www.PHARMAMANUFACTURING.com

pharma™ MANUFACTURING

THE DRUG INDUSTRY'S VOICE FOR MANUFACTURING EXCELLENCE

Automation & Smart Pharma

TABLE OF CONTENTS

Thermo Fisher
SCIENTIFIC

Achieve faster results with precision

What if you could streamline your biotechnology process without sacrificing precision and quality?

With our Prima mass spectrometers, you can. As the standard in gas analysis, our robust instruments provide improved precision, accuracy, long intervals between calibration, and resistance to contamination so that you can optimize industrial processes across many applications.

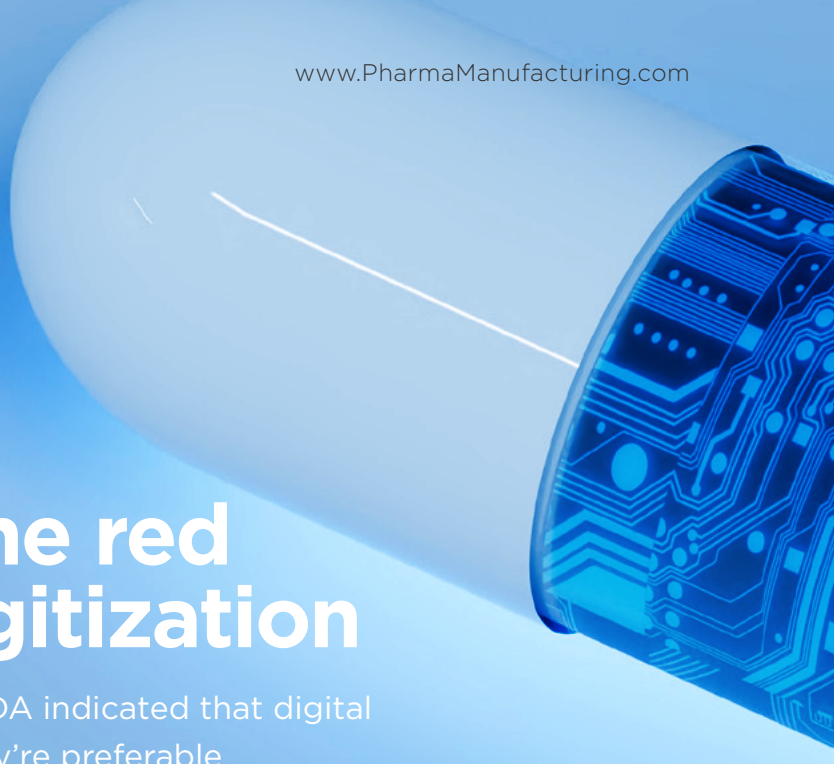
Learn more at **thermofisher.com/primapro** or **thermofisher.com/primabt**

▲ Prima PRO Process Mass Spectrometer

▲ Prima BT Bench Top Process Mass Spectrometer

thermo scientific

AD INDEX



Rolling out the red carpet for digitization

By releasing 21 CFR Part 11, the FDA indicated that digital tools aren't just acceptable — they're preferable

By Erin Wright, Vice President, Product Management, MasterControl

No one would call the U.S. Food and Drug Administration a trendsetter. However, the agency was ahead of the times in 1997 when it released 21 CFR Part 11 regulations on electronic records and electronic signatures.

At the time, records were mostly on paper, and the idea of a binding signature always meant pen and ink. The FDA accurately foresaw how important tech advances would be to the life sciences, however, and decided to officially recognize that digital records and signatures could be just as binding as their physical counterparts. Not only that, but the agency was also wise enough to provide the backbone requirements of an electronic system without hampering industry from innovating with new technologies and approaches.

Part 11 came out over 25 years ago, but electronic signatures and records have never been more ubiquitous — because of this, the guidance continues to be relevant. It is the only reason life sciences companies can use software to create, update and store records, as long as that software is Part 11 compliant.

Part 11 rolled out the red carpet for digital systems in regulated industries. This is the broadest, most dramatic effect that it's had. Technology would have progressed regardless, but by releasing this regulation, the FDA indicated that digital tools aren't just acceptable — they're preferable.

Today, pharma manufacturers that have fully committed to digitizing have seen the benefits of Part 11 in multiple areas

Part 11 is a signed permission slip from the FDA to embrace technology that encourages innovation while allowing firms to remain compliant.

of their business and those that haven't will likely find it increasingly difficult to stay compliant.

DATA INTEGRITY FOR BETTER PRODUCT DEVELOPMENT

Per Part 11, "Persons who use closed systems to create, modify, maintain or transmit electronic records shall employ procedures and controls designed to ensure authenticity, integrity, and when appropriate, the confidentiality of electronic records."[1] This aligns with good data practices and ensures data integrity.

Data has always been vital to developing and manufacturing pharmaceuticals. In 2020, then-FDA Commissioner Stephen M. Hahn, while speaking about developing treatments for rare diseases, emphasized the role of data in the drug development process.

Hahn said, "Ensuring the availability and high quality of data allows us to maximize the extraordinary potential of science, better support the development of new medical treatments and cures, and increase the knowledge patients and consumers have to make informed decisions about FDA-regulated products."[2]

That data would be much harder to access and analyze if it were still on physical paper because regulations didn't allow electronic signatures. Part 11 essentially granted permission to pharma companies to use the technology they need to ensure data integrity and make drug discoveries faster.

AUDIT TRAILS

Part of good data management is ensuring you can track who entered or changed data. That's why Part 11 also requires "secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify or delete electronic records."[1] Any change to data needs to be trackable.

According to an FDA guidance document on data integrity, "FDA expects processes to be designed so that data required to be created and maintained cannot be modified without a record of the modification."[3]

This requirement doesn't mean pharma companies have to use digital systems for

21 CFR Part 11 compliance checklist

If your company is planning to convert to an automated system for managing documents and business processes, make sure that the new system meets the needs outlined in this 21 CFR Part 11 compliance checklist.

- ☑ **Authentic electronic records:** Part 11 requires assurance of the authenticity of electronic records. Your system must include functionality to delineate user permissions for every document vault in the system, as well as be able to generate an audit trail.

