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Current Trends in Regulatory Outsourcing Models

Biologics and Biosimilars Market Key Trends in 2021

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Biosimilars and Biologics
Opportunities for blockbuster growth

The COVID-19 pandemic has impacted many industries alike and the impact on biosimilars market was no different. Lockdowns causing short fall of resources, delays in clinical trials, slowdown in FDA approvals of non-COVID drugs have influenced the R&D activities and the biosimilars pipeline. This has been a great challenge to the pharmaceutical companies focused on biosimilar development. However, as companies began to resume their operations at full scale, development of biosimilars appears to be on track .

Several blockbuster biological drugs have expired, and many are inching towards their patent expiry in the next year or two, highlighting a huge opportunity for biosimilar manufacturers. Factors like rising prevalence of chronic diseases, patent extensions, cost-saving initiatives by governments and third-party payers have also driven the growth of biosimilars. With biosimilars showing equal efficacy and safety in comparison with original drugs at much lower costs, several countries are looking to make the switch to biosimilars by enacting favourable regulations.

Since the first biosimilar of a monoclonal antibody for treating autoimmune diseases such as ankylosing spondylitis, rheumatoid arthritis gained regulatory approval from the European Medicines Agency in 2013, biosimilars have come a long way to offering clinical outcomes equivalent to the original drugs. Be it chronic, immunological diseases or rare diseases, biosimilars have in a way brought a rapid change in the treatment of diseases. Recent trends indicate clinicians actively suggesting the use of biosimilars for treating several diseases (including…). From a cost savings and market share standpoint, the more recent biosimilars are indeed known to faring well in comparison to their predecessors. According to McKinsey's biosimilars market model, biosimilars have shown a remarkable growth from 2015 to 2020 and could see a double-digit growth to touch US$30 billion by 2025 and US$60 billion by 2030.

North America, with a large number of key players in the market, could witness a significant CAGR over the forecast period. Leading biosimilar companies like Pfizer Inc., Mylan NV, Amgen Inc., and Coherus Biosciences Inc., along with others in developing countries, are focussing on innovations for novel biosimilar drug developments, especially in the treatment of the present coronavirus pandemic. With the highest geriatric populations, Europe is contributing its share in the biosimilars market followed by the Asia-Pacific region.

As the world continues to fight the outburst of several diseases, cost effectiveness and clinical efficacy offer bright promise for biosimilars. However, educating and communicating the benefits of biosimilars on a large scale is essential for a widespread awareness for the health systems to become more sustainable.

This issue presents the article by *Ayaaz Hussain Khan, Managing Director, Global Head-Generics, Navitas Life Sciences* that details key trends that will drive growth in the biosimilar and biologics market across the globe. I believe you will find the articles very insightful.

Prasanthi Sadhu
Editor

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Current Trends in Regulatory Outsourcing Models

Globally, the outsourcing of services for drug development and commercialisation is increasing. Regulatory services are often included in this, and regulatory activities are increasingly the subject of specific, dedicated FSP (functional services partnership) projects. This article overviews a number of the more common models, including cost models, that can be deployed for the outsourcing of regulatory services. We assessed the appropriate criteria and advantages of these models, illustrating with examples from our experience. Interestingly, over the life of a single project, different models may be used, depending on a number of factors and aimed at maximising the benefits to both the supplier and the recipient of these services.

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Sarah Mullen, Director, PPD

Pharmaceutical companies of all sizes are increasingly outsourcing elements of the development process, including regulatory affairs. This helps them to access specific technical, regulatory or geographic expertise, to flexibly augment staffing levels without adding to headcount, and to deliver key operational outputs enabling internal staff to focus on strategic elements. Outsourced expertise and alternative experiences can

significantly inform client strategy. This approach can also provide resources for special projects and support clients for finite periods before their workload enters a predicted 'trough,' avoiding the need for the client to reduce its own headcount.

The overall global market for contract research organisation (CRO) services is forecast by ResearchandMarkets to reach US$66.1 billion by 2028, with a compound annual growth rate (CAGR) of 6.6 per cent from 2021 to 2028. A survey by Avoca in 2019 found that clients outsourced 61 per cent of clinical development work and anticipated maintaining that level of outsourcing through 2021.

In regulatory affairs, the global outsourcing market is forecast at US$14.9 billion by 2028, with a CAGR of 11.9 per cent from 2021 to 2028, according to Grand View Research. A driving factor in this growth is the rise in the fixed costs of in-house regulatory affairs functions, including training, technology and facilities.

Large biopharma companies' use of functional services partnerships (FSPs) – which bundle and conduct repetitive, high-volume tasks across multiple projects – is increasing at more than 13 per cent annually. FSPs can lower sponsor drug development costs by reducing redundant activities, providing scalable expertise and offering resourcing flexibility. Other benefits include simplicity of financing and reduced operational burden.

Typically, outsourcing can be provided either under a full-service offering (FSO) or an FSP model; FSOs generally involve a single protocol or project with multiple services and include project management of the study. FSPs usually involve multiple protocols, products or projects around a single service or a limited set of complementary services such as regulatory and pharmacovigilance, data management, or medical writing. Clients allocate an estimated 45 per cent of outsourcing spend to FSPs and the remaining 55 per cent to full-service offerings. While FSPs are often viewed as a way for a client to gain access to a specific service, these engagements increasingly involve multiple services to ensure a smooth and integrated delivery of projects.

Regulatory services are often the subject of dedicated FSP projects, with quality and success measured using well-established parameters, so that clients can compare results achieved by various providers.

Typical regulatory affairs outputs for FSP services include staff augmentation for specific teams (e.g., CMC), end-to-end delivery of single or multiple MAAs/NDAs, managing activities in specific countries or regions, and responsibility for post-approval activities for specific products or regions. Services in these areas can range from project leadership, planning/strategy, authoring, publishing, submissions, interactions with regulatory authorities, and database and system maintenance.

Choosing the best FSP model

There are five main types of FSP cost models (Figure 1):

- In a **fixed price model,** the total cost to complete all tasks specified in the contract is agreed in advance. This has the clear benefit that sponsors can budget for known costs, which are spread predictably over the duration of the

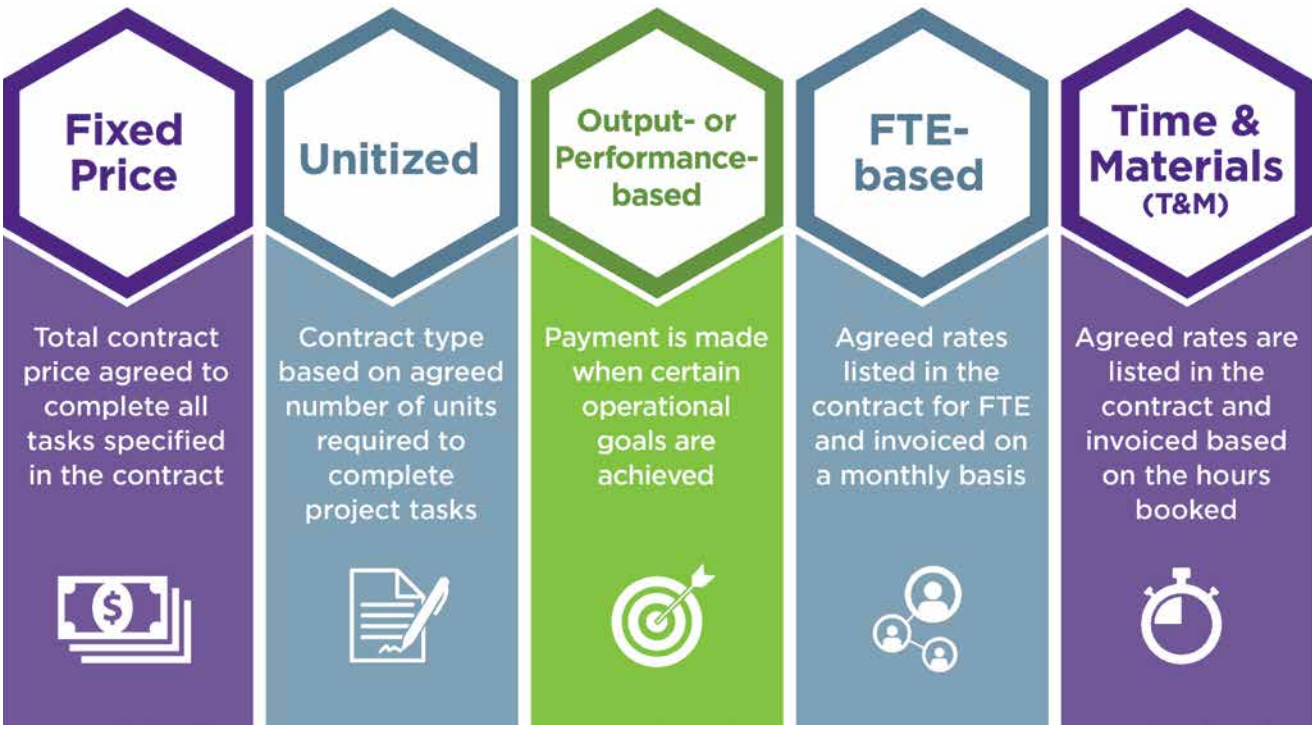

Figure 1: Available outsourcing contracting models

study lifecycle. This could be highly applicable to a client with a known budget or budget cap and where the tasks are well established and understood.

● **Unitised models** involve clients paying for units of work or tasks delivered. This might be best for a client where the volume of work flexes up or down over time, where the hours per unit and volume of work are well established and predictable, or the units involved are well established and understood. Where units are not well understood, and/or the process by which units are generated and delivered is not yet understood, a pilot phase can be helpful. Here, unit delivery, hours and resources are carefully measured and can be used to establish robust units. This model incentivises all parties to find efficiencies.

● For **output or performance-based models,** fees depend on the achievement of pre-specified milestones with or without associated timelines and may include bonus or penalty options. This would be helpful where the client has planned key milestones, and also allows budget to be aligned to the overall timelines for deliverables. As an example, a provider is hired to prepare and to submit a Marketing Application Authorisation (MAA) to a specific regulatory authority on or before a predetermined date. This model might include a bonus for meeting the target timeline and/or a penalty for failing to do so. This model incentivises the provider to deliver to the specific target milestone, though it needs to take into account that unforeseen circumstances beyond the control of the provider may impact the outcome (e.g., unexpected Phase 3 results or delays in provision of data by the client).

● A **full-time equivalent (FTE)-based model** provides the client with a variable number of FTEs, who may be 100 per cent or a part-assigned to development efforts across one or more functional areas. This model can provide expert services in all areas, including regulatory affairs, and might suit a project where the number of units or outputs is hard to predict, but the workload is reasonably well established. This approach is often used when there is a short- or mid-term need to supplement a client's own staff due to shortages, turnover or large influxes of work. This model incentivises the client to carefully consider what resources really are required, at what level and for how long. In addition, it ensures that the provider carefully forecasts and plans resource allocations.

● A **time and materials (T&M) model** is common for projects with tasks where the time needed to perform each task is not easy to predict. As a result, the client receives an estimate upfront, but is only charged for the actual time spent. This might be appropriate for a client looking for consulting services or a one-off project with a small number of units or where complexities may increase or decrease the hours taken to complete a task. Sometimes, a T&M model is used as a pilot, in order to measure time taken and then establish robust units for a subsequent contract. An advantage of this type of model is ease of contracting and administration for both parties.

In addition, a hybrid model consisting of more than one of the above models offers the flexibility to create optimised, highly tailored solutions that may have the greatest impact on key operational metrics and deliverables. Effective use of metrics and key performance indicators (KPIs) can inform ongoing outsourcing decisions and drive process improvements. There also is flexibility to change models during the life of a single project.

Strategic approaches to maximise quality and efficiency

Staffing throughout product development – from early development plans and pre-clinical stages, through to clinical trials and peri- and post-approval activities – requires a strategic approach. This involves examining the portfolio and available internal talent resources, and then determining the best solution to ensure successful delivery for a given asset or program. As client teams evaluate the options, they should consider staffing models that optimise quality and efficiency.

A strong governance structure is of vital importance for a successful partnership. This should be built on transparency and flexibility to support the unique needs of each client. Key elements include provision of a customised and high-touch relationship to clients, with robust oversight from the provider and client leadership teams, and well-defined overarching expectations, requirements and processes. In addition, by acknowledging the mutual desire for enhanced productivity and efficiency, a culture of continuous improvement can be instilled. This should be underwritten by rigorous KPIs, clear communication, risk management, and effective escalation pathways, to maintain compliance and quality throughout the life of the partnership.

Focus on China

Significant expansion of the Chinese pharmaceutical market continues, with sales forecast to rise by 9.8 per cent in 2021. Pharmaceutical innovation is strong in the Asia-Pacific region overall, with more than 5,500 drugs in development as of late 2019.

The many startups in China and the Asia-Pacific region will need to consider outsourcing regulatory services to broaden their global footprint and achieve worldwide registrations for their assets. Here, experienced CROs can provide staff and expertise in locations such as the U.S. and European Union, significantly increasing the capacity of these emerging companies to submit and market their products globally.

A third case study describes successful provision of regulatory resources in China. ▶

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Case studies of various FSP models

The following three case studies provide real examples of the different types of FSP models in action.

FSP Case Study 1

Proven Partnership: Lifecycle Management and Post-Approval License Maintenance

Model type: Unit-based, maturing to FTE-based after six years

Background

- Partnership has been in place since 2013.
- Over 48,700 lifecycle management (LCM) submissions were delivered for 54 products in 165 countries by the end of Q1 2021.
- Managed through established processes, KPIs and training.

Solution

- Dedicated individuals lead portfolio management and planning/delivery of regulatory submissions.
- Flexibility, quality and predictable cost helps smooth peaks and troughs in work volumes.
- Established KPIs are monitored, with timely intervention and resolution if there are deviations.

Benefits

- Partnership provided cost savings of approximately 25 per cent to the client over eight years.
- Cost per unit was reduced by up to 60 per cent in the first five years of the partnership.
- Quality of delivery is guaranteed through effective monitoring and oversight.
- Flexible model transitioned from unitised to FTE as the project evolved.

FSP Case Study 2

Exceeding a Client's Corporate Goals: Faster Successful Delivery of U.S. and EU Marketing Applications

Model type: Mixed (with some FTE staff and initial SME T&M tasks that transitioned to unitised tasks)

Background

- A PPD client needed support for marketing submissions to the U.S. and EU (centralised procedure) for three development programs.
- The client required strategic input, subject matter expert (SME) authoring and review, quality review, document publishing, and post-submission support.

Solution

- An FTE-based project management office set strategy, resolved issues and applied efficiencies.
- Compound-level workstreams were developed.
- FTE-based regulatory affairs leads and functional SMEs focused on deliverables, with dedicated resources for authoring, CMC, nonclinical and management roles.
- SME support was provided initially through a T&M model, which evolved into a unitized model.

Benefits

- High-quality EU MAAs were filed within nine months of project initiation, compared with a typical 12-month timeline. The client exceeded its corporate goals for launch.
- Services were later expanded to support additional markets and tasks.

Case Study 3:

Rapid Onboarding in Challenging Hiring Location Model type: FTE

Background

- Client needed six regulatory FTEs in China for six months of support.
- Traditionally challenging to hire qualified candidates needed in China with short notice, with an average of 60+ days' time to hire in this competitive market.
- FTEs needed to start ASAP upon award.

Solution

- PPD's China leadership ensured sufficient support and resourcing from top-level management.
- PPD HR implemented an aggressive recruitment plan, led by a dedicated recruiter.
- Two FTEs moved from existing teams to lessen hiring burden.
- RA team customized a streamlined onboarding/training plan.
- Clear communication and rapid decision-making.

Client benefits

- Six FTEs identified and onboarded one month sooner than agreed.
- Client extended contract for an additional six months to meet continued needs.

Conclusions and lessons learned

The various FSP models in regulatory affairs provide a wide range of benefits and integrated client-provider partnerships offer efficiency and flexibility to manage regulatory workflows. These increase capacity, add capabilities, and free up in-house resources. FSP models enable specific expertise to be leveraged with flexibility to expand and extend the services and contractual model. Keys to success include clarity upfront for both parties on the scope of work involved, the need to devote time at the outset to ensure expectations are clear, and continued transparent communication throughout the engagement.

As the regulatory environment continues to evolve and as clients seek effective solutions to ensure regulatory compliance and the earliest possible approval of assets globally, these models offer flexibility to deliver both regulatory success and financially prudent contracts. ■

References are available at www.pharmafocusasia.com

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ALISTAIR DAVIDSON serves as executive director of regulatory affairs at PPD. Before joining PPD, he spent nearly 25 years in regulatory affairs in a number of pharma industry roles, such as biological and vaccines, including leadership of regulatory functions with significant international exposure.

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BIOLOGICS AND BIOSIMILARS MARKET

Key trends in 2021

The Global Biosimilars Market is estimated to reach US$240 billion by 2030, with the Indian market at US$35 billion. The considerable increase in reference products, with the USFDA adding 90 molecules and India approving 70 biosimilars, promises to usher in further growth. The Biopharma industry seems keen on investing in the biosimilar market with a focus on improving healthcare and health care costs for diseases of interest like COVID-19, cancer, immunologic diseases, and diabetes. This is evident in the projected growth of the oncology biosimilar market at 17 per cent CAGR, and the growing demand and importance of monoclonal antibodies such as tocilizumab, sarilumab, and itolizumab for testing on COVID-19 patients. Patent expiry for certain biologics like Levemir, Avastin, and Humira have also helped drive growth. Another factor for increased popularity is that the Indian population is cost-sensitive, with domestic sales at nearly US$250 million. Export to other emerging markets is another vital aspect, estimated at US$51 million. Our expert Dr Ayaaz Hussain Khan details key trends that will drive growth in the biosimilar and biologics market across the globe.

Ayaaz Hussain Khan, Managing Director, Global Head-Generics, Navitas Life Sciences a TAKE Solutions Enterprise

The first Biosimilar was approved in the year 2006 in the European Union, and since then, there have been more than 700 biosimilar drugs that have been approved. Not surprisingly, there has been phenomenal growth in the biosimilars market; an Assocham report states that the global biosimilars market is estimated to reach US$240 billion by 2030, while the Indian biosimilar market is expected to reach US$35 billion. According to the U.S Food and Drug Agency (FDA), biosimilars are approved as they are found to be identical to a referenced approved product with no clinical difference when compared to the biological product.

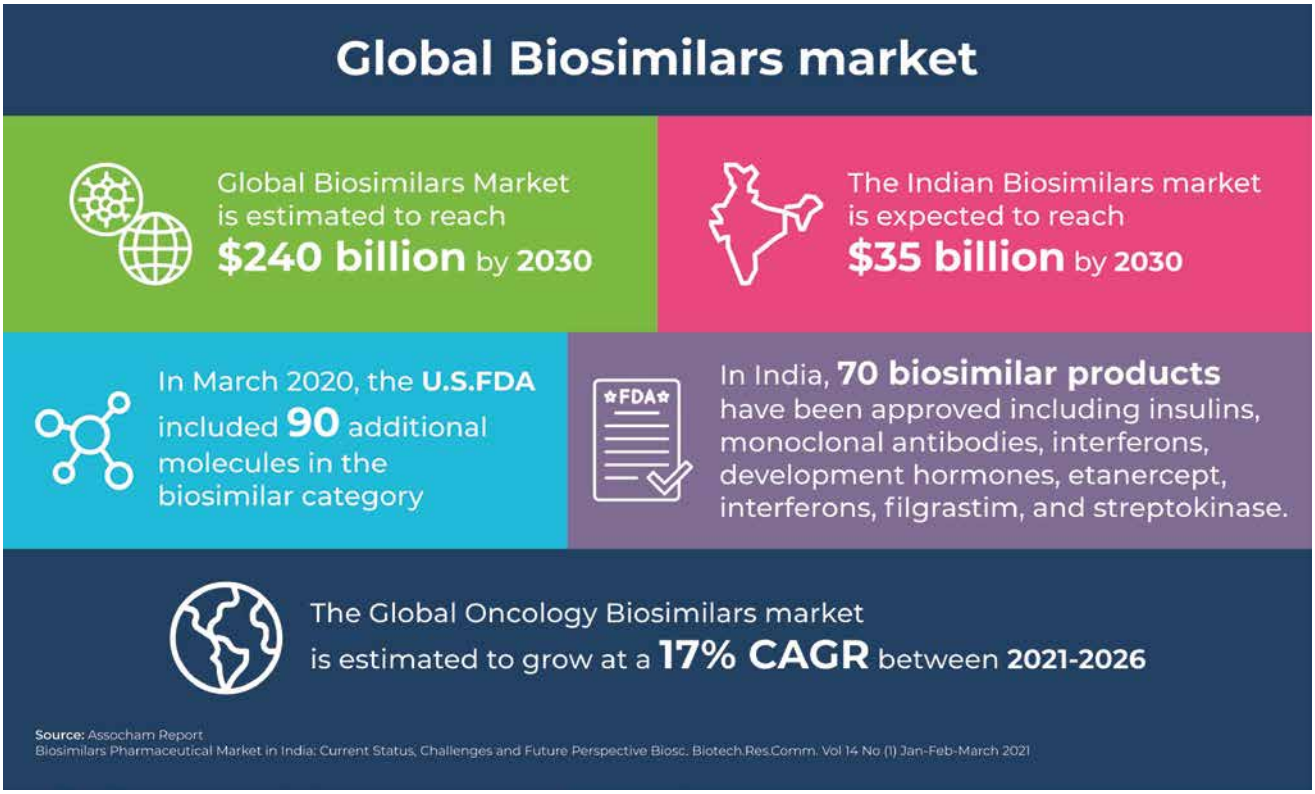

Figure 1

The meteoric rise of the biosimilar market

A systematic literature review conducted on over 90 studies showed that there were no great differences in immunogenicity, safety, or efficacy in biosimilars when compared with biologics. This has been an important factor for the growth of the biosimilar market, with the future of this sector looking right.

The key growth drivers and trends in the Biologics and biosimilar market include:

1) Valued addition of reference molecules: Biosimilars are developed based on approved reference drug products. Omnitrope (somatropin) was the first biosimilar medicinal product, that was approved by the European Commission in the year 2006, upon approval by the European Medicines Agency (EMA). Since then, there have been significant strides in the number of reference molecules that have been added.

Significant expansion of biosimilar Category in the U.S.: In March 2020, the FDA included 90 additional molecules in the biosimilar category. This is a significant step as it increased the number of therapies to be used as biosimilar reference products. Apart from an increase in the biosimilar category, there has been increased approval of biosimilars too in the U.S, highlighting the renewed interest in this sector. In 2018, there were seven biosimilars that were approved by the FDA, which was nearly as many as the previous three years, while ten biosimilars were approved in 2019.

Largest market share in europe: In terms of revenue, Europe has the largest market share as it has a well-defined regulatory framework that large pharmaceuticals use to get their products into the market. Other reasons for continued growth include a good health care system and multiple product launches. As a pioneer in the biosimilar regulatory landscape, Europe continues to play a significant role, with 60 biosimilars that have been approved. The European Medicines Agency put forward stringent rules which need to be adhered to by biosimilars manufacturers for evaluation and approval.

India shows promise in numbers: In India, the number of biosimilar products that have been approved has reached 70, including insulins, monoclonal antibodies, interferons, development hormones, etanercept, interferons, filgrastim, and streptokinase. Greater clarity on the general uptake of biosimilars is evident in the fact that, with an onus on therapy for common diseases like cancer, immunological disorders, and diabetes, there are more than 60 biosimilars that are currently being developed.

