BIKASH CHATTERJEE
Pharmatech Associates, USA

Pharma 4.0 supply chain:
security and data integrity for advanced therapies

KEYWORDS: Pharma 4.0, personalised medicine, IoT, AI, zero trust, advanced therapies, compliance through science, ICHQ10, Pharma Supply Chain.

ABSTRACT

Pharma 4.0 offers efficiency at scale, based on data, security, and automation. Exploiting data from across the overall supply chain, Pharma 4.0 will use predictive analysis techniques that enhance business performance. Yet, by inserting the patient into the supply chain, advanced therapies complicate data acquisition and introduce global privacy requirements. The threat profile is higher from the perspective of data integrity and network security. This article examines key points to consider in a Pharma 4.0 supply chain, for organisations looking to bring advanced therapies to market.

Driven by digitalisation, Pharma 4.0 is envisioned as the next step in the evolution of pharmaceutical manufacturing. It reflects a shift to improving business performance through data analyses and structured decision-making across the entire pharmaceutical manufacturing value chain. At the centre of this new vision is the promise of ICH Q10, as it describes a comprehensive model for an effective pharmaceutical quality system implemented throughout the different stages of a product lifecycle, including good manufacturing practice (GMP) regulations.

By connecting the core elements across the business value chain, Pharma 4.0 is poised to create new levels of transparency and speed on the factory floor and in the supply chain, as shown in Figure 1.
Pharma 4.0 will also require higher levels of security, since connected systems heighten vulnerability, and solving these problems provides further new opportunities for the pharma industry.

Figure 1. Pharma 4.0 Digitalisation Value Proposition.

The ambition of Pharma 4.0 to transform the development and manufacturing value stream from a reactive framework to a predictive framework is based upon analytics that address and anticipate potential problems in the entire supply chain. In that regard it is very different from an automation strategy—the hallmark of Industry 3.0. It is the basis for what we call "smart factory." Figure 2 illustrates the differences.

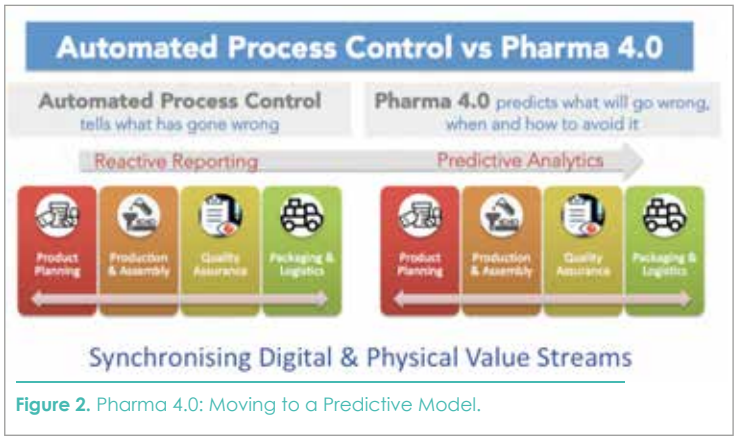

Figure 2. Pharma 4.0: Moving to a Predictive Model.

Today's pharma manufacturing operations are designed to gather information, and then evaluate historical performance and relevant trending using control charting, normality evaluation, regression analyses, to name a few common techniques. In the context of Pharma 4.0, algorithms will be developed that predict the performance of the desired value stream being measured to anticipate issues before they happen.

TAKING THE PULSE OF DRUG DEVELOPMENT TODAY

Pharmaceutical companies are locked in a perpetual race against time to innovate and bring new drug therapies to market as quickly and cost-effectively as possible, and innovator companies find their patent protection eroding. While a patent can provide a company intellectual property protection for twenty years, over half of that time will be spent turning the ideas embedded in a patent into a marketing product, leaving only a few years to recover what is often billions spent in development. An MIT[1] study published in April 2019 determined, after analysing more than 21,000 clinical trials between 2000 and 2015, that only 13.8 percent of drugs successfully pass clinical trials. Combine this state of reality with a development engine that struggles to bring drugs to the market and the need to improve the current model is obvious.

