tetrascience

The data tenets of Pharma 4.0

Transform biopharmaceutical manufacturing through data maturity

WHITE PAPER

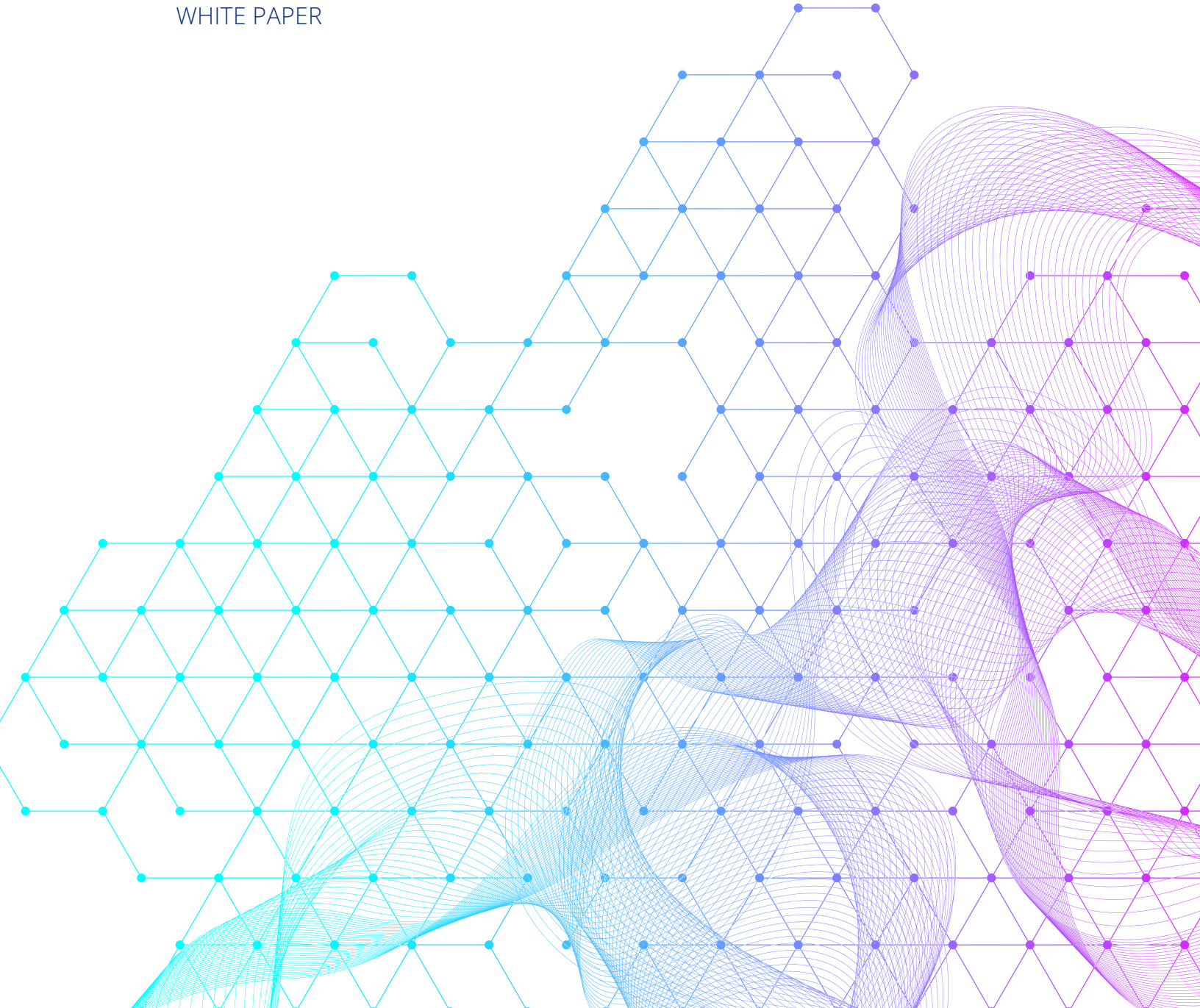


Table of Contents

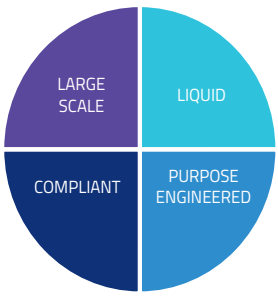
Executive Summary

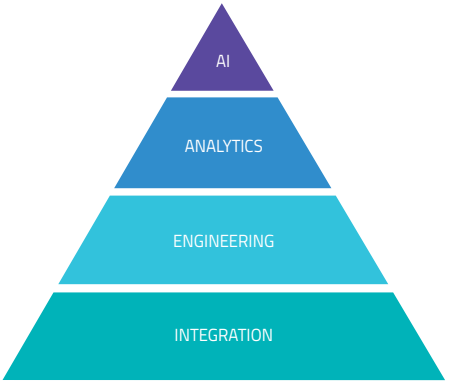
DATA MATURITY IS NO LONGER AN OPTION FOR BIOPHARMACEUTICAL MANUFACTURERS

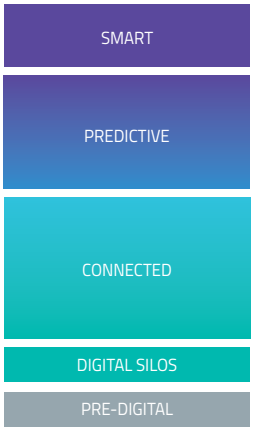
In response to increasing demands on biopharmaceutical manufacturing facilities, many companies are looking toward "smart" factory, or Pharma 4.0, solutions. Smart factory capabilities promise to increase efficiency, improve product quality, and provide a dynamic environment that can respond to the complex requirements of modern therapeutic modalities.