2) Therapy for prevalent or chronic diseases: According to the World Health Organization (WHO), globally, noncommunicable diseases (NCDs), like cancer, heart disease, diabetes and chronic lung disease result in 70 per cent of death. A significant proportion of the affected live in low- or middle-income countries, with

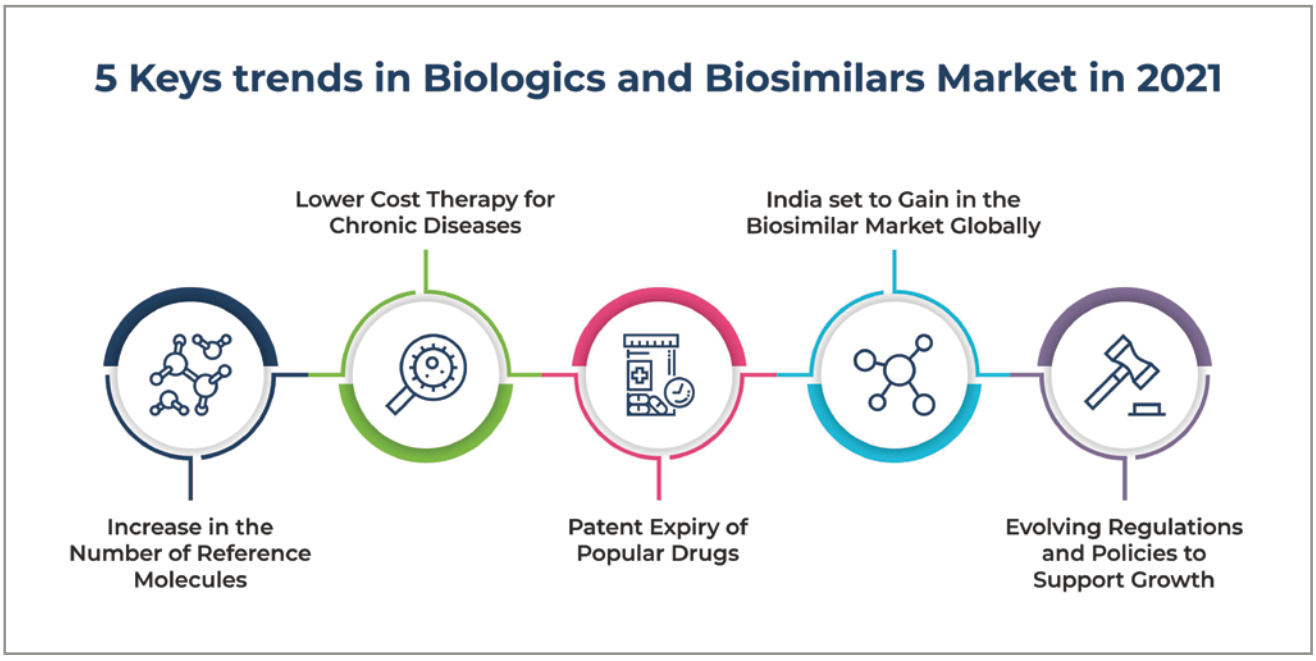

Figure 2

likely lower ability to afford expensive biologics.

In a bid to control the epidemic of NCDs from affecting the health of millions and also to prevent the health care systems from being inundated, developing suitable therapy is imperative. In India, there are nearly 60 biosimilars that are in the process of being developed, focusing on diabetes, immunological disorders and cancer. Product segments in the Indian biosimilar market include insulin, erythropoietin, interferon-alpha, G-CSF, vaccines, fibrinolytic, hormones and plasma proteins. Insulin has the biggest market share, behind which erythropoietin and GCSF have their significant shares too.

There has been renewed interest in biosimilars with the use of monoclonal antibodies as therapy for COVID-19. Biosimilars for cancer too have been rising in popularity, confirmed by projected estimates provided by Businesswire that the global oncology biosimilars market will grow at a 17 per cent CAGR between 2021-2026.

The demand for biosimilars is higher in the Indian domestic market for remedial action and for the treatment of chronic conditions like kidney ailments, rheumatoid pain, cardiovascular disease, cancer, inadequacy in developmental hormone and in haematological maladies.

Key Expertise Drives Partnerships: The lower cost of clinical trials, the deep scientific expertise and a large number of people with chronic illness have brought in renowned global pharmaceutical firms to partner with experienced clinical research organisations to test the efficacy of biosimilars and generics. A global pharmaceutical company required a well-known clinical research organisation to test the safety and efficacy of an anti-parasitic drug against COVID-19.

3) Embracing continuous innovation on patent expiry of popular drugs: There are nearly 17 drugs that will be coming off patent between 2020 and 2026, according to predictions. There has been considerable interest in developing biosimilars for leading biologics like Levemir, Humira and Avastin as their patents expired recently.

The crux in developing biosimilars that meet patient needs is to develop them using the most efficient systems so that they reach the market quickly. The key to maintaining a successful biosimilar in the market is to ensure that viable systems and innovative methods are adopted to bring multiple biosimilars into the market, for improved reach and sustainability.

4) India as a significant player in the biosimilar market globally: Biosimilars enjoy long term growth in the developed markets like Japan, Europe and the United States, as patients can afford the same. The main impediments in such markets are the acceptance from doctors, with respect to safety and efficacy, with stringency in regulatory compliance. However, the main impediment for faster adoption in emerging markets is the inability of patients to pay for the biosimilars. The expertise and resources required to manage biosimilar clinical trials results in the cost of biosimilars being just 10 per cent lower than biologicals.

The cost of the biosimilars, therefore, is a big driving factor, at least in the emerging markets. This same cost sensitivity has been the biggest factor for driving growth of the biosimilar market in India. The lower cost in conducting clinical trials in India, the significant

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number of USFDA approved manufacturing plants present out of US, and the presence of highly skilled and knowledgeable scientists provide the ideal backdrop for developing biosimilars. Cost efficient clinical trials will help in lowering costs of biosimilars. Further, the regulations put forward by EMA and WHO are the biosimilar guidelines of India.

Export to emerging markets shows a positive trend: Another vital aspect that plays an important role in establishing India as an important player is in export to other emerging markets. Cost is an important deciding factor in other emerging markets as well, which may be the driving factor for export of biosimilars from India to other emerging markets, estimated at US$51 million.

5) Evolving regulations and policies driving growth: Each country's central governing body is responsible for approvals and indications of new biologics. Every country can also specify the price, utilisation as well as the interchangeability of biologics with biosimilars. There has been a mixed level of penetration of biosimilars In Europe where the markets are developed. The improved acceptance is largely due to better awareness among the doctors and the pharmacists, incentives, policies, and the varied distribution channels. The penetration level, however, varies from one country to another, even within Europe. There is increased penetration of biosimilars in countries like Poland, Finland and Denmark, when compared with UK, Germany and France.

In the US better financing has played an important role in driving interest towards biosimilars, with Medicare advantage plans updated to determine the most cost-effective treatment measure. Till date, biosimilars are provided via the physician's office, but this is expected to change by 2023, when certain biosimilars, like for adalimumab, are expected to be available through retail pharmacy. Such changes will also help in driving growth in this sector.

Overcoming the intricacies in the production of biosimilars: The living system or genetics play a key role in the development of biosimilars, affecting the safety and efficacy. Relatively small changes in the process of drug development or in the formulation of the drug product could result in significant changes to the therapeutic molecule, when compared with generics. This has resulted in greater hesitancy by physicians to utilise the drugs unless there are conclusive studies determining efficacy. Biosimilars are more expensive to develop when compared with generics, as the process of development is complex. It involves copying of the original structure of the biologics, and the need for capabilities like immunogenicity testing. Addressing such aspects will help in ensuring improved growth.

Clinical trial efficiency to be first-to-market: As many biologicals get off patents and with the collective need to lower burden of disease, there are multiple biosimilars that are expected to be launched.

However, the early market entrants are the biosimilars that will be most successful. According to a McKinsey report, the cost for developing biosimilars is between 100 to 300$, with clinical trials resulting in half of the costs. The adoption of agile methods and the ability to scale up resources at the right time will help in better managing trials. The regulators too have been bringing in regulations to better support the existing systems. For example, the need for immunogenicity trials was waived under certain conditions by the EMA in 2015, while the FDA brought forth similar conditions in 2019. Strategic partnerships will help improve the pace of biosimilar development aided by the right technological capabilities.

Vital insights for clinical trial success: The determining factor for growth in the biosimilar industry is lowering the time to market using innovative and commercially viable models. Agile companies that can rapidly evolve to changing needs and regulations while adopting data platforms and analytics will become strategic partners. Clinical trial complexity can be better managed with the near-real-time data insights gained from artificial intelligence tools as they can be used to take proactive corrective action to resolve critical clinical trial issues at the onset. Such key inputs help in the intelligent deployment of resources which can save time and money.

There are various factors that drive the growth of the biosimilar market like the need to reduce health care costs and to reduce the burden of disease. This is a dynamic sector which has witnessed rapid growth while ensuring a great impact on the health systems. With a large set of biologicals coming off patent and with expected changes to the market and regulatory structure, there is a surge in momentum that is expected. Deep channel analytics and iterative processes will help in strengthening this growing trend, and in transforming human health.

References are available at www.pharmafocusasia.com

AUTHOR BIO

Ayaaz Hussain Khan is an authority in BA/BE domain of generic drug industry. He brings with him a rich experience of conducting over 1000 Bioavailability/Bioequivalence studies. Khan is an authority in BA/BE domain of generic drug industry. He brings with him a rich experience of conducting over 1000 Bioavailability/Bioequivalence studies. He has been a gold medallist in his academics and completed his M. Pharm in Pharmaceutics from Birla Institute of Technology & Science, Ranchi.

ARAGEN

A trusted partner

The Year 2021 is a defining milestone for Aragen in its journey so far. It marks the 20th anniversary of GVK BIO's resilient growth story and its transformation into Aragen, a trusted R&D and manufacturing partner to the global life sciences industry. With Aragen, a new brand identity has been unveiled, an inspiring purpose, and a promise to customers: Together Ahead.

One of the biggest challenges confronting pharma and biotech companies globally is the ever-increasing R&D costs to bring new drugs into the market. The regulatory approvals are also getting more stringent which stretches the overall time required for new launches. The complexity of personalised care and treatment makes this even more complex and challenging. According to a recent study by Tufts Center for the Study of Drug Development and published in the Journal of Health Economics, developing a new prescription medicine that gains marketing approval is estimated to cost drug makers US**$2.6 billion.** and on an average it takes at least **ten years** for a new medicine to complete the journey from initial discovery to the marketplace, with clinical trials alone taking six to seven years on average. The number of blockbuster drugs being launched are also diminishing. All these factors have led to a paradigm shift in the strategies

pharma companies adopt to drive their innovation for discovering new drugs.

Externalisation of R&D is one of the strategies adopted globally to drive innovation. Gone are the days of companies having extensive in-house R&D infrastructure to conduct all their research activities internally. With the growing need of being agile to drive efficiencies in the delivery of new therapeutic options, pharma companies are more open to partner with contract research organisations, universities and even with other pharma companies to leverage on the plethora of new approaches used in modern drug discovery for both small molecules and large molecules.

Contract Research Organisations (CROs) now play an increasing role in such strategic partnerships and are a key component in the discovery-development-manufacturing continuum. Aragen Life Sciences, formerly known as GVK Biosciences, is one such organisation that makes a difference to the research programs of its pharmaceutical customers globally. These companies see Aragen as their trusted R&D and manufacturing partner. Right from 'concept to commercial', Aragen helps transform ideas into solutions for better health. Over the last two years, Aragen has always adopted a partnership approach, providing solutions led by an innovation mind set and enabling technologies.

Aragen is well poised to provide this critical partnership in the concept-to-commercial continuum. Aragen recognizes that such research work is vital, urgent and impacts lives. Through its purpose, 'In every molecule is the possibility for better health' Aragen motivates every employee in the organisation to drive the success of sponsor programs, so that together it helps transform hope into health for millions of people around the world.

Aragen offers services ranging from Discovery to development to manufacturing, from chemistry to biology and across both small and large molecules. Aragen has invested in world class facilities at multiple locations to accelerate the development process. Aragen has invested in proprietary technologies and operational efficiencies to compress development timelines, offer a secure and seamless experience, and accelerate speed to market of customer products. With all of these steps, Aragen is an end-to-end, full-service partner to customers, offering scalable and flexible solutions along the biopharma value chain.

With partnerships around the globe, Aragen ensures that a culture of compliance is built across the organisation to meet global expectations. Robust quality systems across its various facilities ensure that customers can expect the same quality standards irrespective of location. While a quality leadership team with over 180 years of combined experience anchors the solutions offered, Aragen firmly believes that quality is everyone's responsibility. From senior management to the shop floor, all are equally committed to delivering zero-defect products to customers, on time, and in full. Aragen has been audited and approved by leading regulatory agencies from around the world, including the USFDA, EDQM, ANVISA, PMDA and WHO.

The 20-year journey

The humble beginning of GVK Biosciences was a realisation of a dream of a 20 year old engineering student at Purdue University, by Mr. G V Sanjay Reddy, who aspired to create a global company to provide Pharma services. During the initial years, the company was an informatics company. With every passing year, the company reached new heights. In 2002, the company got its first breakthrough when the company signed its first FTE contract. With time the company grew, and in the year 2004, started with clinical pharmacology operations.

In 2005, GVK Biosciences partnered with Wyeth Research to establish a dedicated Discovery Chemistry Research Center at Nacharam, which eventually expanded into an integrated R&D campus for discovery, development, and manufacturing solutions; and from 2006, started offering biology solutions to our clients. The expansion attracted Sequoia capital to invest in GVK Biosciences, which helped the company to deepen its roots in the pharma market and begin its first integrated discovery program in 2008. With enough funds and recognition in the market, the company took another leap and expanded its Chemistry, Biology, and Integrated Discovery services to cover more therapeutic areas in 2010. With every passing year, the brand equity of GVK Biosciences increased, and in 2012, it established itself by starting India's largest Isotope Labelling Facility in Hyderabad. The same year the company received PMDA (Japan) approval for Inogent Manufacturing Facility, and in 2013, it received approval from the USFDA, EU, and KFDA.

GVK Biosciences reached new heights as it established the Formulation Development Labs in Bengaluru, India in 2014; and inaugurated its second R&D Campus at Mallapur, Hyderabad, to commence the Discovery and Development operations in that

year. While ensuring better infrastructure for the company, it acquired Aragen Bioscience Inc., a US-based preclinical with CRO specialisation in high-value biologics services, in January 2014, which became operational at Vivarium in Morgan Hill, CA in 2016 and received its AAALAC accreditation in 2017. The acquisition strengthened the company in the global pharma market. This acquisition opened a whole new window of opportunity.

The acquisition of Aragen Biosciences attracted ChrysCapital to invest in the company, and with the fresh investment the third R&D Campus in Bengaluru in 2016 to offer the Chemistry solutions was established. With access to more capital, the company expanded its wings and was able to set up a Fine Chemical Manufacturing Plant in Hyderabad in 2017.

The years 2018 and 2019 saw expansion of the laboratory and manufacturing facilities. The company inaugurated its Analytical Development Labs at Mallapur R&D Campus and established the second manufacturing facility at Visakhapatnam. It also established Formulation Development Center in Mallapur R&D Campus in January 2019. Inogent Laboratories was merged with GVK BIO to augment the manufacturing infrastructure for APIs and intermediates.

In May 2021, Goldman Sachs invested in GVK BIO. The rebranding to Aragen Life Sciences coincided with Goldman Sachs investment. This development underscores the tremendous opportunity that lies ahead and with Goldman Sachs as investors, Aragen is well equipped to become a global leader in end-to-end solutions for drug discovery, development and manufacturing.

Caring for the employees

Aragen Lifesciences believes in offering professional services with a humane touch to both clients and its employees. In 2020, the company won Asia's best employer award from the World HRD Congress and also became a 'Great Place to Work' certified™ organisation.

The new identity embodies the brand promise, Together Ahead.

The seamless coming together of two forms and their collaborative movement, perfectly indicated in the symbol of Aragen, the "AURA," and represents Aragen's partnerships that enable infinite possibilities for better health.

The colours evoke Aragen's brand purpose, "In every molecule is the possibility for better health". Deep blue conveys the possibilities of science, and vibrant orange symbolizes life and better health. The AURA also represents its ambitious, resilient approach to serving its client.

With this renewed energy and focus on the strong employee base, Aragen Lifesciences stands strong to continue to serve its existing and new customers across the globe, with a promise to work with its partners and make them successful in the race for good health.

COMBINING SAFETY AND EFFICIENCY IN RECONSTITUTED DRUGS IN THE FAR EAST MARKETS

Can advanced dual-chamber solutions help?

The article focuses on the peculiarities of the Chinese pharmaceutical market, characterized by high growth rates. In particular, reconstituted drugs are one of the highest growth market segments, with the increasingly growing need of dedicated solutions to protect drugs from moisture, which Bormioli Pharma has addressed presenting cutting-edge, advanced solutions.

Valiant Chen, China Sales Manager, Bormioli Pharma

Latest figures show that China is the second pharmaceutical market in the world after the United States, with an overall value amounting to about 103 billion dollars in 2020. A further leap forward is expected for 2021, with estimates forecasting Chinese pharmaceutical market to outperform the global market both in the short term (+13 per cent) and in the long term with a +5.6 per cent compound annual growth rate compared to the global value of +5 per cent. Latest estimates also show that China is likely to become the first pharmaceutical market in the world in 10 years, even though the figures show that the market has still a lot of consolidation to do before surpassing the United States, that now accounts for 40.4 per cent of the total revenues worldwide, compared to 11 per cent of China.

Indeed, demand for healthcare services and products in China continues to grow, alongside the government's effort to advance the sector's development with increased investments – up to 8 per cent of the domestic GDP in 2026, compared to 6.5 per cent registered in 2020 - in related infrastructure, pharmaceutical research, medical

diagnostics as well as preventive treatment. Moreover, growing demand is coming from the national middle class, increasingly asking for quality medical services and products.

Besides the rapid growth, China has distinguished itself in the global pharmaceutical market as a country where more and more high value-added drugs and medications are produced. For example, in 2020 disease-wise Oncology has been the leading segment both by size and growth rate. Moreover, in order to save more lives, for urgent clinical cases, the government grants exemption from duties on drugs produced outside of China.

The production and consumption of such precious, high value-added APIs requires increasingly strong protection against atmospheric agents, such as light, oxygen and especially from moisture.

One of the answers that the pharma supply chain has developed is to increase APIs' protection against atmospheric agents is drug reconstitution, meaning with it the freeze-drying process of the APIs that subsequently needs to be properly mixed with a solvent before being administered or consumed by the end user.

Reconstitution segment showed a growth of +4,6 per cent in the 2018-2019 period globally, but its growth rate is definitely more significant in the Far East and in particular in China.

In China, parenteral applications retain the largest share of the national market (more than 50 per cent), driven by the growth of pre-fillable syringe, in line with the global market trend, followed by the oral applications: in this segment, oral solid still account for the largest share but, it is outperformed in terms of value growth by the reconstitution segment, that grew +24 per cent year on year in 2019.

Globally, more than 900 million units of drugs are sold every year to be reconstituted, for an overall value of about US$3 billion. Among these, orally administered drugs are the most common.

Globally, more than 900 million units of drugs are sold every year to be reconstituted, for an overall value of about US$3 billion. Among these, orally administered drugs are the most common.

But what does reconstitution mean in terms of steps to be undertaken by the end user and in terms of main risks that are related to this process? With standard reconstitution, a powdered drug is packaged in a glass or plastic bottle and the patient must add the solvent – which could be water, but also other liquids – by themselves. This represents a considerable risk, both for the safety of the drug to be administered and for the therapy adherence, since the patient could be untrained or not capable of administering it properly.

Secondly, after receiving the medicine, the patient goes home and opens the drug package. At this stage, our patient runs into two different kinds of packaging configurations: we could have a bottle with a level mark, accompanied by an instruction leaflet. This is the case of a glass or plastic bottle containing the powder, where the patient has to add water up to the level mark by following the instructions, properly mix and consume.

In this case, the patient has to check the correct quantity of solvent in the instruction leaflet, autonomously dose it using external and not controllable measuring devices and add it to the bottle.

In both cases, but especially in the latter, the risk of a human error is very significant. Indeed, an untrained patient often undervalues the importance of some critical elements for drug reconstitution, such as the quality and the correct dosage of the water used during the procedure.

A patient could use too little water, causing the powder to be mixed incorrectly or even overdose, while others could dilute the API in a larger amount of water, causing the drug to be not efficient in terms of therapy adherence. These mistakes could be both accidental or voluntary and might have a negative impact on the drug's safety and efficacy.

Involuntary mistakes are primarily caused by incorrect assumptions or fundamental misunderstandings of the product. For example, some people add more water than required because they believe this would help in making the drug last for longer, allowing them to save money.

Needless to say, it is fundamentally important to fully comply with the indications stated on the leaflet in order to reconstitute a drug properly and safely, also ensuring its efficiency. On one hand, the direct consequence of adding too much water is a disproportionate dilution of the active ingredients, resulting in a loss of effectiveness. On the other hand, not using enough water can lead to serious problems of toxicity, as the active ingredients would show a higher level of concentration than required.

Moreover, when discussing reconstitution, water quality is a critical factor, especially when access to safe drinking water is difficult. A contribution from the American University of Sharjah, in the United Arab Emirates, underlines all the possible concerns about the use of the wrong type of water while reconstituting.

First of all, it is uncommon for patients to be aware that, depending on the particular pharmaceutical process at play, different type of water ▶

is required (e.g. purified or highly purified, mineral, spring, drinking, distilled) and that the wrong type of water can negatively impact on the drug's effectiveness. Secondly, patients often reconstitute drugs with tap water, which might be not safe to consume, due to contaminants over specific limits and as a result may lead to several types of health problems.

This consideration is all the more true for those countries dealing with water pollution issues. A study conducted by the World Health Organization (WHO) shows that deaths due to unsafe water are a daily concern in many countries.

Beyond these complexities, reconstitution also creates an issue in terms of drug protection. Powder, by its very nature, is highly sensitive to moisture, and a failure to protect the powder can result in a loss of drug efficacy, particularly when it comes to particularly sensitive APIs. In particular, moisture can interact with the stability of the drug causing changes in the chemical structure of the formulation (e.g., oxidation, hydrolysis) or in the physical structure (e.g., polymorphism), or causing microbial growth.

That's why pharma packaging manufacturers are developing dedicated solutions to understand, address, and tackle the challenges presented by reconstitution, namely, complexity, dosage errors, poor safety features, and APIs protection, by designing brand new, innovative packaging solutions. Specifically, this refers to the design of dual chamber systems that allow for the reconstitution of the oral drug directly in the container, simply following a guided procedure and providing the right choice and the right amount of solvent.

A dual-chamber system is normally composed of a plastic or glass bottle pre-storing the solvent and a cap pre-storing the powder. When the packaging is closed, both the solvent and the powder are unavailable to the patient, who has no possibility of tampering with the pre-stored doses. The integrity of the packaging is ensured by a tamper-evident ring, which has to be removed to make the reconstitution possible. After removing the ring, the patient can reconstitute the drug activating the mechanism, consuming it afterwards.

At this point, the advantages resulting from such a system should be self-evident. Firstly, a dual-chamber system leaves no dosing choice to the patient, as both the powder and the solvent are pre-dosed, ensuring a precise and accurate reconstitution and avoiding any occurrence of human error. Secondly, the solvent is chosen and provided directly by the pharmaceutical company. According to research conducted by the American University of Sharjah, providing pre-packaged water with all oral formulations that require water for reconstitution is the best way to avoid any confusion and health issues. Furthermore, the pharmaceutical company is free to choose what solvent to provide inside the packaging, allowing greater flexibility in drug formulation, since it will not be tied to water as a solvent anymore.

Chamber systems also offer other remarkable benefits in terms of drug protection: unlike the process required for standard drug reconstitution, dual-chamber systems eliminate the possibility for powder loss, unless the packaging is completely destroyed. This is because the powder is safely stored and sealed inside the packaging and thus well protected from

That said, even though dual chamber systems offer a higher level of protection from external agents than standard packaging solutions, there are still particular cases in which the sensitivity of the drug or particularly extreme weather conditions require higher performance solutions. This is true in all the markets worldwide, but particularly for far east countries, given the specific climate conditions of the area, with a higher mean level of moisture when compared to other global areas. That's why further solutions have been developed to properly address this issue, ensuring enhanced moisture protection to safeguard the efficiency of APIs.

These solutions usually feature an active barrier technology, able to maximise moisture performances on a multiple scale compared to standard dual-chamber solutions available on the market.

Enhanced moisture solutions are identical to standard dual-chamber systems, featuring an active material layer in the chamber containing the API, regulating the level of moisture in the container below safety levels, enhancing performances and the product's shelf life. These products are not just concepts, they're already available for industrial production in different formats featuring different moisture absorption performances.