The global nature of the supply chain complicates the drug development process, with the introduction of innovative drug therapies such as personalised medicine, and cell and gene therapies. These therapies bring paradigm-breaking technical, quality, and regulatory challenges that require an alternative approach within the overall manufacturing value chain. Quality initiatives need to evolve to address new data management risks and to adapt to new advanced therapies that do not conform to historical development and regulatory frameworks for only manufacturing.

PERSONALISED MEDICINE: THE PATIENT IS PART OF THE SUPPLY CHAIN

One advanced therapy drug modality that exemplifies a significant shift in the management and the value of the supply chain is personalised medicine. Personalised medicine refers to the tailoring of medical treatment to the individual characteristics of each patient using the patient's own blood as part of the delivery system. It relies upon our understanding of how a person's unique molecular and genetic profile makes them susceptible to certain diseases. Today's companion diagnostics, based upon next generation gene sequencing (NGS) technology, make it possible to ensure that the genetic abnormality behind the disease state responds to the treatment provided.

A prominent approach to personalised medicine is the family of drug therapies based upon the Chimeric Antigen Receptor-T Cell (CAR-T) drug modality. T cells are extracted from a patient's blood then re-engineered in a lab to recognize and kill cancer cells, and re-infused back into the patient. Single-use technology allows small-scale tailored batches to be manufactured for each patient for the duration of their treatment.

The immediate supply chain starts with apheresis, where the patients' blood is harvested for downstream processing. However, processing the blood takes place in a separate manufacturing facility from where the blood is modified. A tailored drug treatment that is only manufactured once for a specific patient poses a regulatory conundrum, especially as it pertains to demonstrating process capability. Blood processing presents manufacturing challenges to the cold chain and could require multiple shipments of different materials at various sub-zero temperatures, all for one batch for one patient. The task is to harvest, process, evaluate, release, and return the drug to the patient within 30-35 days. This is a problematic time constraint given the current state of characterisation assays that often take several weeks to complete. When combined with a quality assurance data review and release process, the cycle time is rapidly bumping up against the 35-day target.

SUPPLY CHAIN EXTENDS FOR ADVANCED THERAPIES

The personalised medicine supply chain will also impact the extended supply chain involving third party contract manufacturing organisations (CMO). Most leading logistics service providers (LSPs) employ pharmacists and patient coordinators who deal with apheresis sites, and interact with hospitals, clinics, and patients. CMOs will have to navigate a new world of personalised medicine by improving their ability to clearly articulate the benefits of advanced treatments and their value to the patient, to help them feel comfortable with the costs. With advanced therapies, the immutable fact is that the risk proposition increases with the complexity of the raw material (Figure 3), partially because of the capability of new characterisation assays, and partially because of the cost and complexity of executing them.

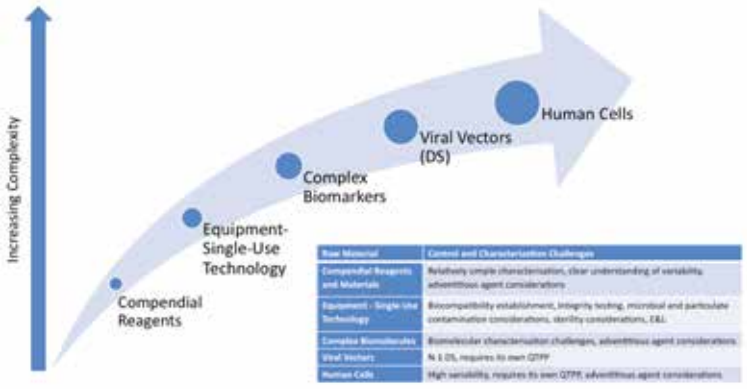

Figure 3. Raw Material Risk Increases.

The additional complexity associated with cell and gene therapy drug modalities cascades into establishing predictive algorithms, and larger data sets are required to have confidence in any desired outcome. As we said earlier, it is the lack of scalability that complicates the supply chain for personalised medicine. The current state is cumbersome at best for the cell line manufacturing of the lentiviral vector (Figure 4), not to mention the difficulty of scaling a personalised medicine supply chain (Figure 5), as this requires a network of clinical sites to support regional drug product manufacturing sites.

