction and collection of participants' background information (e.g., age, injection experience, impairments). Consider digging into the ease or difficulty of each step of device use, perhaps with a numerical rating and an open response for participants to describe the rationale behind their rating. You can also seek more general feedback, such as overall impressions of device use, use safety or instructions.

Data analysis

After you have collected HFE data, it is time to synthesise it into valuable information that you can use to improve your device's design and, if all goes well, boost your commercial success. With formative data, focus on trends rather than one-offs to uncover design refinements that benefit many rather than tailoring the device design to a single user. Document your findings in a report that could describe, for example, the strengths and opportunities for improvement for the device and instructions. With this information, you can improve the design of the device and/or instructions and, if time allows, conduct further formative research to reveal if the changes are effective or require more refinement.

Notably, depending on the clinical trial participants' characteristics, HFE data collected alongside the clinical trial might not fully represent all intended users or how the device is used in a natural environment. For example, participants might have more intensive training on the device in the clinical trial than they would in the real world. In such cases, collecting additional HFE data outside of clinical trials is essential to capture the full scope of realistic interaction with the device by your intended users.

Conclusions

Though clinical trials are often a primary focus of drug development, consider conducting HFE research to ensure that people can use your device safely and effectively. Integrating HFE into clinical trials provides an opportunity to collect valuable insights from users, ultimately leading to improved commercial device design. With the proper preparation and data collection techniques, you can successfully combine both activities. ■

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REVOLUTIONISING CLINICAL TRIALS

Harnessing data and real-time action for better healthcare



Positive progression of clinical trials in the Asia-Pacific region over the last decade (contributing almost 50 per cent of new clinical trial activities globally) has turned the region into a hotspot for clinical research. While the region leverages its vast population as the ultimate power tool, it also faces challenges owing to the huge geographical, socio-economic and cultural differences in the population. To streamline the industry and continue with strengthened efforts, the first step is to create a patient recruitment ecosystem that is driven by data, and runs on real time action, thereby giving strong impetus to not just the number of clinical trials but also the cost of it.

Preetha Vasanji, President-Emerging Markets, Doceree

The past five years have seen the Asia-Pacific (APAC) region emerge as a global hub for clinical trials, attracting pharmaceutical companies, research organisations, and healthcare professionals from around the world. With a diverse population, access to cutting-edge medical facilities, and a growing emphasis on healthcare innovation, APAC countries have become key players in the development of new drugs and therapies. Out of 27,000 clinical trials initiated in the year 2021, nearly half of them were done in multiple areas of the APAC region. One of the most significant advancements in this arena is the utilisation of real-time data in clinical trials. This article explores the impact of real-time data on clinical trials in the Asia-Pacific region and how it is revolutionising the way healthcare is delivered and research is conducted, accelerating the drug development process, enhancing patient outcomes, and reshaping the future of healthcare.

Before delving into the method of shaping the future of clinical trials, it is imperative to understand the current APAC landscape, importance of clinical research and trials in the region, emer-



> Real-time data collection and analysis streamline various aspects of clinical trials. Researchers can quickly identify patient recruitment challenges, protocol deviations, or data inconsistencies and address them promptly. This leads to faster trial completion and reduced costs, especially in the APAC that homes a huge and diverse population.

gence and transformation in trials, and the factors driving the change.

Understanding the APAC hub

Clinical trials in the region are particularly significant for several reasons. APAC is home to a diverse population with varying genetic backgrounds and healthcare needs. This diversity makes it both ideal and a challenging location for conducting clinical trials, as results can be more representative of global diverse populations. With a growing middle-class population and increasing healthcare expenditure, countries also offer pharmaceutical companies access to untapped markets. Clinical trials conducted in the region can help companies understand the unique healthcare needs and preferences of these populations.

Even when compared to the United States and Europe, APAC has a larger urban population and an increasing number of trial sites, which is a key indicator of a region's potential for growth. The density of trial sites in APAC is 3.1 per million urbanised population, which is significantly higher than the next lowest density in Europe, 22.2 per million. This indicates that APAC has a great deal of potential to offer to sponsors looking to benefit from growth.

Furthermore, conducting clinical trials in APAC is often more cost-effective compared to western countries, which can be a significant advantage for pharmaceutical companies looking to optimise their research budgets. Many countries in the region have historically been supportive of biotech research and development, with incentives such as rebates offered in Australia and ongoing investment from the Chinese government in biotech development. Hence, despite the current global economic and industry uncertainty, APAC is expected to remain a promising and resilient market.

Evolving Landscape of Clinical Trials

Historically, clinical trials in the region (and globally) have followed a rigid and sequential process. Researchers design a protocol, recruit participants, collect data over an extended period, and analyse the results after the trial concludes. This approach, while being scientifically rigorous, is slow and expensive. Moreover, it does not always reflect real-world patient experiences or account for the dynamic nature of diseases and treatments.

The COVID-19 pandemic has accelerated the digitalisation and modernisation of healthcare systems, web-based solutions have enabled clinical trials to become decentralised or virtual across the globe, providing access to patients that were previously unavailable. The use of advanced technologies has allowed for continued trial participation, storage and data collection during difficult times. In Asia-Pacific (APAC) alone, the number of decentralised Phase I trials increased by 60 per cent from 2017 to 2022, in comparison to the global average of 10 per cent-20 per cent. Additionally, APAC had the highest prevalence of In-Home Devices for Clinical Trials in 2022 of any region. ▶

However, looking at the global landscape, the fact remains that the interlinked industry can fail any time with minimal imbalance in its ideal setup. This calls for more agile and resilient structures than ever before. Hence, it has become imperative that investors and sponsors take a more dynamic approach towards predicting and planning trials, and building strong structures backed by data and technology, to protect against regional or global natural or man-made disruptions, more appropriately.

Role of Data in Clinical Trials

Data is the lifeblood of modern clinical trials. It provides insights into patient demographics, disease characteristics, treatment outcomes, and safety profiles. The use of data in clinical trials can be categorised into several key areas:

Patient recruitment: Traditional recruitment methods rely on site-based strategies and can be slow and inefficient. Data-driven approaches use electronic health records (EHRs), patient registries, and artificial intelligence (AI) algorithms to identify potential participants more quickly and accurately.

Trial design: Data analytics can help optimise trial design by identifying the most relevant endpoints, patient populations, and treatment arms. This ensures that trials are more likely to yield meaningful results.

Real-world evidence: Beyond the controlled environment of clinical trials, real-world data (RWD) from sources such as wearables, mobile apps, and telemedicine can provide valuable insights into how treatments perform in the real world. This can complement traditional clinical trial data.

Safety monitoring: Continuous monitoring of patient data, including adverse events and lab results, allows for early detection of safety concerns, enabling rapid response and intervention when necessary.

Endpoint assessment: Digital biomarkers, such as patient-reported outcomes collected through mobile apps, can provide real-time data on treatment efficacy and patient experiences.

Real-Time Action in Clinical Trials: Real-time action refers to the use of data as it is generated to make informed decisions during a clinical trial. This approach contrasts with traditional methods, where decisions are typically made retrospectively.

Power of Real-time Action

Like real-time data, real-time action has also had a demonstrated history of bringing efficiencies in the clinical trial process. Here are some ways in which real-time action is transforming clinical trials in the region with huge and diverse population:

Advantages of Real-time Data and Action

Traditionally, clinical trials relied on periodic data collection and analysis, which could be time-consuming and result in delays in decision-making and patient care. Real-time data collection and analysis have transformed the landscape of clinical trials. It allows researchers and healthcare professionals to make informed decisions quickly and respond to emerging trends or safety concerns promptly.

Real-time data also allows for continuous monitoring of patient responses and adverse events, enabling early intervention if safety concerns arise. This proactive approach is particularly crucial in clinical trials involving vulnerable populations or experimental treatments. Italso improves the collection of individual patient data, enabling the development of personalised treatment plans, which is particularly important in the era of precision medicine, where therapies are tailored to a patient's unique genetic makeup and characteristics.

Real-time data collection and analysis streamline various aspects of clinical trials. Researchers can quickly identify patient recruitment challenges, protocol deviations, or data inconsistencies and address them promptly. This leads to faster trial completion and reduced costs, especially in the APAC that homes a huge and diverse population. Advances in technology have also enabled remote monitoring of clinical trial participants through which patients can provide data from the comfort of their homes, reducing the need for frequent clinic visits and improving overall trial participation rates.

Furthermore, the entry for live data reduces the risk of transcription errors and data discrepancies, thereby enhancing data quality. Electronic data capture systems, coupled with immediate data validation, ensure data accuracy and integrity, which is vital for regulatory submissions and decision-making. Timely data capture and analysis also facilitate compliance with regulatory requirements. Sponsors can maintain rigorous documentation and submit necessary reports promptly, reducing the risk of regulatory delays.

Real-time data also empowers researchers to adopt adaptive trial designs. By assessing fast accumulating data, they can modify trial protocols, treatment arms, or sample sizes in response to emerging trends, increasing the likelihood of trial success. Lastly, the real-world evidence gathered during data-driven trials provides insights into a treatment's effectiveness across diverse patient populations and settings like in the APAC region, enhancing the generalisability of trial results.

Adaptive trial design: Adaptive clinical trials allow for real-time adjustments to various trial parameters, such as sample size, treatment arms, and patient inclusion criteria. This flexibility can lead to faster, more efficient trials and better outcomes for patients.

Early stopping rules: Real-time data analysis can trigger early stopping of a trial if it becomes evident that one treatment arm is significantly superior or inferior to another. This not only saves time and resources but also ensures ethical treatment of participants.

Dose optimisation: For trials involving dose-finding, real-time data analysis can help identify the optimal dose more quickly, leading to better treatment outcomes and reduced patient exposure to ineffective or toxic doses.

Patient-centricity: Real-time data collection and analysis enable a patient-centric approach, where the patient's needs, preferences, and safety are continually monitored and considered throughout the trial.

The various technologies and innovations driving the adoption of real-time data in clinical trials in the region are electronic health records (EHRs), wearable devices such as fitness trackers and smartwatches, mobile apps, telemedicine platforms and platforms using Blockchain Technology, etc.

Challenges and Considerations

While the use of data and real-time action in clinical trials holds great promise, it also comes with several challenges and considerations. We know that the accuracy and reliability of data are paramount when it comes to clinical research. Ensuring data quality, especially in the context of real-world data sources, can be a significant challenge. Furthermore, integrating data from various sources, such as EHRs, wearables, and apps, can be technically challenging due to differences in data formats and systems.

Another major challenge is safeguarding patient data. Collecting and using patient data raises ethical and privacy concerns. Robust data security and informed consent procedures are essential. Even the researchers and organisations must implement robust data security measures to safeguard sensitive information.

> The use of advanced technologies has allowed for continued trial participation, storage and data collection during difficult times, like COVID-19 pandemic.

Countries in the region have varying regulatory requirements, and navigating this complex landscape can be another big challenge. While regulatory bodies like the FDA are adapting to these new approaches, there is still uncertainty and variation in regulatory requirements for data-driven trials.