- ☑ **Multiple password authentication:** The potential for a signer to repudiate an approval must be minimized. An automated system should require users to enter two passwords — one for login, another for approvals — to approve any type of document collaboration.

- ☑ **Computer system validation:** Any electronic system used to manage compliance-oriented documents and processes must be validated. Implementation of an electronic system with a proven track record can drastically reduce the time and money a company devotes to overall validation efforts.

- ☑ **Integrated personnel training:** All users approved to use the electronic system must be sufficiently trained to perform assigned duties. A system that incorporates automated training capabilities can automatically trigger new training courses when an essential quality document is revised to ensure sustained organizational compliance.

- ☑ **Effective change control management:** Document controls must provide revision controls, change controls and time-based system modifications.

- ☑ **Electronic signatures:** Signed electronic records must include the following data: name, date and time of signing, and meaning of signature. An effective electronic system should provide fields for all such required information.

- ☑ **Interconnected records/signatures:** Electronic (and handwritten) signatures must be able to be linked to their corresponding electronic records. An established electronic system should easily be able to link every signature with a specified record.

their records. But digital systems that are designed with this in mind do happen to make it much easier to provide an audit trail. When pharma companies use software that is Part 11 compliant, this information is created automatically and can be pulled whenever necessary.

Not only does having an audit trail keep companies regulatory compliant, it also prepares them for data-driven decision making when formatted appropriately. If all of the data, corrections and change reasons are defined and understood within a company's systems, it puts the company that much closer to being able to infer insights and make data-driven decisions about products.

Since Part 11 was released, document management systems have become more commonplace in pharmaceutical manufacturing environments. These systems fulfill the requirements for data integrity and audit trails while relieving quality and regulatory professionals from the stress of having to ensure these requirements are being met through a manual system — at least, that is the case when the system does what it is designed to do.

HOW PHARMA CAN IMPROVE VALIDATION

Ensuring software works the way you need it to work is the whole point of computer system validation (CSV). After all, if software plays a part in compliance, pharma manufacturers need assurance that it performs as advertised. The key to not becoming overwhelmed by validation is to determine the part it plays in your organization. Not every single system used by a pharma manufacturer needs CSV.

An FDA guidance document suggests that businesses "take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability and authenticity of required records and signatures."[4]

Unfortunately, CSV is commonly seen as a burden that can take months of time. This doesn't have to be the case if companies use the approach recommended by the FDA. When pharma companies use risk to determine where to focus their validation efforts on their intended usage, validation can be done in a matter of hours or even minutes. This more efficient version of CSV still ensures compliance with Part 11 and other regulatory requirements and aligns with what the FDA has been asking for over the last twenty years. It also means manufacturers can update with every software release instead of continuing to use a much older version for fear of the validation burden — putting them at risk for data integrity concerns and security breaches.

Part 11 had the potential to revolutionize how pharma manufacturers store batch records, SOPs, work instructions and other documents.

DOCUMENT RETENTION AND RETRIEVAL

Part 11 had the potential to revolutionize how pharma manufacturers store batch records, standard operating procedures (SOPs), work instructions and other documents. The FDA was trying to enable companies in regulated industry to use digital systems in the widest sense possible, but this isn't the reality that played out. In theory, a pharma company that has completely digitized its systems should be able to immediately pull up any document the FDA needs to see. And with file sharing, sending a document to the FDA should also be an easy task.

Twenty years ago, this is the future that Pharma Manufacturing magazine had in mind. In the brand's inaugural issue, one article noted, "But these electronic records have even bigger benefits — they allow manufacturers to share information quickly and easily, store and analyze information in ways not possible with paper, and improve documentation quality and security by decreasing human access and error."[5]

Unfortunately, while this is technologically feasible, it isn't always how the industry operates. This was very apparent during the COVID-19 pandemic when the FDA had to resort to using remote tools for inspections in lieu of showing up on-site. Records requests were not optional when it came to the pharma industry. Under Section 704(a)(4) of the Federal Food, Drug and Cosmetic Act, refusing a records request carries the same weight as refusing an inspection.

Paper-based pharma companies that received a records request during the pandemic found themselves hunting down physical paper and scanning those documents to send to the FDA electronically. While this did fulfill the needs of the FDA and the pharma companies were complying by providing records in this manner, it took considerably longer than if those records had been electronic. Just as with the original Part 11, the FDA is not forcing companies to digitize, but compliance is easier by digitizing.

PART 11: MORE RELEVANT THAN EVER

Part 11 is a signed permission slip from the FDA to embrace technology that encourages innovation while allowing firms to

remain compliant. The agency is embracing digital solutions and moving into the future. This trend is obvious in the FDA's attitude toward the remote inspection tools previously mentioned.

One of those tools is remote regulatory assessments (RRAs). RRAs were a side effect of the pandemic, but not one that will disappear when the pandemic is over. According to the FDA, RRAs are to be "incorporated consistently across all FDA-regulated products beyond the current COVID-19 public health emergency."[6] By nature, an RRA runs smoother when the company in question is using electronic systems.

Apart from the FDA, the industry itself is steadily moving in this direction, although it's clear that not every organization has fully embraced Part 11-compliant digital systems. Recent research from Cicero and MasterControl indicates that in life sciences as a whole, 64% of organizations prioritize digitizing their manufacturing departments.

This is definitely an ongoing process for most life sciences companies. Respondents indicate that 52% consider their companies to be digital, and 35% say they are connected, meaning they have multiple systems communicating with each other.

Part 11 deserves a place of honor alongside every software that allows pharma manufacturers to move faster and be more innovative because of compliant electronic signatures and records. There is certainly no obligation for these companies to use digital systems, but as those systems become more common, the FDA will likely continue to produce guidance and regulations on the assumption that pharma manufacturers have digital capabilities. The FDA's attitude toward electronic systems and increased pressure from competing pharma companies that have digitized indicates that this needs to be a priority for pharmaceutical decision-makers.