Figure 4. Complexity in the Current State of Lentiviral Production.

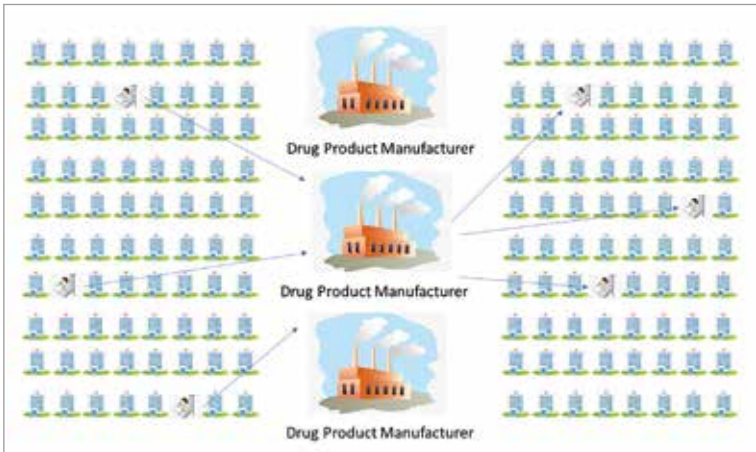

Figure 5. Scalability Challenges in the Personalised Medicine Supply Chain.

The many technical and manufacturing challenges associated with CAR-T therapies must be overcome before they can become a core component of most biologic portfolios. Inserting the patient into the supply chain also raises many data security issues—including HIPAA and GDPR compliance—which greatly escalates the risk exposure of data acquisition.

DATA INTEGRATION AND THE INTERNET OF THINGS

Compliance with the FDA Unique Device Identifier (UDI)[2] and the Drug Supply Chain Security Act (DSCSA) in the U.S. is just one of many compelling reasons to deploy Internet of Things (IoT) technology within the supply chain. Manufacturers—both drug sponsors and contract manufacturing organisations—should be in compliance with the act[3] today as the FDA extended the compliance deadline by one year to November 2018. In a global marketplace and supply chain where more than 70 different serialisation standards and regulations exist, a patchwork solution architecture is not viable in the long term.

Yet, data integration has proven to be the most perplexing problem in IT. Much of pharma's data is trapped in isolated islands of automation and disparate databases, and this complicates and limits the effectiveness of predictive analysis. Ontological databases have matured to a point where they can address, manage, and analyse siloes of disparate data. Technical solutions exist that allow data to be utilized in its raw state, to curate it, apply security and governance, and make it accessible for analysis as needed. These systems can provide pharma with a single portal and interface to all relevant data across the business value chain without disassembling any of the solutions in place. The reluctance to migrate away from legacy systems is one of the biggest organisational hurdles faced by cross-functional data management initiatives.

ZERO TRUST NETWORKS FOR PHARMA 4.0

In the modern supply chain we are describing, the need for ensuring data integrity is elevated because advanced therapies have additional requirements, including privacy issues. Basic principles of data and cGMP records (Attributable, Legible, Contemporaneous and Accurate—known as ALCOA) must be demonstrated as part of the final data acquisition and information management architecture. In a Pharma 4.0 smart factory we are adding "data" as a product being generated, so making certain the data is not adulterated moves to the forefront of any solution being considered. The immediate and extended supply chain must take into account the security and data integrity requirements of the data being acquired. In this scenario, modern IT solutions strive to address three basic requirements:

1. Segregate users, devices, data, and services, within a trust framework, to ensure every access request is validated and deliberately permitted or disapproved;
2. Be resistant and resilient to attack without a large administrative burden; and;
3. Be able to easily and rapidly (if not automatically) adjust to an ever-changing service environment also without a large administrative burden.