Oral drugs, such as antibiotics, syrups or other high-value treatments, represent an important segment of the global pharma industry. However, the standard reconstitution process still seems to be too complex, potentially unsafe or not completely safe, being subject to accidental or voluntary human errors. Packaging manufacturers and pharmaceutical companies can work together in order to develop effective solutions to make reconstitution more precise, safer and easier. Amongst the potential solutions, innovative dual-chamber systems appear to be a strong alternative to standard packaging methods. In particular, this has been demonstrated in our outreach to the Far East and Chinese market, collecting very positive feedback and in-depth technical requests that represent a good parameter of the market interest in such solutions. ■

AUTHOR BIO

With more than a decade experience in pharma packaging in China, Valiant built his career path in global pharmaceutical packaging companies, covering roles of increasing responsibilities, and leading relevant business development projects. He is now in charge of Bormioli Pharma's business development in China.

ClinPro RESEARCH EMPOWERING SOLUTIONS

Your CRO partner for effective Drug Development in India

Can you provide an overview of ClinPro Research?

ClinPro Research, established in Feb 2020 is an ISO 9001:2015 certified, full-service capability CRO, headquartered in Mumbai; India. We cater to the clinical requirements of both domestic and international pharmaceutical companies, biotech companies, medical device companies, ayurvedic and nutraceutical companies with our exceptional suite of solutions, which includes end-to-end project management and functional standalone services as well.

We provide cost effective options to custom-curate the requirements for projects to our prospective and existing clientele.

What is the current state of clinical research in India?

The clinical research industry is a significant parallel of the health care sector. The covid-19 pandemic also brought about a wave of awareness on clinical trials and its relevance in the drug development process. India has accounted for 8.3 per cent share of global clinical trials activity in 2020, and this figure is only going to upsurge with the numerous opportunities this country provides, in terms of skilled medical and paramedical professionals, large and diverse genetic pool of treatment-naive population, lower operational cost, multidisciplinary well-equipped sites and much more!

Furthermore, the regulatory landscape in India has evolved with the new NDCT (New Drugs and Clinical Trials) Rule 2019, to advantageously place India as one of the preferred hubs for conducting clinical trials.

Can you elaborate more on the company's capabilities and services that you provide?

ClinPro Research has accomplished several projects across various domains like Clinical Data Management, End to End Clinical Trial Conduct and Management, Site auditing, Medical Writing, eTMF, Clinical Analytics etc. Our leadership team has over 15 years of robust clinical trial experience across various submissions viz; India, APAC, UK, EU, LATAM and the US. We have core expertise across a gamut of therapeutic indications. Our strong technical acumen enables us to conduct various types of trials like phased trials, patient-based PK studies and BA/BE trials with an appreciative turnaround time and exceptional quality.

Our extended service arm includes medical coding, safety and pharmacovigilance, clinical trial supplies management, biostatistics, strategic consulting etc.

ClinPro Research is now one of the emerging service providers in the clinical trials space. Can you share an insight into the market drivers and the needs that ClinPro is responding to?

Patient enrollment and retention is one of the crucial aspects along with efficient study start up and regulatory barriers in any clinical trial.

Our recruitment specialists assist the PI in providing insights to upkeep with the recruitment

demand. They work closely with the investigator and site staff to identify recruitment challenges (if any) and come up with appropriate resolutions. Our diligent team of CRCs works towards subject retention by meticulously tracking subject visits, enquiring about subject safety and well-being, and being available for their assistance/queries etc. With this, we ensure good subject retention rate and minimal/negligible dropouts.

We expedite study start up process through our pre-assessed network of investigative sites. Each site is evaluated for infrastructure, qualified professionals, potential subject pool, ethics committee availability & compliance etc. prior to enrolling in our network. These factors play pivotal role in hassle free start up and conduct.

Our regulatory advisors are well versed with the Indian regulatory guidelines and have considerable experience in seeking approvals and addressing regulatory queries with excellent turnaround time Thus, enabling us to provide exceptional regulatory compliance for our projects.

TARANNUM KASHMIRI is a seasoned clinical research leader with over 15 years of extensive experience in managing domestic as well as global clinical trials, across a wide spectrum of therapeutic indications. She has strong technical acumen across Clinical Analytics, GCP Auditing, Clinical Data Management and Clinical Operations. Innovation is her inbuilt forte; she has accomplished several cost-effective lean projects during her professional tenure.

AUTHOR BIO

How well prepared is ClinPro Research to support large scale clinical trials?

We have an elaborate network of multispecialty clinical sites; including hospitals, research institutes and laboratories across various urban and suburban locations in the country to open doors to a diverse subject pool. Our team of experienced clinical professionals are adept in managing large scale clinical trials with great ease. We are competent in various e-clinical systems like EDC, CTMS, eTMF, IVRS etc. which aid in seamless execution of large-scale trials. Additionally, comprehensive trials involve smooth coordination and rapport building with a host of third-party vendors. We, at ClinPro are cognizant of this, and have built excellent collaborations and seamless working relations with our vendors, who have been meticulously selected via our robust vendor evaluation and selection process. This empowers us to meet our goal of providing proactive, prompt and proficient services to our customers.

AI has become a focus area for drug R&D. How has ClinPro been responding to this market trend?

As AI and digitalisation have also entered the medical world with a compelling intention to stay and are also the need of the hour, our team of technologically advanced clinical researchers are adopting newer technologies like decentralised trials, virtual and hybrid trials.

Electronic data capture (EDC), Clinical trial management systems (CTMS), electronic patient reported outcome(ePRO), digital wearables are being integrated in data collection, site operations and management to offer an enhanced engagement for the participants and a logistically and economically advantageous experience for us and the sponsors.

How does ClinPro handle challenges like recruitment, poor site performance/response, quality and compliance issues, etc.?

These challenges are the part and parcel for every functional business.

The credit for always being on the forefront for observing and resolving these short comings has to go to our skilled team for their ever so positive approach towards our goals, extensive experience in the industry and zeal to bring about a positive

change in the healthcare industry. We have a robust Quality Management System with well-defined SOPs, work instructions and policies. We have a strong CAPA mechanism to ensure that gaps are addressed on time and not repeated. We also practice predictive analysis to identify potential risks and proactively take preventive measures to evade their occurrence or minimise the impact. In addition to the above, at site level, our QA team conducts in-house site audits to ensure the study is progressing as intended and with the expected quality and compliance.

What is your Unique Selling Proposition (USP) and how would you add value being an emerging CRO?

Our USP is that we provide client-oriented tailor-made solutions, specific to each customer. We are agile and can adapt to a customised approach best fit for the project and the client. Customer delight is our topmost priority, and we go that extra mile to provide cost-effective and quality services with excellent turnaround time. Our team's varied and extensive experience is another asset which keeps us at the forefront. Another unique practice that we follow is that we adopt lean principles on our assignments. We constantly review our processes to eliminate redundant tasks/procedures which proves to be cost effective for our clients and acts as a catalyst for us in meeting/expediting the turnaround time with optimum results.

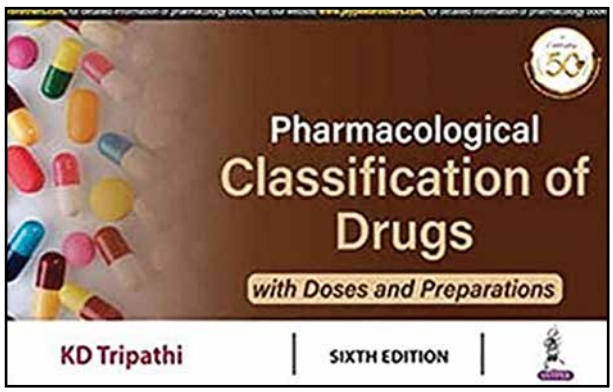
What are the strategic objectives you envision ClinPro to achieve, over the next couple of years?

We would like to work harder and keep ourselves apprised of the latest nuances in the clinical research field and incorporate them within our services to provide a quality experience to our clients throughout the project and even after. We would like to cater to a wider clientele and welcome the opportunity to provide unmatched services to them.

Making healthcare affordable and accessible to the masses by playing a humble part in accelerating the drug development process is our core goal and we desire to keep working towards it with honesty and integrity.

We look forward to overcoming the roadblocks in this journey and stride past them with our improved performance, teamwork, innovative ideas, customer focus and ineffable passion for clinical research.

BOOKS



Pharmacological Classification of Drugs By [sixth edition]

Author:	K D Tripathi
Date of Publishing:	2020
No of Pages:	259

Description: Provides an invaluable aid for remembering drug names, identifying the class and subclass to which they belong, and provides easy access to core prescribing information. You can use this book for basic knowledge also and this book pharmacological classification of drugs by kd tripathi is a well known book available in exams.

PRACTICE MAKES PERFECT

Adopting industry best practice requires three crit

Many pharma industry executives think that success can be found in 'best practice' – imitating the behaviour of successful companies. Many consultancy companies make good business selling the idea of 'best practice' in business models, strategy or organisational structure. Yet the concept has no evidence base and runs counter to the ide that every firm is different and faces a differen market situation.

In this article, I'll describe why the idea of 'best practice' is a myth and why the mantra 'what works is what fits' is the only one that acknowledges the realities of your firm's uniqueness and your market's characteristics Using examples in from business model design, strategic planning processes and organisational structuring, it will explain how to address these challenges in a firm-specific way, avoiding the consultants' cookie cutter.

Brian Smith, Principal Advisor, PragMedic

THE THREE LESSONS OF BEST PRACTICE ADOPTION

- **1. SAY WHAT YOU MEAN:** If the best practice you want to emulate contains fashionable jargon or terms with imprecise meaning, define those terms tightly and make sure everyone knows what they mean.
- **2. RESPECT DIFFERENCES:** If the best practice you want to emulate comes from another firm, ensure you understand the differences between the two situations and ask whether that affects the transferability of the practice.
- **3. WHAT WORKS IS WHAT FITS:** If the best practice you want to emulate requires significant change in your current practices, ask how that will fit with your external market and internal culture and try to ensure two-way fit.

Every life science company is eager to find and absorb industry best practices — and for good reason. In a business environment that is changing quickly, no firm can afford to be left behind and relying on internal experience and lessons is too slow. It is essential to imitate as well as to innovate. But, as any experienced business leader will tell you, assimilating the processes and methods of other firms, even apparently successful ones, is fraught with difficulty. The devil is in the detail of the differences between the exemplar and the emulator, and a transplant of best practice can often be rejected.

In my work, which focuses on how life science firms evolve in response to changes in their technological and sociological environment, the reasons for this failure resolve into three critically important lessons. In this article, I'll illustrate them with examples, taken from my research, of three common attempts at embracing best practice.

Say exactly what you mean

Consider the case of a research-driven, primary care pharmaceutical company trying to adopt a new business model. Driven by intense competitive pressures on its current model, the firm looks around and sees a firm in a related market that is being successful with a service-led business model that creates most of its value – and its competitive advantage – 'beyond the pill'. Pushed by growth targets and pulled by envy of the exemplar company, our would-be emulator tries to copy the business model of its more successful peer.

But it fails. For reasons that it does not fully understand, its attempts at value beyond the pill don't seem to impress its customers. Extra costs, associated with added-value services, do not achieve their intended return on investment. Competitive pressure intensifies and results do not improve.

There are many possible explanations for this failure, which has been repeated by a number of life science companies, but the obvious ones – incompetence or under-investment – are not usually supported by the facts. In this case, the emulator saw the visible aspects of the exemplar firm's model – high levels of service – and imitated those very well.

Instead, it was matter of semantics. Our emulator's leaders had to narrow a definition of the term 'business model'. This modish phrase is actually an umbrella term that includes strategy, structure, monetisation methods and other things. But by conflating the expression with only a narrow part of the value proposition, the emulator's leaders forgot to pay attention to the other necessary parts of the model. So, they failed to target those market segments that valued – that is, would pay for – service, they failed to structure themselves for service delivery and they neglected to find a way to create revenue from service. All because of the way they defined 'business model'.

This failure, and others like it, would have been avoided if someone on the leadership team had asked a simple question: What exactly do we mean when we say 'business model' and how is it different from other, related ideas like strategy? Amongst academics, who are taught and paid to think critically, this issue is known as'construct definition'. In plain English, it translates to a simple lesson that is critical to the successful adoption of best practice: When you use a term, say exactly what you mean.

Respect differences

For our second example, consider an in-vitro diagnostics company that is classed as 'small to medium' but which, thanks to innovative and patented technology, is growing very rapidly. Faced with managing a larger business and flush with cash flow, the flourishing firm decides to invest in its strategic marketing capabilities. It picks one consultancy from the long line queuing up to take its money and commissions a 'Marketing Excellence' programme.

It is expensive but the consultancy can claim, honestly, that its strategic marketing planning process is based on that of one of the most successful large firms in the same industry. They truly do offer 'best practice' in strategic marketing.

Again, the transplant fails. The new process is much more laborious than the one it has replaced. It absorbs a lot of time and effort but does not produce a significantly different output. True, the marketing department now produces some splendidly professional looking presentations. And there is a lot of new jargon, which sounds like that heard in the corridors of multinationals. But there is no real-world impact and, to a significant degree, the new jargon and process creates division between marketing and their colleagues in medical affairs, sales and other departments.

It is not always easy to explain the expensive failure of a process that was so successful elsewhere. Again, the obvious explanations can be ruled out; the importation had senior leadership endorsement, was supported by a very generous investment of time and money and the consultancy was world famous. Yet the project was a failure – expensive in both direct and opportunity costs – despite being best practice imported from the industry's leading player.

But the failure can be explained. The strategic marketing planning process miscarried not despite its origins in a successful big company but because of those origins. By assuming that what works in one diagnostic company would work in another, the emulator's leader ignored the reality that every firm is different from every other. In this case, the main difference lay in the nature of the markets that the strategic marketing planning process had to address. The large, exemplar firm operated across several related but very different sub-markets within the in-vitro diagnostics sector. And each of those markets, being quite mature, had segmented into numerous different customer types. As a consequence, the exemplar firm needed

> What life science firm, faced with rapid change, can afford not to borrow good ideas from elsewhere? But best practice is only valuable if it is chosen well and assimilated thoroughly.

and had developed a very complex and sophisticated strategic marketing planning process that exactly matched its needs. By contrast, our emulator firm was tightly focused on one sub-market of the in vitro diagnostics sector and that market, being relatively immature, was relatively homogenous and unsegmented. Although the complex, imported process could be applied to this simpler situation, it was not needed. It was, as one of the emulator's leaders said to me, akin to buying a Ferrari to do the school run. It looked good but it was extravagant and unnecessary.

This failure to adopt best practice would have been avoided if the leadership team of the emulators had applied a critical test that is beaten into young academics. Is the success in one setting (in this case, the large, complex market of the exemplar) likely to happen in another setting (in this case, the simpler market of the emulator)? This piece of critical thinking – the test for external validity as my academic colleagues call it – would have made the emulator pause before signing a large cheque for the consultants. They would have reduced the risk of transplant rejection by looking for an exemplar from a smaller, simpler market. This provides a second lesson for those who would adopt best practice: When you import ideas from one context to another, respect the differences.

What works is what fits

For our third example, consider a speciality pharmaceutical company that wants to become 'patient-centric'. The firm can cite many rational reasons for this. Being customer-oriented has long been the mantra of every marketing professor. And the concept of customer-centricity fits well with the mission statements that hang on the wall in the firm's reception area. But, if they are honest with themselves, the firm's leaders are also influenced by the fashion for patient-centricity that is sweeping the industry. After all, as the emulating Chief Marketing Officer said to me, what are we centred on if not the patient?

In this case, failure was slower and less visible but none the less it became clear both externally and internally. In the market, relationships with important Key Opinion Leaders eroded. At the same time, payers complained that the firm's commercial leaders were not listening to their needs. And it was noticeable that the firm's value proposition to the market, formerly crystal-clear, became blurred. Internally, communications within brand teams between marketing and some of the more technical functions, such as market access and regulatory affairs, became strained. Team cohesion eroded.

Because the concept of patient-centricity seems so intuitively right, it was hard to understand why it was failing in practice. Obviously, the patients' needs are important and obviously they should drive what the company does. And the company had manifested the concept in its goals, metrics, strategy and tactics. How could that be wrong?

This slow, imperceptible failure was not understood until a new leader arrived with fresh eyes and an interesting turn of phrase. 'What works is what fits' she would say, in recognition that every initiative, process or strategy had

to align with both the market's needs and the firm's own culture. In this case, patient centricity was not aligned to either. The patient was important but, in a market where they had little influence, success depended mostly on meeting the needs of the specialist physicians and the payers who had to justify the costs of the firm's effective but costly products. Internally, the company had a culture, embedded over decades, of scientific prowess and excellence in understanding the disease and its treatment. That culture struggled to change priorities to include relatively nebulous, unscientific ideas such as the patient experience and non-clinical benefits. Patient-centricity did work in other contexts but, in this firms, was a doubly-misaligned to both the culture and the market.

This pernicious and slow failure would have been avoided had the new leader, with her characteristic chant, had arrived earlier. Rather than blindly adopting the new, fashionable idea of patient-centricity, the emulator firm might then have asked how it fit with the firm's external market and internal culture. The influential academics Burrell and Morgan called this two-way fit idea 'bicongruence' and saw it as essential to any business initiative. Translated from the academic, bicongruence is expressed as our third lesson of best practice adoption: What works is what fits.

Three lessons to learn

As these real, but disguised, examples show, the idea of adopting best practice is a good one. What life science firm, faced with rapid change, can afford not to borrow good ideas from elsewhere? But best practice is only valuable if it is chosen well and assimilated thoroughly. Firms who are good at this have learned three critical lessons (see box 1) that, unsurprisingly, have been observed by business academics like me and given fancy names. But whether you choose to use academic argot or plain language, these are critical lessons for leaders in the life sciences. ■

AUTHOR BIO

Brian D Smith is a world-recognised authority on the evolution of the life sciences industry. He welcomes comments and questions at brian.smith@pragmedic.com

Novo Nordisk Pharmatech A/S

Ensuring Quality Assurance

Enabling better medicines by using cGMP Quats as excipients in topical, nasal or ophthalmic applications, Ulla Grove Krogsgaard Thomsen talks about product quality and how to ensure a superior quality control.

Ulla Grove Krogsgaard Thomsen
Managing Director & CEO, Novo Nordisk Pharmatech A/S

Can you explain the role of formal documentation in quality assurance?

In the highly competitive pharma market, quality has become the key differentiator for almost all products and services. Quality control is essential for building a successful business that delivers products that meet or exceed customers' expectations. It also forms the basis of an efficient business that minimises waste and operates at high productivity levels.

With this in mind, we are continuously working on improving our product quality.

Standards have become a symbol for products and service quality, and the majority of customers are now only buying a product or service from a certified manufacturer. Therefore, Novo Nordisk Pharmatech is regularly audited by major and minor pharmaceutical companies and inspected by the Danish Medicine Agency as we are a supplier of EU cGMP manufactured (ICH Q7) quaternary ammonium compounds. We are also complying with and certified according to standards such as ISO 9001 and ISO 14001.

We understand that quality control is a product-oriented process, whereas quality assurance is a process-oriented practice. When it comes to quality control, we make sure that the end product meets the quality requirements, and via quality assurance, we make sure that the process of manufacturing the product does adhere to standards. Therefore, quality assurance can be identified as a proactive process, while quality control can be perceived as a reactive process.

Besides quality monitoring, what else can you suggest to ensure the quality of materials and products?

We always strive to develop and provide high-quality products and services that emphasise the health and safety of our consumers and customers.

With more than 70 years of experience, we want to ensure that the products reaching our customers meet the highest levels of quality and safety. Therefore, we must ▶

incorporate the highest standards across the supply chain – from raw materials to manufacturing, packaging and distribution.

Controlling quality by utilising product inspections throughout the production cycle reduces sourcing risks and cost and ensures high quality.

> We do not compromise on quality, which is why our pharmaceutical grade Quats, recombinant Insulin for technical use and enzymes are manufactured follow the highest standards; The cGMP Guide ICH Q7 for API.

But a good plan is only as good as its foundation, so comprehensive and detailed product specifications are critical to success. An essential component of product quality is knowing your product and having good process knowledge. In addition, it requires detailed product specifications that identify precisely how the item or items should turn out.

Can you explain the benefits of using cGMP Quats as excipients in topical, nasal and ophthalmic applications?

An innovative synthesis process makes Novo Nordisk Pharmatech a leading supplier of cGMP Quaternary Ammonium Compounds (Quats) for a wide range of applications. High purity levels for Benzalkonium Chloride, Cetrimide and Cetrimonium Bromide (CTAB) make them particularly suited for pharmaceutical applications. They act either as preservatives or active ingredi-

ents in many ophthalmic, nasal, oral and topical drugs and in various solutions, ointments and creams. They can also be used as lysing or precipitating agents in vaccine production.

Our Quats are effective at all pH levels. However, their effectiveness increases when the pH increases. The higher the pH, the lower the concentration needed to obtain an antimicrobial effect. As opposed to bacteriostatic/fungistatic compounds, which only prevent micro-organisms from dividing (growing), Quats are bactericidal/fungicidal, meaning they will kill micro-organisms whether they are in a growth phase or not.

Our Benzalkonium Chloride has been tested against several relevant microbial strains and has shown to be effective against a wide range of micro-organisms at low concentrations.

Our production and process know-how allows us to offer Quats with an entirely well-defined alkyl chain length distribution, whether it is with our standard chain length or with customised chain length distributions. Our customers also receive a regulatory package, which will help the approval process of their product when using Benzalkonium Chloride.

How does Novo Nordisk Pharmatech stay on top of fast-paced technological changes?

We have a clear vision and strategy to develop the business over the coming years. Our customers see us as the market leader and innovator in the industry, and to meet the future challenges requires vision and direction. We will continue to match and outperform the market as needed.

How does Novo Nordisk Pharmatech ensure that industry standards are met, if not exceeded?

We do not compromise on quality, which is why our pharmaceutical grade Quats, recombinant Insulin for technical use and enzymes are manufactured following the highest standards; The cGMP Guide ICH Q7 for Active Pharmaceutical Ingredients. Furthermore, we analyse according to relevant multicompendial pharmacopoeias (e.g. Ph.Eur., USP/NF, JP, BP and ChP). Both Novo Nordisk Pharmatech and Novo Nordisk, our parent company and supplier of our Insulin Human AF, are regularly audited by major and minor pharmaceutical companies, the Danish Medicine Agency, and the FDA. Our products are used in many different pharmaceutical and biopharmaceutical drug products approved by regulatory bodies worldwide. For some products, we also supply a complete regulatory package.

> **Our definition of success has not changed; we still want to maintain our position as the market leader in the industry.**

What are the biggest challenges currently facing the pharmaceutical/healthcare markets; how does Novo Nordisk Pharmatech approach them?

We see significant legislative and regulatory changes coming to the industry. In addition, there is an increase in regulatory expectations from Innovators and Generics to be able to guarantee patient safety due to today's expanding global market.

We aim to be the best supplier of pharmaceutical ingredients by providing excellence at every step of the supply chain. It begins with a consistently high quality of our products, ensuring continuous availability and a secure global supply chain, and ends with extensive regulatory documentation living up to the highest available standards.

By delivering excellence at every step, we help our customers do the same – whether they're developing a cure for cancer or a new ophthalmic. We deliver a proven record of product purity, reliability and consistency and can help tailor products to enable future therapies.

How has your definition of success changed over the years? Where do you think the industry is headed?

Our definition of success has not changed; we still want to maintain our position as the market leader and innovator in the industry.

The pharmaceutical industry quality functions are continuously trying to keep up with the rising demands of regulators. In addition, the increasing relevance of global markets (beyond the United States, European Union, and Japan) is adding the complexity of multiple quality standards and regulatory regimes. Compliance, the robustness of processes, and efficiency will, therefore, need to be squared in one equation. That is why we need to be at the very forefront of meeting the industry standards and ensuring patient safety. ■

AUTHOR BIO

Ulla Grove Krogsgaard Thomsen started as a Researcher in Novo Nordisk A/S in 1997. In 2003 she became the Vice President of the Protein Engineering Research area. In 2009 she started as Corporate Vice President heading up the Biopharmaceutical API production area in Novo Nordisk A/S. Finally, in 2021 she became the Managing Director & CEO at Novo Nordisk Pharmatech A/S.