REFERENCES

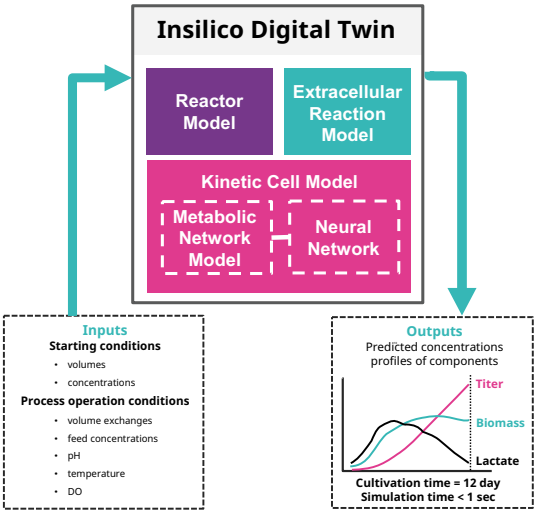
1. FDA. Part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures. (1997).
2. Hahn, S. FDA. Remarks by Dr. Hahn to the Public Meeting on Rare Diseases, FDA. (2020)
3. FDA. Data Integrity and Compliance With Drug CGMP. (2018).
4. FDA. Part 11, Electronic Records; Electronic Signatures – Scope and Application. (2003).
5. Palus, T., Norz, C. Six Steps to Part 11 Compliance. Pharma Manufacturing. (2002).
6. Califf, R, McMeekin, J., FDA Details Optimized Approach for Regulatory Oversight Tools to Better Protect Public Health. FDA. (2022).

Yokogawa Insilico Biotechnology

Transform your data into new opportunities through virtual experimentation.

Yokogawa Insilico Biotechnology provides software solutions for predictive biomanufacturing using digital twins. The biopharma industry uses our software to accelerate time-to-market, to mitigate risks, and to capitalize on the value of data.

- SELECTOR
  Identifies top clones
- COMPOSER
  Optimizes media composition
- FEEDER
  Optimizes feeding strategy
- SCALER
  Scale-up/Scale-down
- CONTROLLER
  Model-predictive control
- NAVIGATOR
  Characterizes the design space



Let our experts guide your digital transformation journey
insilico-biotechnology.com

YOKOGAWA
Co-innovating tomorrow™

Circling back to digital initiatives

Three priorities for re-strategizing digital transformation post-COVID

By Matt Weaver, Senior Manager, Digital Technologies Industry Lead, Rockwell Automation

It's well established that digital transformation is revolutionizing pharmaceutical development and manufacturing. But what may come as a surprise is that only 2% of life sciences leaders are realizing the full benefits of their digital transformation initiatives across the core processes of their organization.[1] Many organizations have been busy on the front lines of retooling processes and production capabilities to meet pandemic-related needs, and consequently, digital transformation has taken a back seat.

As pharma manufacturers adjust to the new normal of post-pandemic operations, they're increasingly circling back for more comprehensive assessments on how best to accelerate their digital transformation efforts. In doing so, many companies are finding that the key is to embed these initiatives more fully into companies' overall strategy for a smoother transformation toward a more productive digital environment.

CATCHING UP ON THE TRANSFORMATION TO-DO LIST

After scrambling to implement measures to maintain safe operations on the factory floors while also adapting production toward medicines urgently needed during the pandemic, many pharma companies are finally able to take stock of how their businesses have fundamentally changed. It's especially critical for the sector to catch up, given the likelihood that new public health crises will place similar pressures on the industry in the future.

The good news is that, as pharma refocuses on the marketplace and strategic choices in

The wrong approach to digital adoption risks broadening the potential attack surface as companies move from tightly guarded on-premises data management towards a new world.

transforming their information technology and operational technology systems, digital transformation teams in the industry are finding an increasing number of options available for structuring and implementing these transformations. The Industrial Internet of Things (IIoT), augmented reality (AR) and related innovations have shown their value to connect people, products and processes together for a more orchestrated and cost-effective operation.

These powerful building blocks for digital transformation enable companies to connect, monitor, analyze and act on data in new ways. AR, in particular, is a highly visual and interactive method of presenting relevant digital information in the context of the physical and operational environment — streamlining the flow of information and instruction to operators to improve efficiency and effectiveness.

However, with these enhanced choices comes the enhanced need for strategy in implementing them. Investment in the technologies alone doesn't guarantee that the organization will experience the full potential of manufacturing innovations. For that to happen, they cannot just be bolted on; they must instead be fully integrated into the desired business approach and the IT/OT processes that support that approach.

The challenge is compounded by the nature of pharma manufacturing. Production must happen in highly sterile and climate-controlled environments. This creates increased cost, complexity and compliance hurdles. For these reasons, it's crucial that pharma manufacturers plan and design their implementation strategically and in accordance with their broader business operations.

3 priorities for success:

1. Embrace a holistic view of transformation
2. Let the desired business outcomes drive the technology choices
3. Address the workplace culture and digital transformation management components

THREE PRIORITIES FOR SUCCESS

While there's no single path to success, here are three key priorities that pharma manufacturers must keep in mind when charting the way forward in their digital transformation journeys:

1. Embrace a holistic view of transformation

The true value of connected technologies isn't simply what they can do for specific operations, but how technologies can enable an entire connected ecosystem. That requires a more holistic view of the design and benefits you want to reap from your connected platform and how this integrates with a broad range of business priorities and stakeholders.

The scope of digital transformation goes well beyond the manufacturing process and analytics. This holistic view of transformations must include comparative analytics across both the organization and its broader network of partners, suppliers and logistics service providers. This will help inform how companies shape a more collaborative digital ecosystem enabled by enhanced access across any location; more options for orchestration and ability to manage devices as separate layers to existing operational equipment; and connectivity with modern tools for practical adoption, such as via tablets, smartphones or AR headsets.

Critically, this holistic mindset must extend to the industry's view of security. Given that pharmaceutical operations involve tremendous amounts of intellectual property and sensitive information, the wrong approach to digital adoption risks broadening the potential attack surface as companies move from tightly guarded on-premises data management towards a new world of cloud, remote working and internet-enabled devices. It is important to take a comprehensive and proactive approach to security via clear processes around handling, sharing and storing data.