However, most biopharmas lack the data maturity to achieve smart factory capabilities. Artificial intelligence (AI), advanced analytics, and enterprise interconnectivity cannot function without **large-scale, liquid, purpose-engineered**, and **compliant** data.

By incorporating these new "data tenets" into their operations, biopharmas can advance their data maturity and provide the infrastructure that enables digital plant maturity and the impactful use cases associated with that evolution. These include: optimized tech transfer, collaborative data supersets, advanced process controls, continuous manufacturing, digital quality monitoring, recursive data exchange, continuous process verification, real-time release testing, agile manufacturing, and predictive maintenance.







Introduction

Modern biopharma manufacturing is a marvel of science, engineering, and cooperation. As of 2021, over 20,000 prescription drugs were being produced by 10,000+ human drug manufacturing facilities in the United States alone[1]. Each of these therapies requires:

- A unique manufacturing procedure
- A means to transfer that procedure from development to a commercial facility, and from facility to facility
- A compound-specific quality assurance/quality control (QA/QC) process
- Specific process controls and compliance protocols

Managing these workflows becomes more difficult as novel modalities with complex manufacturing processes enter and dominate markets.

In this landscape, one of the foremost challenges for creating consistent and safe medicines for patients while achieving profitability is optimizing manufacturing. Biopharma leaders are looking to other industries to see what best practices can translate to the biopharmaceutical space.

However, optimization in biopharma manufacturing has unique challenges compared with other industries. Biopharma products, processes, and data management are highly regulated for quality, efficacy, and safety. Meanwhile, the runway for profitability is limited due to competition and finite patents[2]. The result is a manufacturing environment where experimentation is simultaneously difficult and absolutely vital to product and organizational success.

Biopharmas are presented with a unique and meaningful challenge. How do you optimize manufacturing processes so medicines reach the market faster, without sacrificing quality and safety, all while saving time and money?

ENTER PHARMA 4.0

Industry 4.0 is a term that has been in use since 2011. It refers to the fourth industrial revolution that was set in motion by digital technology. Pharma 4.0 generally refers to the application of Industry 4.0 concepts to the biopharmaceutical space. However, there is one significant difference, and that is how Pharma 4.0 approaches data.

In Pharma 4.0 data is collected from all aspects of the manufacturing process, from raw materials to finished products. This helps create a holistic approach to manufacturing. In these facilities, people, systems, data, and AI seamlessly converge to enable better predictions, automated processes, and optimized drug development and production. The end result of Pharma 4.0 is often referred to as an adaptive, or "smart" biopharmaceutical factory.

Interest in smart factory techniques has grown over the years and most biopharmaceutical factories have some advanced capabilities. However, even with organizational alignment and plentiful funding, biopharma companies are struggling to evolve their manufacturing plants. One of the primary (and sometimes surprising) challenges is the quality and usability of scientific data.

SCIENTIFIC DATA IN MANUFACTURING

Biopharma leaders have discovered that the limiting reagent of digital plant maturity isn't solely the presence of data technology such as advanced analytics or AI. Rather, it is the maturity of the data itself.

Organizations have discovered that without large-scale, liquid, purpose-engineered, and compliant data, analytical applications and AI can't access or leverage data sets, limiting their ability to make accurate predictions and drive informed business decisions.

> ***"The first thing we've learned is the importance of having outstanding data to actually base your ML on. In our own shop, we've been working on a few big projects, and we've had to spend most of the time just cleaning the data sets before you can even run the algorithm. That's taken us years just to clean the datasets. I think people underestimate how little clean data there is out there, and how hard it is to clean and link the data."***
>
> **—Vas Narasimhan, CEO, Novartis**

Once the issue of data maturity was diagnosed, biopharma leaders quickly learned that creating and maintaining smart-factory enabling data infrastructures is difficult. These infrastructures require integrations with numerous instruments and software, which typically generate data in vendor-proprietary formats. Disparate data formats need to be engineered and contextualized so analytical applications can access and interpret that data.

Solutions for these challenges must adapt to the ever changing data ecosystem, as systems are continuously updated with new software and equipment. While there are some technologies that assist with data workflows, most can't cover end-to-end use cases (from data ingestion to data utilization). The result is digital siloes, cumbersome error-prone processes, and significant costs.

Fortunately, by leveraging a mature data model strategy, biopharmas can empower their AI and analytical applications, effectively enabling Pharma 4.0 principles and evolving manufacturing facilities toward smart factories.

What you'll find in this whitepaper

In the following pages, you will find an overview of the current state of manufacturing and QC processes along with a list of optimization parameters.