Implementing data-driven clinical trials requires significant investments in technology infrastructure, analytics expertise, and staff training. While the region has many developing and underdeveloped countries, infrastructure and resources availability also poses huge challenges at times. Access to reliable internet connectivity and technology infrastructure can vary across the Asia-Pacific region. Ensuring that all trial participants have access to the necessary technology can be a logistical challenge. Further, standardising data collection methods and formats is crucial for effective real-time data analysis and comparison across trials. Establishing common data standards can be a complex task.

To conclude, real-time data in clinical trials is revolutionising healthcare in the region. It offers the potential to accelerate drug development, improve patient care, and enhance the efficiency of clinical research. As technology continues to advance and regulatory frameworks evolve, the Asia-Pacific region is poised to play an even more significant role in shaping the future of healthcare through real-time data in clinical trials. By overcoming challenges and embracing innovations, stakeholders in the region can continue to drive progress in medical research and patient care. ■



AUTHOR BIO

Preetha Vasanji is part of the senior management team at Doceree, working as President – Emerging Markets. She has over two decades of experience in the Healthcare Communications and Marketing space. In her illustrious career, she has had the experience of working with multiple multinational and home-grown organisations. Prior to joining Doceree in 2021, Preetha served as Sr. Vice President and General Manager-McCann Health, Mumbai where she was responsible for leading a team of 30+ people, driving the company's growth and managing its business. Preetha takes pride in being a specialist in managing business and people.

How to Overcome The Hurdle of Immunotherapy

Immunotherapy is the most popular treatment for diseases due to the high specificity and low toxicity of the approach. However, the high cost and low treatment efficacy are key factors that impede its translation into large-scale application. The utilisation of a precision and personalised medicine strategy should be the best solution to address this pressing problem.

Chuanhai Cao, Full Professor, Taneja College of Pharmacy



For most people, only vaccines come to mind when they think of immunotherapy. But in fact, immunotherapy encompasses more than just vaccines – it refers to a disease treatment method that has health benefits or prioritises disease modification while working through the immune system (or taking effects through the immune system). Therefore, immunotherapies can be largely grouped into several categories including vaccines, antibodies, and other methods that take effect through the immune system.

Active immunotherapy, also called vaccines, refers to delivering an antigen into the body with or without an adjuvant to initiate an immune response. This approach needs the stimulation or activation of the immune system (antibody production and T cell activation) to occur in order to generate an immune response. It can be traced as far back as five centuries ago, but Jenner was the first man to test this method to protect against smallpox in a scientific manner in 1796, and he named this approach as a vaccine. However, it was William B. Coley, MD, who is recognised as the Father of Immunotherapy for his treatment of cancer patients by injecting bacteria into tumours in 1891. Though Coley was famous for having successfully treated different cancer patients using this method, no one knew the mechanism of the approach at that time, and hence it

was not popularised. Bacteria injection as a cancer treatment was used again in 1976 by using dead BCGs. Since then, scientists and clinicians have noticed the value of immunotherapy and have been inspired to continuously work on it. As for the component of a vaccine, it contains the antigen (protein-based vaccine, such as viral protein or subunit of the viral protein or peptide, or a small molecule linked to a big protein, DNA based vaccine, such as viral vector, plasmid DNA and RNA based vaccine) plus an adjuvant. The antigen will drive the antibody production, and the antibody will have specific binding for the antigen (therapeutic target). The role of the adjuvant is to non-specifically prime the immune system to enhance the function of the antigen.

Passive immunotherapy refers to giving anti-sera or antibody to the patient to treat the disease. The most recent example is the use of monoclonal antibodies against COVID-19 that has saved many lives during COVID-19 pandemic. It is worth noting that antibodies exist in our body even before we are born because mothers can pass the antibodies through the umbilical blood to the foetus to protect the baby from diseases. Passive immunotherapy was first used in the 19th century for the treatment of infectious diseases, such as through the use of anti-sera to treat diphtheria and the use of horse anti-sera to treat rabies. Now, it has been used to treat both infectious diseases and noninfectious diseases such as cancer (anti-PD1/PDL1 antibody) and arthritis (anti-TNF alpha antibody). Now, most passive immunotherapies use recombinant human or humanised monoclonal antibody for disease treatment. Antibody therapy is highly specific, but the cost is much higher compared to that of vaccines.



The other type of immunotherapy treats diseases by using immune cells or cytokines, or small molecules that can regulate or activate immune function to fight diseases, such as NK cell, antigen-specific T cell or modified T cell therapy and IL2, G-CSF as a treatment for diseases. Cells can be isolated from patients or healthy individuals, and cytokine, growth factor that are produced as recombinant proteins. This approach may be expensive or very cost-effective depending on availability. The treatment is less specific compared to vaccine and antibody therapies.

With the advancement in knowledge and understanding of immunotherapy and the immune system, immunotherapies are now becoming a more popular therapeutic for different diseases since they are considered as safer and more specific treatments. The major advantage of immunotherapy is that most of the molecules used for the therapy are derived from our body or produced by the human body, so there is a smaller chance of rejection by our body compared to methods such as NK or T cell therapy. Another major feature of immunotherapy is due to less toxicity to the body since it is normally produced by our body to against diseases, such as cytokines and antibodies.

The benefits of immunotherapy to human health is clear, such as its potential for vaccines against infectious diseases and antibody treatments for cancer (PD1/PDL1 antibody). The success and promise of immunotherapy have motivated many investors and pharmaceutical companies to jump into this field. However, recent progress in clinical trials has pushed most of them to hold their steps, because of the high investment and high failure rates. This situation has warded off many pharmaceutical companies and stirred up hesitation in making investments on immunotherapy. Many investors have begun to question the function of immunotherapy. The key factor causing this dilemma should not be attributed to technologies but rather to our understanding of the mechanism of immunotherapy. In other words, most immunotherapies should work if they were tested properly. Unfortunately, most are wrongly transferred into clinical settings and lead to failed outcomes.

Before moving forward, it is important to understand how our immune system works and the role the immune system plays in disease onset. In short, there is the innate immune system (also called the adopted immune system) that we adopt from our parents and the acquired immune system (also called the adapted immune system) that we gradually develop after birth. Both innate and acquired immunity are varied among people and change with ageing, so some people may be resistant to certain infectious reagents because they inherited sound innate immune systems from their parents, but this may change with ageing. Importantly, the genes passed down from our parents plays a very important role in immune responses and will determine the effects of immunotherapy.

As immunotherapy develops, we should identify the therapeutic target and targeted population. In other words, we should be familiar with the mechanism through which it works. Particularly, how our immune system will use the molecule, and even need to know whether our body could handle these molecules or is able to uptake and initiate proper immune response and how to manage the adverse response. Two popular terms, precision ▶

> Passive immunotherapy was first used in the 19th century for the treatment of infectious diseases, such as through the use of anti-sera to treat diphtheria and the use of horse anti-sera to treat rabies.

medicine and personalised medicine, are very important and critical to immunotherapy. They determine the success of immunotherapy if we can understand what immunotherapy is and how to use it properly. As introduced earlier, immunotherapy works through the immune system by modulating immune responses, such as through strengthening the hypo or minimising hypered immune response. The efficacy of immunotherapy will rely on the association of the root cause of the disease. However, most diseases are associated with multiple factors or determined by more than one factor, including infectious diseases like COVID-19. It is well known that the virus is the causative factor, but not everyone who is exposed to the virus under the same circumstances will be infected, even if they are all exposed to the same dose at the same time. This is mainly due to the soundness of the individual's immune system which can prevent them from being infected. Hence, the status of our immunity is the critical factor to the success of viral infection. Another factor is that the level of receptor expression and the degree of affinity to viral protein are also important for viral entry. From this simple example, it is easy to understand the role of immunity and the multiple factors related to a disease.

However, since our innate immunity is inherited, we do not have total control over the strength of our immunity. Thus, the immunity of our parents partially decides the condition of our immune system. Intriguingly, our life span is also related to that of our parents because it is associated with our genes, thus our genes impact our immune system and our life span. We know that our age will impact our immune system, and the immune system will determine our response to immunotherapy. Therefore, when we apply immunotherapy to treat a disease, we should consider the following factors: the condition of the immune system, age, and genetic factors to reach the best therapeutic effects. Why these are determined factors for the successful immunotherapy, it will be very difficult or even impossible to have any treatment effect if the patient has impaired or poor immune system, or it can even cause life threatening issues if the immune system overreacts to the treatment. Both conditions can cause major problems for immunotherapy and may force the cessation of clinical trials.

What can help guide immunotherapy development? As introduced in the beginning, immunotherapy is a personalised medicine and precision medicine because the variety of immunotypes will determine the different responses to the same treatment, and the responses to treatments differ due to age and health conditions. How do we ensure immunotherapies are applied to the right subjects? We need to understand the target population of the therapy first, so this is the precision medicine aspect of the approach (selecting and assigning patients into different groups). This means that we should find a way to select the right population that will have the best responses to the treatment. Our group has tested different vaccines on people with different immunotypes and collected important information. Another major factor for the success of immunotherapy is the physical condition of the person who will receive the therapy, such as age and the health condition. For example, the treatment and the preventive therapy should not apply to the same person. The treatment should apply to a person with a good immune system for active immunotherapy, but the same dose may cause severe adverse effects if it is used on a patient who has a poor immune system. The preventive vaccine should only be applied to healthy people because they can tolerate a higher immune response, but it may be life-threatening to older people who cannot not tolerate any over response.

To summarise, immunotherapy is a very promising approach for disease treatment or prevention and is likely to dominate the future pharmaceutical market given our ageing society. However, we should understand that it is a precision medicine and a personalised medicine, thus we should preselect the right target populations before it is translated into clinic application. Meanwhile, immunotherapy is also a highly personalised medicine, therefore, we should bear this concept in mind while we apply the therapy to patients. Monitoring the drug levels (PK/PD) is very necessary to reach ideal treatment benefits. This will ensure the success of clinical trials if we can create a monitor or selection method for immunotherapy. ■

AUTHOR BIO



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Deuterated Drugs In The Covid-19 Pandemic



Coronavirus disease 2019 (COVID-19) continues to ravage populations globally. In seeking a potential treatment for COVID-19, deuterated compounds have been (and continue to be) explored as therapeutic agents and internal mass spectrometry standards. We review these in this article, including the drug 'VV116', approved as a COVID-19 treatment in December 2021.