2. Let the desired business outcomes drive the technology choices

Technologies such as AR, machine learning and predictive analytics can be applied to a wide range of use cases. So the questions that should be asked are: which specific functionalities would offer the most benefit your plant, and where should they be applied? The focus should be on what you want to achieve, and then the technology choices follow as a means to do that. Pharma facilities can take advantage of new Process Analytical Technologies (PAT) to

improve quality and efficiency, IIoT connectivity to consolidate data for electronic batch records, extended reality technologies to enable their workforce, or digitized tech transfer processes to improve time to market.

Once the focus areas are defined, drill down to consider specific user requirements and iterate backward to define the functional and technical specifications. This can best be achieved by using agile methodologies to prioritize and dynamically update the list of features to be included in applications — with ongoing testing and verification to ensure they are in line with expectations. Strategic piloting and scaling can then follow as the broader organization is reshaped.

Zeroing in on the right capabilities means also zeroing in on the right data — its nature and usability —to power these capabilities. Think through, for example, how production performance data might be useful both to the line manager seeking to boost efficiency and to the engineers seeking to ensure the machinery is operating at optimal levels. It's a strategic and proactive approach to help companies better track, contextualize and monitor real-time data against pre-defined measurement criteria.

3. Address the workplace culture and change management components of digital transformation

Implementing new technology capabilities is part of a bigger move to fundamentally change an organization's mindset. That means workforce culture plays a role at every stage, and the right change management programs must be developed and implemented as part of the transformation. This is essential to demonstrate the effectiveness of the digital transformation program.

Workforce culture is included among the four key areas of consideration laid out in the National Academy of Science and Engineering's Industrie 4.0 Maturity Index, with which all digital transformation teams in manufacturing should be familiar. Along with resources, organizational structure and information systems, culture is listed as a key area that requires its own strategy and approach that must be finely balanced for a successful transformation.

It's rarely the case that a digital transformation program fails because the business chose one set of technology specifications over another. Rather, it's almost always that the organization's culture wasn't supportive of change. In assessing an organization's readiness for change, make sure that those on the shop floor have the necessary support to adopt these solutions to enhance their own productivity and drive progress in a successful digital transformation strategy.

Pharma companies and other life sciences manufacturers may have lagged in their overall digital transformations in order to focus on immediate pandemic needs, but now they're charting beyond current circumstances to consider how digitalization transformations can be undertaken in more strategic and powerful ways.

It's a welcome trend toward more resilient operations, stronger supply chains and enhanced efficiency in production. As this happens, we can make the industry better at bringing the latest treatments to market — driving favorable health care outcomes and making a positive impact on the patients that need them.

REFERENCES

1. Ulrich, P., et al. Will your digital investment strategy go from virtual to reality? (2020).

HYGIENIC PUMPS FOR FLUIDS & PASTES: FROM <0,1 ML

- Repeatability of > 99 %
- For one & two component materials
- Gentle handling: Low-shear & pulsation-free
- No dripping due to adjustable suck back
- For low to high viscosity materials
- GMP-compliant hygienic dispensers

Solutions for supplying and dosing or filling of difficult to handle fluids and pastes – for semiautomatic or fully automated packaging lines.

viscotec.com

Digitize to curb staffing challenges

Modern manufacturing solutions can spare pharma the worst of ongoing labor shortages

By Dave Edwards, Chief Revenue Officer, MasterControl

Pharmaceutical manufacturers face unique challenges, all of which are exacerbated by the ongoing shortages of skills and staffing in the manufacturing industry. As demand soars, the number of job candidates declines, and it is increasingly difficult for pharma manufacturers to rapidly produce safe, effective products in a tightly regulated market that has no margin for error.

The National Association of Manufacturers (NAM) reports that between 2023 and 2031, the U.S. labor pool will only grow 0.2% per year. Left unchecked, the issue of having a disproportionate number of jobs compared to qualified candidates could have an overwhelming impact on the economy. The 2021 Deloitte and NAM talent study estimates that we could reach 2031 with 2.1 million unfilled manufacturing jobs, and in that year alone, the skills and staffing shortages will cost the U.S. economy $1 trillion.

It's important to understand that if changes are made today, these numbers do not need to become a reality. Addressing the full scope of the problem will take time, but one of the most effective steps to take right now is adopting a modern manufacturing solution. The outdated business model of relying on manual, paper-based processes is no longer sustainable because the industry is running low on its most valuable resource: people.

Pharma manufacturers need to employ systems that create efficiencies for workers so they can do more in less time. Digitization also makes it possible to retain and engage

current employees, attract tech-savvy talent and meet growing demand.

RETAIN AND ENGAGE

In the midst of a labor shortage, workers with skills specific to pharma manufacturing operations are in high demand, which makes it critical for pharma companies to retain current teams and make the best use of their time. The most effective way to do this is to ensure employees have opportunities to become engaged by investing their time in meaningful work, which ultimately adds to the success of the company.

According to a report by Gallup, there is a strong correlation between employee engagement and retention. Additionally, companies where at least 70% of employees are engaged see improvements in growth and profits.

Using paper-based processes hinders an organization's ability to engage workers and optimize their time and skills. Manual tasks performed using paper are repetitive and can take hours to perform, and it isn't uncommon for the work to include fixing mistakes created by using paper in the first place. For example, paper batch records are subject to human errors including incorrect or illegible entries, missing signatures or even lost or damaged records. The result is additional time spent addressing these mistakes.

With the technology available today, manual work that is dependent on paper

Digitization can save pharma manufacturers a significant amount of time, and this empowers employees to work on more meaningful tasks, which can include product improvements or other innovations.

and does not engage employees is largely unnecessary. By removing paper and digitizing, many tasks are automated, and the potential for human error is greatly reduced or eliminated entirely. Returning to the example of batch records, electronic batch records improve efficiency and reduce delays because incorrect, missing or out-of-date information is not allowed by the system.

Digitization can save pharma manufacturers a significant amount of time, and this empowers employees to work on more meaningful tasks, which can include product improvements or other innovations that make the product more effective. The next big idea that puts a pharma manufacturer on the map could come from an existing employee who has time to leverage their experience and add value. It's just a matter of empowering workers by digitizing so they can find the time to contribute in new ways.