You will then find a discussion on how data tenets in biopharmaceutical manufacturing are being updated, a review of the data maturity model and how this impacts digital factory maturity, and the specific use cases that data maturity and plant digitalization unlock, such as:

- » Optimized tech transfer
- » Collaborative data supersets
- » Advanced process controls
- » Continuous manufacturing
- » Continued process verification
- » Digital quality monitoring
- » Automated quality monitoring
- » Recursive data exchange
- » Real-time release testing
- » Agile manufacturing
- » Predictive maintenance

The state of biopharmaceutical manufacturing

Where biopharmaceutical manufacturing is today

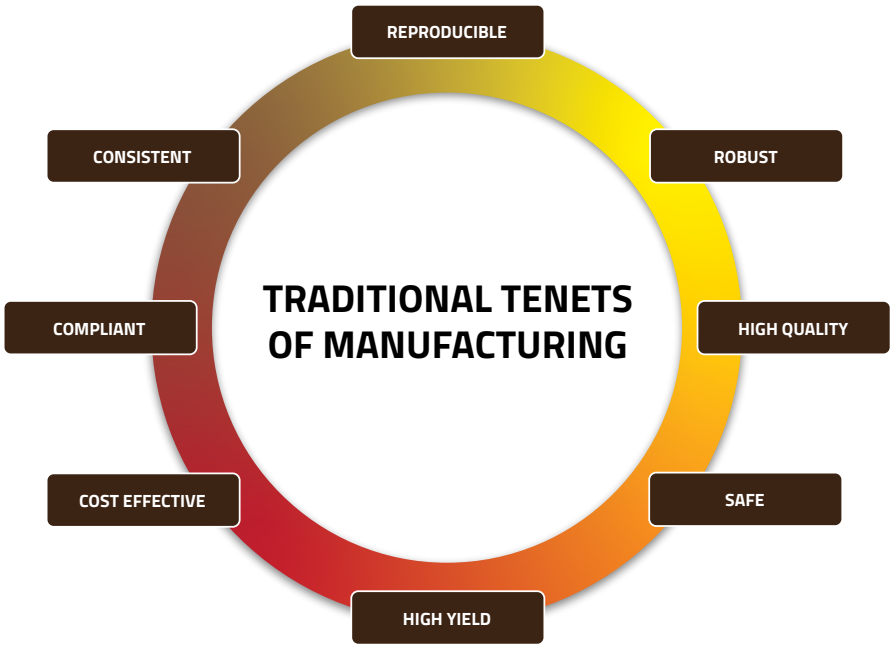
SCALE AND COMPLEXITY

Biopharmaceutical manufacturing requires the coordination of extremely complex, industrial-scale chemical and/or biological processes with supply chain management, ever-evolving techniques and technologies, and vast amounts of scientific data. Any variation within these systems can have outsized impact on downstream processes, product quality, safety, availability, and profitability.

REGULATION AND SAFETY

Biopharmaceutical manufacturing is highly regulated to ensure product quality, efficacy, and patient safety. To achieve this, QA/QC is essential and indispensable when compared with other industries.

Biopharmas rely on core tenets to manage key variables and execute effective biopharmaceutical manufacturing.

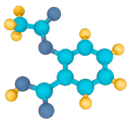
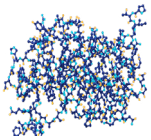
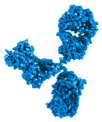


With the advent of new, more complex therapeutic modalities, adhering to these tenets has become difficult. Biologics, cell and gene therapies, drug conjugates, and personalized medicines require a significantly more complicated manufacturing process than traditional small-molecule compounds. Moreover, yields are smaller, costs are exponentially higher, and for targeted therapies, there's a definitive cap on scalability.

One need only look at the composition of therapeutic molecules to observe this change. The molecular weight of biologics, such as IgG antibodies, is 1,000 times larger than that of Aspirin. As a consequence:

- The number and scale of processes designed to ensure high-quality products is expanding
- Data volume is increasing
- Data management is becoming exponentially more difficult

Size and relative complexity of creating therapeutic compounds

Small-molecule drug	Large-molecule drug	Large biologic	Cell-based therapy
 **Aspirin** 21 atoms	 **hGH** ~3000 atoms	 **IgG antibody** ~25,000 atoms	 **CAR T-cell** ~100,000,000,000 atoms
 **Bike** ~10 kg	 **Car** ~1500 kg	 **Business jet** ~15,000 kg	 **Boeing factory** ~13,400,000 m^3

Adapted from Small Molecules, Large Biologics, and the Biosimilar Debate. https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate. AZBio.

INCREASED EFFICACY, BUSINESS VALUE, AND COST

The high efficacy and wide application of many recent biologics have assuaged industry skepticism around advanced molecule production. As of 2023, 6 of the top 10 biopharmas have a large-molecule biologic as their lead product. Many therapeutics achieve such high value by transcending their original indication, becoming a "pipeline in a product." At the time this paper was written, Humira boasts 9 indications while Keytruda touts 30[3,4].

Despite their impressive efficacy, the business value of these products remains closely tied to cost management. The raw materials, process complexity, technology, and data management required for manufacturing complex molecules increase the price per manufactured batch by as much as 1200%[5]. Furthermore, yields for traditional small molecules are often measured in kilograms, whereas large-scale production for a biologic, like a monoclonal antibody, is anything over 100 grams[6].