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Luka Jedlovcnik, PhD student in organic chemistry, University of Ljubljana

Since the recent (2017) approval by the FDA to commercialise and administer deutetrabenazine (registered name Austedo®) (CAS 1392826-25-3) (**1, Figure 1**), the first for a deuterated pharmaceutical, there has been a surge of interest in the preparation and testing of deuterated pharmaceutical compounds with improved medicinal properties (safety, efficacy, bioavailability) compared to their non-labelled counterparts. (Figure 1)

This is largely due to C–D bonds requiring slightly more energy to break compared with the C–H bonds. Thus, when situated at the point of metabolism in a drug, the C–D bonds are harder to break (by enzymes, typically cytochrome P450s), therefore, slowing down the drug metabolism. This can result in an increase in the drug's bioavailability and reduction in the requisite dosage quantity. Altering the bonds at the point of metabolism can also modify the metabolism pathway, resulting in different metabolic products ("metabolic shunting"). Sometimes these alternative metabolites are less toxic than with the original non-labelled drug, making the D-labelled drug safer for use. In most cases, the inclusion of deuterium does not alter the pharmacodynamics of a drug, only its pharmacokinetics. This means that the labelled drug is just as potent as the non-labelled analogue and has the added advantages already described. However, D-labelling can also ▶

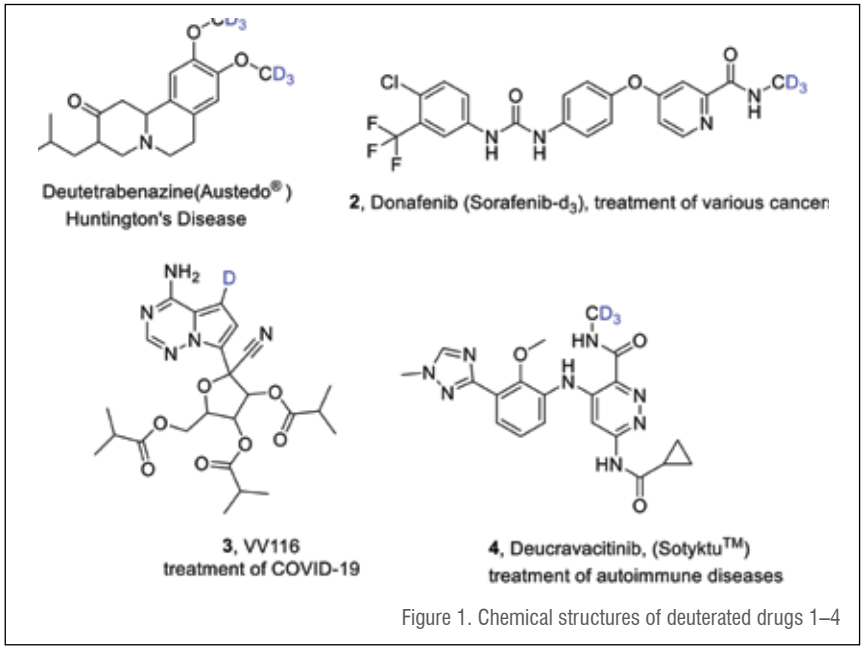

Figure 1. Chemical structures of deuterated drugs 1–4

have a complex effect on intermolecular interactions and binding to enzymes.

The use of D-labelled drugs is also gaining attraction as fluorinated drugs (which offer some of the advantages offered by deuterated drugs) are likely to slowly be phased out because of the persistence and toxicity of trifluoromethyl groups, a component of most metabolites of fluorinated drugs (Hammel 2022).

Since 2017, three other drugs have been approved for prescription and usage [Donafenib/ Sorafenib-d^3 (2, CAS 1130115-44-4), VV116 (3, CAS 2647442-33-7), and Deucravacitinib/ Sotyktu (4, CAS 1609392-27-9] while 19 compounds are under clinical investigation for potential future approval (di Martino 2023). Of the three approved deuterated drugs, the oral remdesivir derivative VV116 was approved in December 2021 for emergency treatment of COVID-19. During the COVID-19 pandemic, many research groups and small industrial companies mobilised resources towards the synthesis and testing of deuterated drugs and biomarkers to find a potential cure for COVID-19 (many companies/groups are still researching in this area). There is a chance that some of these deuterated compounds are still undergoing clinical trials and could, too, meet criteria for approval.

Deuterated drugs explored as treatments for COVID-19 are either repurposed or novel drugs. These have been summarised in the table below. (Table 1)

Table 1. Deuterated drugs tested as therapeutic agents for COVID-19 [a]

Drug	Role in targeting COVID-19	Role played by deuterium
REPURPOSED DRUGS		
VV116 **(3)**	RNA-Dependent RNA Polymerase (RdRp) inhibitor i.e., the drug binds to the RdRp protein at the enzyme active site, therefore interfering with the RNA synthesis step.	Inhibits enzymatic degradation
Deupirfenidone or LYT-100 **(5)**	Treatment of patients suffering from long COVID-19	Inhibits the metabolism of the drug and enables less frequent dosing
deuterated analogues of GS-441524 **(6a–e)**	RNA-Dependent RNA Polymerase inhibitor. The parent nucleoside of remdesivir.	Might improve antiviral activity of GS-441524 against SARS-CoV-2
ACH-3422 **(7)**	RNA-dependent RNA polymerase inhibitor	Improves the safety profile of the parent drug by enabling a more stable drug concentration and reducing the production of toxic metabolite
dexamethasone-d_2 **(8)**	Corticosteroid and anti-inflammatory agent	Might improve bioavailability and safety profile (hindered metabolism)
NEW DRUGS		
Arachidonic acid ethyl ester-d_6 **(9)**	Reduction of oxidation products which tend to induce inflammatory responses in lung tissues	Decreases the rate of drug oxidation therefore increasing its bioavailability
Y180 (e.g., **10**)	Mpro inhibitor	Deuterium-enabled chiral switch
Deuterated analogues **(11)** of S-217622 (Ensitrelvir), compound YY-278 **(11a)**	3CLpro inhibitor	Increased bioavailability and plasma exposure
GC376 deuterated analogues (e.g., **12**)	3CLpro inhibitor	Enhances activity due to tighter binding to the target or improves physicochemical properties of the drug

[a] For chemicals structures of compounds, see Figures 2 and 3.

Deuterated Drugs as Internal Mass Spectrometry (MS) Standards to aid Drug Discovery

Processed internal standards are used to correct errors in detection when using Gas Chromatography (GC) /Liquid Chromatography (LC) coupled with (tandem) Mass Spectrometry (MS) for bioanalysis. This procedure is needed for the development of drugs, for example to understand drug pharmacokinetics and metabolism. The development of drugs for treatment of COVID-19 is no exception. Thus, we list compounds 13–25 as deuterated drugs that have been prepared as internal standards for studies of repurposed drugs for the treatment of COVID-19 in the table below. (Table 2)

In addition to the deuterated drugs or their metabolites used as internal MS standards for studies on the action of their non-deuterated analogues for the treatment of COVID-19, there are also many molecules that have been studied as biomarkers for the detection of COVID-19 or the severity of the disease.

Commercially available deuterated lipids are mostly used for these purposes, as molecules such as lipids, triglycerides and free fatty acids are often indicators (biomarkers) of various (inflammatory) diseases in the body and potential targets for therapeutic agents. Some structures and uses of these compounds can be seen in the review paper by Jansen-van Vuuren et al. 2022.

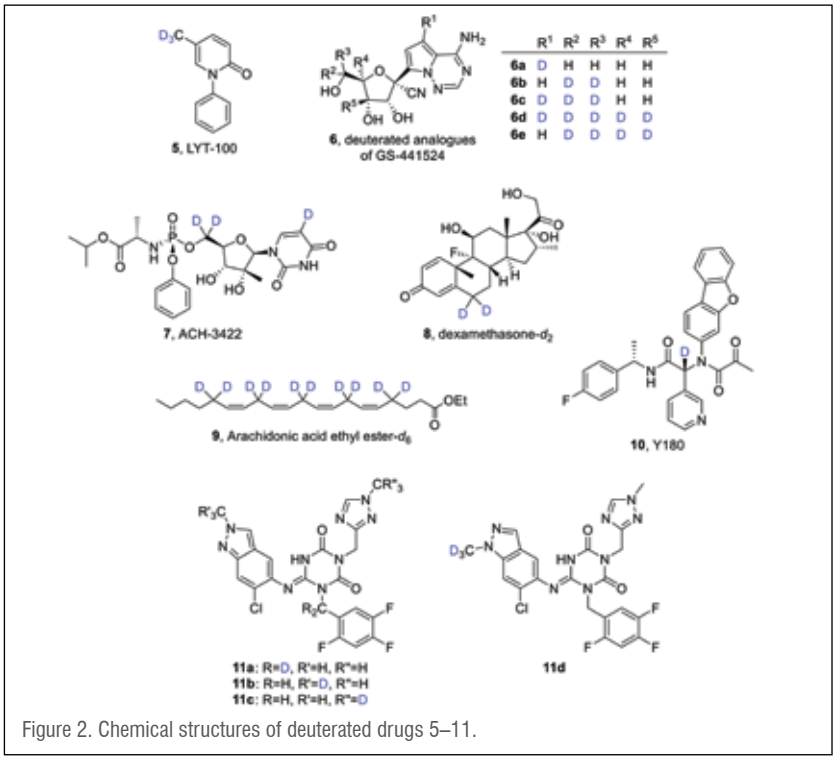

Figure 2. Chemical structures of deuterated drugs 5–11.

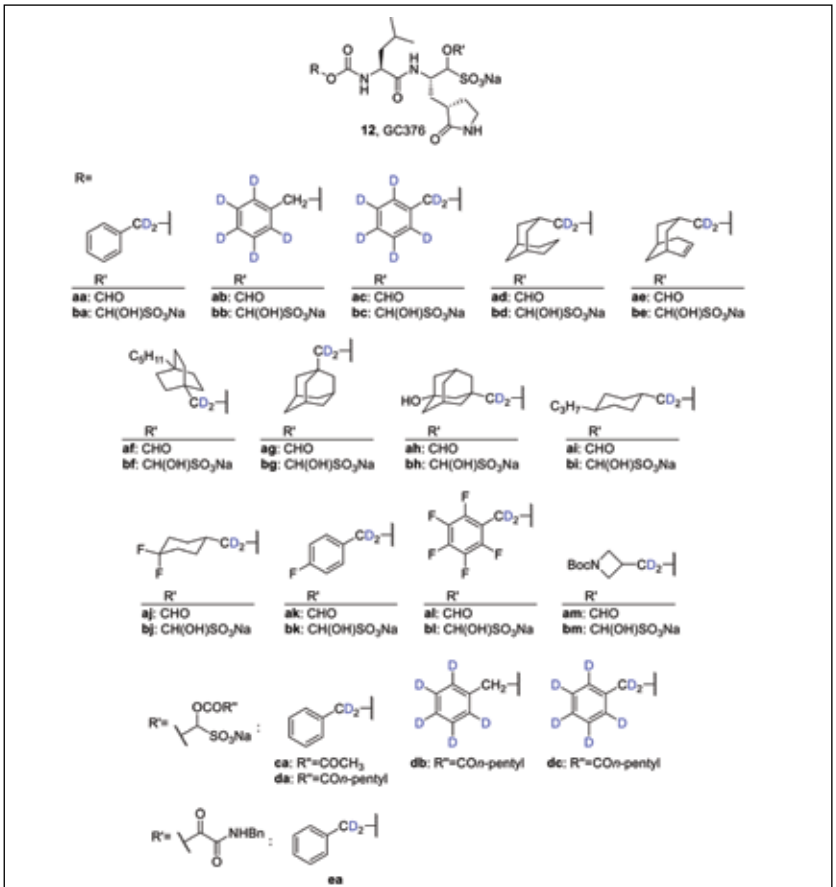

Figure 3. Chemical structures of deuterated drugs 12.