A New Strategy to Predict Neurovirulence Risk Associated with Covid-19 Vaccines

For seamless adoption

SARS-COV-2 is a continually evolving threat. Containing it requires that we reimagine drug and vaccine development and testing strategies. The COVID-19 vaccine is an achievement, given its speed of development, and given the circumstances, but there is room for improvement still. Questionable legacy tests for safety, such as the Monkey Neurovirulence Test are not fool-proof, as the neural disorder in some recipients of a COVID-19 vaccine attests. It is a good time to leverage the impetus for change that the pandemic has engendered to improving technique.

We propose here an artificial-intelligence powered, stem-cell platform-based, bench-top workflow and strategy for reliably predicting the neurovirulence of vaccines, quantifying risks and preventing adverse events. It is fast, accurate, precise, and modular; it can be seamlessly integrated into any existing workflows, is amenable to automation and standardisation, and is cruelty-free. We believe this strategy marks an inflection point in vaccine safety testing scheme for safe immunisation programs.

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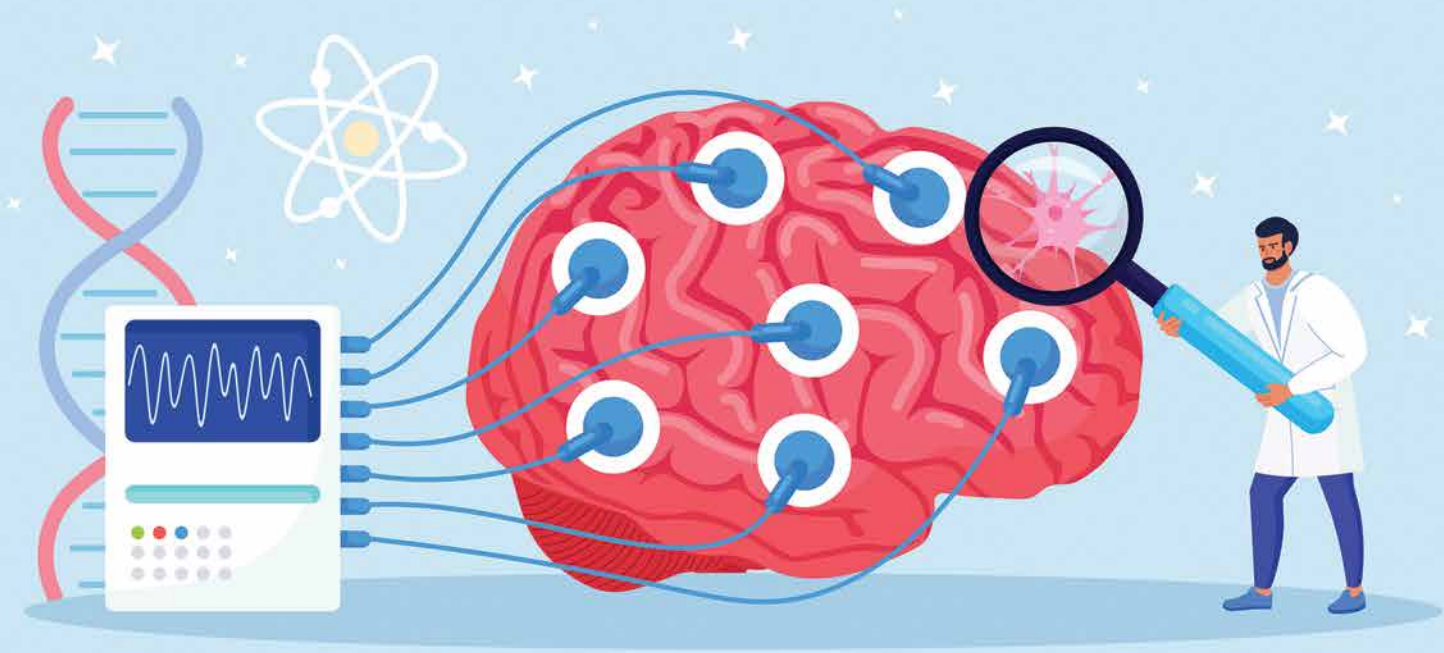
Saikat Biswas, Global Head – Life Sciences, iCORE, Wipro Limited

Lakshman Varanasi, Academic Consultant Transcell Oncologics
Assistant Professor of Biological Sciences, Krea University

Vaccines derived from live attenuated viruses are required by law to be subject to tests for residual neurovirulence before use. This applies to vaccines which comprise whole neurotropic viruses, vaccines which have a neurotropic component, or those which have been passaged in neural tissue. The vaccine's viruses may occasion a neurological adverse event, ranging from muscular weakness to paralysis and death. The Guillain Barre syndrome, caused by Johnson & Johnson's single-shot vaccine- and promptly reported- is the most recent instance of vaccine neurovirulence. The Adverse Events Following Immunisation (AEFI) program in India and the US Vaccine Adverse Event Reporting System surveil vaccine use for safety concerns such as these. More than 60 neurotropic viruses have been introduced into the market since 2001 and the check for neurovirulence is imperative.

The test for neurovirulence has conventionally been done by the inoculation of the candidate virus into the brain or spinal cord of monkeys of the Macaca or Cercopithecus genera and observation of the animals for symptoms of neural damage over a 17 to 22



days period; brain and spinal cord tissue is also examined for viral lesions. The Monkey Neurovirulence Test, or MNVT as it is called, has been the neurovirulence test of choice for the poliomyelitis, measles, mumps, rubella, varicella, influenza, and yellow-fever viruses, and more recently for the COVID vaccines, the rationale for the model being the phylogenetic distance between humans and non-human primates. For want of a better model, the vaccine industry has persisted with the MNVT despite the lack of demonstrable relevance to the human system.

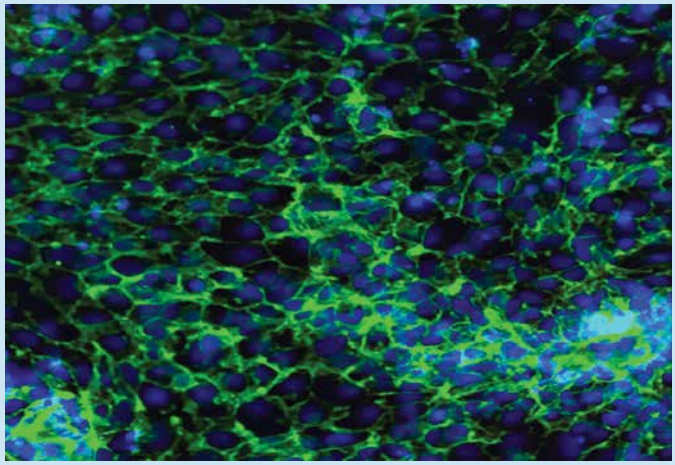
In response to ethical objections to animal use in the lab, attempts have been made to develop in vitro or small animal models for neurovirulence testing, but the transition has been sluggish for various reasons. The transgenic mouse has been approved for poliomyelitis virus (OPV), as has the PCR based MAPREC test for the same vaccine. Next Generation Sequencing (NGS) has been proposed as an alternative to the MAPREC. More recently, induced pluripotent stem-cell (iPSCs) derived cell-culture assays have been considered for various virus-host interaction studies, and have found their way into in vitro safety testing platforms. We daresay these will comprise the test reagent of choice in the near future.

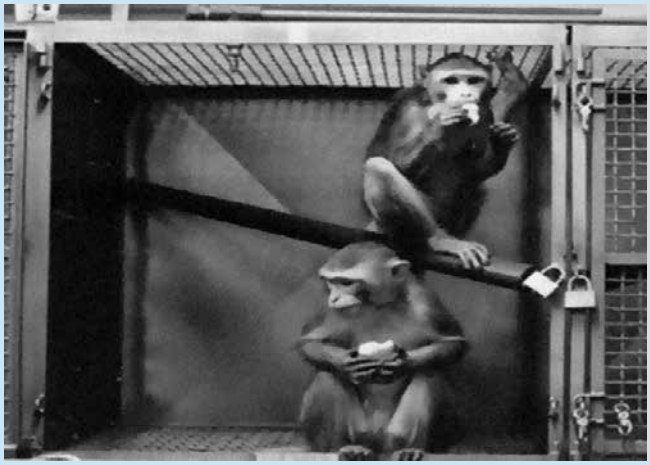
NeuroSAFE is a new strategy and method/ system for evaluating/ predicting the neurovirulence of a live attenuated viral vaccine, or of any other vaccine or drug candidate, and ascertaining its safety for human use. The procedure is straightforward and uses reagents that are readily available utilising a human biological discard sourced and derived iPSC in vitro system, treating with different concentrations of the potentially neurovirulent candidate vaccine or drug in one or more multi-well plates, incubated for different periods of time. Cells are subsequently examined under a microscope and photographed, and the micrographs are contrasted with those of control cells. This iPSC in vitro system is established to have genes participating in pluripotency feature with an ability to differentiate to all the three lineages of embryo development including that of neuronal lineage – Precisely the reason behind the choice of iPSC in vitro system as real time platform (human surrogate) complementing the in-silico tools (artificial intelligence and machine learning).

The system is 'taught', using various training cohorts, to recognise test cells whose gross cellular morphology differs from the control upon treatment with/ when administered the candidate vaccine. It derives its cognitive intelligence from the training data, and can discern healthy cells from sick ones, and cells from artifacts; it can also assess the magnitude/ degree of the damage in the treated cells and class them as Cells-in-shock, Infiltrated, Apoptotic, Necrotic, and Dead read outs. The primary outcome is cell death, and the overall effect of the vaccine candidate is represented by a prediction score backed by the event related genomics barcoded predicting the Neurovirulence risk.

The pertinent AI system follows FDA guidelines and is designed for best-in-class accuracy. The solution can analyse the phenotype and the corresponding genotype readouts. Phenotype predictive algorithms are based on semantic segmentation and advanced computer vision. Options are available for deriving insights from single cell gene expression. Algorithm is exposed to sufficient set of data points and their labes, and the performance is analysed to ensure accuracy. AI can see things that the human ▶

Monkey neuro virulence test

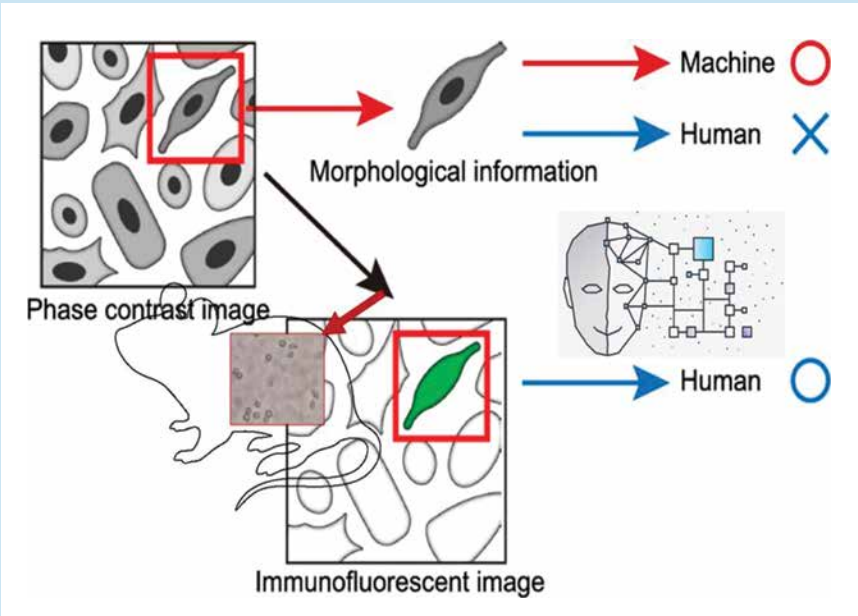




eye can't, which helps in reducing false negatives. A trustworthy AI framework is utilised to evaluate the data, algorithm and the predictions for bias and explainability. The data is from multiple population samples, the algorithm undergoes conformity assessment for explainability and results are compared with those derived by human experts for a given dataset. This AI based workbench generalises well beyond the training set with the capability to monitor any drift and also has interfaces to integrate additional data from different sources. The user can enjoy the best-in-class prediction accuracy, which is evaluated using confusion matrix in terms of sensitivity, specificity and precision. Another important aspect of the solution in in discussion is scalability and seamless integration into the existing vaccine production workflow classifying it as a workbench method.

The complimentary NeuroSAFE-PV detects any untoward effect at the physiological level and enables pharmacovigilance post vaccine licensure. It works like this: This system is trained on physiological symptoms of neurovirulence collated from the clinical literature and designed into/ embedded in a client vaccine company's website. The vaccine recipient or attending medic reports adverse events on the company's website using a form or chat bot. This data is analysed by the platform to stratify the recipient, i.e. place into one of several grades of risk, and the pharmacovigilance officer notified by email subsequently on the signals detected in their repository.

NeuroSAFE is designed for easy implementation in a company's QC existing workflow/ standard operating protocols, requires reagents and hardware that are easily available, does not require additional training, and is inexpensive; these are not trivial benefits as protocol changes and training cost time, money, and effort. It obviates the ethical dilemma, as it does not require experimental animals or biopsies, and is in keeping with the 3Rs of animal testing. It reduces testing time from 28 days to a few hours and enables massive throughput; such agility is conducive to COVID-19 pandemic like situations, where the pathogen evolves faster than vaccines can be developed. Because the test is based on human healthy stem cells, the test result is, in principle, expected to be more relevant to the human physiology mimicking the immunised population, than is the MNVT; at the very least vaccine candidates that fail the NeuroSAFE test can be discontinued. The test can be tailored to any racially distinct population that the vaccine is intended for, or to check for any genetic basis/susceptibility for neurovirulence while being agnostic to mutations occurring in the pathogen. The test format will possibly also find application for other vaccine related toxicities such as



renal-toxicity, hepato-toxicity, and so on. Furthermore, the quantitative nature of the test reduces the technical variability between measurements.

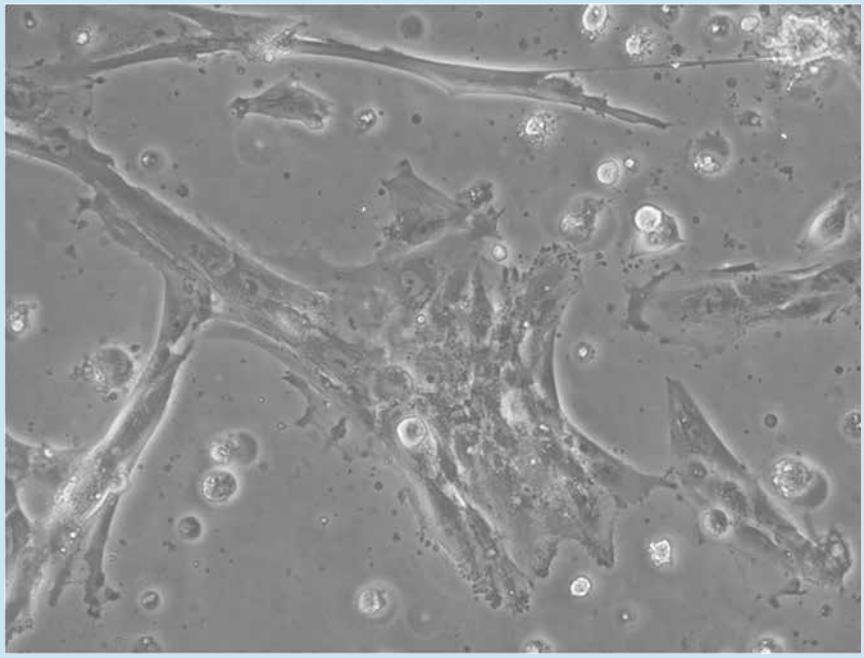
Importantly, it is, to our knowledge, the first time that neurovirulent potential has been quantified on iPSC system (human surrogate) for the purpose of safety testing and risk analysis. The quantitative nature of the test is perceived to reduce the technical variability between measurements and opens the door to comparison of neurovirulence measurements from other formats, such as the MNVT.

There are questions though. For one, can an in vitro system like NeuroSAFE simulate better than the non-human primate the whole-body physiology of the human, with its functional immune and nervous system? This question bears extensive experimentation; the stem-cell based assay is obviously unlike the whole-body assay, but experience from other stem-cell based in vitro testing platforms have indicated that the cellular nature of the primary reagent is not a disqualification; results from such platforms are highly relevant, and predictive of the human system when iPSC system is the real time platform choice. Research also supports the translational potential of stem cells in the study of viral infections of the CNS, although reports of the effect of live attenuated viral vaccines on this model are lacking. Results from Neurosafe-type platforms are relevant, and predictive of the human system.

The proposed novel strategy is proofed against the future. As research on virus-host interactions advances and our knowledge of them becomes more granular, newer cellular and molecular endpoints for neurovirulence will be revealed, and can be incorporated in NeuroSAFE; iPSC system can be engineered to suit the tests' purpose, and NeuroSAFE's AI powered algorithm made progressively more intelligent through input from orthogonal testing formats. ■

References are available at www.pharmafocusasia.com

Tested for neurovirulence



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Predicting Quality Risks in Pharmaceutical Production

Incorporating internal and external signals

Quality risk management plays a key role within pharmaceutical production. Being able to predict quality issues and proactively maintain regulatory compliance prevents production downtimes and disruptions of medicine supply. This article outlines a comprehensive approach how to address and predict quality risks by utilising internal and external metrics.

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Ritz Marten, Institute of Technology Management
Friedli Thomas, Director, Institute of Technology Management

Proactive quality risk management provides numerous advantages to pharmaceutical companies, such as less rejected batches, and less drug shortages (FDA, 2021a). It helps to minimise and predict potential negative impact on patients caused by quality issues, and it encourages manufacturers to adopt suitable continuous improvement programs. The combination of quality standards and good manufacturing practices constitutes the guidance for industry ICH Q10 Pharmaceutical Quality System (PQS), which sets the basis to establish a holistic quality system and a continual improvement of product quality (ICH, 2008). Academics addressed quality risks in pharmaceutical production with a special focus on two subject areas: analysing the methods and tools for managing and reducing quality risks in the processes (Altamuro et al., 2017; Ball et al., 2017; Seiss, 2018) and identifying context factors influencing quality risk at the plant level (Gray et al., 2015a; Gray et al., 2015b; Gray et al. 2016).

However, both industry and academia are lacking a comprehensive approach to measure, operationalise or quantify quality risk. Regulatory programs, such as the quality metrics initiative showed that the effectiveness of a PQS cannot be assessed based on a few single key performance indicators (KPI) (Friedli et al., 2019). Similarly, a quality risk assessment

should consider the site's characteristics, operational data sources, and external data sources (ICH, 2019). Moreover, the Covid-19 pandemic has shown that also regulatory authorities might be forced to perform remote inspections and prioritise oversight activities (FDA, 2021b). These newly raised regulatory efforts to better evaluate quality metrics and risk underline the importance of predicting instead of reacting to potential menaces to quality.

Predictive quality risk assessments can address the needs of different parties: pharmaceutical companies benefit from improved quality systems, regulators can ensure oversight in a more efficient way and academics apply new methods to an established field of research. Discussing predictive quality risk assessments in the following, we will differentiate between internal and external quality risk perspectives. Internal perspective describes factors related to the manufacturing site while the external perspective is connected to the environment, which is surrounding the establishment. We will present early findings of researching the internal perspective on predictive quality risk assessments, outline approaches for addressing the external perspective afterwards, and underline the importance of integrating both subsequently. Lastly, the article will provide an outlook to future research activities in this area.

Internal quality risk assessment

Manufacturing facilities are routinely inspected by authorities to minimise patients' exposure to unsafe drugs. The U.S. Food and Drug Administration (FDA) already assesses risk to schedule inspections and identify firms that may incur quality violations and prioritise these for inspections. FDA's risk assessment is based on the site type, time since last surveillance inspection, FDA compliance history, foreign regulatory authority inspectional history, patient exposure, hazard signal, and inherent product risk (FDA, 2018). Combining the compliance history with broader risk factors is expected to be a key lever to improve risk forecasting accuracy. Seiss (2018) showed how compliance history data does help to predict future inspection outcomes, especially if combined with additional parameters. For this reason, the FDA aims to leverage additional data in combination with compliance history to optimise the inspection schedule (FDA, 2021b).

The selection of appropriate data to combine with compliance history is a crucial element for better quality risk prediction. Thus, different parameters and signals must be analysed to reveal telling risk predictors. According to the ICH (2005), contributions to quality risk management at the plant level should cover all steps of the value chain and all stages of a drug's lifecycle. A simple consideration of a single production process or department is, therefore, not sufficient to determine the quality risk entirely. A comprehensive plant quality risk assessment shall consider both manufacturing and quality control (QC) lab testing processes. In addition to fulfilling its role as a safeguard for product quality and adherence to specifications, robust quality control is crucial to ensure reliable and timely release of medicines to supply the market (Ritz, 2021).

Site's quality risk assessment can be operationalised by detailing two major dimensions: Quality maturity and performance. At the same time, these two dimensions provide a categorisation of different sources of risks. Moreover, they provide a structure for the different data sources to subsequently characterise a predictive model.

A site's Operational excellence (OPEX) maturity is an umbrella term that summarises all initiatives driving continuous improvement along the manufacturing chain (Friedli & Bellm, 2013). OPEX initiatives have been started in the pharma industry for several reasons, one of them is to directly improve process and product quality. The implementation of lean concepts provides advantages in terms of operational performance and enables plants to achieve better results in quality if implemented correctly. In the final report after supporting the Quality Metrics Initiative for three years, Friedli et al., (2019) analysed the relationship between OPEX practices (defined as Overall Enabler, Total Quality Management Enabler, Just-In-Time Enabler, and Quality Maturity) and compliance status of pharmaceutical production facilities. The results are displayed in Figure 1, inspection outcomes are clustered in two categories: No Actions Indicated (NAI) and Actions Indicated (AI) comprising of voluntary and official actions indicated. Within all four diagrams, sites showing a maturity level below the median in the respective category reveal a higher amount of AI results compared to the sites above the median. The implementation of higher

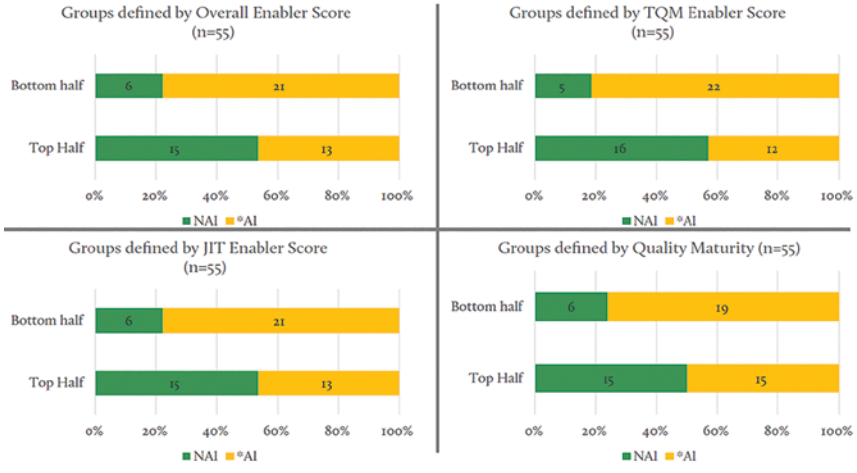

Figure 1:Site's Inspection Outcomes by Maturity Implementation Level (Friedli et al, 2019)

maturity in all categories provides confidence for a statistically significant relation with NAI inspection outcomes. (Figure 1)

Subsequent research confirmed the preliminary findings of Friedli et al. (2019). Eich & Friedli (2021) disclosed that sites with a higher implementation of OPEX practices, especially in total quality management, show better inspection outcomes. Another important internal signal that is leveraged by FDA (2018) and mentioned by ICH (2005) is the inherent product risk. Drug products carry a different level of inherent risk depending on their characteristics. For example, large molecules products are more complex and carry higher risks compared to small molecule products (Basu et al., 2013). Moreover, a product's risk is influenced by its lifecycle stage. A product in the initial phase does carry a higher inherent risk per definition compared to a very established medicine.