The increased market demand, high operating costs, and high value-per-mg/mL place immense pressure on biopharma manufacturers to optimize their processes. Unfortunately, they face significant challenges:

Biologics	Personalized therapies	Cell and gene therapies
Complicated to produce	Small patient populations	Complicated and expensive production
Low yield compared with traditional small molecule production	Demands on plant agility are unprecedented	Tumultuous regulatory environment
Inherent variability due to being biologically derived	Value of product (per mL or gram) is high, making efficiency demands extreme	No scale due to limited patient volume
		Coordination between multiple facilities required

SIX PARAMETERS FOR BIOPHARMA MANUFACTURING OPTIMIZATION

To improve manufacturing processes, get therapies to market faster, save time and money, without sacrificing quality and safety, biopharma companies need to optimize around six key areas but are held back by current practices.

Parameter	Current roadblock
 **Human Work**	• Manual data processes such as transcription, processing, QA/QC, and harmonization are slow and error prone • Escalating data volume and automation increase the amount of manual data transfer/ transcription events • Deviations from standard operating procedures (SOPs) and their impact on out-of-trend/out-of-specification (OOT/OOS) events are difficult to track
 **Process Performance**	• Despite producing terabytes of data per day, manufacturing facilities struggle to derive insights that can optimize performance • The lack of large-scale, liquid, engineered, and compliant data inhibits the success of AI models that promise to optimize process performance

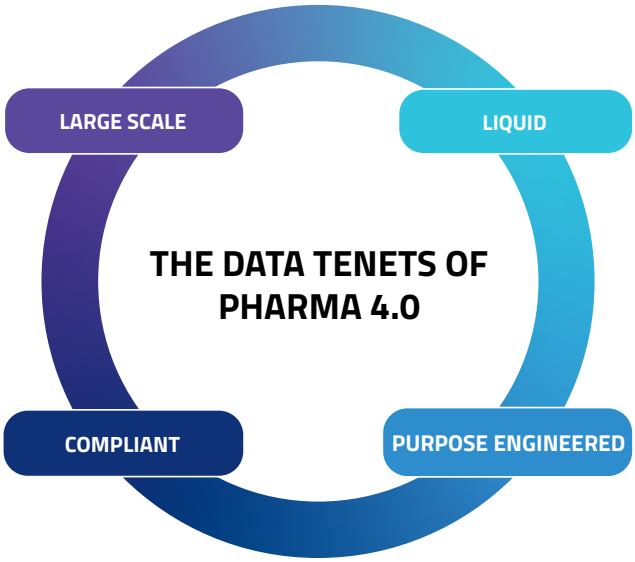
Parameter	Current roadblock
 **Asset Performance**	• Predictive and proactive asset maintenance is difficult without streamlined data workflows and near-real-time data. This leads to unplanned downtime • Environmental monitoring and deviation prediction are challenging due to lack of accessible and analytics-/AI-ready data
 **Network Performance**	• Supply management and cross-facility comparisons require seamless data transfers that current data infrastructures can't support • Most biopharmas don't have the centralized, accessible, and near-real-time data that is required to optimize decentralized production (e.g. COVID-19 vaccine manufacturing)
 **Regulatory Compliance**	• Compliance efforts are high • Optimization requires change. But once processes are set, users are disincentivized from changing parameters due to regulatory risk • Costs associated with revalidation are high
 **Environmental Sustainability**	• Traditional processes are often paper based, which necessitates shipping, storage facilities, and frequent on-site visits • Inventory tracking and monitoring are typically decentralized, making it difficult for organizations to control product loss and minimize supply chain waste • Variability in process and environmental conditions can lead to faulty batches, wasted materials, and wasted energy • Unoptimized manufacturing workflows require more raw material and produce less potent outputs

Adapted from "The biopharma factory of the future," by L Pernenkil, M Humphreys, S Laaper, A Deshpande. Deloitte. 2019.

Achieving digital plant maturity through data maturity

Augmenting biopharma data—the lifeblood of digitalization in manufacturing

The common thread across manufacturing optimization roadblocks is scientific data. Unfortunately, many biopharmas are discovering that these roadblocks persist throughout digitalization and Pharma 4.0 efforts. AI, analytical tools, and visualization applications all rely on a foundation of large-scale, liquid, purpose-engineered, and compliant data. In other words, if biopharmas want to build "smart" factories, data maturation is no longer optional. Organizations must prioritize scientific data management and adhere to the 4 data tenets of Pharma 4.0.