Conclusions and Implications for Future Research

The discussion around the deuterated pharmaceuticals (therapeutics and internal standards) included in this article can be read in greater detail in a review we published last year (Jansen-van Vuuren 2022) as well as in subsequent articles (Yang 2023; Zhou 2023).

The development of deuterated pharmaceutical compounds is a rapidly growing area of research, especially in known drugs that have failed clinical trials but whose unfavourable properties can be corrected by the incorporation of D. There is also increasing interest in the design of *de novo* deuterated drugs. The position of the D is crucial for improving the efficacy and lowering the toxicity of the drugs. However, this is not always predictable and/or straightforward, and researchers in this area must be prepared to run the necessary biological studies on the drug, such as metabolism studies (Zhang 2018). Furthermore, methods to prepare deuterated drugs need to meet certain criteria (e.g., reproducibility, precision deuteration) if they are to be patented and transferred from medicinal to process chemistry. Similarly, for drugs to qualify as active pharmaceutical ingredients (APIs), they must undergo a rigorous process of assessment to meet the standards set by the World Health Organization (WHO), see https://extranet.who.int/pqweb/medicines/active-pharmaceutical-ingredients-0.

COVID-19 has taught us many things, amongst these the creation of therapeutics for future infectious-disease outbreaks. There is no doubt that deuterated drugs will play an increasing role in this sphere, and there are many opportunities for developing new or repurposed drugs to meet these needs. 90 per cent of drugs fail clinical trials. These failures occur for various reasons including, for example, poor solubility or ineffectiveness (versus a placebo). In cases where a drug fails a clinical trial based on rapid metabolism, high toxicity effects, epimerization to an ineffectual epimer, or low bioavailability, the strategic incorporation of D may 'resurrect' the drug and give it a second chance.

References are available at www.pharmafocusasia.com

Table 2. Deuterated drugs or metabolites used as internal MS standards[a]

Deuterated Drug or metabolite	Role played by deuterium
DEUTERATED DRUGS OR METABOLITES AS INTERNAL MS STANDARDS	
Chloroquine-d_4 phosphate **(13)** Hydroxychloroquine-d_4 sulfate **(14)** Ritonavir-d_6 **(15)** Lopinavir-d_8 **(16)** Azithromycin-13_C-d3 **(17)**	Enables quantification of analogue non-deuterated repurposed COVID-19 drugs in human serum by ID-LC-MS/MS
Azithromycin-d_5 **(18)** Hydroxychloroquine-d_4 **(19)** Desethyl-hydroxychloroquine-d_4 **(20)** Bisdesethylhydroxychloroquine-d_4 **(21)**	Enables LC-MS/MS quantification of non-deuterated repurposed drugs in EDTA-treated human blood plasma to support clinical trials and assess the pharmacokinetics and pharmacodynamics of this repurposed drugs
M2-d_6 **(22)**	Enables LC-MS/MS quantification of 'M2', the major BS1801 (ebselen analogue) metabolite
Baricitinb-d_5 **(23)**	Could enable LC-MS/MS quantification of baricitinib
Remdesivir-d_5 **(24)**	Enables LC-MS/MS quantification of remdesivir in human plasma
Teriflunomide-d_4 **(25)**	Enables LC-MS/MS quantification of teriflunomide, the active primary metabolite of leflunomide in plasma

[a] For chemicals structures of compounds, see Figures 4 and 5.

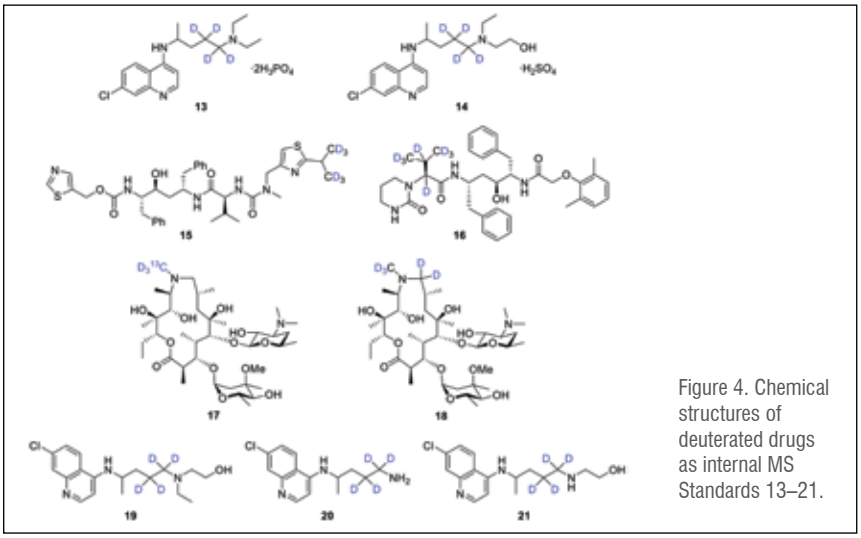

Figure 4. Chemical structures of deuterated drugs as internal MS Standards 13–21.

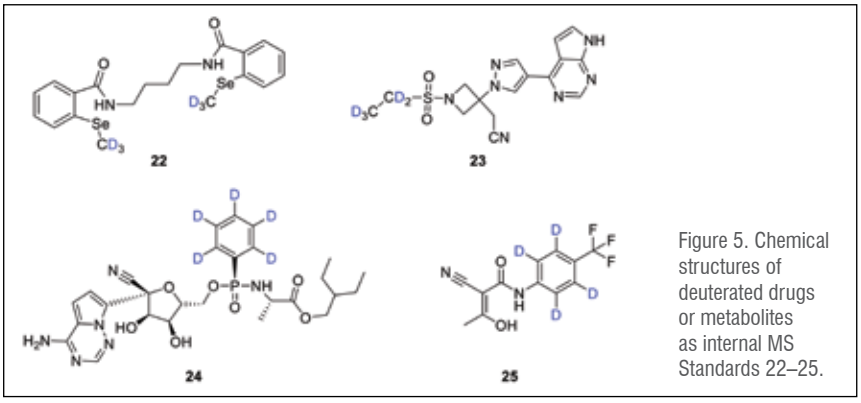

Figure 5. Chemical structures of deuterated drugs or metabolites as internal MS Standards 22–25.

AUTHOR BIO



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Mr. Luka Jedlovčnik is a PhD student under the supervision of Prof. Janez Košmrlj at the University of Ljubljana. He is working with Dr. Jansen-van Vuuren and Prof. Košmrlj to develop sustainable catalytic solutions for hydrogen isotope exchange (HIE).

ANTS: NON-INVASIVE TECHNIQUE FOR EARLY DETECTION OF CANCER

Cancer is a significant contributor to premature mortality globally, ranking among the top causes of death in numerous countries. Improvements in treatments have led to higher survival rates, with more people living with cancer as a chronic condition. Currently it was found that ants can detect the scent of several types of cancer.

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Early detection of cancer is critical for successful treatment and improved patient outcomes. Unfortunately, many existing methods for early detection are invasive and expensive, limiting their accessibility to a broader population. However, recent research has focused on identifying unique cancer-specific volatile organic compound (VOC) profiles in exhaled breath. These VOC profiles are generated by tumour cells due to their altered metabolism and physiological changes associated with cancer development. This has opened up a new frontier in cancer diagnostics and health inspections, offering the potential for developing rapid, noninvasive, and cost-effective cancer screening tools.

The analysis of VOC biomarkers in exhaled breath shows promise in its ability to serve as a noninvasive and affordable method for cancer screening. VOCs are small molecules released from metabolic processes in the body, and their unique patterns in cancer patients' breath can potentially be used as indicators of the disease. The advantages of breath analysis as a cancer diagnostic tool include its non-invasive nature, rapid screening capabilities, cost-effectiveness, and ability for repeatable testing. However, it's important to note that this approach is still an area of active research and faces challenges in terms of sensitivity, specificity, standardisation, and large-scale validation. Despite these challenges, breath analysis for cancer detection holds the potential to revolutionise early diagnosis and monitoring, leading to improved patient care and reduced healthcare burdens. As research and technology progress, breath analysis may become an essential component of cancer screening programs, benefiting individuals and healthcare systems alike. Previous research has indicated the potential use of dogs for tumour detection in body-odour samples. Additionally, studies have shown that Caenorhabditis elegans, a type of nematode, exhibits chemotaxis towards certain cancer-related VOCs. However, recent experiments employing in vivo calcium imaging with the proboscis extension response have indicated that neither honey bees nor dogs could effectively detect cancer odours, despite attempts at olfactory conditioning. In light of these findings, scientists are now considering alternative options and have turned their attention to insects as potential bio-detectors for various types of odours, including those related to cancer.

Insects present several advantages in this regard: they are abundant, making them suitable for large-scale screening, relatively easy to manage in laboratory settings, and do not require expensive rearing facilities, thus reducing overall costs. It's worth noting that this area of research is still in its early stages, and the potential use of insects as ▶

bio-detectors offers exciting possibilities for early cancer detection and other applications. However, further studies are needed to fully understand and validate their effectiveness in this role. Research on utilising animals' sense of smell for cancer detection has been an active area of study. Scientists have been exploring the potential of using animals such as dogs and rats, known for their highly sensitive olfactory abilities, to detect cancer from samples like urine, breath, or tissue. These animals have shown promising results in identifying certain types of cancer based on VOCs produced by cancer cells, which can be detected by their keen sense of smell. If successful, this approach could offer a cost-effective and non-invasive method for early cancer detection. However, further research is required to validate and understand the specific molecular signatures of cancer that animals are detecting. While animal-based detection methods might not replace standard diagnostic techniques like biopsies and imaging, they could potentially supplement existing methods and provide additional screening options, particularly in areas with limited access to advanced medical facilities.

Ants are known for their exceptional memory capabilities, forming long-lasting memories and exhibiting strong retention. In an intriguing study, researchers trained individual ants to recognize the scent of mouse urine by associating it with a sweet solution reward. The ants were placed in a circular arena and underwent three training sessions, during which the time taken to find the reward was measured. Over time, the ants learned to associate the specific smell with the reward, becoming more efficient at locating it during subsequent tests. The research also highlighted the ants' ability to generalise their memory by recognizing a mixture of different smells associated with the reward. This demonstrates that ants can learn specific associations and respond to more complex scent combinations to find the reward. Furthermore, the study revealed the ants' impressive memory retention. Even after multiple tests without any reward (up to nine times in the experiment), the ants continued to respond accurately. This suggests that their memories are stable and can last for several days. Overall, this research provides valuable insights into the cognitive abilities of ants and their capacity to navigate and adapt to their environments. Additionally, it contributes to a better understanding of memory and learning processes in various organisms, including humans. "The use of animals, such as ants, for cancer detection through their ability to detect specific VOCs is a promising area of research. Cancer cells can release distinct chemicals that differ from normal cells, making VOCs potential biomarkers for cancer detection. Animals can be trained



through olfactory associative learning to differentiate between cancerous and non-cancerous samples based on their highly developed sense of smell. This approach offers several potential benefits, including early cancer detection, non-invasiveness, cost-effectiveness, portability, and complementary use alongside existing diagnostic methods. However, there are challenges to address, such as standardising training protocols, accounting for variations between individual animals, and considering ethical aspects related to animal use for this purpose." In recent times, there has been a growing interest in leveraging animals' highly developed sense of smell for various applications, including medical diagnostics. Canines have been successfully trained to detect certain diseases, such as cancers, by sensing specific VOCs present in human breath, urine, and other bodily fluids. Similarly, certain insects, like ants, have displayed remarkable olfactory capabilities and have shown potential for rapid training in scent detection tasks. Training insects, such as ants, may offer certain advantages compared to dogs, such as potentially being less resource-intensive in terms of time and cost. Ants can be trained using classical conditioning techniques, where they form associations between specific scents and rewards, making them capable of detecting particular VOCs associated with diseases like cancer. However, it is crucial to acknowledge that while insects have shown promise in research settings, the practical implementation of ant-based scent detection systems for medical diagnostics is still in its early stages. There are various challenges that need to be addressed, including developing reliable and consistent training methods, ensuring accuracy and specificity in detecting disease-related VOCs, and accounting for individual differences in ants' detection abilities.