An additional font of information about current quality status at the site level can be drawn from operational performance metrics. Eich (2021) demonstrated that the integration of operational KPIs improves the predictability of the risk assessment providing a better capability of forecasting the outcomes of compliance inspections. Figure 2 shows how the reliability of the logistic regressions improves by adding new parameters to the model. Starting only from the compliance history (left) the model is not too reliable, by adding the product type (middle) the model is improved. Finally, by combining compliance history, product type and operational KPIs (right) the model soundly predicts inspection results. The analyses support the overarching idea of integrating manifold perspectives when designing sufficient predictive quality risk models.(Figure 2)

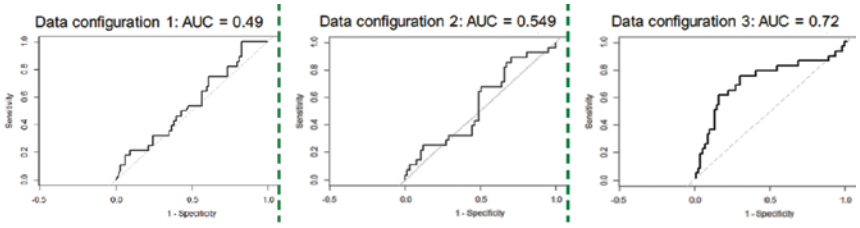

Figure 2: ROC Charts for Logistic Regression Models with different data configuration (Eich, 2021)

External quality risk assessment

As previously discussed, early attempts to assess quality risk and predict future inspection outcomes have mainly focused on the manufacturing site level. The state of the art on data-based quality risk evaluation at the site provides some insights on how different parameters are related to inspection outcomes. The sole quantification of internal related risk would not be sufficient to provide a comprehensive plant risk assessment because of the numerous external risk factors. External drivers for quality risk have been analysed less, if not almost ignored regarding the pharmaceutical industry. Therefore, considerations on external signals can only be based on initial reflections. Research in this particular field was recently started and is among the priorities of the OPEX team at the university of St.Gallen.

Since every manufacturing facility is connected with the external environment, the external originated risk might impact the internal production processes. Supply chain issues are one major cause of drug shortages and raise the risk for patients (FDA, 2019). Further external factors might have a critical impact on a plant's risk level but are hardly manageable from a plant perspective: A manufacturing site has only a limited capability of influencing external factors. Nevertheless, the ability to screen external signals in search of possible quality risks for the plant is the key to prepare the site to face and reduce the impact of these events. External signals can be leveraged to be matched with site internal parameters, such as performance or maturity, to support their validity and improve the predictability of the assessment. Additionally, external data can be used to surrogate the consequences of internal process issues which are difficult to measure, such as using data from online employee satisfaction portals to assess the company culture.

External factors can be crawled by analysing publicly available data from the web and searching for specific signals related to the site or products. The research approach is structured as follows: At first, select clusters of relevant information to provide the structure for the data gathering process to follow. Secondly, define an ontology approach, such the Columbia Ontology for Pharmaceutical Engineering (COPE) developed by Remolona et al. (2017). The ontology organises the different information sources and associations to generalise the multiple data sources relevant to the risk factors. Finally, raw data gathered is processed aiming to extract semantically rich information from the multiple data sources and make them appropriate for the particular risk prediction.

The major challenge in managing such an amount of unstructured data is to provide a clear structure that can both reduce complexity but is still flexible to develop numerous scenarios. For this reason, a data lake provides broader opportunities compared to old-fashioned databases (Khine et al., 2019). Using a data lake, the researchers can store different types of data in a centralised way, and not just a fraction of the gathered data stored in a structured format in relational databases. Additionally, the data lake offers great flexibility facilitating and supporting the development of statistical models analysing the lake's content in detail. Nevertheless, it is important to carefully tailor the data lake to its purpose and avoid turning into data swamps due to redundant, incorrect, and wrong classified data.

Development of a balanced risk score

Once concepts are in place for both measuring and analysing risk from an internal and an external perspective, this information will be integrated into an aggregated score. By calculating an overarching risk score, it is possible to reduce the complexity and provide a clear and user-friendly risk measurement system. The prediction model will rely on a central data lake, where all information is stored and then aggregated to build the final risk score based on context factors. Context factors describe the environment and the specifics of an establishment. They provide the conditions that must be taken into consideration when assessing the risk and therefore are used as a weighting system. Context factors are a fundamental part of the risk model since the consideration of global phenomena level does not provide a sufficient level of granularity to industry socially related phenomena. The specific context of a particular manufacturing site needs to be adequately represented in the model.

Leveraging the contextual factors, the most suitable internal and external data are selected and extracted from the data lake. Successively, machine learning algorithms will combine historical compliance data with the information extracted from the data lake to generate predictive models. Resulting risk models aim to generate insights to understand the contributions of various factors to the final risk score without compromising the accuracy of the predictive model. The goal is to define the minimum set of internal and external signals that must be incorporated to obtain a reliable and suitable quality risk prediction depending on the context factors that have been set.

Outlook

The St.Gallen understanding of internal and external risk signals while considering context factors supports the development of predictive quality risk models able to calculate different scenarios and adapt in real-time. Following such a system-thinking based approach provides numerous benefits to the different stakeholders. The model will improve companies' ability to assess current risk levels, better fulfil regulatory requirements and inform management decisions to assign resources to the most urgent initiatives at the right point of time. Regulators will benefit from better inspection scheduling system, based on the current risk and its possible development. Moreover, the transparency within the industry will improve. Finally, research can truly profit from a sharpened understanding of the roles of internal and external signals in influencing and predicting different risk levels in pharmaceutical production.

Building on the experience gained in projects for risk prediction at the site level, the research team currently focuses the efforts on three fields of priority. Firstly, expanding the understanding of inherent product risk parameters and the creation of product health metrics. to identify the right parameters able to depict the current status of different product and therefore its risk for the production site. Secondly, screening and clustering publicly available data to classify sources for external signals. Finally, integrating the signals in a comprehensive predictive model that considers both internal and external perspectives to provide a ready-to-use tool industry's quality system and management professionals. ■

AUTHOR BIO

Matteo Bernasconi is a research associate at the University of St.Gallen. At the Institute of Technology Management, he works in the Operational Excellence team with a special focus on the pharmaceutical industry. Currently, his academic work concentrates on preventive risk quality management and data-driven decision-making.

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Applying PAT to the Continuous Digital Biomanufacturing of Monoclonal Antibodies

Biomanufacturing is moving toward digital manufacturing with increased application of process analytical technology (PAT) and continuous manufacturing. This article describes experiences in the modelling, design, control, and operation of continuous monoclonal antibody (mAb) manufacturing processes. Fully automated processes employ in-line and at-line PAT that are used to build mechanistic models to confirm process understanding and design real-time feedback control of critical quality attributes (CQAs).

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Monoclonal antibodies (mAbs) are the highest selling class of biologics due to their specific action and reduced immunogenicity. As the use of mAbs promotes treating many diseases (e.g., cancer) with better targeted immunological approaches, the development of mAbs will continue to increase.

Process analytical technology (PAT) is increasingly applied in biopharmaceutical manufacturing. PAT is "a system for designing, analysing, and controlling manufacturing through the timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." On-line measurements of critical quality attributes (CQAs) lead to increased process understanding and facilitate construction of process models, with most of the PAT being implemented in upstream processing. Standard sensors provide in-reactor analysis of optical density, dissolved oxygen, temperature, and pH. Moreover, online analytics of in-vessel Raman, viable cell density via capacitance, and off-gas and weight control

for bioreactor and feed streams can be included. Also, through the use of an autosampler, samples can be sent to at-line cell culture and metabolite analysis.

Another trend is increasing use of continuous operation of biomanufacturing to improve product quality and reduce manufacturing costs. Moving to end-to-end continuous biopharmaceutical manufacturing, from continuous perfusion bioreactors to continuous downstream processes, is also of interest, and several experimental implementations have been reported. The upstream can consist of multiple perfusion bioreactors in parallel, to better balance the flow through the unit operations. Such end-to-end biomanufacturing, when unit operations are tightly integrated, requires that the control strategy is designed to address the propagation of disturbances. The overall process operations can be optimised by using a plant-wide control strategy, such as demonstrated for small-molecule pharmaceuticals.

These trends ultimately lead biomanufacturing towards digital manufacturing, which refers to manufacturing that is centred around a computer system and enhanced by using modern systems engineering tools (e.g., modelling and simulation, process optimisation, and process control) acting in concert. Below are examples of the application of digital manufacturing to continuous bioprocessing.

> Process measurements from PAT are used for development and validation of mathematical models for biopharmaceutical manufacturing processes, to provide insights into multivariable interactions and dynamics from the bioreactor through protein capture, viral inactivation, and polishing.

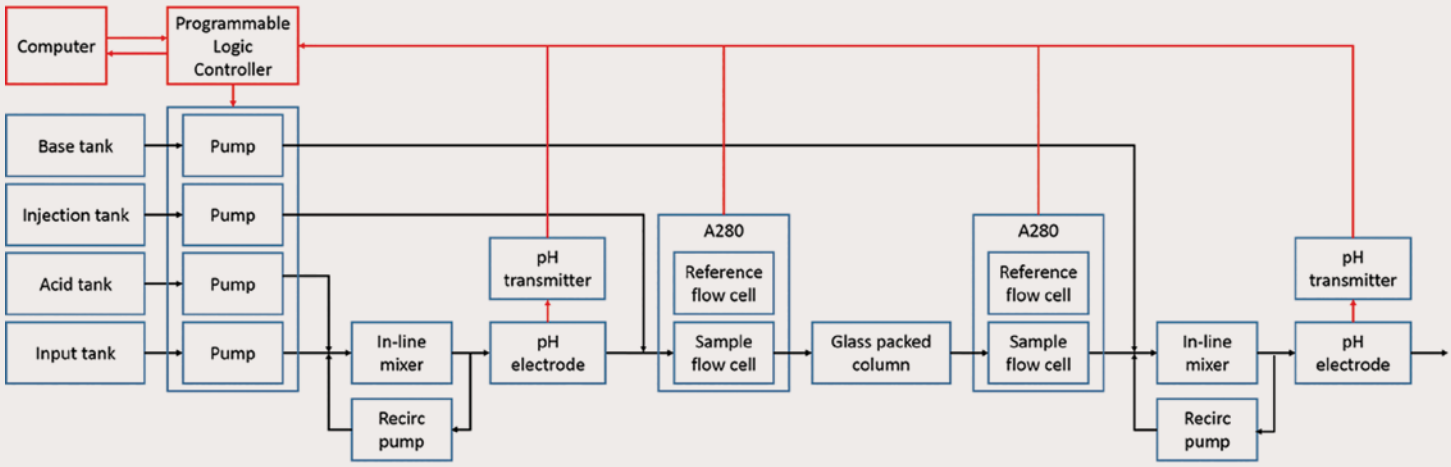

Figure 1: Schematic diagram of the colum-based continuous viral inactivation system

Mechanistic modelling of perfusion bioreactors

Mechanistic modelling can be developed for all of the unit operations in a continuous biopharmaceutical manufacturing plant. The material balances for the bioreactor are typically modelled as well-mixed,

$$\frac{dy}{dt} = \frac{F_{in}}{V_L}(y_{in} - y) - \frac{F_{out}}{V_L}(\delta y - y) + r_y$$

y is the concentration of species of interest in the bioreactor, V_L is the liquid medium volume, F is the media flow rate, the subscripts in and out referring to inlet and outlet streams, δ is the separation factor at the outlet, and r_y is the volumetric reaction rate. The separation factor for the cell density is equal to one for fed-batch operation and zero for perfusion operation.

For perfusion operation of Chinese hamster ovary (CHO) cells producing mAbs, differential balances for viable cell density X_V and concentrations of substrates S, inhibitors I, and monoclonal antibody P are

$$\frac{dX_V}{dt} = -\frac{F_{in} - F_{out}}{V_L}X_V + (\mu - \mu_d)X_V,$$

$$\frac{dS_i}{dt} = \frac{F_{in}}{V_L}(S_{i,in} - S_i) - q_{S_i}X_V,$$

$$\frac{dI_i}{dt} = -\frac{F_{in}}{V_L}I_i + q_{I_i}X_V,$$

$$\frac{dP}{dt} = -\frac{F_{in}}{V_L}P + q_P X_V,$$

μ is the specific growth rate, μ_d is the specific death rate, q_S is the specific substrate consumption rate, q_I is the specific inhibitor production rate, and q_p is the specific monoclonal antibody production rate. Typically, critical substrates involved are glucose for carbon source and glutamine nitrogen source, and critical inhibitors produced as side products are lactate and ammonia.

For product characterisation, mammalian N-linked glycosylation is important as glycosylation profiles impact activity, immunogenicity, and efficacy of therapies. Glycosylation is a complex biological process beginning from addition of a precursor oligosaccharide in the endoplasmic reticulum (ER) to a series of enzymatic reactions converting the precursor oligosaccharide into a complex carbohydrate in the Golgi apparatus. Many variables have been identified to impact the glycoform distribution including host cell machinery, process conditions, and medium components. For example, important carbon sources such as glucose and galactose impact glycosylation by affecting the nucleotide synthesis. Metal cations facilitate an increase in glycosylation as they act as co-factors for glycosylation enzymes. Metabolic waste products such as ammonia impact culture conditions such as intracellular pH, which in turn affect the glycosylation.

Mechanistic models of glycosylation can contribute to the understanding of these effects and provide a better basis for process design. Glycosylation can be modelled as material balances, considering the Golgi apparatus as a plug flow reactor operating at quasi-steady state conditions,

$$\frac{\partial OS_i(z,t)}{\partial t} = -\frac{4Q}{\pi D^2}\frac{\partial OS_i(z,t)}{\partial z} - \sum^{n} v_{i,j}r_j,$$

OS is the concentration of oligosaccharide structure, Q is the volumetric

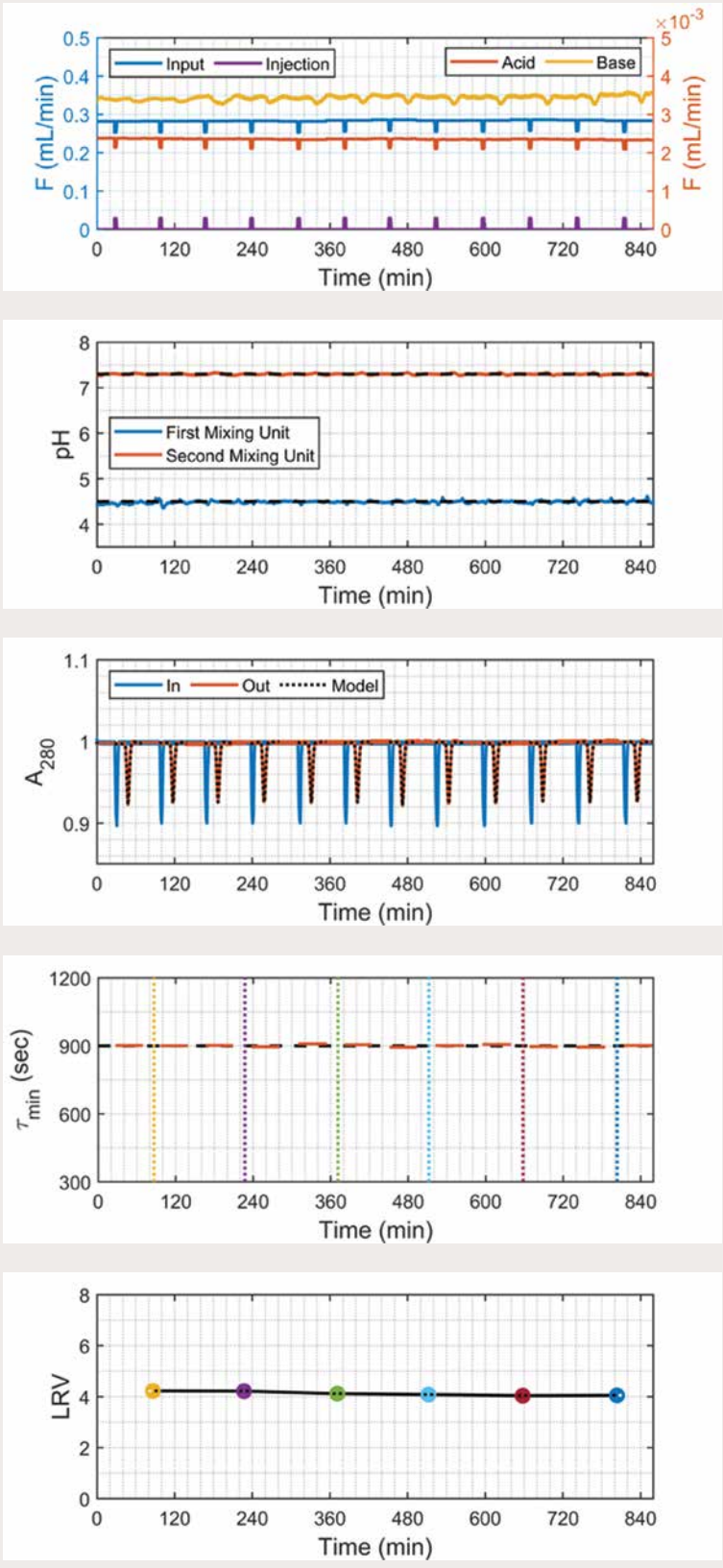

Figure 2: Experimental demonstration of the column-based continuous viral inactivation system. (a) Flow rates specified by the controllers in the system, (b) pH measurements, (c) absorbance measurements at the inlet and outlet of the column, and (d) the estimated minimum residence time. Set points are indicated by black dashed lines. Samples are taken for the phage plaque assay at the times marked by the vertical dotted lines. (e) The logarithmic reduction value (LRV) of the samples from varying the operation time was consistent. Adapted from Ref. 12.

flow rate through the Golgi apparatus, ***D*** is the diameter of the Golgi apparatus, ***n*** is the number of glycosylation reactions, ***v*** is stoichiometric coefficient, and ***r*** is the reaction rate. The effect of the operating conditions on glycosylation is simulated by the effect of the concentrations of sugar precursors, co-factors, and ammonia on enzyme kinetics. These concentrations are taken as input variables from the aforementioned bioreactor model. Assumed reaction mechanisms can be implemented in the mechanistic model first, and then validated or invalidated by comparisons to experimental data, to improve process understanding.

Completing the continuous downstream operations

Continuous tangential flow filtration, chromatography, and diafiltration are commercially available for continuous downstream processing, as described in recent review, but are not commercially available for viral inactivation. To address control challenges with operating the system, we invented a low-cost column-based system (Figure 1) that provides precise control over the pH and residence time, which are critical parameters to ensuring product safety and quality. Model-based pH control is implemented with Bayesian estimation to account for the nonlinearities and variations in the operation. The residence time distribution through ▶

the column is periodically estimated during operation as a parametric distribution based on the model through inverse tracer experiments to quantify the minimum residence time and adjust feed flow rates. The system is experimentally demonstrated for tight control of the operating pH, minimum residence time, and logarithmic reduction value over extended operation (Figure 2).

The first stage brings the fluid to a low pH by mixing the input stream with an acidic solution using a mixing unit and an in-line pH electrode. The mixed stream then flows into a column packed with inert glass to incubate at the low pH for a specified residence time for viral inactivation. UV absorbance sensors are placed at the column inlet and outlet to measure the residence time distribution from periodic injections of UV-transparent solution. The pH of the fluid leaving the column is raised by mixing with a basic solution using a second mixing unit and a pH electrode. Programmable logic controller provides low-level control of the system and is connected to a computer to collect data, estimate parameters online, and provide a human-machine interface.

Closing

Mechanistic modelling, design, and control are described for the continuous biopharmaceutical manufacturing of mAbs, including the roles of on-line and at-line PAT and basing the designs around modern computer-based tools. Process measurements from PAT are used for development and validation of mathematical models for biopharmaceutical manufacturing processes, to provide insights into multivariable interactions and dynamics from the bioreactor through protein capture, viral inactivation, and polishing. Such plant-wide models enable the design of advanced control strategies for manufacturing products of the highest quality. ■

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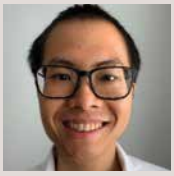
Moo Sun Hong is a postdoctoral associate at the Massachusetts Institute of Technology (MIT) in the group of Prof. Richard D Braatz. Moo Sun received a B.S. from Seoul National University and an M.S. and Ph.D. from MIT. His research is in the mechanistic modelling and model-based design and control of biopharmaceutical processes.



Amos E Lu was a postdoctoral associate at MIT in the group of Prof. Richard D Braatz. Amos received a B.S. from the National University of Singapore and an M.S. and Ph.D. from MIT. His research is in mechanistic modelling and model-based design and control of biopharmaceutical processes. In 2020 Amos moved to Sanofi where he is a Data Scientist.

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Richard D Braatz is the Edwin R Gilliland Professor of Chemical Engineering at the Massachusetts Institute of Technology (MIT). He leads the process analytics, modelling, design, and control activities of many biopharmaceutical manufacturing efforts at MIT, which are primarily in continuous manufacturing. He is a member of the U.S. National Academy of Engineering.

Formulation and Evaluation of Solid Dispersion Containing Simvastatin

Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin belongs to BCS class II drug. To overcome this shortcoming, a solid dispersion is prepared using a carrier of PEG 6000 to potentially enhance the dissolution rate and extend drug absorption. The objective of the study is to increase the solubility by solid dispersion method and to compare dissolution of pure drug and solid dispersions. The present study is an attempt to enhance the solubility of Simvastatin by fusion (Melt) method using polyethylene glycol 6000 as carrier. The complex of Simvastatin with polyethylene glycol 6000 shows enhanced solubility than the pure drug in the ratio between drug: carrier is 1:2. The dissolution rate studies were performed in phosphate buffer pH 7 and the dissolution rate was found to be 99.94 ± 2.17 per cent for optimised formulation F5 at the end of 50 mins. It is concluded that dissolution of the Simvastatin could be improved by the solid dispersion and PEG 6000 based solid dispersions were more effective in enhancing the dissolution.

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Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. The poor aqueous solubility of drugs is still now a challenge in formulation and development. Due to the poor aqueous solubility, the dissolution as well as bioavailability decrease which may be insufficient. Bioavailability of poor water solubility drugs that undergo dissolution rate limited gastrointestinal absorption can generally be improved by formulation techniques, such as preparation of solid dispersions. Solid dispersion, in which compounds are dispersed into water-soluble carriers, has been generally used to improve the dissolution properties and the bioavailability of drugs that are poorly soluble in water. In the biopharmaceutical classification system (BCS) drugs with low aqueous solubility and high membrane permeability are categorised as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. Drugs disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug to form a solid dispersion. The carrier of solid dispersion dissolves in water very quickly. The drug release is high due to more surface area of particles which causes high bioavailability of poor water-soluble drugs. Polyethylene glycols (PEGs) with molecular weights of 1,500–20,000 are extensively used as water-soluble carriers for preparation of solid dispersions of many poorly water-soluble drugs. The carriers show low melting point, rapid solidification rate, low toxicity, low costs, and good solubility in water and most of organic solvents. The aim of a present study was to compare ▶

solubility of Simvastatin alone, complexes of aspirin with PEG 6000 using solid dispersion technique.

Materials and methods

Materials

Simvastatin was obtained from Researchlab fine chem. Industries India. PEG 6000 was purchased from S D fine-chem limited India. Methanol from SD fine-chem limited was used. All reagents were of A.R. grade. Double distilled water was used throughout the experiment.

Methods

Preparation of solid dispersion

Melting method was used for the preparation of solid dispersion. Accurately weighed carrier (PEG 6000) was melted in a water bath at 70°C, the drug was added in the solid state and the mixture stirred until homogeneity was obtained. The mixture was then cooled rapidly in a freezing mixture of ice and stored in a desiccator for 24 hours. Subsequently, the dispersion was grinded in a mortar and sieved through 80 #. The required drug to carrier ratio for formulations was shown in table 1.

Batches	Drug: carrier
F1	1:0
F2	1:0.5
F3	1:1
F4	1:1.5
F5	1:2

Characterisation of solid dispersions

Micromeritic characterisation

Angle of repose:

Fixed funnel method determines angle of repose. The required quantity of granules was taken in funnel where funnel tip touched the granules heap. The granules were permitted to fall through the funnel. Powder cone radius was determined and followed by determination of angle of repose using given equation.

$$\tan \Theta = h/r \quad \ldots\ldots (1)$$

$$\Theta = \tan^{-1}(h/r) \quad \ldots\ldots (2)$$

Where Θ is the angle of repose, h is the height of cone in cm and r is the radius of the cone base in cm.