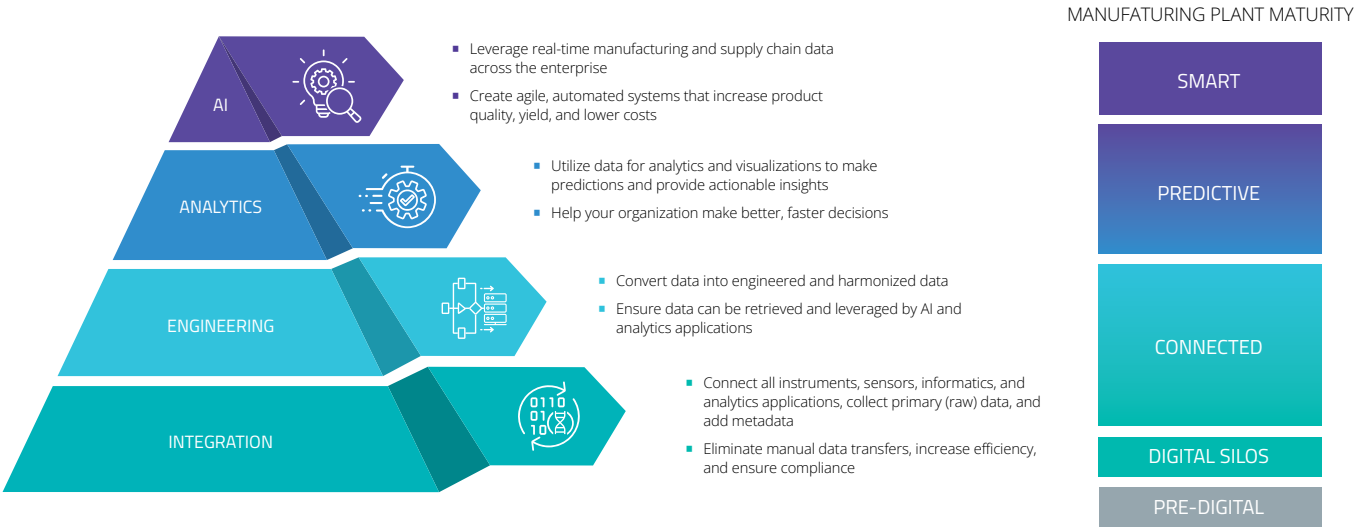


Large scale	The insights and value produced by AI, advanced analytics, and data applications are directly correlated with the amount of data they can access. Data must be collected and centralized in a single-source-of-truth rather than distributed in silos.
Liquid	Data must seamlessly flow across instruments, applications, departments, and organizations. Data must be searchable and usable for users no matter where they are within an organization.
Compliant	At every step of the data journey data must be compliant with regulatory standards. Organizations must have the ability to prove data integrity and traceability to comply with 21 CFR Part 11, EU Annex 11, and GxP guidelines.
Purpose engineered	Scientific data ecosystems generate data in numerous proprietary data formats. These various formats cannot be read or interpreted by AI or analytical tools. Data must be engineered into formats that AI and data applications can locate, read, and interpret. This requires a deep understanding of the underlying science and the scientific workflow that might include AI or a specific scientific application.

Unlocking the power of smart factories

Adhering to and implementing these data tenets within manufacturing facilities has become a top priority for leading biopharma companies, especially as the promise of AI edges its way from concept to industry best practice. This process is known as data maturation, and it works in lockstep with the digital maturation of manufacturing facilities, as each stage of the maturity model unlocks smart factory use cases.

It is best to approach data maturity in a stepwise fashion, beginning with a foundational infrastructure that ensures all systems (lab instrumentation, processing equipment, machinery sensors, LIMS, ELNs, analytics applications, etc.) are connected to a platform and data is centralized. Next, data must be contextualized and harmonized so it can be found, accessed, and analyzed by the high-value applications atop the data value pyramid.



While for many organizations the north star of AI is clear, the data infrastructure and engineering needed to reach that goal remain somewhat obscure. This will be the defining issue for biopharmas looking to advance their manufacturing facilities. AI and smart factories are not possible without connected ecosystems, centralized data stores, and harmonized, enriched, analytics- and AI-ready data.

Assessing digital plant maturity—on the road toward "smart" plants

Alongside data maturity rises digital plant maturity, where facilities can move from pre-digital spaces with manual data processing and paper-based storage toward the fully autonomous and self-optimizing "smart plants" of the future.

Currently, most facilities have some aspects of "digital" and "connected" plants, while industry leaders may have aspects of the "predictive" plant. Smart plants stand as the ultimate target, consisting of systems with mature data infrastructures, properly leveraged AI, and effective optimization protocols.

Stage of digital plant maturity	Description	Data maturity
Pre-digital plant	• Data is manually processed and paper-based storage and archiving is predominant • Lab instruments, plant machinery, and informatics applications are not connected • Compiling information for batch release and inter/intra-site transfers is time consuming and tedious • Lead times are long • Predictive and proactive asset maintenance is inhibited • Tracking and diagnosing root causes for OOT/OOS events is cumbersome • Proving GMP compliance through paper-based submissions and on-site visits is a burden and slows down processes	None
Digital silos	• Some integration between instruments and applications has been achieved • Lack of harmonization and centralized data storage results in digital silos across the plant • Automated systems used for quality management, lab management, and compliance processes are disconnected • Decentralized controls result in inconsistent SOPs and processes across the enterprise • Data-based decision making through AI or analytics requires significant efforts	Integrated

Stage of digital plant maturity	Description	Data maturity
Connected plant	• Instruments and machinery are connected to a centralized location allowing global systems to be established for quality management, lab management, and compliance • Data is harmonized across sites, enabling automated descriptive analytics, with automated controls to ensure data integrity • High level of plant automation, integration, and systems standardization • Semi-automated batch review	Integrated Engineered Analytics
Predictive plant	• Completely streamlined plant network with pervasive, real-time, predictive analytics • Integrations across internal and external plants and labs provide a near-real-time, end-to-end view of quality management and lab operations • At-line testing, automated batch release, and review by exception (plus some in-line testing with real-time release [RTR]) • Automated archiving of reports and records for regulatory review • Analytics embedded in lab management and quality management processes	Integrated Engineered Analytics AI
Adaptive (smart) plant	• Autonomous, self-optimizing systems • Supply chain management is fully optimized as integrations extend to external stakeholders and field-generated quality information • Plug-and-play, self-configuring instruments integrated into modular manufacturing units • In-line, real-time automated process monitoring and release eliminate the need for a traditional QC lab • Automated regulatory inspections eliminate the need for site visits • Multivariate prescriptive analytics with AI/ML learning adjusts parameters to avoid deviations and optimize outcomes	Integrated Engineered Analytics AI

Adapted from A best practice guide to using the BioPhorum digital plant maturity model and assessment tool. M Dubs, H Vilas, Y Berthouzoz, S Banerjee, I Helliwell, J Selva. BioPhorum. 2018.