Insects possess several advantages over dogs and other vertebrates in certain research or practical applications, particularly in controlled conditions and behavioural studies. One notable advantage is their ease of rearing in controlled laboratory environments. With short lifespans, rapid reproduction, and minimal space and resource requirements, insects are a convenient option for experimental purposes. Moreover, their cost-effectiveness compared to larger animals like dogs makes them appealing for scientific research and various applications. Insects' strength lies in their well-developed olfactory system, especially observed in species like fruit flies (Drosophila melanogaster). This makes them valuable subjects for investigating sensory perception and olfaction mechanisms. Additionally, their ability to be bred in large numbers allows researchers to conduct experiments with significant sample sizes, leading to more robust and statistically significant results. Insects' simple nervous systems enable fast learning and conditioning, making them suitable for studies involving associative learning or classical conditioning paradigms. Furthermore, using insects for research or practical applications often raises fewer ethical concerns than using vertebrate animals like dogs, making them a more attractive option in terms of animal welfare.

The concept of using ants as bio-detectors for cancer is fascinating and warrants further investigation. The initial study demonstrated that ants can be trained to detect a specific type of cancer, raising the question of whether they can apply this ability to other kinds of cancer as well. This potential shows promise for developing an efficient and cost-effective method for cancer detection in the future. However, it is essential to conduct thorough research and validation, including using human samples to verify the ants' abilities accurately. The idea of ants being fast learners and easy to maintain as bio-detectors is intriguing, but it is crucial to note that this is still a 'proof of concept' at this stage. Further studies are required to evaluate the reliability and effectiveness of using ants for cancer detection. Moreover, ethical considerations and regulatory approvals should be taken into account before considering its application in real-world healthcare scenarios. In conclusion, while the notion of using ants for cancer detection holds promise, extensive research and testing are necessary to ensure its accuracy, safety, and practicality in clinical settings. ■

AUTHOR BIO



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ExpertTalk

UNIFYING DRUG SAFETY

The significance of harmonisation in pharmacovigilance

In the world of pharmaceuticals, harmonisation in pharmacovigilance is paramount. Organisations such as ICH have standardised regulations, streamlined drug submissions, and improved adverse event reporting. Harmonisation involves aligning regulations, data collection, and reporting standards across countries and regions. This enhances the sharing of adverse event information, streamlines drug monitoring, and ensures patient safety through consistent, evidence-based decision-making in the pharmaceutical industry. The interview will uncover the nuances of Harmonisation in Pharmacovigilance.





Nikesh Shah
VP and Global Head, Safety and Pharmacovigilance, Indegene

Dr. Siva Kumar Buddha
Director - Safety and Pharmacovigilance, Indegene

1. Could you explain what harmonisation in pharmacovigilance means and why it is important in the context of global drug safety?

In pharmacovigilance, harmonisation refers to the collaborative effort among regulatory authorities, pharmaceutical companies, and stakeholders to standardise and align processes, regulations, and standards related to drug safety monitoring and reporting on a global scale. It ensures consistent and uniform practices across different regions and countries. This consistency simplifies the exchange of critical information regarding adverse events, allowing for earlier detection and response to potential safety issues, which can improve patient safety. In addition, harmonisation enhances the efficiency of new drug applications and regulatory submissions, reducing duplication of efforts and expediting the approval process. This, in turn, accelerates patients' access to new and potentially life-saving medications. Moreover, harmonisation promotes transparency and collaboration in the pharmaceutical industry, fostering the sharing of best practices and the pool-

ing of resources to improve overall drug safety. It also facilitates international research collaborations, leading to a more comprehensive understanding of drug risks and benefits. Organisations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Pan American Network for Drug Regulatory Harmonisation (PANDRH) are working towards bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop guidelines. ICH has been around since 1990 and has grown to include more members and observers from around the world. ICH aims to create global guidelines for the pharmaceutical industry so that safe and effective medicines are developed, registered, and maintained in the most efficient way possible. ICH's guidelines are used by many countries to assess new medicines. Currently, it includes 21 members and 36 observers, representing regulatory authorities, pharmaceutical companies, and other stakeholders from around the world.

2. How does the global regulatory landscape impact the need for harmonisation in pharmacovigilance practices?

The global regulatory landscape has a significant impact on the imperative for harmonisation in pharmacovigilance practices. This globalisation of the pharmaceutical industry necessitates a unified approach to drug safety. The European Medicines Agency (EMA) especially in the EEA regions has been very instrumental in harmonising at the European Union (EU) level from lab to patient activities concept.

Several key factors highlight the impact of the global regulatory landscape on pharmacovigilance harmonisation. Some countries have unique pharmacovigilance regulations, such as REMS in the USA, Analysis of similar events requirements for SUSARs in the USA and a few other countries, and French imputability for causality for cases submitted to ANSM, to name a few. There are still differences in guidelines pertaining to definitions, causality scales, frequency of the literature search, and signal statistical method for quantitative analysis etc.. Asia is the most populous continent with nearly 60 per cent of the world's current population; yet, there is no centralised data system, PV regulations and harmonised reporting rules. This heterogeneity creates challenges for pharmaceutical companies, which must navigate a complex web of regulations to ensure compliance. This also increases their costs in maintaining compliance with diverse regulations. The primary objective of pharmacovigilance is to safeguard patient health. Global harmonisation consistently ensures that drug safety data is collected, analysed, and acted upon, regardless of geographic location. This uniformity is crucial in promptly identifying and mitigating potential safety concerns. With the globalisation of clinical trials, often conducted in various countries, harmonisation becomes a logistical necessity. It streamlines the process of reporting adverse events and standardises the evaluation of safety data. The COVID-19 vaccine situation is a good example where the safety data published from other countries were taken into consideration by the public to make decisions on the choice of the vaccine.

> Despite its implementation challenges, the benefits of harmonised pharmacovigilance practices, such as improved patient safety, streamlined operations, and enhanced regulatory compliance, make it a worthwhile pursuit for pharmaceutical companies.

3. What are the key benefits that pharmaceutical companies and regulatory authorities can gain from harmonised pharmacovigilance processes?

Harmonised pharmacovigilance processes offer pharmaceutical companies and regulatory authorities several key benefits. Mainly, the harmonised processes streamline drug safety reporting and data exchange, reducing administrative burdens and ensuring consistent, efficient operations. In addition, harmonisation enhances global collaboration, enabling quicker detection and mitigation of safety concerns, and ultimately safeguarding public health.

Additionally, it expedites the regulatory approval process, accelerating patients' access to safe medications while reducing costs for pharmaceutical companies. Furthermore, standardised practices foster transparency and trust, promoting industry compliance and regulatory confidence. Overall, harmonised pharmacovigilance not only improves patient safety but also enhances operational efficiency and regulatory effectiveness for both pharmaceutical companies and regulatory bodies. ▶

4. How does harmonisation in pharmacovigilance contribute to enhanced patient safety and better healthcare outcomes?

Standardising safety-monitoring practices globally ensures timely and consistent reporting of adverse events, enabling rapid identification of potential risks associated with medications. Early signal detection can prompt regulatory agencies and pharmaceutical companies to take prompt actions to mitigate and safeguard patients. It also brings more transparency in the safety data, which can enable better benefit-risk analysis. Streamlined processes can give patients quicker access to new medications through faster regulatory approvals. This also contributes to better health outcomes via optimised treatment plans, and reduction in medication errors, therefore building patient trust and compliance.

5. In what ways does harmonisation streamline reporting and data management processes, leading to more efficient resource allocation?

Currently, there are multiple reporting rules like timelines, formats, criteria (seriousness, listedness, country, etc.,) and medium for submission of the individual cases. This causes a lot of administrative burden and additional resources to manage and monitor. This can lead to multiple chances of missing the timelines and reporting as necessary, leading to diminished visibility of the risk profile of the drug for the regulators. This burden can also cascade to the downstream activities where the requirements like aggregate reports submission timelines and medium of submission are different. Harmonisation initiatives need simplification and centralization of reporting rules at a global level. This can reduce the administrative burden and allow resources to be redeployed for more important activities like signal and risk assessments. Centralisation of data leads to more efficient data management, making it easier to identify safety signals and trends. Not only this the collaboration on harmonisation initiatives encourages knowledge sharing among pharmaceutical companies and regulatory authorities.

6. How does harmonisation influence the submission of safety data to regulatory authorities? Are there specific requirements or guidelines that companies should be aware of?

Harmonisation in pharmacovigilance significantly influences the submission of safety data to regulatory authorities. It promotes a standardised and streamlined approach to reporting, ensuring consistency in the information provided to regulatory agencies across different regions. Most of the time the regional PV guidelines are built based on the ICH PV guidelines (E2A to E2F), which promotes some sort of standardisation. These guidelines cover aspects like ICSRs, periodic safety update reports (PSURs), Pharmacovigilance Planning and Developmental safety update reports (DSURs). Adhering to these standards simplifies the submission process, as companies can follow a single set of guidelines for multiple markets. This alignment reduces the burden on pharmaceutical companies, allowing them to efficiently compile and submit safety data while ensuring compliance with global regulatory expectations. Recently, TransCelerate Biopharma Inc., which is funded by 20 organisations dedicated to making research and development, including pharmacovigilance monitoring and reporting, published an article on ICSR replication with different health authority databases and its impact on the quality analysis of the safety information. They have found that the average ICSR is replicated 3 times. However, some ICSRs are replicated in 10 or more databases leading to inconsistencies in the data and the exposure data inaccuracy. There is an opportunity for implementing a centralised database with integration between multiple databases to avoid them. On similar lines, MSSO MedDRA is based on a terminology belonging to the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK; this was developed using the ICH process by the ICH partners, including WHO to facilitate a standardised medical terminology. This has very much helped to maintain consistency in the coding of adverse events, medical history, drug indications, lab tests etc.; recently they have also mapped the ICD-10 with MedDRA, which also gives room to integrate the real-world data into the safety analysis.