*Bulk density (**e**b):*

Bulk density apparatus (Sisco, India) was used to determine bulk density of granules. First granules mass (m) and bulk volume (Vb) was noted. The given equation was used to calculate bulk density.

$$e_b = m/V_b \quad \ldots\ldots (3)$$

*Tapped density (**e**t):*

Bulk density apparatus (Sisco, India) was used to determine tapped density of granules using standard procedure. First granules mass (m) and tapped volume (Vt) was noted. From the given equation 4 tapped density was calculated

$$e_t = m/V_t \quad \ldots\ldots (4)$$

Compressibility index (Carr's index):

Carr's index is used to estimate powder flow characteristics. The Carr's index can be calculated by the following equation 5.

$$\%\ \text{Carr's index (C.I)} = \frac{et-eb}{et} \times 100 \quad \ldots (5)$$

Where et is the tapped density of granules and eb is bulk density of granules

Hausner's ratio:

Hausner's ratio is another parameter to estimate powder flow characteristics. It is the ratio of tapped density to bulk density. It is shown in equation 6.

$$\text{Hausner's ratio (H.R)} = \frac{et}{eb} \quad \ldots\ldots (6)$$

Physical characterisation

Solubility studies

To evaluate the solubility of Simvastatin in the presence and absence of carriers, saturation solubility measurements were conducted. An excess amount of plain Simvastatin and dispersion powder were added to 20 ml of freshly prepared phosphate buffer pH 7 containing 0.5% Sodium lauryl Sulphate (SLS) in clean vials with continuous shaking at 25 ± 0.5°C for 24 hours to achieve equilibrium. The filtered solutions were suitably diluted and analysed for Simvastatin at 247 nm on a UV spectrophotometer (Shimadzu, model no. 1800 , Japan).

Drug content

The drug content in each solid dispersions and physical mixture was determined by the UV spectroscopic method. The simvastatin solid dispersions were prepared and tested for drug contained. From each batch of solid dispersion (prepared in different ratios) equivalent to 10 mg of simvastatin were taken and analysed by proposed method for drug content.

Percentage Yield

To determine the efficiency of solid dispersion production percentage yield was calculated. In this method preweighed solid dispersions were collected to determine practical yield. The percentage yield can be calculated using the given equation 7.

$$\%\ \text{Yield} = \frac{Practicalyield}{Theoreticalyield} \times 100 \quad \ldots (7)$$

In vitro dissolution study

Dissolution studies were performed in phosphate buffer pH 7 containing 900 ml at 37 ± 0.5°C, using USP type-II apparatus with paddle rotating at 75 rpm. Sample of pure drug, solid dispersions of various batches each containing 40 mg equivalent of drug were subjected to dissolution. Aliquots of 5 ml were withdrawn at time intervals of 10, 20, 30, 40, and 50 mins. were filtered and spectrophotometrically analysed at 247 nm.

Accelerated stability study

Stability study was conducted on optimised formulation. The formulations were packed in an airtight container and stored in stability chamber at 40 ± 2°C and 75 ± 5% RH for a period of 3 months. The samples were then withdrawn at interval of 30, 60 and 90 days and were evaluated for drug content and In-vitro dissolution studies.

Results and discussion

Micromeritic characterisation of SD formulations:

All the granules were evaluated for micromeritic properties (Table-2) such as angle of repose bulk density, tapped density, Carr's index and Hausner's ratio. All were found to be acceptable limits.

Table 2: Micromeritic characterisation of solid dispersion granules

Batches	Angle of repose(degree) a ± S.D	Bulk density (gm/ml)a±S.D	Tapped density (gm/ml)a ± S.D	Carr's Index (%)a ± S.D	Hausner's Ratioa ± S.D
F1	28.78 ± 0.14	0.528 ± 0.12	0.562 ± 0.11	6.05 ± 0.14	1.06 ± 0.09
F2	27.82 ± 0.12	0.524 ± 0.14	0.567 ± 0.12	7.58 ± 0.12	1.08 ± 0.11
F3	26.19 ± 0.11	0.525 ± 0.11	0.571 ± 0.12	8.05 ± 0.14	1.08 ± 0.09
F4	25.01 ± 0.12	0.526 ± 0.04	0.558 ± 0.06	5.73 ± 0.05	1.06 ± 0.03
F5	25.19 ± 0.14	0.525 ± 0.11	0.571 ± 0.12	8.05 ± 0.14	1.08 ± 0.09

N.B. All values are expressed as mean± S.D, a n = 3.

Physical characterisation

All the granules were evaluated for physical characterisation such as solubility, drug content, and % yield. It is shown in Table 3.

Table 3: Physical characterisation of solid dispersion batches

Time (Mins.)	F1 ± S.D	F2 ± S.D	F3 ± S.D	F4 ± S.D	F5 ± S.D
0	0	0	0	0	0
10	18.73 ± 2.43	29.79 ± 1.49	38.34 ± 1.43	42.66 ± 1.42	47.34 ± 2.43
20	25.46 ± 1.55	45.88 ± 2.36	49.46 ± 3.22	55.46 ± 1.28	60.46 ± 1.25
30	31.96 ± 2.67	55.96 ± 2.67	60.75 ± 2.32	61.93 ± 2.65	74.96 ± 2.67
40	48.98 ± 3.07	78.02 ± 1.79	81.32 ± 2.11	85.98 ± 1.04	87.92 ± 1.21
50	68.73 ± 2.45	84.73 ± 1.66	87.82 ± 1.76	91.06 ± 1.43	99.76 ± 1.49

In vitro dissolution study

The in vitro drug release was carried out in phosphate buffer of pH 7 to found out cumulative drug release (CDR). The % CDR from formulations F1, F2, F3, F4 and F5 at the end of 50 mins were found to be 68.73 ± 2.45, 84.73 ± 1.66, 87.82 ± 1.76, 91.06 ± 1.43, and 99.76 ± 1.49 % respectively.

Table 4: % CDR of Simvastatin of different batches

Batches	Solubility (mg/ml) ± S.D	Drug content (%) ± S.D	%Yield ± S.D
F1	0.420 ± 0.36	----	----
F2	0.726 ± 0.67	98.42 ± 1.09	78.73 ± 1.43
F3	1.231 ± 0.39	99.02 ± 1.11	85.46 ± 1.55
F4	1.576 ± 0.45	99.06 ± 1.02	91.96 ± 2.67
F5	1.652 ± 0.34	99.87 ± 1.15	98.98 ± 1.07

N.B. Mean ± SD, n=3

Stability studies

From short term stability studies of optimised formulation F5, it was confirmed that there was no significance changes in, drug content and % CDR. Hence it was concluded the formulation was stable in storage condition.

Conclusion

The solubility and dissolution studies showed there is a possibility of improved solubility of Simvastatin through solid dispersion with PEG 6000 by fusion method. A maximum increase in dissolution rate was obtained with Simvastatin in F5 due high concentration of carrier. Finally, it is concluded that solid dispersion of Simvastatin using hydrophilic polymers improved the solubility, dissolution rate and thereby enhancing its systemic availability. ■

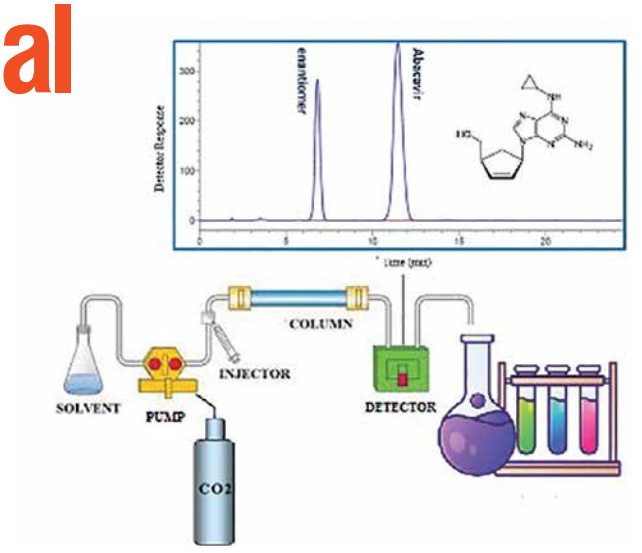
AUTHOR BIO

Subrat Kumar Tripathy is working as Assistant Manager in Zydus Cadila Healthcare Ltd., Kundaim, Goa. His main areas of interest is in validation of different dosage forms like injectables and OSD. He has more than 10 years of experience in pharmaceutical field and expertise in validation, qualification etc.

Chinmaya Keshari Sahoo is working as Associate Professor of Pharmaceutics at College of Pharmaceutical Sciences; Puri, under Biju Patnaik University of Technology (BPUT), Odisha. His main areas of interest in research includes in controlled drug delivery systems. He has published 99 articles (Google Scholar Citations 370, h-index=15 and i10-index 11) in various international and national journals as well as represented more than 21 papers in various international and national conferences. He has authored 3 books in his credit.

Chiral Chromatography in Pharmaceutical Analysis

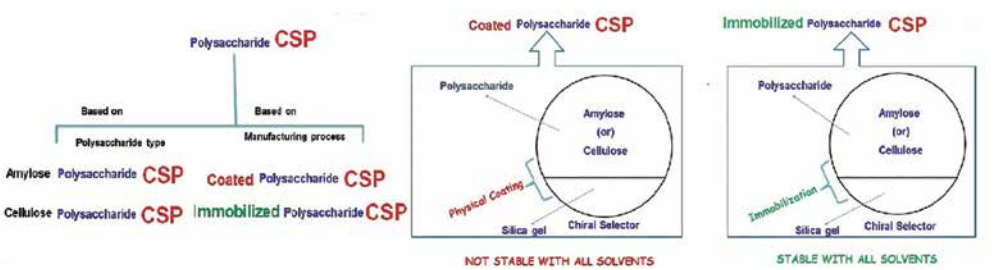
Advances and applications

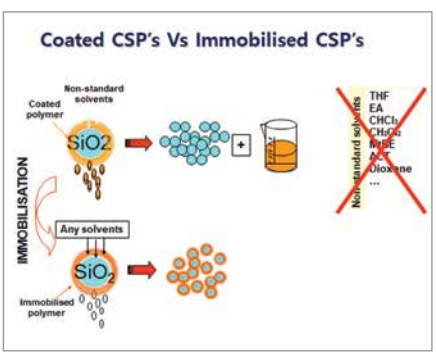


This article mainly focuses on the recent advances and applications of Chiral HPLC, LC-MS and SFC applications in Pharmaceutical Analysis.

M V Narendra Kumar Talluri,
Head, Dept of Pharmaceutical Analysis, NIPER

Polysaccharide derivatives are extensively used in chiral stationary phases. They provide multiple advantages including broad enantioselectivity, better resolution ability, easy availability, and high loadability under preparative separation conditions. Commercially available chiral stationary phases (CSPs) of this type are usually coated onto a silica matrix (or) covalently bonded to the silica matrix (immobilized). However, coated CSPs swell or dissolve and finally destroy the enantioselective capacity of the phase with some forbidden organic modifiers. The use of forbidden organic modifiers, such as chloroform, dichloromethane, acetone, ethyl acetate and tetrahydrofuran, in the mobile phase is, therefore, prohibited. To overcome these limitations, new immobilised CSPs were developed, containing polysaccharide derivatives covalently bonded to the silica matrix.

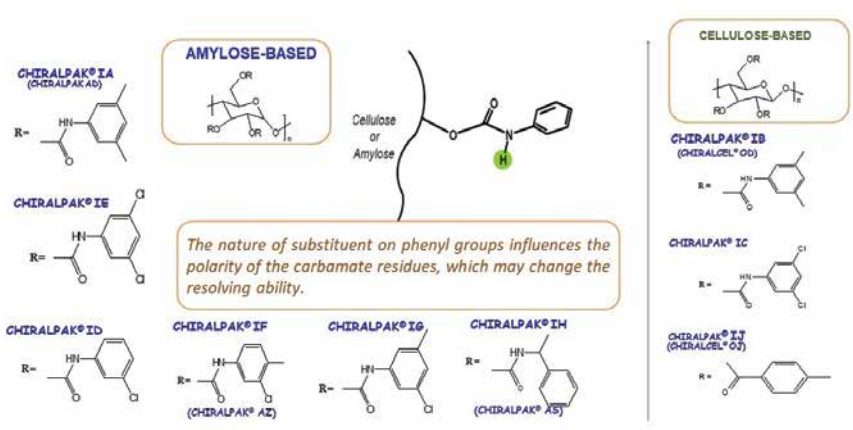




Coated vs Immobilised Chiral Stationary Phases (CSPs)

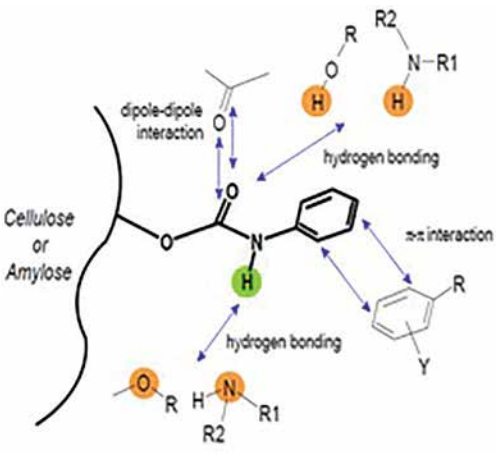
At present, nine immobilised polysaccharide-based CSPs are commercially available Chiralpak IA, IB, IC, ID, IE, IF, IG, IH, IJ. The chemical structures of these selectors are given in the below figure. Different approaches were reported to fix the chiral selector chemically linking the polysaccharide derivatives to the silica matrix, which is considered to be a prerequisite for enantioselective recognition. Consequently, the enantioselective recognition abilities of polysaccharide CSPs may be different. The immobilised CSPs are robust and can be used with a broader variety of solvents, as mentioned above. This extends the application range of these selectors in terms of enantioselectivity, but also in terms of mobile-phase solubility of compounds, offering benefits at both analytical and preparative scales.

Chiral selectors present in amylose and cellulose based CSPs



Chiral recognition mechanism :

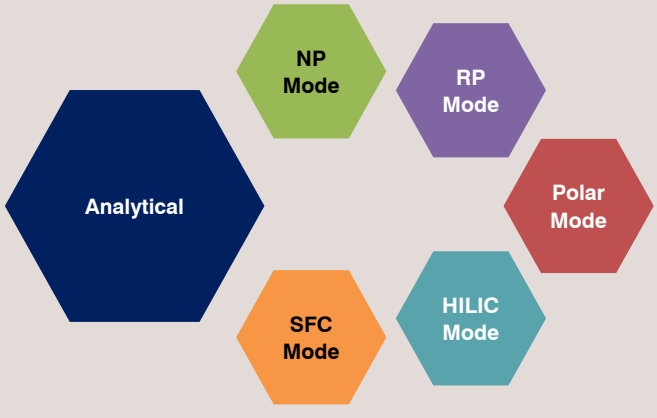
- Chiral selectors have special types structures (grooves/cavities/baskets)
- Enantiomers become stereo specifically interacted



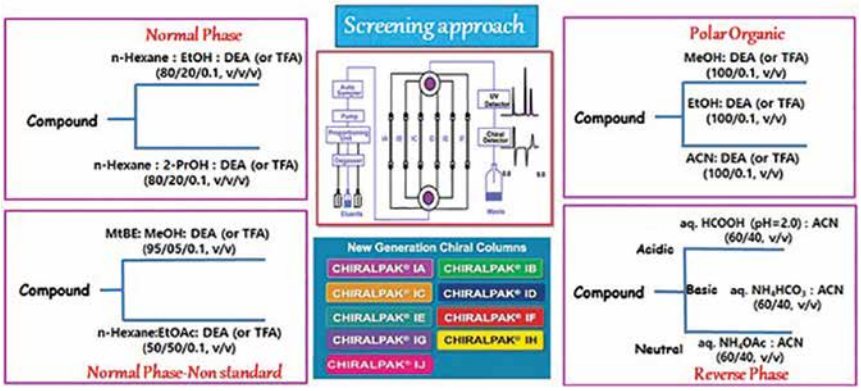
- The enantiomers is stabilised by various forces…
- Hydrogen bonding, π-π interactions, Dipole induced Diploe attractions etc…
- The combination of these forces is entirely different in each chiral selector
- The enantiomers fit sterogenically into the chiral grooves at different extents
- As a result of these combined effects, the enantiomers elute at different time intervals and mobile phase try to elute them.

Chiral method development & mobile phase elution modes

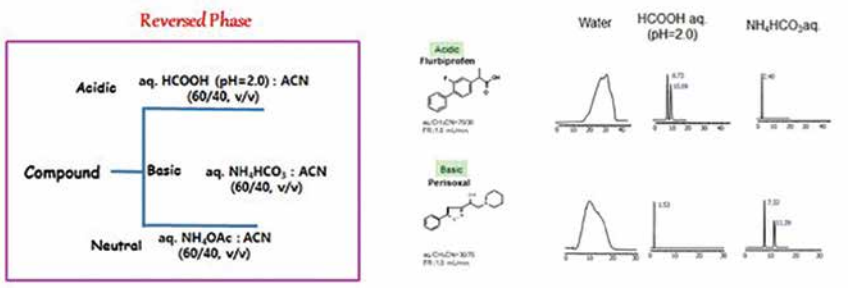
- The success rate on each immobilised stationary phase is some what different for each MP.
- Chiral HPLC is a very versatile technique for the determination of chiral impurities in bulk actives and pharmaceutical formulations.
- Using polysaccharide derived CSPs on chiral HPLC, separations can be explored in three common modes: normal phase (NP), polar organic (PO) and reversed phase (RP) chiral LC.
- For both 'coated' and 'immobilised' CSPs, in NP mode, typically alkane and alcohol mixtures are used as mobile phases.
- In case of 'immobilised' CSPs, additionally, solvents such as methyl tertiary butyl ether, ethyl acetate, tetrahydrofuran, dichloromethane, chloroform, 1,4-dioxane etc can be used.
- In PO mode, polar organic solvents such as methanol, ethanol, acetonitrile are used as mobile phase for both 'coated' and 'immobilised' type CSPs.
- In RP mode, water/buffer in combination with organic solvents such as acetonitrile and methanol are used as mobile phase.
- HILIC mode is suitable for separating polar compounds. Polar samples always show superior solubility in the aqueous mobile phase used in HILIC, which overcomes the disadvantages of the poor solubility often encountered in NP-LC. it can be easily coupled to mass spectrometry (ESI-MS) analysis.
- In view of difficulties in predicting the chiral separation based on the chemical structures, standard screening approach is in practice using HPLC connected with column switching valve as shown in Fig.

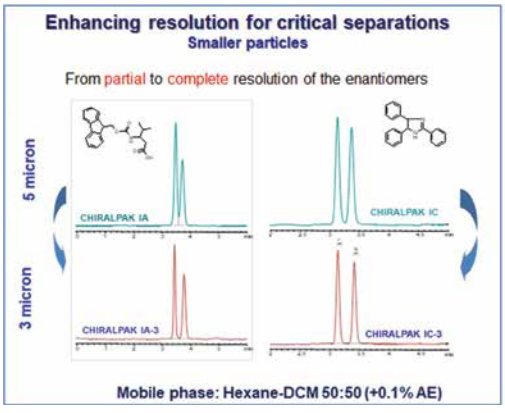


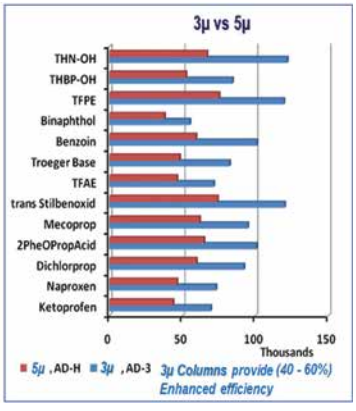
Method development-screening approaches

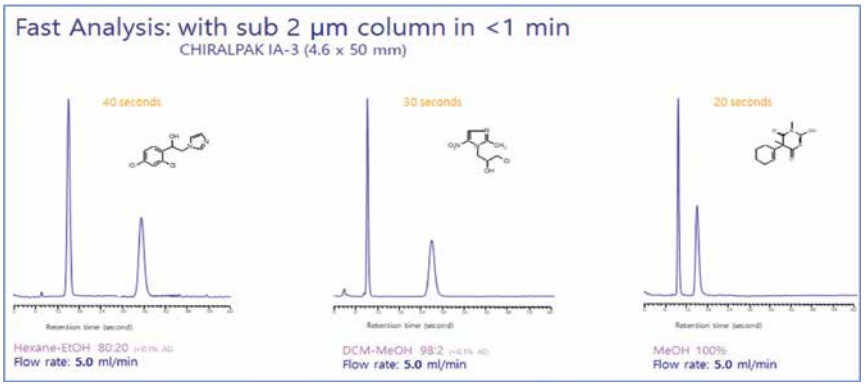


Example: Reversed phase screening and advantages









Advantages of reversed phase mode:

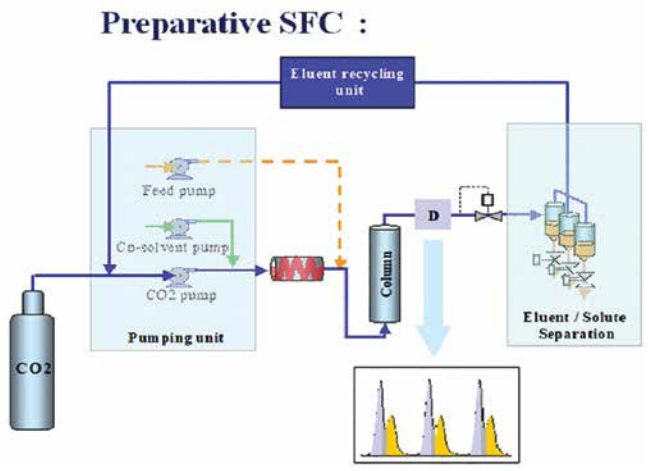
- Better solubility of analytes in salt form
- Less use of toxic solvents
- Compatible for Bio analytical and formulation samples
- Compatible with LC-MS/MS

Advanced CSPs (3 and 2µm particle size) for critical resolution of drug enantiomers:

- Reduce analysis time. So more number of sample analysis posible in shorter times.
- Less efforts in method development as run time is less.
- Cost reduction due to less consumption of mobile pase solvents and time saving.
- Save capital investment and operating costs
- Excellent tool for rapid dvelopments in R&Ds, Drug Discovery research and CRO environments.

Supercritical Fluid Chromatography (SFC): Green analytical chemistry tool

Although SFC has repeatedly proven itself as a performant separation technique for chiral separations, HPLC remains dominant in this field. This is likely due to the limited range of available SFC equipment. However, day to day, the number of reports on chiral SFC applications also increasing in pharmaceutical analysis. Chiral SFC separations can be achieved with high efficiency and minimal mobile phase solvent consumption in a short time span. SFC also has benefits in the context of upscaling to preparative scale, since returning to ambient conditions after analysis evaporates the main eluent (CO_2) from the mobile phase. Due to these reasons, interest remains in SFC for enantioseparation of pharmaceutically important compounds and drug substances till now.



When a substance is brought above its critical temperature and pressure, coexisting both phases disappear and a new state called the supercritical fluid is formed.

The physical properties of a supercritical fluid are intermediate between those of a typical gas or liquid

- Supercritical fluid is formed if temperature and pressure of a gas or liquid exceed their critical values. CO_2 are easily attainable.(TC = 304.12K, pC = 73.74bar)
- CO_2 is non-toxic, non-flammable, can be easily purified and is relatively cheap.
- Supercritical fluids have unique features lying between gas and liquid states.
- Liquid-like densities and dissolving capabilities together with gas-like viscosities and diffusion properties make them ideal candidates for major mobile phase components
- Its high molecular diffusivity considerably enhances mass transfer.
- The majority of SFC separations take place in subcritical region due to the addition of organic modifiers
- SFC can substitute both normal phase and reversed phase HPLC separation modes
- Pressure, temperature, mobile phase composition enable the separation of more compounds in reasonable analysis time.
- Wide variety of possible organic modifiers facilitates the optimisation of separation
- The SFC mobile phases enable high flow rates and therefore fast analyses
- Post-analysis evaporation of CO_2 keeps products concentrated in the organic modifier
- Better soluble in mixtures of supercritical fluids and organic modifiers than in pure organic solvents.