To illustrate this point, one pharma manufacturing customer estimated that each week, 30% of each operator's time was spent on paper inefficiencies. Digitization eliminated the need to perform paper-based tasks, and thus every operator gained 12 hours per week to invest in engaging activities to help drive the company's success.

In some cases, a portion of the time made available by more efficient processes should be dedicated to training, which will help employees get up to speed on the technology included as part of a modern manufacturing solution. This too is an important component of an effective retention strategy.

A recent McKinsey report noted that digitization is one of the most significant disruptors in pharma operations. In part, this is because technology changes how work is being performed, and as a result, new skills are required to perform certain jobs. The report stated, "Reskilling employees to address talent gaps can help a company retain the bulk of its operations workers and empower them to take advantage of a new world."

Just as current employees are one of the strongest assets pharma manufacturers

have to address the labor shortage, the same is true for acquiring the new skills required as part of digital transformation. Employers that adopt a modern manufacturing solution and dedicate the necessary resources to engaging and training their workforce will see a significant return on investment.

ATTRACT TECH-SAVVY TALENT

As you work to appeal to digital natives and individuals who have built careers around their ability to work intuitively with technology, digitizing operations and having a truly paperless shop floor can be a powerful recruiting tool. AMS, a workforce solutions firm, reports, "Transformative technology allows the candidate to understand the company culture and values so candidates can make informed choices as to whether the company is one they want to work for."

Among other things, a modern manufacturing solution indicates that a company fosters a culture where employees are given the tools they need to be successful and innovative. It also signals to candidates that a company is invested in being an industry leader while making a commitment to producing a high-quality product that can change lives. Top talent is drawn to these organizations.

You're ultimately building an adaptable workforce that is comfortable with change. This is key when it comes to adopting a modern manufacturing solution and being able to take full advantage of the flexibility it provides. In pharma manufacturing, demand for certain products is always fluctuating, and you need the right people with the necessary skills so you can adapt quickly.

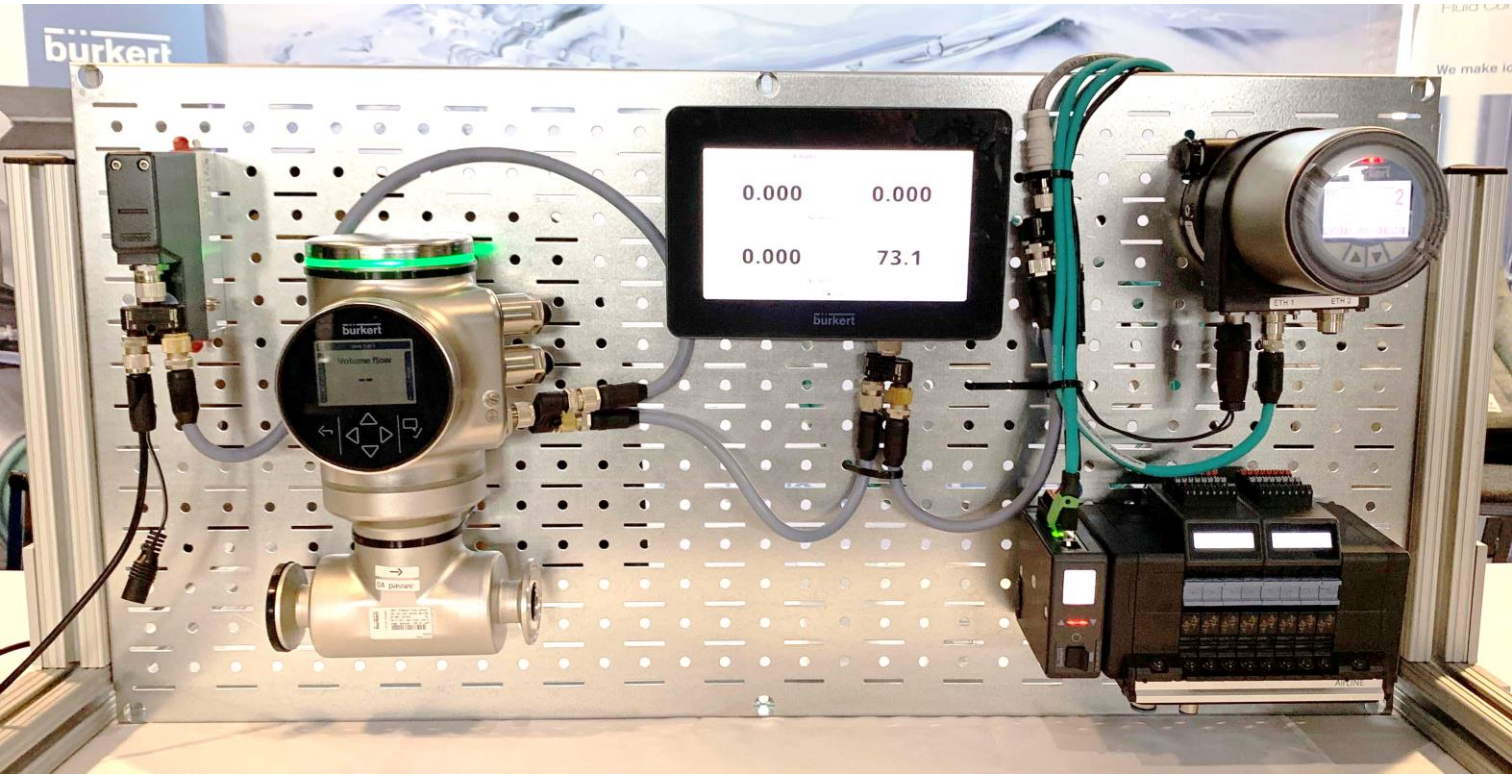
DIGITIZE NOW

Within a decade, the manufacturing industry could face a shortage of skills and staff that will cost the U.S. economy $1 trillion in 2031 alone — but it doesn't have to be that way.

By digitizing now, manufacturers can streamline operations, leverage the skills of existing employees, and attract tech-savvy talent. Pharma manufacturers who accomplish this will be able to keep up with inevitable changes in the industry, and not only will they be able to meet current demand, but they will be flexible enough to move faster than the competition.

Complete Communication Packages

When devices are connected seamlessly and communication protocols are coordinated together, the entire process is more efficient and cost effective.