One approach to the problem of ensuring data integrity across the supply chain that is slowly gaining traction is the concept of zero trust network architecture. Zero-trust networks, first used in enterprise security, satisfy the above characteristics by treating all users, devices, data, and service requests in the same manner. This shifts from the traditional security policy of all assets in an organisation being open and accessible, to requiring continuous authentication and authorisation for *any* asset to be accessible. Much more than a single piece of hardware, "Zero Trust" is an architectural design approach to security, and a strategy for the modern pharma supply chain, where every device, user, and network flow is authenticated and authorized.

In general, Zero Trust:

- Provides a consistent security strategy of users accessing data that resides anywhere, from anywhere, in any way;
- Assumes a "'never trust and always verify" stance when accessing services and/or data;
- Requires continuous authorisation no matter what the originating request location, and;
- Increases visibility and analytics across the network.

The basic premise of Zero Trust is that the network is always assumed to be hostile and that external and internal threats exist on the network at all times. Because locality is not sufficient for deciding trust in a network, policies must be dynamic, and calculated from as many sources of data as possible. Large technology companies and the U.S. Federal Government have adopted Zero Trust[4] as their next-generation security model and Siemens[5], the largest industrial manufacturer in Europe, is now looking at zero-trust architecture as the next-generation solution for mission-critical business sectors.

ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING

If the IoT involves connecting devices to gather data, then artificial intelligence (AI) makes the decisions based upon that data. As such, the applicability of AI is not limited to the shop floor or the manufacturing supply chain. The potential applications of AI span the spectrum of drug discovery and molecule identification to post-approval pharmacovigilance. Almost every major market in the world, and many secondary countries have formal AI strategies underway.

AI is a broad term that applies to any technique enabling computers to mimic human intelligence. To fully understand its utility, it is important to look closer at the two subsets of AI: Machine Learning and Deep Learning.

Machine learning is not used solely to optimize performance on the shop floor. Applications of machine learning exist in the drug discovery phase that improve the success rates of new drug therapies and drug modalities as they move through the clinical pipeline. Novartis, for example, is using machine learning to improve their molecule selection process. By building large libraries of digital images of cells treated with different experimental compounds machine-learning algorithms are used to screen compounds faster with a higher rate of success.

CREATING A NEW FUTURE

To sum up, Pharma 4.0 aspires to harness data across the overall supply chain as a basis for operation, using predictive analysis techniques to enhance business performance. Advanced therapies complicate data acquisition by inserting

the patient into the supply chain, raising the threat profile from a data integrity and network security perspective, and by introducing global privacy requirements required by some major markets. Zero-trust networks are a secure approach to network architecture that could be advantageous when deploying IoT and when considering advanced therapies such as personalised medicines. Cell and gene therapy processes are still in early stages of development, but the ability to scale them will result in a tremendously complex supply chain.

For Pharma 4.0 to be fully effective in this context it will need to implement data acquisition and analysis solutions that provide data integrity in the near term, and the flexibility to accommodate the next generation of advanced therapy processes, as they evolve to mimic more conventional biological processes in the future.

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Bikash Chatterjee *has 30 years' experience in the design and development of pharmaceutical, biotech, medical device, and in vitro diagnostic products. His work has guided the approval and commercialization of over a dozen new products in the U.S. and Europe. Chatterjee is a member of the USP National Advisory Board and a past-chairman of the Golden Gate Chapter of the American Society of Quality. He is the author of Applying Lean Six Sigma in the Pharmaceutical Industry (ISBN-13: 978-0566092046) and a keynote speaker at international conferences. Chatterjee holds a B.A. in biochemistry and a B.S. in chemical engineering from the University of California, San Diego.*

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Integration of the new high-pressure reactor array module enables scientists to run a mix of reactions simultaneously, with each experiment conducted under different conditions. This extends the utility of the Integrity 10 reaction station, maximising efficiency and saving precious fume hood space. Manufactured as standard from durable 316 Stainless Steel - Asynt is also able to fabricate the system from exotic alloys such as Hastelloy or Inconel.

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Using the Integrity 10 reaction station allows scientists to design automated reaction profiles for each individual experiment; with variations in temperature, pressure, stirring and time possible. All data is captured and recorded electronically and stored automatically.

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