7. What are some of the challenges or barriers that companies may face when attempting to implement harmonised pharmacovigilance practices?

As with any big change, with the harmonisation of pharmacovigilance processes across the globe, there are also challenges to tackle. Some of them are Data privacy and security issues and laws in different countries, resistance to change within the organisations and regional regulators, cultural differences, data compatibility issues and budget allocation, amongst others. Despite these challenges, the benefits of harmonised

pharmacovigilance practices, such as improved patient safety, streamlined operations, and enhanced regulatory compliance, make it a worthwhile pursuit for pharmaceutical companies. Effective change management, strategic planning, and collaboration with regulatory bodies are key strategies to overcome these obstacles and achieve harmonisation successfully.

8. What role does technology play in enabling harmonisation in pharmacovigilance? Are there specific data standardisation initiatives that are particularly impactful?

Yes, technology plays a pivotal role in facilitating harmonisation in pharmacovigilance by enabling streamlined data management and reporting processes. One particularly impactful initiative is the adoption of the ICH E2B (R3) standard for Individual Case Safety Reports (ICSRs). This standard defines a consistent format for reporting adverse events, making it easier for pharmaceutical companies to submit safety data to regulatory authorities worldwide. Furthermore, the use of advanced data analytics and artificial intelligence (AI) contributes significantly to harmonisation efforts. AI can process large datasets and identify safety signals more efficiently, enhancing the ability to detect emerging risks consistently across different regions. Similar to MedDRA, the adoption of WHO DD in pharmacovigilance systems ensures that the names and attributes of drugs are uniform across regions.

9. Can you discuss the importance of global collaboration and knowledge sharing in achieving harmonisation goals in pharmacovigilance?

Global collaboration and knowledge sharing are pivotal in achieving harmonisation goals in pharmacovigilance - for reasons like standardisation of best practices, enhanced patient safety, more visibility for the regulators on the risk profile of the drug, enhanced data analytics application on the centralised data, common goals with common data, consistency in the data standards, early detection of signals with red flags within the system, resource optimization and also room for more real-world data integrations. It promotes transparency, consistency, and collective problem-solving in pharmacovigilance. They not only advance the harmonisation of safety practices but also enhance patient safety by facilitating the early detection and management of medication risks on a worldwide scale.

10. What emerging trends or technologies do you see playing a significant role in advancing harmonisation efforts in pharmacovigilance?

With the proven use cases in other industries and within PV, regulators are also very positive about implementing AI and automation in PV. Newer large language models (LLMs) like ChatGPT and other AI techniques have the potential to analyse vast datasets more efficiently than manual methods through ML and NLP. They can also help integrate the RWD from electronic health records, wearables, and social media, which can provide a broader and more diverse dataset for pharmacovigilance. Particularly in terms of data security and privacy concerns, technologies like Blockchain offer secure and transparent data sharing. Its decentralised nature can simplify global data exchange and enhance the reliability of safety data, promoting harmonisation. In addition, Telemedicine and Remote Monitoring can enable remote patient monitoring, offering a broader view of medication safety and side effects, particularly relevant in the era of decentralised clinical trials. These advancements are integral to achieving global harmonisation in drug safety monitoring and ultimately improving patient health outcomes.

11. Any other comments?

In totality, harmonisation in pharmacovigilance requires collective action and cooperation among regulatory authorities, pharmaceutical companies, vendor companies, healthcare professionals, patients, and international organisations. Vendor companies, in particular, have a crucial role in providing the technological infrastructure and solutions necessary to support harmonised practices in data management and reporting.

AUTHOR BIO

Nikesh Shah, heads the Safety and Pharmacovigilance business at Indegene. He is also responsible for Marketing, Presales and Strategic Initiatives for the Enterprise Medical Business. Previously, he led the Corporate Strategy function at Indegene. He worked with the CEOs office and the Founding team on identifying and executing strategic initiatives within the organization including M&A, BU strategies and corporate planning initiatives.

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ExpertTalk

UNVEILING THE EVOLUTION

A thought leader's insights into the pharmacovigilance industry



You have been in the pharmacovigilance industry for nearly 23 years, and were an early pioneer of this area in India. As a globally recognised thought leader, how have you seen this evolve in the past two decades?

Getting exposure very early on, in the science and business of pharmacovigilance was a very fortunate thing for me. In the early 2000s this area was all about the fascination of doing something new and different for some of us because clinical trials were the usual area of interest and a natural career inclination given the growth trajectory it was on then. We started it as a small nest in the year 2005 in Ranbaxy then and then never

As the sea of data continues to surge, demanding more resources and investments, the industry must navigate treacherous waters, contending with outsourcing challenges while striving for consolidation and standardisation. In the next five years, an exhilarating journey awaits as the industry gears up for monumental growth, laser-focused strategies, and the embrace of ground-breaking technologies. Brace yourselves, for these exciting times that herald the dawn of automation, artificial intelligence, machine learning, and the birth of co-development partnerships that will redefine the landscape forever. Service providers armed with comprehensive solutions will shape the future of pharmacovigilance.

Vivek Ahuja, Pioneer in Pharmacovigilance

looked back. By the year 2010, Indian pharma companies and International clinical research organisations (CROs) had all begun to set up a base in India and India was beginning to get recognized as the outsourcing destination for worldwide pharma given the significant cost arbitrage of doing work in India. By 2015, not only was the majority of work in this area begun to be offshored and outsourced to India but also the nature of the work being done also began to change character and besides the manual data entry and management related work, India also became the preferred destination for work requiring higher intellectual expertise like benefit risk assessment and medical review also. The next five years until 2025 saw further expansion and evolution of this space, with technological advances like adoption of cloud computing, experimentation with automation and so on.

Was India a 'rightshoring–outsourcing' destination for this ?

I see India as a strong established destination, with significant future investments being made by not only the Indian tech companies who evangelised the concept of running this work as business process outsourcing shops processing terabytes of data but also by large pharma who have set up captive bases in India and are increasing their investments. Not many may know this fact, but the top 2 companies who hold majority of the market share of the pharmacovigilance software were started by Indian entrepreneurs based in the US in the 1990s. Their back end offices were based in India then. The tech software and service industry around pharmacovigilance has now mushroomed and there are several successful start up ventures who have made a significant mark in this area.

What in your opinion are the top issues faced globally by major pharma to fulfil their pharmacovigilance compliance needs today?

In my opinion, the locus of problems has moved further down the value chain now, however the character of the problems has not changed. In fact, they have got compounded now with additional problems. Let's take a step back to understand the subject. Ten years ago the problem was to find good talent, the problem is still the same, we are always looking for better talent. Five years ago we were looking for better technology, we are still looking for better technology. We have always been looking to achieve higher quality, it is no different even now. Regulations have been evolving very significantly every now and then since the past ten years, right after the introduction of the EU GVP modules and then the introduction of the R3 standards. That is the only area that appears fairly silent and maturing to the level that there are no upcoming major changes visible on the horizon.

What in your opinion is the reason for all of this?

Data has been burgeoning since ever, and there is no respite from it —there is never going to be. And the science of pharmacovigilance feeds on the data by looking at the cumulative data rather than the incremental delta data. More the data, more the probability of finding a statistically stronger correlation between an adverse event and a drug. To manage the data better, regulators evolved the data standards.

Do you see this as a concern?

So, fundamentally more data is good for us and helps us take better decisions. But more data also means ▶

more resource requirements, greater expense, need for higher quality, better talent, and greater investments into technology. Besides this, the locus of the focus has increasingly shifted from reactive to proactive pharmacovigilance. In anticipation of the risks, greater focus is now on prevention of these risks via the introduction of the risk management programs and introduction of risk minimization measures, targeted follow ups. This requires additional investments in both technology and resources.

What are the other areas that the industry is grappling with?

Another area that the industry is grappling with but not yet consciously acknowledging is that every company is outsourcing work in bits and pieces to multiple vendors and then further investing in multiple manpower resources to manage this multiplicity. Simple principles like drawing on economies of scale, consolidation and standardization of approaches, being technology agnostic will go a long way in tackling these challenges.

How do you see this panning out over the next five years?

Like in every industry there will be the usual lifecycle of the stages of scaling up, focus and consolidate and then balance and alliance. There is an element of unpredictability with respect to how much the technology will turn out to be the panacea for all these problems and in turn create a fresh wave of problems like job losses, requirement for newer kinds of skills. In such situations, speculations rule the roost and exercising prudence is the most prudent thing to do. Open mindedness to experiment and take risks for adoption of newer technologies will determine who gets to this goal post first.

Besides this, service providers who can offer everything under one roof, all the services ranging from the infrastructure and talent to handle the first complaint call that comes from the consumer right up to the last product label update or the additional risk minimization measure implemented. Incidentally, that is just only a hundred and eighty degrees of support that a marketing authorisation holder needs to fulfil its compliance obligations. Just that one side. The remaining hundred eighty degrees of the spectrum or the other side is formed by the technology behind the scenes i.e. the hosting and upkeep of the safety database and the automation that galvanizes this engine. Add to that the services like literature monitoring, translations capability, QPPV services, local country pharmacovigilance associates, regulatory intelligence services that must also come from the same stable. If you think the list got over, provision of all these services in Japan adds a completely new additional dimension to the requirement list.

Any closing remarks from you ?

These are very exciting times to be in the world of pharmacovigilance. It's going to be a watershed moment in the history of pharmacovigilance when the industry will undergo a tectonic shift and roll over into a new era revved up by robotic process automation, artificial intelligence, machine learning on one hand and vendor consolidation to complement it. Over the years,the relationship with these vendors will transform into co-development partnerships. ■

AUTHOR BIO



Vivek Ahuja is a pioneer in pharmacovigilance in India. With over 22 years of experience, he established the country's first global pharmacovigilance unit. He is a renowned thought leader, who has worked in drugs, biologics, device and vaccine safety. He is passionate about AI, ML, and NLP, and is actively involved in policymaking. Notably, he was the co-author of the Pharmacovigilance Program of India. Currently, as a Senior Vice President at EVERSANA, he drives Delivery Excellence, Strategy & Growth in the organization's growing Pharmacovigilance, Regulatory and Quality teams.

ExpertTalk

Enabling the delivery of the poorly soluble and unstable drugs to the site of action



Effective delivery of the difficult to solubilise and labile (unstable) drugs has remained a great challenge for a formulation scientist. Low solubility of the drug leads to incomplete dissolution in the GI tract and hence lower bioavailability. Current drug discovery pipeline is composed of almost 60-70 per cent of the molecules indicating low solubility and thereby lower bioavailability. Formulation technologies such as amorphous solid dispersions, micronization, nanosuspensions, lipid-based delivery systems (SMEDDs/ SEDDS), mesoporous silica particles are extensively studied to enhance the in vivo dissolution rate and bioavailability in the clinics. The optimisation of the formulation and scale up is a complex task and must be designed meticulously.

Drugs which are unstable in the GI tract (drugs sensitive to acidic or basic pH) and sensitive to hydrolytic/ oxidative degradation can be delivered at the target site if formulated in an optimum manner. Stabilising excipients such as antioxidants, chelating agents, complexing agents (cyclodextrins) and pH modifiers are reported to stabilise the drug in the final formulation (with the anticipated shelf life) and also during in vivo passage

Formulation technologies also play an important role to extend the life cycle management of the marketed drugs and to obtain additional IP protection of the drugs under development.