Fully Compatible Devices Include:

Type ME43 Fieldbus Gateway

Type 8652 Valve Island

Type ME61 Process Display

Type 8098 Acoustic Flowmeter

Type 8653 AirLINE Field Valve Island

Type 8692 Top Mounted Digital Positioner

Type 8792 Side Mounted Digital Positioner

Whether it be pharmaceutical, food & beverage, packaging, or even an automated car wash - there are hundreds of thousands of applications in a vast sea of industries that rely upon automation. From pneumatic actuation panels, process controllers, mass flow meters, valves, and sensors - the communication and control of these separate devices can be complex and costly. Fortunately, Burkert has unique and creative ways to circumvent these challenges.

Coupled with the wide range of communication protocol options available, each with its own benefits and caveats, Burkert is constantly working on producing system solutions that ensure a complete control package with synchronized communication and a range of devices that partner together seamlessly.

bürkert
FLUID CONTROL SYSTEMS

Connecting labs to power digitalization

Developing a holistic data strategy will enable pharma to create a fully integrated ecosystem

By Dr. Moussa Saleh, Senior Project Manager and Dr. Christian Mueller, Director Service & Support for EMEA, Thermo Fisher Scientific

A fully integrated network of laboratories can deliver significant benefits to the pharmaceutical industry. By facilitating improved connectivity and collaboration between their network of laboratories and manufacturing plants, pharma companies can become more productive, strengthen their resilience to disruption and offer greater job satisfaction for their scientists. To this end, digital transformation programs are underway in pharmaceutical companies worldwide.

Well-integrated data systems are a critical component of the connected laboratory, providing a single source of truth accessible across the organization. At present, however, data silos and unconnected systems represent a significant hurdle for many pharma manufacturers, limiting their transformation efforts.

Improving data integration is a challenging process. Attempts to address single gaps between instruments, systems or laboratories won't necessarily deliver data harmonization — and could even hinder future transformation efforts.

By creating a holistic data strategy and implementing advanced data solutions to connect their laboratories to each other, as well as integrating quality data from the manufacturing plant, pharma organizations can overcome data silos in manufacturing and continue their digital transformation journey.

THE DRIVE TO ADDRESS DATA SILOS

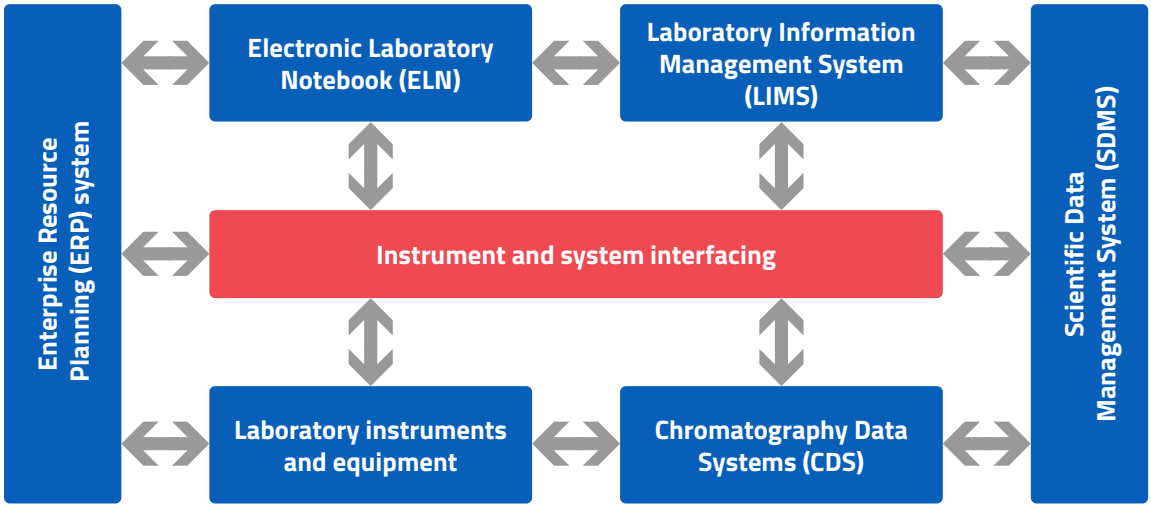
Data management is critical in pharma manufacturing, for both compliance and timely workflow decisions. High volumes of data both from QA/QC laboratories as well as from Enterprise Resource Planning (ERP) systems must be safely and appropriately stored, so that information can be accessed by the right people at the right time.

However, pharma manufacturers often face data silos. A combination of the disparate data formats of lab instruments, isolated software systems, unintegrated workflows and past acquisitions mean that many organizations have a fractured information landscape. Data may be isolated on one system or available to just one group, limiting communication between individual labs, sites, regions and even external collaborators. Information that could be critical to plant managers waiting to release product, or when collated with other details might provide a crucial answer to a manufacturing issue, is often left adrift.

These data silos also pose significant challenges for the manufacturing process by creating gaps in data integrity. This could compromise the completeness or consistency of datasets, and the accuracy of the insights discerned as a result. Equally, disparate systems require the manual transfer and input of data, which can represent a sizeable drain on efficiency, particularly where data needs to be transferred between international sites. The productivity of scientists is therefore reduced by needing to spend time on these highly repetitive and error-prone tasks.

EXHIBIT 1

A harmonized system connecting laboratory and manufacturing data



Without an integrated, standardized system to share information between the laboratories and plants, pharma manufacturers may not be able to realize improvements to manufacturing processes and workflows. Meanwhile, at a strategic level, decision-makers may lack a holistic view of the business to inform the choices that will guide the future of the organization.

ACCELERATING INTEGRATION

The drive to create fully integrated data systems and strengthen data integrity has accelerated over recent years and even months. Establishing a single data repository improves data tracking, storage and reporting; that in turn enhances efficiency, facilitates scalability and flexibility across the organization, and improves decision-making. There has also been clear support from a regulatory perspective, with the U.S. Food and Drug Administration establishing the ALCOA+ principles for data integrity in pharmaceutical manufacturing, stating that data must be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

Pharma manufacturers are now more aware of the potential of cloud-based storage and applications to support the delivery of data integration. The cloud helps facilitate a single source of truth for data and enables easier data sharing across teams and global sites. Importantly, pharma manufacturers have growing confidence in data security in the cloud.