The only way to achieve smart factory transformations is by establishing a mature foundation of large-scale, liquid, purpose-engineered, and compliant data.

Use cases

Use cases for digitally mature biopharma plants

Biopharmas that achieve data and digital plant maturity will quickly realize significant scientific and business benefits. It is one of the reasons Vas Narishman, the CEO of Novartis, stated that we are in the middle of "the fourth industrial revolution," enterprise IT spending will reach $240.5 billion in 2023, and McKinsey estimates that generative AI could unlock potential value equal to 2.6 to 4.5 percent of annual revenues across life science industries.[7-9]

Both capital patterns and biopharma leaders anticipate the powerful capabilities for enterprises that successfully leverage the combined emergence of medical, instrument, and data technologies. Below, we review several but not all of the capabilities empowered by data and digital plant maturity.

OPTIMIZED TECH TRANSFER

Successfully migrating process parameters and quality control (QC) test methods from one facility to another requires the seamless transfer of massive amounts of data. This is true whether you are transferring data from a development to a commercial facility, transferring data between commercial facilities, or between sponsors and contractors.

Process knowledge management is crucial if organizations want to maintain quality across their enterprise. However, each transfer makes process knowledge management more difficult. Duplicative data sets and interfacility data silos bar organizations from maintaining a single source of truth for their scientific data. Meanwhile, many facilities still use tedious, error-prone paper documentation for their tech transfers.

Smart plants leverage centralized repositories of contextualized data that enable teams to quickly search for and identify relevant data. This could include raw material information, instrument information, instrument group information, end-to-end workflow data, etc. Using this data, the receiving site can see precisely how a batch ran at the donor site. Harmonized data will then allow seamless data comparisons and data interoperability, even if manufacturing and/or lab equipment is from different vendors. This accelerates first-to-manufacture times, enables first-right-time execution, eliminates error-prone manual processes, and significantly reduces costs.

COLLABORATIVE DATA SUPERSETS

CDMO facilities and biopharmas each collect, store, and manage manufacturing data separately. However, as data is centralized into large-scale stores and engineered into liquid formats, both parties can begin to leverage data across all their data sets simultaneously. These data supersets contain comprehensive insights into historic timelines, effective models of production, production volume, data volume and type, input/output specs, and more.

By pairing these large-scale and liquid-data supersets with AI models, CDMOs and biopharmas can unveil

hidden insights such as undetected failures or deviations, improving overall product quality and throughput speed. Data-superset-powered AI models can also significantly improve how biopharmas manage, structure, and predict workload and turnaround time by fine tuning scheduling and enabling greater predictability. This helps them avoid "empty suite" issues, where suites are underutilized due to projection and scheduling inefficiency. It also helps them avoid "full suite" issues, where projects must be turned away due to overcapacity.

System predictability and data insight will improve over time as data is continuously fed into larger-scale stores and more advanced AI models. These capabilities will empower sponsor/contract teams to boost overall production and reduce cost.

ADVANCED PROCESS CONTROLS

Advanced process controls (APC) refers to the complex algorithms that use plant data (instrument, sensor, etc.) to create predictive, adaptive, and optimized techniques to control manufacturing processes. Applications of APC include model predictive control, fault detection and diagnosis, condition-based monitoring, and real-time process optimization.

In essence, these applications enable real-time monitoring of process outputs/inputs and real-time prediction of process endpoints and product attributes to determine deviation from the predetermined ranges. They can also calculate how process inputs or equipment settings should change in order to reach desired outputs.

These capabilities offer unprecedented levels of efficiency, improved product quality, lower common cause variations, greater product consistency, improved yield, and cycle time improvements as well as optimized energy/raw material consumption and costs. This is why APC is one of the foundational pillars of the adaptive plant, the highest level in the digital plant maturity model. It's important to note, however, that APC also requires the highest level of data maturity. The AI and advanced analytical models that power APC require large-scale, liquid, engineered, and compliant data to generate value.

CONTINUOUS MANUFACTURING

Empowering a facility to produce a single product in one, non-stop, continuous fashion dramatically reduces hold times and costs. In an ideal state, continuous manufacturing also represents a synthesis of multiple smart factory capabilities operating simultaneously, including continuous process verification (CPV), real-time release (RTR) testing, automated quality monitoring, and advanced process controls (APC). Since the first approval of continuous manufacturing for an active pharmaceutical ingredient in 2020, biopharma has trended strongly toward continuous versus batch release techniques.

To provide these capabilities, factories require a plantwide control strategy that monitors multiple product and process attributes throughout successive operations. These processes need to be closely linked and monitored in real time. This requires sophisticated plantwide controls and rigorous adherence to evolving

regulatory standards.