Fluid	Density (g/cm^3)	Viscosity (cP)	Diffusivity (cm2/s)
Gas (CO_2)	$< 2.10^{-3}$	0.01	0.2
Supercritical CO_2	0.3 (35°C/75 bar) 0.8 (40°C/150 bar)	0.03	> 0.0001
Methanol	0.789	0.54	< 0.00002
Water	1	1	

Properties of Fluids : SFC and Elution

Eluent system: CO_2 (60-95%); Co-solvent: Polar solvents (5-40%) Eg: MeOH, EtOH, IPA, ACN

Elution mode : Isocratic / Gradient

Flow Rates : Typically 3-4 times higher than LC flow

Col Temperature : 10-40°C

Additives : Acidic Analyte: No additive

Neutral Analyte : No additive, Basic Analyte : 0.1-1% DEA / EA / IPA / BA

SFC – applicable for analytical & preparative separations:

- Complementary selectivity
- Faster separations and high productivity
- Preparative separations ranging from g to multi Kg scale
- Easy evaporation of fractions
- Lower operating costs and Green technology.

AUTHOR BIO

M V Narendra Kumar Talluri associated as Head-pharmaceutical analysis NIPER, Scientific Manager-Biocon-BMS R&D. PhD from CSIR-IICT, published 90 articles, guided 50 MS & 4 PhD scholars, membership in RSC, Asian Council of Science Editors. Awards: Science Direct- "Top 25 hottest articles", IDMA-"Young Pharmaceutical Analyst Award 2011", Associate Fellow of A.P. AS(2014), Best Research Scientist Award-NIPER, 2016. Bharat Vikas Award, JPBA Quality Award2017, reviewer: 25 Journals, invited talks in conferences.

CYBER-PHYSICAL SECURITY TOOL FOR CONTINUOUS PHARMACEUTICAL MANUFACTURING PROCESS

The pharmaceutical manufacturing process and critical quality attributes (CQAs) are not only needed to control tightly but also required to be protected from any vulnerability in real-time. Currently, pharmaceutical manufacturing companies are facing enormous challenges to protect their plant from possible cyber-physical security (CPS) threats. Cyber-physical security is essential not only to protect the plant from any mechanical damages but also to assure the product quality and thereby, patient safety. The quality of the pharmaceutical products can be improved significantly by implementing advanced model predictive control (MPC) systems if an appropriate cyber-physical security defense is in place. However, much less attention has been paid to implementing a cyber-physical security system inside the pharmaceutical manufacturing plant.

In this work, a systematic framework, including the methods and tools, have been developed for proactive identification and mitigation of potential cyber-physical attack risk on the continuous pharmaceutical manufacturing process. The cyber-physical security-relevant software tools such as Snap 7, Wireshark, and Tripwire have been applied to CPM. A novel software tool named CPS (Cyber-Physical Security) has been developed for cyber-physical security of continuous pharmaceutical manufacturing. It has various features for improving the security level in the pharmaceutical plant. The integrated commercially available and developed (in house) cyber-physical security tools have added an extra layer of security of continuous pharmaceutical manufacturing pilot-plant for any unexpected attacks.

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Over the years, there have been many expensive and notorious incidents that have prompted the necessity of cyber-physical security of manufacturing plants. Stuxnet, Duqu, Flame, and Gauss were malware specifically designed to target industrial control systems (ICS) and cause physical damage to the equipment and inhibit processes from executing normally. In the case of the Stuxnet disaster, which degraded the integrity of uranium centrifuges, and prompted their destruction through software, while inhibiting security measures and monitoring software from accurately displaying the current situation of the machinery. As a result, the centrifuges were led to spin at unusually high rates, destroying the plant (Chipley, WBGD;). Because of incidents like these, respondents to the Global State of Information Security Survey - 2016 reported budgets for cyber-physical security to have increased by 24 per cent that year alone, suggesting a robust recent trend in the general industry towards prioritising the security of software and network (Williams, COPA-DATA UK;). Although many competitors in the industry have decided to invest more in cyber-physical security, many control systems currently used in the professional world were installed over twenty years ago. The old systems are opting out of reinstalling and migrating control systems due to financial costs but opening them up to several security risks. This realisation has prompted a more open study of continuous pharmaceutical manufacturing and CPS logic for this more experimental system, which holds a high initial investment. Still, it serves as a modern investment that can replace the outdated hardware currently being used.

According to the Business Advantage State of Industrial Cyber Security 2017 Report, 54 per cent of companies in the survey experienced some cybersecurity incident in their control system within the past twelve months, with 16 per cent claiming more than two incidents, prompting the necessity of a network monitoring and autonomous response system, in addition to localised software installation. Within the pharmaceutical manufacturing industry, the integrity of the compound often depends on the precise and consistent regulation of hundreds of parameters, from feeding, mixing to compaction. Pharmaceutical plants are now becoming the most targeted facilities for attacks, acting as a delicate system with great consequences for global safety, as well as holding incentive for attackers with invaluable formulas for drug manufacturing. Even minor parameter alterations can result in a wide variety of disruptions, ranging from inefficiencies like production downtimes or more damagingly, poisonous drug distribution, and hazardous waste handling (Perelman, Indegy). Especially due to the direct impact on public safety and health as an ingested medical compound, tablet production holds many legal and moral restrictions, prompting high-grade security to ensure the integrity of machinery and products.

In the continuous manufacturing process, tablets are produced continuously, and product quality relies on real-time monitoring and implemented control systems. However, the attackers can modify and collect information from PLC (programmable logic controller) communication without directly accessing to HMI (human-machine interface). If the attack happens at the PLC level, it means the attacker could directly control all the unit operations and devices that are connected to the PLC system. Therefore, it is necessary to monitor data directly from the data block instead of collecting data from other sources that could be infected by cyber-physical attacks. There are existing data capturing software that can access data from HMI memory block, like Snap 7. However, after accessing data from the memory block, it is not readable for operators to understand which parameter has a potential problem in the ▶

CM process. Therefore, an advanced tool is needed, which can access the data blocks, decode it quickly, and take the security actions in real-time. Such a software tool has been developed in this work, and its applications have been demonstrated.

PLC is a server connecting plant and the host operating PC (a control platform). For PLC system, security is the main concern because the information and data flow is not under direct supervision of the operators. Supervisory control and data acquisition (SCADA) is one of the most commonly used systems for controlling and monitoring the data. The continuous manufacturing plant considered for this study is for drug production, and the plant uses both SCADA and PLC. In the process of producing drugs, eliminating the cybersecurity threat is essential because the attacker could counterfeit the pharmaceutical drugs by gaining confidential information relating to the formulation as well as qould affect the CQA's.

In this work, a systematic framework, including the methods and tools, have been developed for proactive identification and mitigation of potential cyber-physical attack risk on the continuous pharmaceutical manufacturing process. We applied the cyber-physical security-relevant software tools such as Snap 7, Wireshark, and Tripwire to CM plant. We have developed a software tool named CPS (Cyber-Physical Security). The developed tool is complementary to the existing tools, and it should have a broad range of applications in the cyber-physical security of the continuous pharmaceutical manufacturing process.

The rest of the paper is organised as follows. The systematic cyber-physical security framework is described in section 2. The functionality of the developed CPS tool is presented in section 3. The integration of the CPS tool with the plant is explained in section 4. Building the security database is presented in section 5. The applications of the CPS tool are demonstrated in section 6 through a case study. The future expansion of the CPS tool is described in section 7. Finally, the manuscript is concluded in section 8.

The systematic cyber-physical security framework

Overview of the cyber-physical security system of the continuous pharmaceutical manufacturing plant

As shown in Figure 1, the PLC is in the server that controls communication between devices and the host PC in the continuous pharmaceutical manufacturing plant. Therefore, the PLC is vulnerable. If any hackers want to gain access to the continuous manufacturing plant, PLC could be the best target for them. Therefore, the priority for protecting the continuous pharmaceutical manufacturing plant is to monitor the status of PLC to detect suspicious activities. The data and information flow from the plant to the human-machine interface (HMI) via multiple layers, and a data breach could happen at any of these layers. The conditions of the continuous pharmaceutical manufacturing plant usually are monitored manually through the HMI of the operating PCs assuming that all the intermediate communication layers are secure. However, in the case of the cyber-physical security risk, HMI has limits in monitoring data from PLC data blocks. For example, any modification in the plant operating set points that may have severe consequences on plant safety, and the operator cannot easily detect the product quality via the currently available cyber-physical security system. Therefore, it is necessary to have the CPS tool to monitor and secure the continuous pharmaceutical manufacturing plant.

As shown in Figure 1, the proposed CPS tool developed in the Python programming platform integrates the network monitoring tool and data capturing software with the CM plant via PLC. The network monitoring tool (e.g., Wireshark) gives the real-time status of the data traffic communicating from operating PC to the plant and vice versa. It thereby detects the unauthorised access of the plant. The data capturing tool (e.g., Snap 7 integrated with CPS tool) detect any changes in the data communication with the plant and thereby prevent any unauthorised alterations in the plant operating parameters. We developed a graphical user interface (GUI) to ensure the users to use the tool efficiently.

In the PLC architecture (see Figure 1, middle), data of the PLC is stored into the data block. The function block is for storing the function, the organisation block stores all function block and data block of the process. The PLC is connecting different unit operations (e.g., feeders, blender, tablets press) of CM plant with control platform.(Figure 1)

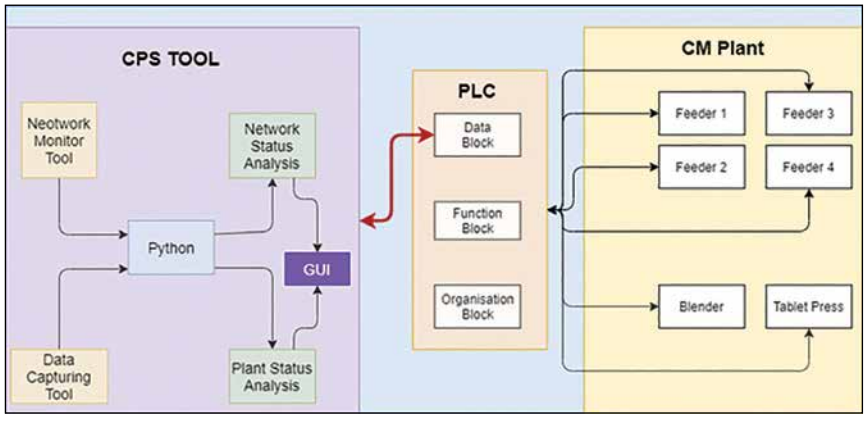

Figure 1: Data and workflow of the cyber-physical security systems of the continuous pharmaceutical manufacturing plant

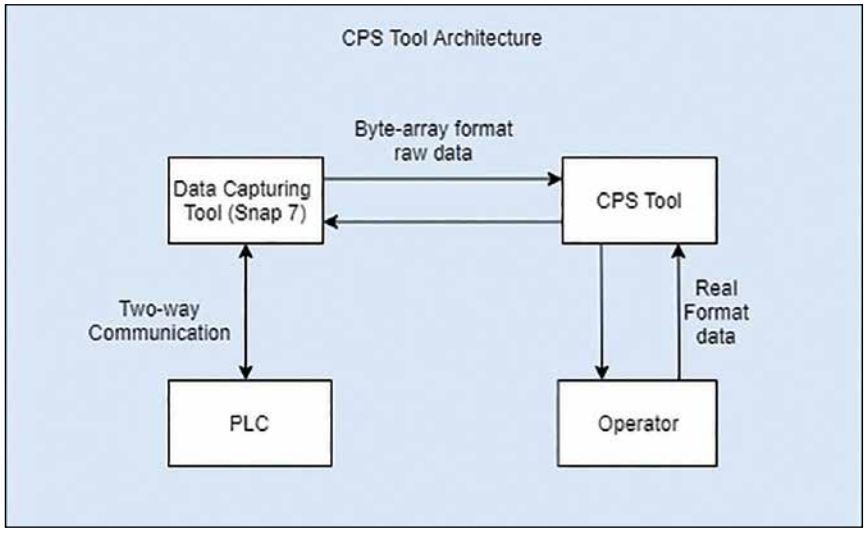

Figure 2: The architecture of the CPS Tool

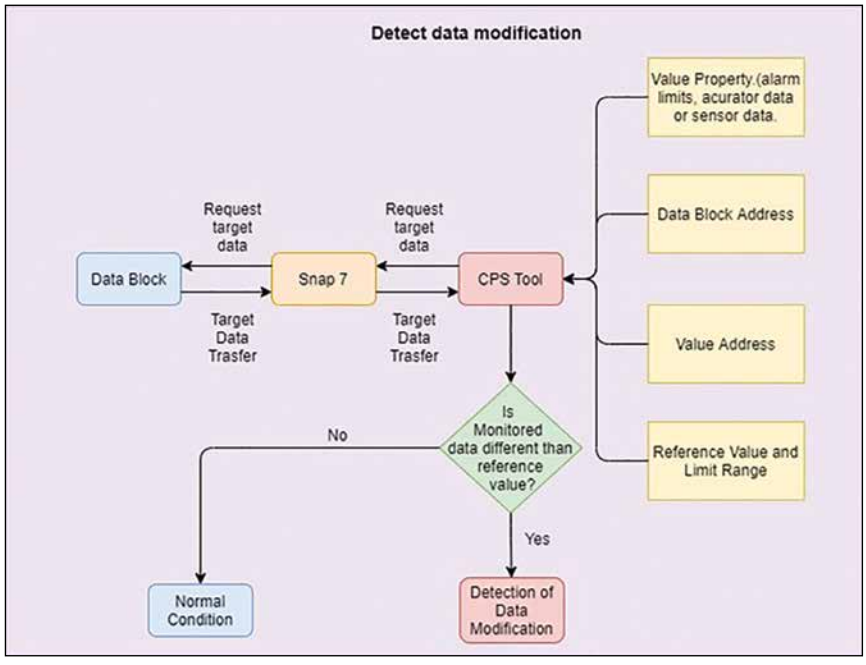

Figure 3: Detection of data modification

The architecture of cyber-physical security (CPS) tool

The architecture of the CPS tool is shown in Figure 2. As shown in the figure, the CPS tool integrates the data capturing tool, such as Snap 7. When 'the raw data' (in byte-array format) is getting communicated from 'PLC Data Block' to HMI, then the data capturing tool is monitoring it in real-time. However, the raw data is in byte array format, and the operator cannot understand it. Therefore, taking any security action either by the control system or operator is not possible. So, after capturing the 'raw data,' the next step is to decode it using the developed CPS tool. The CPS tool can also read and write in the data block; thereby it can take proactive cyber-physical security action in real-time. (Figure 2)

A systematic methodology for cyber-physical security

Proactive detection of cyber-physical attack risk

The systematic methodology for proactive detection of the cyber-physical security risk is shown in Figure 3. The data block is the unit in the control system that stored all the information in a coated form. The information/data stored in the data block directly goes to the plant when the function block uses them. In other words, all the changes (authorised/unauthorised) can only be implemented in the plant through a data block. Therefore, it is a unique place where the security system can be placed to screen the authorised and unauthorised activities. So, if this information/data stored in the data block can be decoded in real-time, then it is possible to proactively detect any attempt to make the unauthorised changes in the plant. In this way, the cyber-physical attacks can be identified and mitigated before it impacts the manufacturing process and product quality. The developed CPS tool is precisely performing these tasks, as described in subsequent sections.

As shown in Figure 3, the starting point is to provide the required inputs to the CPS tool. These inputs are data block address, reference value, the acceptable limit ranges, and other properties, as shown in the figure. The Snap 7, then scan the data block in real-time. The developed CPS tool decodes the data block to get the ordinary numbers (integer format) that can be understood by the operator and programmer (see Figure 4). The decoded number is then compared with the pre-specified reference value. If the actual value is the same as the reference value or within the specified limit range, then no security action is taken. Otherwise, the CPS tool will take the appropriate security actions, as discussed in the next section. (Figure 3 & 4)

Cyber-physical security actions

The systematic methodology for cyber-physical security is shown in Figure 5. If any plant data get modified, then the

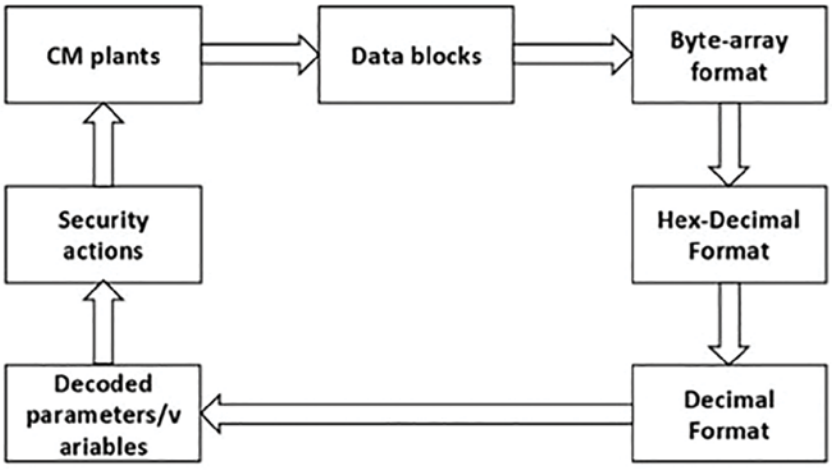

Figure 4: Decoding of the information stored in the data block

'cyber-physical security (CPS) tool' will take the actions according to the flowchart shown in Figure 5. All the purple blocks in Figure 5 referred to operations in the security system.

As shown in Figure 5, the plant is connected with PLC. The data coming from or going to the plant is stored in the 'data blocks,' which is monitored in real-time using developed CPS tool. The CPS tool should be placed in a security PC, which ideally need to be a separate PC to avoid getting infected if the operating PC may get infected. The CPS tool detects any changes in the data in real-time directly from the data block (see Figure 3). Subsequently, a pop-up window is generated to check if this change in the data value is intentionally made by the operator or not. If the operator acknowledges making this change, then it means the operation is regular, and no security actions need to be taken. If the operator has not made the changes, then the security actions will be considered as described in subsequent paragraphs. Note that if the operator does not respond, then the CPS tool will assume that the change has not been made by the operator, and therefore, the appropriate security actions will be initiated.

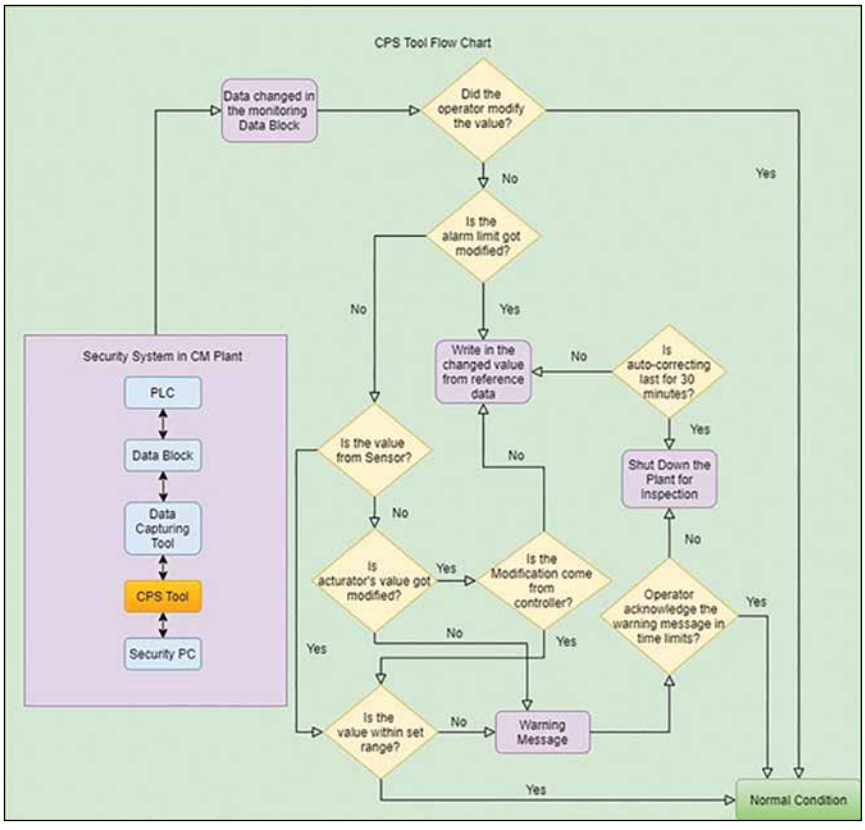

Figure 5: Flow chart of CPS Tool

If the change is not made by the operator, then the next step is to check whether the changed value is within the specified limits or not. If it is outside of the limits, then the CPS tool will auto-correct it by writing the original value of the data. Note that, for repeated changes, the CPS tool will keep on correcting it for a specified period of the time (e.g., 30 mins), and then if the problem still exists, then it will shut down the plant for manual inspection and fault detection.

If the change is within the acceptable limits, then the next step is to find out whether this data is coming from the sensor or not. If the data is not coming from the sensor, the next step is to identify the data belongs to the actuator or not (the signal that goes to the plant). If the data belong to the actuator, then the CPS tool will autocorrect the value irrespective of the magnitude of the changes. The reason is that the signal going to the plant is supposed to be constant unless it is intensionally changing because of the control actions. If the actuator value is coming from the controller, then the next step is to check if the actuator value is within the specified limits or not. If it is within limits, then no action is needed; otherwise, the CPS tool will generate a warning message. If the operator acknowledges the warning message, then no more operation will

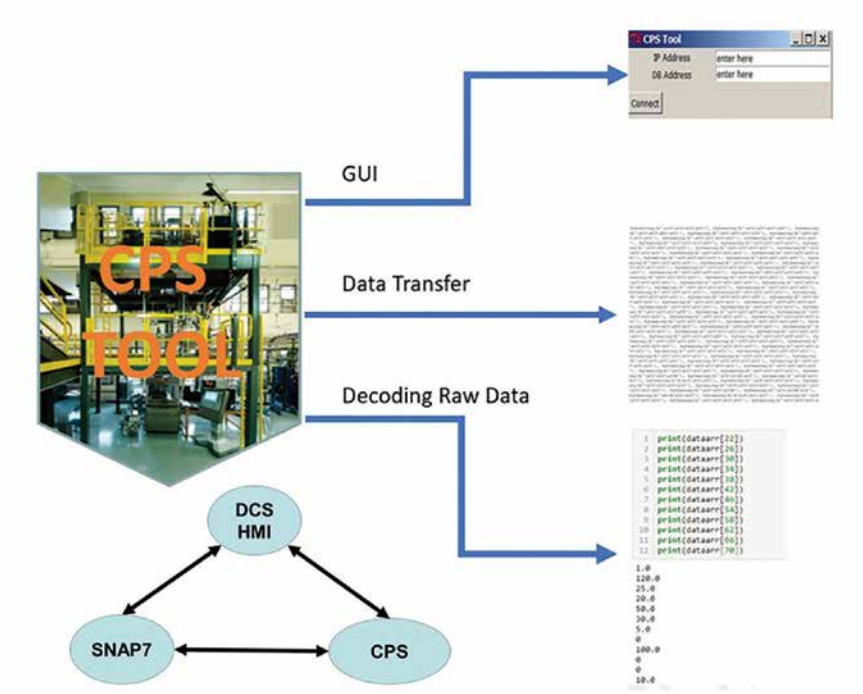

Figure 6: CPS Tool Features. DCS: Distributed control System. HMI: Human Machine Interface

be taken; otherwise, the CPS tool will suggest the operator shutting down the plant for inspection and fault identification.