Yogeshwar Bachhav, Founder and Director, Adex Pharma consultancy Services

1.How do formulation technologies contribute to the development of novel drug delivery systems?

The drug discovery pipeline is composed of around 60-70 per cent molecules with low solubility (compounds from the BCS class II and IV), which leads to low bioavailability following oral administration. Significant efforts are needed to improve the solubility/dissolution rate of these compounds and formulation technologies are of immense help for this purpose.

Techniques such as spray drying and hot melt extrusion are used to develop novel drug delivery systems such as amorphous solid dispersions (ASDs) which are reported to improve the bioavailability of the poorly soluble drugs. Nanosuspension is one of the novel drug delivery systems produced using techniques

like media milling (ball milling), high pressure homogenisation to increase the bioavailability of difficult to solubilize drugs. Advanced drug delivery systems such as mesoporous silica particles are produced using the solvent evaporation technique where the objective is to entrap amorphous form of the molecules within the mesopores of silica particles to improve the bioavailability. Lipid-based systems such intralipid emulsions are produced using high pressure homogenization.

Thus, successful development and scale up of novel drug delivery systems necessitates use of formulation technologies.

2.What are some challenges or limitations associated with formulation technologies and how can they be overcome?

Formulation technologies used to produce novel drug delivery systems or enabled formulation have their advantages and disadvantages. Some of the major limitations of these techniques are the operational cost, impact of the timelines for the development, scale up challenges, degradation of the drug and limited know-how.

Selection of the given formulation technology to develop desired novel drug delivery systems is driven by suitability with the target drug candidate/formulation. If any technique has significant impact on the timelines for development, efforts should be made to explore an alternative which can speed up the overall process. For example, the lyophilization process often needs longer cycle times compared to liquid fill and finish operations in the case of parenteral formulations. This could impact both the timelines, operational cost as well stability of the drug under processing conditions (for drugs with instability issues). Hence, in this case the later option is better suited if the formulation is stable in liquid over long time storage.

Similarly, for heat unstable or labile molecules, selection of the formulation technology is driven by the stability of the drug candidate under the processing conditions. Drug substances with strong tendency for aggregation may not be suited for jet mill technology to produce micronized material, in this case solvent precipitation technique is better suited to obtain the size reduction.

In summary, the selection of the formulation technique will be based on the above-mentioned limitations and alternative solutions at disposal; it could vary on a case-to-case basis.



Yogeshwar Bachhav

3.How does the choice of formulation technology impact the stability and shelf-life of a product?

Often the formulation technologies involve use of extreme conditions such as use of organic solvents, high pressure, or high temperature. There are fair chances that the molecules which are sensitive to these conditions undergo degradation. For example, a drug sensitive to thermal degradation will not be suited for the hot melt

extrusion process used to produce solid dispersion. Similarly, the spray drying process cannot be used for the drugs which may undergo degradation in the presence of organic solvents at high temperature.

Drugs sensitive to oxidative degradation can not be subjected to high pressure homogenization used to produce intralipid emulsions.

Hence, due consideration must be paid for the selection of the technology to produce a formulation to rule out any degradation to obtain a stable product with the desired shelf life. Any undesired formation of the impurities/degradation products will severely compromise the safety and efficacy of the drug product in clinical use.

4.Can you discuss the role of formulation technologies in enhancing the bioavailability of poorly soluble drugs?

Poorly soluble drugs significantly limit the bioavailability upon oral administration. Significant advances have been made to improve the bioavailability of the difficult to solubilise compound with the effective use of different formulation technologies.

Various principles are explored to improve the solubilisation such as converting the crystalline form of drug into an amorphous form with increased dissolution rate, reduction in the particle size to improve overall surface area which leads to increase in dissolution rate, solubilisation of the drug into the lipid-based vehicles to improve in vivo dissolution, complexation of the drug to cyclodextrins which encapsulate the hydrophobic part of the drug molecule in order to effectuate solubilisation.

The following technologies can be used to develop new drug delivery systems to improve bioavailability.

- Hot melt extrusion: Amorphous solid dispersion
- Spray drying: Amorphous solid dispersion.
- Jet milling: Micronisation
- Media milling: Nanosuspension
- High pressure homogenization: nanosuspension and intralipid emulsion
- Anti-solvent precipitation: Nanosuspension
- Solvent evaporation: Mesoporous silica particles
- Complexation: Cyclodextrin complexes

5.What are some emerging trends or advancements in formulation technologies?

The following areas have reported significant advancements in formulation technologies.

Inhalation products (Pills, capsules): Products to be administered by inhalation route represent a big business opportunity. Patients suffering from asthma and other respiratory diseases would not mind paying good money for an efficient inhalable product, as the faster onset of action and reduced incidence of side-effects is highly desired. For each kind of inhalation device, the formulation challenges are different. Droplet size and viscosity of the solution are critical in the case of the metered dose inhaler, When the dry powder inhaler is used, significant optimisation of particle engineering is needed with respect to the particle size, flow properties and polymorphic forms.

Modified/sustained release dosage form: The need for modified release dosage forms is increasing at the same speed at which formulations are developed. For drugs unstable in the stomach or with potential of gastric irritation, intestinal release is highly desired to avoid drug degradation and adverse events. The intestinal release technology can be explored for both new chemical entities as well as for life cycle management of the approved drugs. Patient compliance (due to reduction in the number of pills taken per day) and low incidence of the side-effects (due to low peak plasma concentrations) are two factors driving demand to develop modified/sustained release dosage forms. Many pharma companies are exploring this option of modified release dosage forms to extend patent periods and thereby maintain market share. Formulation technologies such as multi-particulate formulations, pelletization are again of significant importance to develop the modified release dosage forms.

Combination products: The market for fixed dose combinations of products which often contain two or more drugs is growing and its leading pharmaceutical companies to explore this option to develop new formulations for the existing drugs. Reduction in the number of pills taken every day is a preferred option by physicians and patients to improve patient compliance. Combining two or more drugs in a combination product is a significant challenge. And to ensure the stability of the respective ingredients in the formulation to obtain the desired PK/PD response may necessitate the use of the advanced techniques such as layering, pelletization or mini tabulation of the individual drugs.

Paediatric medications formulations: It should be noted that paediatric populations have different needs compared to adults such as smaller doses, inability to swallow tablets or capsules, and adaptation of the dosage form to child weight. Hence, liquid dosage forms are easy to administer compared to the tablets and can also be adjusted as per age, body weight and pathological condition. Taste masking is advantageous while using tablets and capsules compared to liquid dosage forms. Longer shelf life of paediatric formulation can be ensured using dry syrups in bottles.

Abuse deterrents: Regulatory authorities are advising pharmaceutical



companies developing certain types of products such as opioids to explore the technologies which will prevent them being abused. To address this concern, various technologies are explored to prevent tablets from being crushed, melted, or manipulated which could facilitate the API release. The effectiveness of the technology depends on the drug, as one of the technologies prevents dissolution of tablets in alcohol while others prevent the release in response to physical manipulation.

6.How do formulation technologies support the development of personalised medicine or customised drug formulations?

Lastly the personalised medicine concept has been proven to play an important role in the clinics. Personalised medicine modifies conventional dosage forms as per the patient's needs. And this improved concept allows the individual patient to effectuate the best treatment options and decrease adverse effects.

The goal of personalised medicine is to tailor the drug administration to an individual while considering the pathophysiology, response to drug and genetic profile of the patient. Among the several emerging technologies which help to shift from the conventional dosage to personalised medicine, 3D printing is gaining attention. 3D printing deals with the creation of three-dimensional objects (through the formation of layer upon layer) using computer software. This technology can be used to produce a variety of drug delivery systems differing in shape, release kinetics and combination of the ingredients. In future, this technology can be used to dispense the medications based on the individual needs.

7.How does the stability of drugs impact their formulation and delivery?

Drugs sensitive to pH dependent, oxidative, hydrolytic degradation or thermal degradation will limit the choice of the delivery system. Dry powder systems are better suited compared to a liquid formulation for a drug sensitive to hydrolytic degradation and intended for parenteral administration; for oral administration a tablet or capsule formulation is preferred. Use of antioxidants is recommended for the drugs sensitive to oxidative degradation. Photoprotective primary packaging can be a preferred option for the drugs prone to photodegradation.

Also, stability of the drug can impact the choice of the route of administration drugs sensitive to acidic pH of the stomach are often delivered via parenteral route to avoid extensive gastric degradation. Large molecules are sensitive to acid catalysed degradation and hence mostly delivered via the parenteral route. Topical route of administration is often explored for drugs sensitive to degradation via oral route.

8.What are some common issues encountered when formulating and delivering unstable drugs, and how can they be addressed?

The most common problem occurring during the formulation development and storage of the unstable drugs is the degradation of the drug on its own or in contact with the excipients and/or primary packaging components. This leads to the formation of drug degradation products which may produce toxic effects.

This issue can be addressed by conducting the forced degradation studies for a drug candidate alone and in contact with the excipients and primary packaging material. The outcome of these studies will help understand the possible drug degradation mechanism and selection of the appropriate excipients such antioxidants, pH-modifiers, chelating agents, complexing agents. Use of the protective primary packaging materials (e.g., packaging materials with moisture barrier and photoprotective packaging).

9. Can you explain how formulation technologies help protect and stabilise unstable drugs during storage and administration?

As addressed before, the first step would be to understand the degradation kinetics of the drug and possible factors leading to its degradation. Based on this information, the choice of formulation technology can be made which may help to protect the drug during administration and storage. The choice could vary depending on the susceptibility of the drug candidate to the different stress factors such as temperature, water content/atmospheric moisture, pH of the microenvironment, photolytic stress or contact with the primary packaging etc.

For drugs prone to hydrolytic degradation and only stable at acidic pH, intended preferred route will be parenteral administration and lyophilised formulation will be best suited.

10.How do formulation technologies impact the release profile of soluble and unstable drugs in controlled or sustained-release formulations?

Controlled or sustained release formulations are desired for the drugs with short life. In this case, rate controlling polymers such as polymethacrylates, cellulosic polymers are used to control the dissolution rate of the drug during the GI transit. Focus is to obtain the delayed or controlled release over 12-to-24 hours depending on the expected duration of treatment. Conventional tableting techniques may be explored to produce the sustained release dosage forms using these polymers.

Pelletisation is one of the techniques explored to produce a controlled release formulation owing the ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings. Use of sustained release dosage forms is very important in terms of patient compliance, reduction of see-saw fluctuations related to exposure of drug, reduction of total dose of the drug, and improved overall efficacy of the treatment. Acid labile drugs (drugs which are unstable in the acidic medium of stomach) can be delivered using the enteric coating. The oral solid dosage form in this case uses a polymer which is insoluble in the acidic medium and will only release the drug at the intestinal pH. Similarly, the drugs which are not stable at intestinal pH can be delivered effectively using the gastroretentive dosage forms. For example, osmotic tablets (pump) are evaluated to develop gastroretentive dosage form of Diltiazem Hydrochloride.