The importance of data maturity for continuous manufacturing cannot be emphasized enough. The capabilities of plantwide control are predicated on access to real-time data from numerous instruments and sensors. That data needs to be harmonized and automatically enriched with metadata (engineered). This allows advanced analytics and AI models to access the appropriate data, relate it to the correct system, and analyze ongoing operational status against prior or potential future conditions. Systems powered by both advanced analytical instruments and a mature data infrastructure can produce, QC, verify, and self-correct automatically, ensuring product control end-to-end.

The end result is manufacturing plants with small equipment footprints, reduced lead times, shortened times-to-market, lower inventory costs, and safer processes.

CONTINUED PROCESS VERIFICATION

Developing, improving, and validating manufacturing processes and analytical procedures helps accomplish two things: identify conditions that impact variability in product quality, and introduce boundaries to control them. In traditional biopharma plants, these states were predetermined in the process design stage of development and carried forward in a static state that could not adapt to plant or input variations. Furthermore, once the protocol was developed, technicians and operators were disincentivized from making changes. Any deviation from protocol could result in loss of batches, investigation, and subsequent corrective and preventive actions (CAPA), or worse, an FDA Form 483 or other warnings from a regulatory agency. Additionally, any protocol changes would require QA involvement so they can revalidate the new protocol. These processes are very time consuming and costly.

Smart factories, however, provide a more dynamic and cost-effective way to prove that processes have not left their validated state even as the process adapts to variations in raw materials, instruments, and environmental conditions. While a well-defined design space backed by engineered, harmonized data supports a systematic quality by design (QbD) approach, deeper process knowledge and real-time analytics are required for real-time responsiveness, monitoring, control, and prediction. Continued process verification (CPV) encompasses real-time data on relevant process trends and critical quality attributes (CQAs) of incoming materials or components, in-process material, and finished products. Most commonly, system suitability, performance trending, or similar visualizations can be used to show the historical trending of observations or measurements for parameters and attributes of interest. These observations are made possible when instruments and software can store historical trends in a centralized, large-scale data store, while simultaneously moving data seamlessly across workflows, allowing trends and relationships to be analyzed and interpreted in near-real-time.

Data harmonization and contextualization become even more important as manufacturers implement multivariate statistical process controls, which use sophisticated techniques to characterize valid states of a manufacturing process. This characterization, or “fingerprint” of a validated state, can be used as a comparator for future states to help ensure newly manufactured batches are generated by the same validated state, while also providing a reliable benchmark for test models.

DIGITAL QUALITY MONITORING

Consistent production of safe, effective medicines requires strict adherence to product specifications. Organizations must devote significant resources to quality control (QC) processes so they can guarantee the safety, efficacy, and quality of products.

In large enterprises, QC labs need to document tens of thousands of deviation cases per year. However, biopharmaceutical manufacturing ranges in complexity. Intricate systems, such as those associated with biologics and cell and gene therapies, tend to have higher degrees of freedom, behave non-linearly, and exhibit multiple variable interdependencies. This means that identifying the root cause for out-of-spec (OOS) products requires capturing and analyzing interdependencies between hundreds of variables.

Furthermore, the data associated with deviations is generated by dozens of instrument types and models. In traditional labs this data is manually collected and reformatted. This process is extremely time consuming and doesn't make use of all the data available.

Smart factories with mature data infrastructures within their QC labs can consolidate all their data into one easily accessible single-source-of-truth while engineering that data so it can be ingested and interpreted by applications that can run multivariate analysis, such as AI.

Pairing data maturity with high-powered analytics allows organizations to leverage both historical and emerging data from every deviation instance within the lab. Doing so enables organizations to greatly increase the speed of deviation investigation, infer causal relationships to articulate which variables require adjustment, and predict future deviation. By doing so, smart factories greatly increase throughput and reduce lead time

AUTOMATED QUALITY MONITORING

As plants reach digital maturity and production processes become automated, it is crucial for quality control (QC) to also transition to automation.

Smart factories must deploy an approach to validation that provides continual monitoring of automated systems, as well as enabling systems to adjust as necessary. While there are AI systems that perform these types of calculations and controls, proper execution requires heavy investment in the foundational layers of data maturity—integration of instruments and the collection and engineering of scientific data. If those fundamental layers are in place, manufacturing plants have several tools at their disposal.

The first is optimized tech transfer. Analytical methods developed in early stages of development will carry forward and be applied to the commercial facility. The second is the use of continued process verification (CPV) to ensure a process is consistently operating (and producing product) and meeting tight, predetermined standards. Quality monitoring should then assess outputs and use that data to validate the process, while simultaneously preempting and preventing future out-of-spec production.

RECURSIVE DATA EXCHANGE

Every deviation detected within quality control (QC) labs produces high-value data that development labs can use to improve their process experimentation. However, that data is often siloed and difficult to transfer between QC and development lab groups due to disconnected data stores and disparate data formats. These bottlenecks in "local" tech transfers limit development labs to incomplete data sets.

Smart factories solve this issue by leveraging centralized, liquid data to initiate consistent communication between development and QC. This ensures that deviation data generated by QC labs can seamlessly flow back toward development labs. Using this recursive workflow, development labs can analyze data regarding production suite conditions and product quality across every run and batch, supercharging their optimization efforts and greatly improving future development strategies.