More recently, COVID-19 has underlined the need for data management improvements to support resilience in the face of disruption. Laboratories that are heavily dependent on manual data input have seen their operations particularly disrupted by social distancing requirements. This has in turn made it more difficult to provide plant managers with the timely QA/QC data required. Integrated digital processes, together with data automation, can keep labs operational with fewer scientists on site, and maintain a seamless flow of data to manufacturing plants.

It's also true now more than ever that pharma manufacturers need to be well positioned to provide the fastest and most efficient operation to deliver high quality drug products. This can only be possible if all opportunities are taken to automate and streamline processes, and to ensure information is made available to those who need to make critical operational decisions. Collating QA/QC data from labs with manufacturing data from ERP systems provides a more holistic view of operations throughout the organization, enabling continual improvements to maximize production efficiency.

In addition to significant short-term operational benefits, single data repositories will

Collating QA/QC data from labs with manufacturing data from ERP systems provides a more holistic view of operations throughout the organization.

enable pharma manufacturers to conduct more sophisticated analyses of their laboratory and plant data to identify longer term patterns and opportunities. With a standardized, central data set, pharma manufacturers have the opportunity to benefit from utilizing data analytics, including machine learning, to spot trends over time. These insights enable continual performance improvements, enabling organizations to realize the full value of their data.

The opportunities to maximize the value of data for both operational optimization and longer-term transformation are clear. However, the level of complexity in labs combined with other operational requirements can make delivering integrated data systems a significant challenge.

ESTABLISHING A HOLISTIC DATA STRATEGY

The most effective way for pharma manufacturers to establish a fully integrated data system is to develop a holistic data strategy encompassing the whole organization.

In the past, many labs have attempted to address gaps in their data processes individually, with single upgrades or patches that might cover a single integration or section of the organization. However, this approach will leave gaps at the end of the process, and may render it more difficult to integrate new instruments, software or technologies in the future.

By contrast, taking the time to develop a holistic data strategy enables the organization to create a fully connected ecosystem, with a single source of truth from the lab to the boardroom. Manufacturers can map their existing systems, determining where gaps lie and what information needs to be captured and connected to deliver value for the business.

Technology specialists can support this process by providing strategic guidance and identifying the data solutions that will most effectively integrate instruments and software systems, while enabling the adoption of new technologies further down the line.

INTEGRATION IN ACTION

A data integration program was recently undertaken by a large pharma company. The Chemical and Pharmaceutical

Development (CPD) department was using six disconnected systems and over 1,000 disconnected instruments. Importantly, there were large differences between sites and departments, with heterogeneous IT landscapes and inconsistent LIMS usage, which meant the project required significant conceptualization to create one strategy incorporating every system.

The pharma company worked with a technology partner to improve data harmonization. Laboratory Information Management System (LIMS) software was chosen to manage lab data and procedural workflows, and connect with other enterprise systems, instruments and equipment. The built-in integration solution was used to build cross-connectivity between the LIMS, ELN, CDS and SDMS, as well as the instruments and equipment used in the lab. (Exhibit 1)

The higher degree of integration achieved has increased efficiency by 20 percent, with additional improvements to both data quality and integrity. Fewer mistakes are likely through transcription errors, while the labs benefit from the security of a full audit trail, including a risk-based audit system. Information isn't simply captured as "paper on glass," but intelligently linked to improve searchability. Despite the different modules and capabilities, the user experience across the labs is nearly seamless — and scientists now have more time for what they are most passionate about: Science.

This project also highlights the importance of cultural change to a successful data strategy. Scientists are often required to focus on operational tasks, so don't have the time needed to make the transition to new technologies or develop new digital skills. By establishing a holistic strategy that incorporates the people who use the systems, pharma manufacturers can ensure their data integration programs are more effective.

Beyond individual transformation programs, technology vendors have a key role to play in the establishment of a universal data format that will facilitate future integration. Organizations like the Allotrope Foundation and Pistoia Alliance are working to establish standards for common data formats, which will benefit end users going forward.

A PLATFORM FOR TRANSFORMATION

Pharma manufacturers can achieve significant operational advantages by addressing their data silos. An integrated system that connects labs and manufacturing plant quality data across the organization can provide greater efficiency and scalability, facilitate flexibility, and improve decision-making. But importantly, establishing an integrated data system will be a key major step forward for enabling improvements both in the lab and across manufacturing operations to support future transformation. Considering the current need for pharma to be ready to rapidly

deliver a large supply of vaccines and treatments, there has never been a more significant time to advance on this digital transformation journey.

With truly connected labs, pharma manufacturers can establish greater collaboration across the business, identify continual organizational improvements and, perhaps most importantly, enable scientists to spend more time on productive, valuable and rewarding tasks. By establishing a holistic data strategy, with the support of a strategic and collaborative technology partner, pharma manufacturers can improve workflows today and be prepared to quickly make adaptations for their needs of the future.

Building intelligent processes for Pharma 4.0

How to develop a smart cell culture bioreactor

By Shilpa Nargund, Managing Director, Yokogawa Insilico Biotechnology

Market needs for cheaper, safer and better-quality drugs are driving digital transformation within the pharmaceutical industry.

The amalgamation of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and Industry 4.0 has resulted in a new era called “Pharma 4.0.” A key piece to achieving Pharma 4.0 is the enabling of smart manufacturing. This involves developing intelligent processes that can self-adapt.

Smart manufacturing is possible due to advances in technologies such as artificial intelligence (AI), the Industrial Internet of Things (IIoT), sensors, robotics, and virtual reality. The core driver, however, is data. When data is converted to decisions that are automatically executed, we achieve ‘smart’ manufacturing processes.

To convert data into decisions, we need to build models that learn the hidden rules in the data. These models must accurately mimic the behavior of the manufacturing process. The most sophisticated models can predict the outcome of a process and prescribe desired changes to it. Such models are called digital twins. A digital twin is a virtual representation of a physical object that reacts to interventions in a manner that is identical to its physical counterpart. Most digital twins rely on machine learning methods to learn hidden rules in the data. However, it is best to build hybrid models that combine mechanistic knowledge with data-driven knowledge.