11.Any other comments?

The pharmaceutical industry is witnessing the shift from small molecules to large molecules (proteins, antibodies, and vaccines). These molecules are produced using biological systems and that makes overall formulation development a complex process. Large molecules are administered by parenteral route due to the poor stability and absorption following oral route. Hence, significant efforts are needed to develop painless delivery of the biologicals to improve the patience compliance. Also, poor stability of the large molecules in the formulation is a major challenge necessitating cold chain supply, hence there is a need to come up with the formulation technologies which can stabilise these molecules allowing room temperature storage and shipment. ■



AUTHOR BIO

Yogeshwar Bachhav is Pharmacist by training and PhD in Advanced drug delivery systems from ICT, Mumbai (India). He has around 16 years of Post PhD experience in Europe in the field of Pharmaceutical Development of investigational drugs. Currently he is working as Director (Consultant) at AiCuris Anti-infective Cures AG Germany and responsible for Pharmaceutical Development of investigational drugs in the domain of innovative antiviral and antibacterial drugs. He has also started a consultancy firm called Adex Pharma which deals with solving complex issues in the pharmaceutical development of new and approved drugs since 2016.

ExpertTalk

The Rising Importance of Containment and Delivery Systems and Latest Trends in The Space

In this interview with West Korea's General Manager Journey Hong shares his insights on containment and delivery systems, and trends in advanced biologics therapies — in the context of South Korea. He also discusses the strengths of the South Korean market, and some lessons to learn from organisations in mature markets.

Journey Hong, General Manager, South Korea, West Pharmaceutical Services, Inc.

1. What is the role of containment and delivery systems for biologics and injectable therapies? What are some trends in this space?

To properly comprehend the important role that containment and delivery systems play in the context of biologics and injectable therapies globally, it is essential to begin by understanding the dynamics of drug development, commercialization, and utilisation.

In markets across the world, the pandemic in the last few years has drawn significant attention to biologics and biotechnology. Specifically, within the Asia-Pacific (APAC) region, there has been a very notable surge in clinical trials, spanning not only the past three years but through the past decade as well. According to Pharma Intelligence[1], APAC contributed close to half of the world's clinical trial activities in 2021 alone, and this figure has only been growing. Notably, this growth is particularly evident in the biopharma sector. As a result, there is also an expansion in the corresponding manufacturing industries.

The Indian pharmaceutical market is one of the fastest growing within the region, whereas on the other side of APAC, South Korea benefits from robust support from regulatory boards. Concurrently, Singapore is strengthening its very promising position as a leading hub of biomedical sciences in Asia.

The rapid growth of the biopharmaceuticals in APAC can be attributed to several factors — beginning with businesses capitalising on the rising demand for home-based healthcare — a trend further accelerated by the COVID-19 pandemic. Additionally,

1 https://invivo.pharmaintelligence.informa.com/IV146738/APAC-As-A-Clinical-Trial-Powerhouse

the enormous rise in cell and gene therapy research and development has spurred another wave of clinical trials.

The growing interest and expansion of biologics and clinical medication research has paved the way for injectable therapies to emerge as one of the fastest growing segments in the global drug industry. This, in turn, fuels demand for innovative packaging and delivery solutions. In accordance with this trend, the market for containment and delivery systems is projected to witness compound annual growth rate of 11.87 per cent [2]from this year through to 2031. This is in line with how the biotechnology and biopharma sectors are set to grow with an expected compound annual growth rate of 10.3 per cent[3] from 2023 to 2030.

As drug developers across the globe race to bring their products to market and regulators place heightened focus on product quality, the significance of containment and delivery solutions is on the rise.

The implications are two-fold. Firstly, it is imperative for drug developers to carefully select a containment system that ensures the safeguarding of the valuable drug product, thus providing assurance of both low risk and high-quality standards. And for containment and delivery solution providers, this translates to the need for remaining attuned to the latest developments within the drug development domain and innovating their products to cater to the evolving needs of drug developers.

Secondly, in order to ensure both speed to market and adherence to regulatory requirements, drug developers should adopt an open, collaborative approach with containment and delivery solution providers. Discussions concerning packaging decisions should be initiated early within the drug development process between stakeholders. By doing so, the unique needs of a biologic drug and regulatory requirements can be adequately addressed upon the drug's impending launch.



AUTHOR BIO

JOURNEY HONG

Appointed as GM in February 2022, Sung-Yong HONG (Journey) holds 28 years of global bio and healthcare management experience such as from Medidata Solutions, Cytiva, and GE Healthcare Life Sciences in ASEAN and Korea. Before joining West, HONG was VP and General Manager of Sales at Medidata as well as the Korea Representative for GE Healthcare Life Sciences/Cytiva. With close to 30 years of bio and healthcare industry experience in sales and management, he is strengthening West's position in South Korea and driving business growth.

2 https://www.insightaceanalytic.com/report/integrated-drug-containment-and-delivery-solutions-market/1823

3 https://www.grandviewresearch.com/industry-analysis/biologics-market#:~:text=Report%20Overview,10.3%25%20from%202023%20to%202030.

2. The South Korean government has laid out ambitious plans for the biotechnology sector in Korea. What are the challenges and opportunities for Korean companies following these policies?

In South Korea, the biologics sector makes up the majority of the pharmaceutical market whereas generic medicines, therapies and injectables make up the rest of the market. The government has recognized the strong potential for the industry to boom and has strategically fielded more support to foster the growth of the South Korean biologics and biotechnology sectors. For example, most recently, the government has announced its ambition to raise the market's overall production capacity to 100 trillion won and doubling export values by 2030. Following the launch of these favourable policies, there will be innumerable opportunities for pharmaceutical companies to further expand.

These additional investments from the government will also certainly attract more new players to enter the South Korean market, while the current players in the market, homegrown or from abroad, will have a better chance to grow competitively within the APAC region. The boost in investments will also be a gateway to attract fresh talent and an encouraging factor for the current workforce to grow, so we can expect more opportunities within the sector. It will pave the way for upskilling existing talent and allowing South Korean companies to accelerate their growth trajectory for the future.

What these policies also imply, however, is that for many Korean pharmaceutical companies, the ambitious plans launched by the government rely on an increase in customer demands without any compromise in the quality of products. Hence, biopharma companies must rise to the challenge set by the authorities and put in place stringent checks to ensure proper quality control. This will mean pooling more resources into well-backed, innovative research, and consistent development of products. Companies must be prepared to expand and build production pipelines as and when needed to meet expectations and customers' requirements, while staying ready to pivot their business and logistics strategies if unexpected situations and delays occur. The COVID-19 outbreak we have experienced as an industry over the last few years is one such example.

While South Korean pharmaceutical companies meet these expectations, they must also ensure that the demands are properly fulfilled. An effective organisation must prove themselves capable of producing high quality products in time, managing deliveries, and overcoming supply chain disruptions that may impact patients, regionally and globally. South Korean biopharma companies must be ready to come together to tackle these potential disruptions for their delivery lines to stand out, as the entire sector envisions a positive momentum.

As a result, companies must take time to understand how containment solutions work and apply the right long-term forecasting tools to boost the efficiency of delivering these solutions to patients. With the right technologies, fulfilment pressures can be eased. South Korean businesses should also pool resources to optimise lead times of delivery through understanding how containment solutions match with certain types of drugs, and the regulatory complications that impact fulfilment. Coupling this with the customers' value proposition, it will definitely become easier for South Korean companies to earn the trust of their customers while delivering the product they need, with the highest quality of services.

Once this is worked out by the organisations, there will be plenty of opportunities to grow for the pharmaceutical companies. Any company that neglects these issues may end up losing the trust of their key partners and patients they serve, or risk losing out on the market share.



3. What are some of the characteristics of South Korea which makes it stand out in the global biopharma market?

Compared to the global biopharma market, South Korea stands out because of the market's strength in biologics and biosimilars. South Korea has cemented its place as one of the most promising markets where pharmaceutical companies have identified huge investment potentials for research and development processes. Over the years, there has been a growing interest in South Korea's specialisation in biologics.

Moreover, within the same region, most other markets specialise in generic medicines and biopharmaceuticals. South Korea's unrelenting focus on producing high quality biologics has allowed the market to rise above the rest. It has also earned the industry trust to innovate and manufacture cutting-edge medicines and therapies. This trust has extended into the global pharma market as well where South Korean players are well-respected.

On top of these, the substantial policy support from the authorities provides South Korea with another competitive advantage over other markets. The government has chosen the bio-health industry as one of its three future growth engines and has announced a host of policies to foster the industry.

Lastly, alongside the growth of foreign companies entering and setting up their base in South Korea, the country's own domestic biopharma companies have also been expanding and growing rapidly. Locally developed biosimilars are steadily gaining a larger market share in the Korean pharmaceutical sector. For the South Korea market especially, the Botulinum Neurotoxin A (BoNT-A) market stands out. The market, with its high number of quality manufacturers, can produce high quality solutions and injectables for BoNT-A that are competitive in price, for a growing pool of regional audiences.

> As drug developers across the globe race to bring their products to market and regulators place heightened focus on product quality, the significance of containment and delivery solutions is on the rise.

4. What are some key lessons South Korean biotech businesses can learn from the global leaders of the biotech industry?

Industry leaders in markets such as the USA and China are great examples to adapt and learn from.

Despite the different characteristics of these markets, the speed and flexibility to embrace industry trends and changing business models is very impressive and a great contributor to their success. As more treatments are developed and society's needs evolve, global biotech leaders need to quickly adapt and understand patient needs to develop the right solutions. The pandemic served as a strong learning experience when most of the big players quickly pivoted their strategies to innovate and cater to the market needs. Some of these strategies may include directing strong investments to hire the right talent and workforce, or to expand production spaces, and biopharma companies need to have the agility and flexibility.

Being open to collaboration and partnerships is also another key to success. The biotech world no longer exists in a silo, and strong partnerships and collaborations across markets can help drive innovation and development beyond borders. With the proliferation of data analytics and communication tools, it is now easier to work across the world with other leaders in the industry, sharing skills, knowledge, and ideas.

From other markets, we also observe that sharing close partnerships with regulators and policy makers helps biotech businesses to find success in their markets as well. For example, in India, regulators are taking initiative to develop closer partnerships with the biologics and biotech sectors through schemes such as the National Biotechnology Development Plan and Biotechnology Industry Partnership Programme.

As the quality standards and complexities of bio injectables and treatments increase, it is more important than ever to establish good understanding and relations with regulators, and vice versa. This will help keep a stringent check on quality standards and regulatory compliance to bring forward the right solutions and products with sufficient support. Doing so will also help South Korean companies build trust with their valued stakeholders and lay a strong foundation for long-term, sustainable growth within the market.

Whether it is through relationships and collaborations with overseas partners, observations, or interactions via platforms and trade events, there remain many key lessons for South Korean companies to learn and improve on. As the biotech space continues to grow, homegrown businesses can even emulate what players in mature, established markets have done right and adapt their strategies to the South Korean market, to innovate and overcome any potential challenges. ■



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