If the CPS tool detects that the monitored data is coming from a sensor, but the changes are within the acceptable range, then no security actions will be taken. If it violates the limits, then the CPS tool will generate a warning message. If the operator acknowledges the changes, the CPS tool will not take any security action. Otherwise, the CPS tool will shut down the plant for inspections and further investigation as required to determine if it was a false alarm. Note that the operator can specify the time for which the CPS tool should wait before shutting down the plant, which means that the CPS tool does not need to shut down the plant instantaneously to avoid any mechanical damage in the plant. (Figure 5)

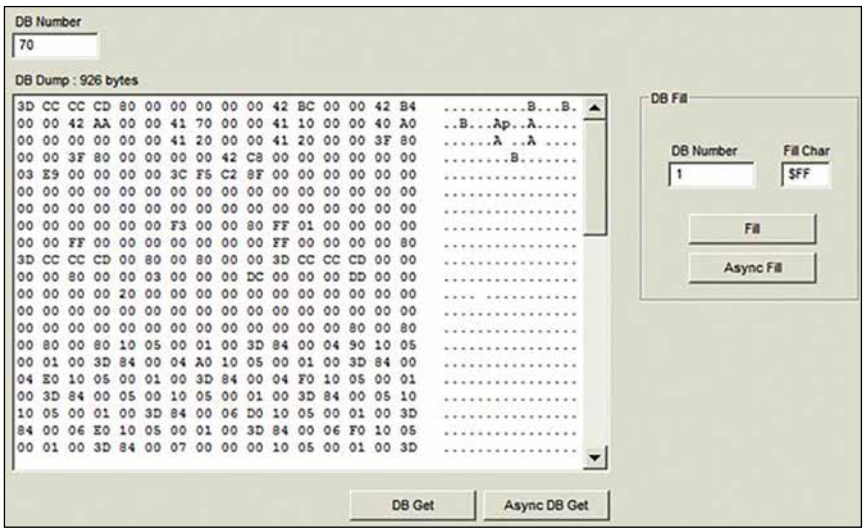

Figure 7: Raw data from data block

Functionalities of CPS tool

CPS tool is for monitoring security data during the manufacturing process. The CPS tool integrates the data capturing software by importing its library. However, since the data format collected from the data capturing software is in byte array format, decoding data from the data block is the first step. CPS Tool has three functionalities (Figure 6): the graphic user interface (GUI) for allowing the operator to input their system's IP address, plant, and control system information (data block address in use). Collect raw data in a data block with an Ethernet connection. The CPS tool is capable of decoding raw data to floating-point data for better understanding the data to monitoring specific data block. (Figure 6)

It is necessary to create a GUI to create a user-friendly environment for non-programmers. After entering the IP address of the plant and the DB address that the operator wants to monitor, it is clicking the 'Connect' button that will allow the CPS tool to access data and track the data in the CM process.

By default, the HMI should be the only way to communicate with PLC. Any other methods that can access to the PLC would be considered as security concerns. Data capturing tool is one way to communicate with PLC. The raw data from the data capturing software does not show much information to the operator without decoding (see Figure 7). Therefore, decoding byte arrays type of data into an understandable format (real number) is necessary. The next steps after decoding the byte array format raw data are storing the decoded values into the CSV files for references and mapping the decoded value from the CPS tool with physical properties. (Figure 7) ▶

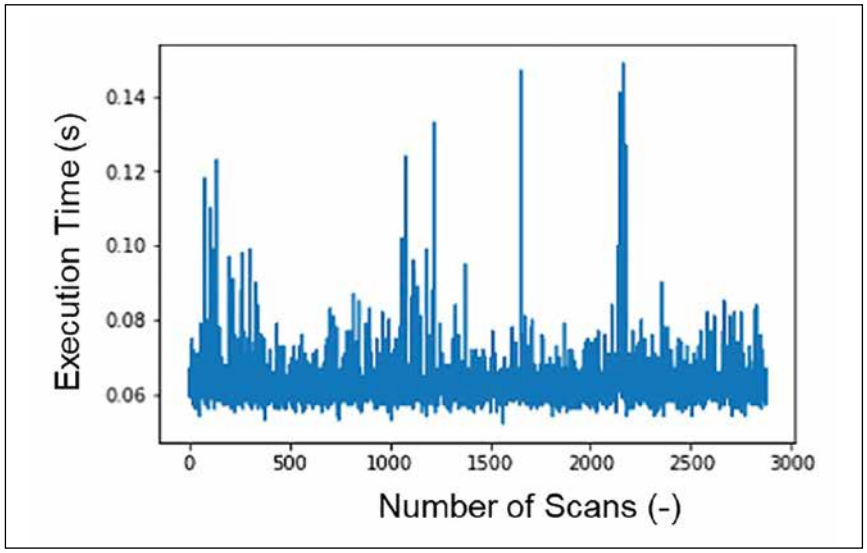

Figure 8: Response time for scanning data blocks

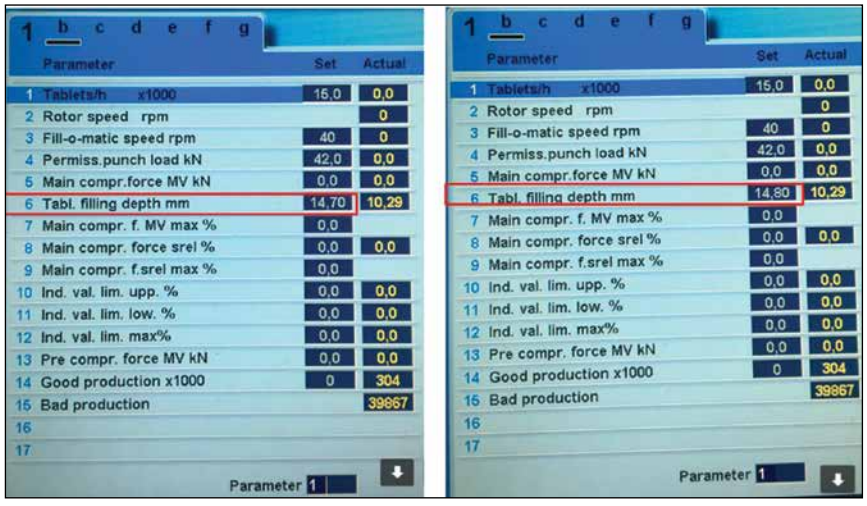

Figure 9: Modify Tablet Fill Depth from HMI

CPS tool connected with CM Plant

The CPS Tool continuously scans the data blocks, decodes values in data blocks, and provides the actual value of the critical process parameters. After the operator sets up the limits for the monitoring parameters, if the monitoring value is out of the set range, a warning message will be displayed. Comparing with the HMI tool's monitor function, the CPS tool's monitoring function is mainly focused on the cybersecurity side. The main distinguishing feature of the CPS tool is the function of monitoring alarm limit changes.

The next rising question about the CPS tool is the response time to scan one data point form the targeted address in the data block. Figure 8 shows the response time for reading data from a single address in a single data block. On average, the CPS tool takes 0.063 seconds to scan and decode one raw data point. The response time is measured by collecting data of one address in data block 71 (tablet press). Therefore, if the attacker modifies the value in this specific address, the CPS tool will detect unauthorised changes within 0.063 seconds. However, the response time varies from different data blocks, which means that it might take longer to read another data block. (Figure 8)

Depending on which parameters the operator is monitoring, the setup of the reference value would be different. The CPS tool sends the warning messages in IDE when the tablet press is in resting condition (see Figure 9). Fill depth and production rate values read from the data block using the CPS tool. When the CPS tool detects the value is out of set limits (The filling depth has a set limit of 15.0, and the production rate has a set limit of 100), the CPS tool displays many warning messages for alerting the operator.

In the CM plant, we performed the experiment about monitoring the tablet fill depth value. We changed the tablet fill depth with HMI in the CM plant and confirm if the CPS tool can detect the modification. In figure 9, the value of table fill depth modified from 14.70 to 14.80. The reference value set in the CPS tool is 14.70 and it detects the modification and sent out the warning message to alert the operator as in figure 10

Storing data into the database

It is important to keep tracking data in real-time by using the CPS Tool. For future reference purpose and regulatory perspective, implemented features in the CPS tool for allowing the operator to save all the monitoring data. The historical data is useful for offline investigation of cyber-physical security to ensure that the plant was not running under attacks at any time interval. The historical information is also helpful to determine if it is necessary to disregard the products which are suspected to be influenced by cyber-physical attacks. For example, when the CPS tool will notice the critical parameters of the tablet press like fill depth, or main compression force is out of range. The CPS tool will generate the warning message, value of the variable, and corresponding time. The actual value recorded from the machine

Figure 10: Warning Messages

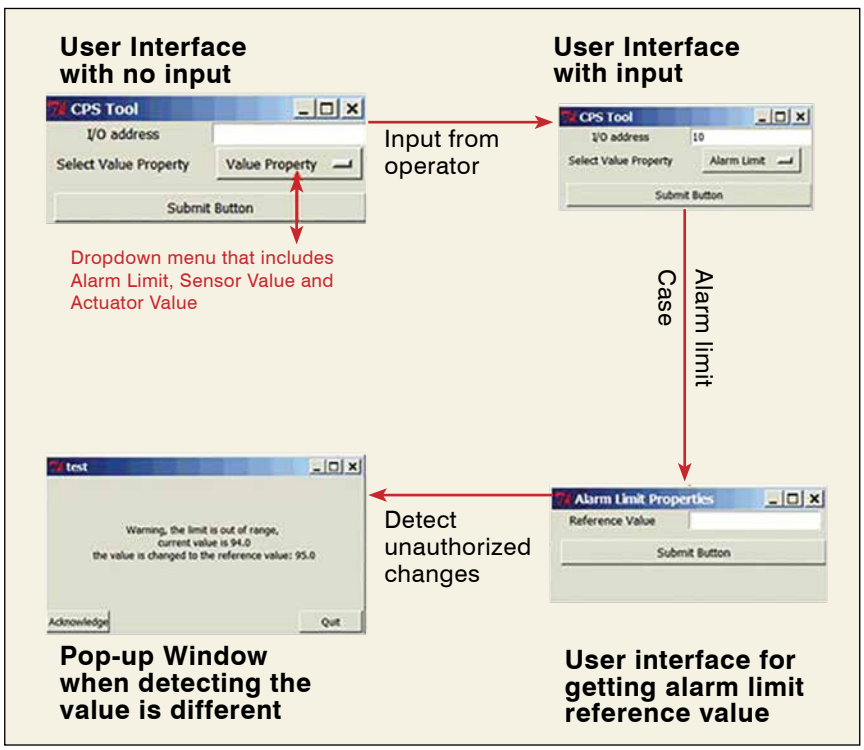

Figure 11.:UI and Pop-up window for Monitoring Alarm Limit

has multiple variables like flow rate or ingredients of the powder that will cause fluctuation and impact the accuracy for determining safety status in the plant. Therefore, a warning message might have false alarm issues, and the operator could not correctly interpret if the situation was outside attacks or not. For having data saved after the operation, if the operator saw many warning messages, then the operator can have reference data set to analyse the suspicious data changes and identify if the situation is a false alarm or actual attacks.

Security concerns regarding with alarm limits modification

The alarm limits are critical in the role of alerting the operator about unexpected situations happening in the CM plant. However, if attackers modify the alarm limits setting, no warning message will be displayed. The reason is that the alarm condition in the previous environment is masked too safe now. Therefore, it is necessary to have a side tool for continually monitoring the alarm limits situation. The Figure 5 shows the flow chart about detecting modification of alarm limits. The alarm limits value does not change during the manufacturing process, unlike other actuator values.

CPS Tool user interface for value property and alarm limit inputs

Before the monitoring process, the operator needs to enter the relevant information about the value that need to be monitored (see Figure 10). The relevant information would be value's property, which is the alarm limit. In this experiment, the reference value is 95, and the I/O address of the monitoring value is address number 10. We developed a GUI, as shown in Figure 11. The GUI allows the user to enter the value's address and the category of monitoring value. Value property is in the form of a dropdown menu that contains 'Alarm Limit,' 'Actuator Value,' and 'Sensor Value.' After entering both the I/O address and the value property ▶

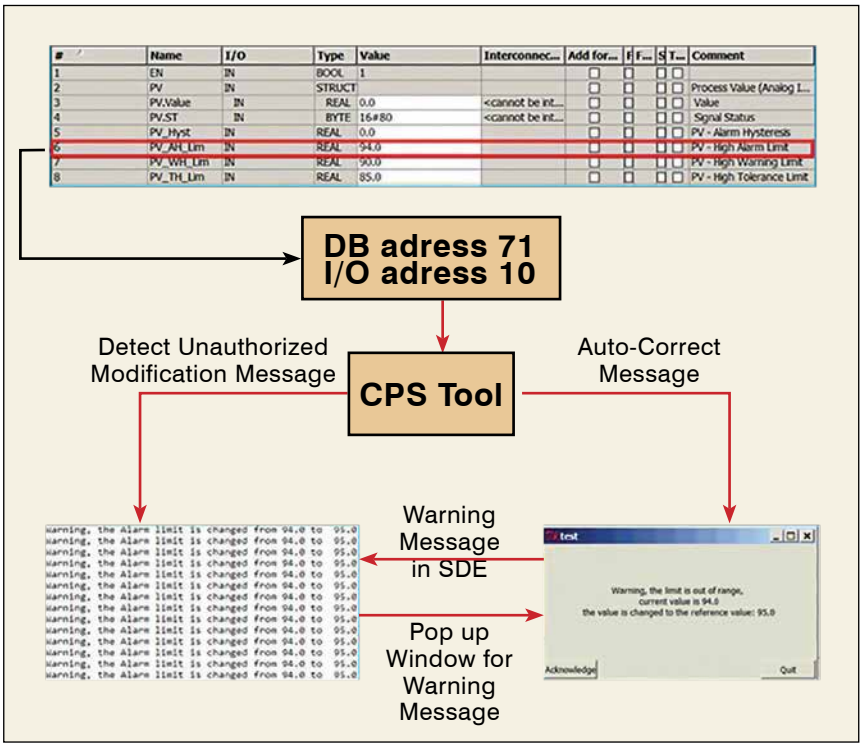

Figure 12: Alarm Limits in Data Block 71

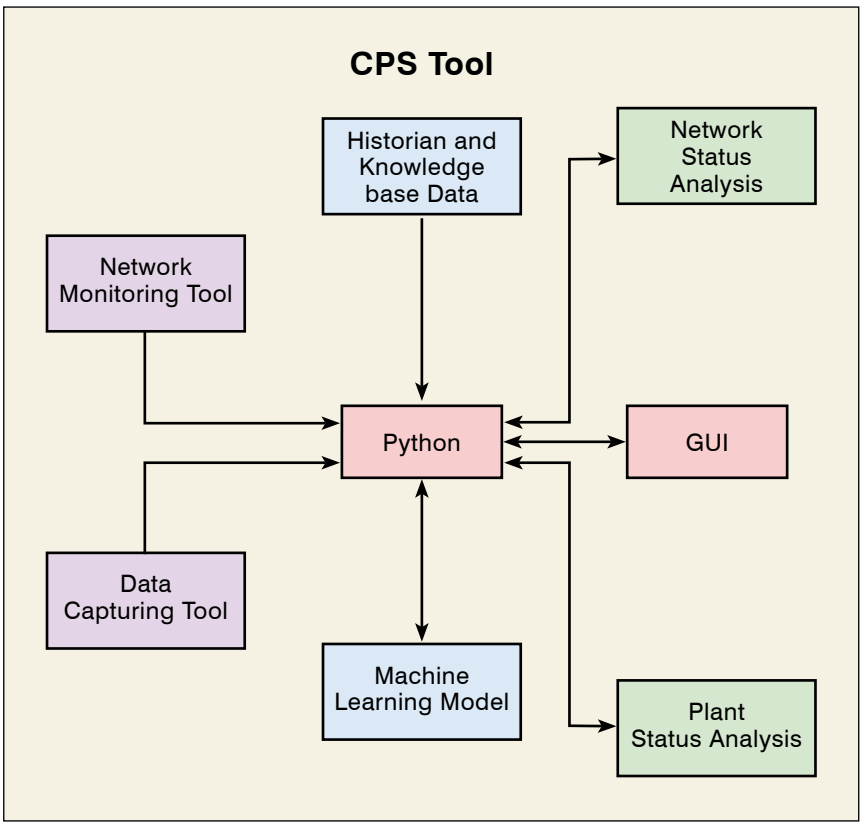

Figure 13: CPS tool Integration with other Commercial Tools

in the GUI, the user needs to click on 'Submit Button' and close the window. Then, the next window will pop up, depending on which value property is entered. In this experiment, the monitoring value's I/O address is 10, and the value belongs to the alarm limit category. The alarm limit properties' window will pop up and ask the operator to enter the reference value, which is 94.0 in this case. After all, based on the inputs that the operator provides, the CPS tool will show the pop-up window as a warning to the operator if the CPS tool detects any modification in the manufacturing process. Since the value property is 'alarm limits' in this case study, the CPS tool will also auto-correct the modified value to the reference value. (Figure 11)

An experiment of monitoring alarm limits

In this experiment, the targeted data block number is 71, and the main focus is to detect any modification in the data block 71's alarm limit setting (upper alarm limits' I/O address in DB 71 is 10). There are two alarm limits in data block 71: one is the upper bound, and the other one is the lower bound. If the monitoring value got out of range, which means the monitoring value is higher than the upper bound or lower than the lower bound limit. Then the CPS tool will display a warning message to alert the operator.

Figure 11 shows the flow chart of the monitoring alarm limit experiment with the CPS tool. In this experiment, the upper alarm limit is modified from 94.0 to 95.0. The CPS tool is monitoring the single address (address 10), which is the upper alarm limit in DB 71. If it detects any changes in the upper alarm limit, it will send a warning message and auto-correct the current value to reference value. (Figure 12)

Possibilities of integrating with other tools

We developed the CPS tool using Python as the programming language.

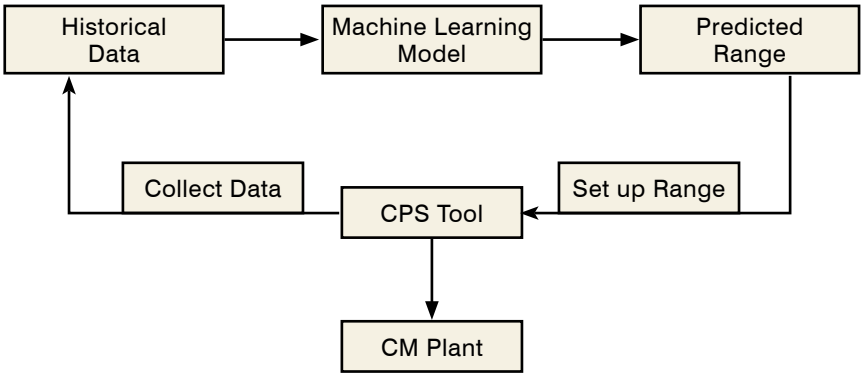

Figure 14: CPS Tool with Machine Learning Models Integrated into CM Plant

Cyber-physical security has multiple areas, including network status, machine learning for data analysis, etc., (see Figure 13). The CPS tool can integrate other functions by implementing existed packages from Python with modification for cyber-physical security purposes. In continuous manufacturing security, multiple devices are working in a single process. Therefore, it is necessary to have a tool for monitoring data and analyse the correlation of data from various devices. Flexibility is critical to implement into the numerous platform, and the CPS tool is capable of fitting into different platforms. After reading multiple devices' data, running a machine-learning algorithm to them will reveal more accurate results for detecting attacks. The most popular programming language for machine learning is Python, which is also used in the CPS tool. For this reason, the CPS tool can enable further enhancements with integrating machine learning algorithms. (Figure 13)

Machine learning models are useful for continuous manufacturing process analysis. In the current state, only the hard limit which is set by the operator is implemented in the CPS tool. However, the hard limit has limitations in handling cyber-attacks because values might get masked and hard limit is not suitable for dynamic analysis. To perform dynamic analysis, creating the soft limit concept is the critical step (see Figure 14). The soft limit is the limit set by using multiple parameters instead of the targeted parameter as reference. Therefore, even the targeted setting is masked; the soft limit is still consisting of the original configuration. (Figure 14)

The CPS tool plays a role in monitoring any suspicious data which are out of soft limit and collect data in every operation if needed. Saved data from the CPS tool is used as input for training machine learning model. The machine learning model sets up the soft limit when the operation is going on. The soft limit will improve detecting malicious attacks with masking values because the masked value is out of range by prediction of other values.Conclusions

A distributed control system has significant impacts on the increasing productivity of the manufacturing plant. However, not paying enough attention to the cyber-physical security side in the manufacturing process would cause severe damages to the plant and clients. To monitor data in the plant, a cyber-physical security (CPS) tool has been developed. The CPS tool's applications have been demonstrated in continuous pharmaceutical manufacturing pilot-plant. Implementing various features in the CPS Tool, including data monitoring and data storage, helps the operator to detect unauthorised modifications in the manufacturing process. The time requires to read data from a single address in a single data block is considerably shorter. With the ability to access the data from the data block, 'monitoring alarm limits setting' become the main difference in comparison to the existing HMI tool. The developed CPS tool is complementary to the existing tools. Therefore, it should have a broad range of applications in various manufacturing industries. The integrated commercially available and developed (in house) cyber-physical security tools have added an extra layer of security of continuous pharmaceutical manufacturing pilot-plant for any unexpected attacks.

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References are available at www.pharmafocusasia.com

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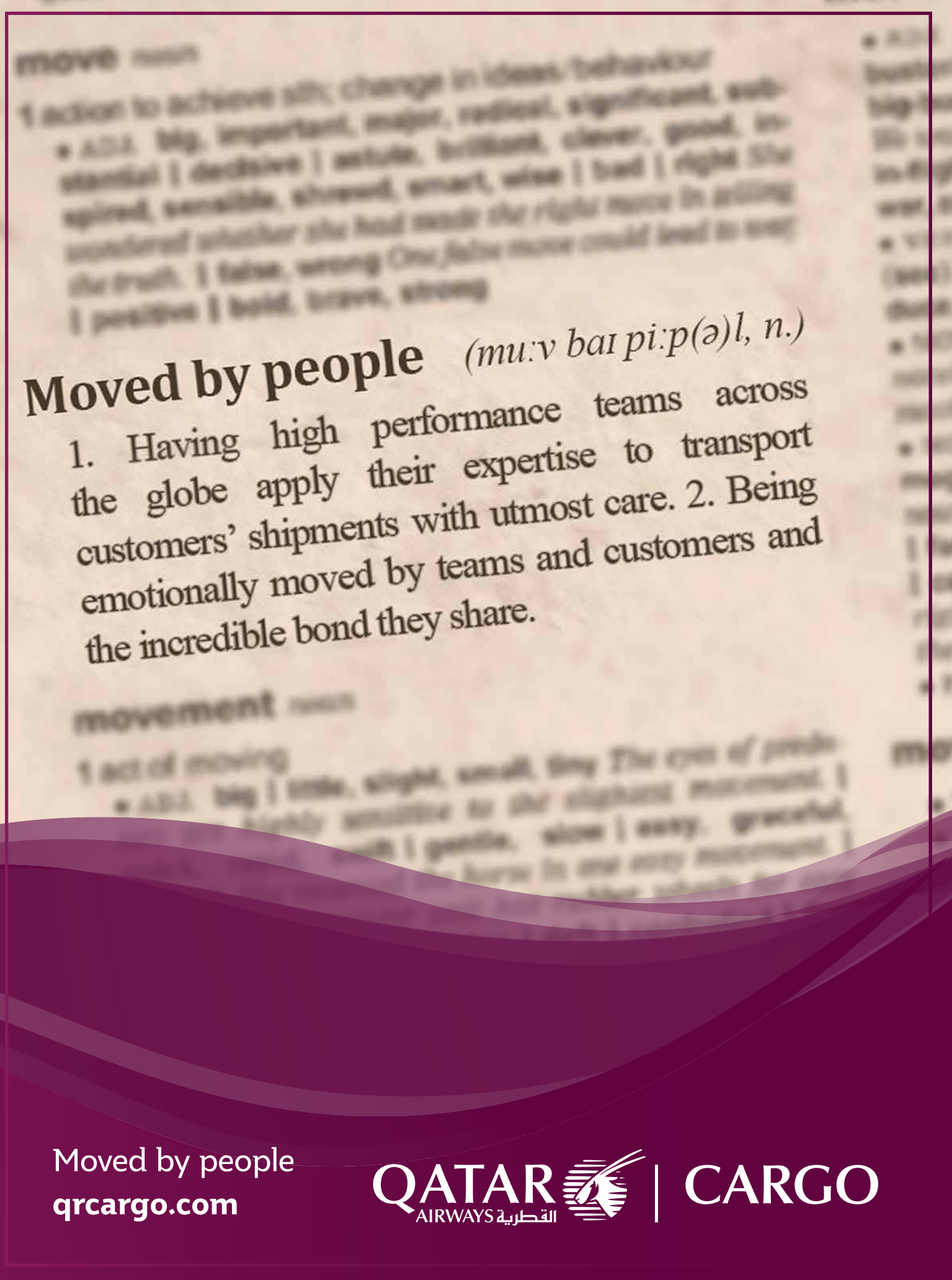

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