REAL-TIME RELEASE TESTING

As plants mature, functions such as continuous manufacturing and continued process verification (CPV) enable new opportunities like real-time release (RTR). RTR is an advanced procedure that utilizes signal conditioning, advanced chemometrics, and multivariate calibration models to accurately determine in-process and final product attributes. If successfully implemented, plants will be able to accurately and compliantly confirm a product's fit-for-use, independent of off-line testing. This will drastically reduce time-to-market and increase product quality.

RTR is a data-based procedure that requires a high level of process understanding, including historical data regarding the impact of process parameters on raw materials or critical quality attributes (CQAs), and connection/access to real-time process data. In other words, the level of RTR quality assurance and compliance adherence is correlated with the size, liquidity, and quality of an organization's scientific data.

AGILE MANUFACTURING

While some biopharmaceutical products benefit from a continuous manufacturing model that is highly centralized in one location, other products require a decentralized model where components of drug products are produced at multiple facilities. This technique was demonstrated by COVID-19 vaccine manufacturing, where bulk drug substances were manufactured at one location and then shipped to other sites for batch formulation and subsequent filling and packaging.

In other cases, new therapeutic modalities like cell and gene therapies may require production of on-demand dosages for small populations or even a single individual.

This manufacturing model demands modularity and flexibility of the manufacturing facilities. Both data and digital plant maturity will enhance these manufacturing modules by centralizing an enterprise's data in one easy-to-access location, enabling automated, near-real-time workflow updates, and providing highly liquid, engineered data. The upshot is seamless migration of scientific data, validated operational states (CPV fingerprints), and analytical models from one facility to another.

PREDICTIVE MAINTENANCE

In addition to acquiring data from instruments and sensors to assess process and product quality, data can help evaluate and predict equipment performance. Most facilities use a production control system or basic sensors for their predictive maintenance data. A subset of facilities still rely on "best guess" practices where instrument usage and wear-item fatigue are estimated based on gut feeling rather than hard data.

However, the wealth of data generated by labs (chromatography for example) and manufacturing systems (throughput speed, fan speed, temperature, number of runs, etc.) can be used to assess the status of specific equipment. By collecting this data in one easily accessible and searchable location, engineering it so it can be compared and seamlessly flow across an organization, data scientists can apply advanced analytics or AI models to the complex, multivariable data sets. This allows facilities to predict when maintenance will be required and when equipment needs to be replaced or serviced.

Ultimately this reduces downtime, conserves resources, and reduces the health, environmental, and quality risks associated with poor equipment performance.

Conclusion

Unlocking Pharma 4.0 through data maturity

Biopharma manufacturing is evolving. Exciting technologies like AI and novel treatment modalities are creating a future of improved therapies and manufacturing quality. But while much of the attention is given to AI, analytical applications, or technological solutions, the primary foundation for a biopharma manufacturing facility's success is its data.

Many biopharma companies have already seen data roadblocks emerge despite investment in high-power technologies. This is because analytical solutions, including AI, rely on massive volumes of accessible and interpretable data. Biopharma companies that adhere to the new data tenets of Pharma 4.0—creating mature data that is large-scale, liquid, engineered, and compliant—will be the first to realize their smart factory ambitions.

The advantages provided by smart factory capabilities are difficult to overstate. Automation, self-correction, and compliance streamlining will provide generationally significant scientific and business advantages. The result will be innovative, high-quality, safe medicines that cost less and reach patients faster.

To learn more about advancing your data maturity, visit tetrascience.com

References:
[1] FDA. "FDA at a glance." April 2023. https://www.fda.gov/about-fda/economics-staff/fda-glance.
[2] Rome, Benjamin; Lee, ChangWon; Kesselheim, Aaron S. "Market Exclusivity Length for Drugs with New Generic or Biosimilar Competition, 2012-2018." Clin Pharmacol Ther. 109, 2 (February 2021): 367-371.
[3] AbbVie Inc. "HUMIRA® (adalimumab). Package Insert." February 2021. https://www.rxabbvie.com/pdf/humira.pdf.
[4] Merck & Co., Inc. "Selected Indications for KEYTRUDA® (pembrolizumab)." https://www.keytrudahcp.com/approved-indications (accessed August 9, 2023)
[5] Makurvet, Favour Danladi. "Biologics versus small molecules: Drug cost and patient access. Med Drug Discov. November 2020. DOI: 10.1016/j.medidd.2020.100075.
[6] National Institute of Health. "Monoclonal Antibody Production." National Research Council (US) Committee on Methods of Producing Monoclonal Antibodies. 1999.
[7] Finelli, Luca A; Narasimhan, Vas. "Leading a Digital Transformation in the Pharmaceutical Industry: Reimagining the Way We Work in Global Drug Development." Clin Pharmacol Ther. April 2020. https://doi.org/10.1002/cpt.1850.
[8] Gartner. "Forecast: Enterprise IT Spending for the Healthcare and Life Sciences Markets, Worldwide, 2021-2027, 1Q23 Update." April 2023. https://www.gartner.com/en/documents/4282399
[9] Chui, Michael; Hazan, Eric; Roberts, Roger; Singla, Alex; et al. "The Economic potential of generative AI." McKinsey and Company. June 2023.

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