Once a digital twin is prepared, we must enable it to automatically execute its prescriptions on the manufacturing process. This means that the twin's outputs need to be converted into control actions by an intermediary. The twin also needs to obtain feedback from the manufacturing process in real-time using this intermediary. Developing these intermediary communicators between the digital and physical counterparts is the last crucial step in endowing 'smartness' to the manufacturing process. Further, in the pharma industry, all components of the smart manufacturing process must comply with ICH guidelines.

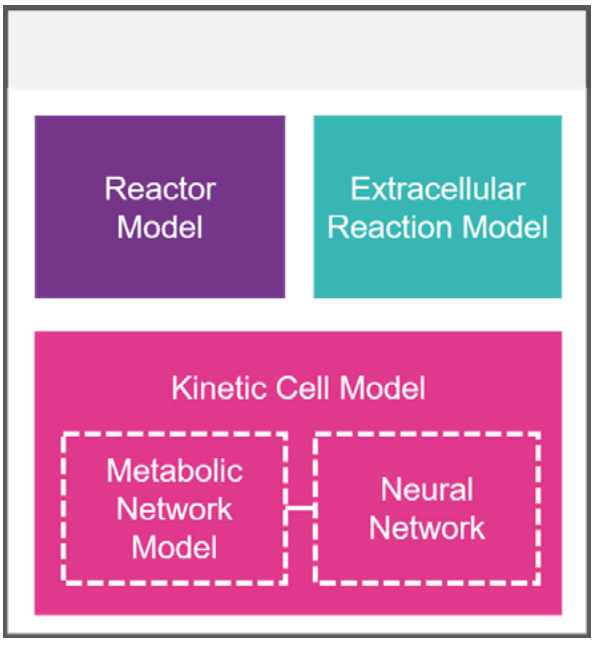


Exhibit 1. Digital twin hybrid model

In the next few sections, we will showcase our approach to developing a 'smart' cell culture bioreactor for biomanufacturing.

BUILDING A DIGITAL TWIN OF A BIOREACTOR

The digital twin predicts the concentration profiles in the bioreactor during a virtual experiment. In our approach, we have built a hybrid model that combines three models – the Reactor Model, the Extracellular Reaction Model, and the Kinetic Cell Model.

The Reactor Model describes batch, fed-batch, or continuous processes by accounting for the changes in volumes and component concentrations in the bioreactor vessel that result from the inlet (feeds, base, antifoam, etc.) and outlet streams (samples, cell bleed, harvest, etc.). The Extracellular Reaction Model tracks concentration changes due to abiotic reactions such as degradation of glutamine in the cell culture media.

The Kinetic Cell Model tracks concentration changes in the bioreactor that result from cell metabolism and growth. This is arguably the most critical part of the digital twin. Here, a genome-scale metabolic network model is combined with an artificial neural network. The time-series data from cell culture processes (e.g. viable cell density, titer, amino acids, lactate, ammonia, etc.) is used in two ways when training the digital twin. It is first used by the metabolic network model to identify the active

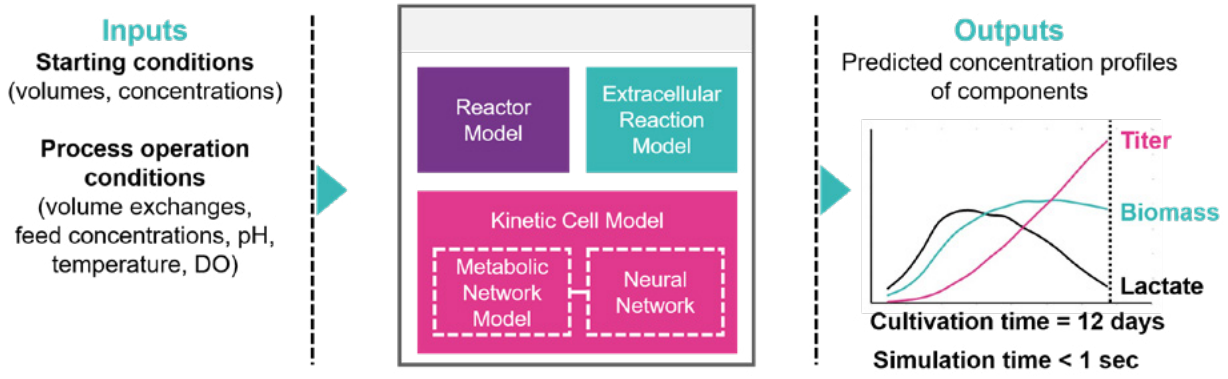


Exhibit 2. Digital twin hybrid model inputs and outputs

metabolic pathways in the cells by methods such as flux balance analysis. Thus, the known rules such as the law of conservation of mass and biochemical pathways are explicitly modeled. The second way we use the data is to allow the neural network to learn the kinetics of the active metabolic pathways. The reader may appreciate that the most difficult challenge when modeling cell metabolism is the estimation of the rates of metabolic reactions. Our hybrid approach ensures that the neural networks are burdened only with this task. This helps us build accurate digital twins with less data than would otherwise be required.

VIRTUAL EXPERIMENTS WITH THE DIGITAL TWIN

Once the digital twin is trained, it can be used for virtual experiments at any stage of the drug substance life cycle. To conduct a virtual experiment, the digital twin needs inputs such as the starting conditions and the process operating conditions. These include information on concentrations of basal and feed media, feeding and sampling volumes, feeding and sampling timepoints, and set points of pH, temperature, and dissolved oxygen. At every time-point, the twin calculates the changes in concentrations due to process operation, extracellular reactions, and cell metabolism and growth.

The outputs of the digital twin are the time-series concentrations of key components in the bioreactor such as biomass, product titer, lactate, amino acids and ammonia. The twin can simulate a 12–14-day process in less than one second. We can conduct thousands of virtual experiments in a few hours. Further, we have built Prediction Apps that conduct these virtual experiments intelligently. For example, if the objective of an experiment is to maximize product titer, the Prediction App uses an optimization algorithm to search media compositions and feeding schemes that lead to the highest product titer.

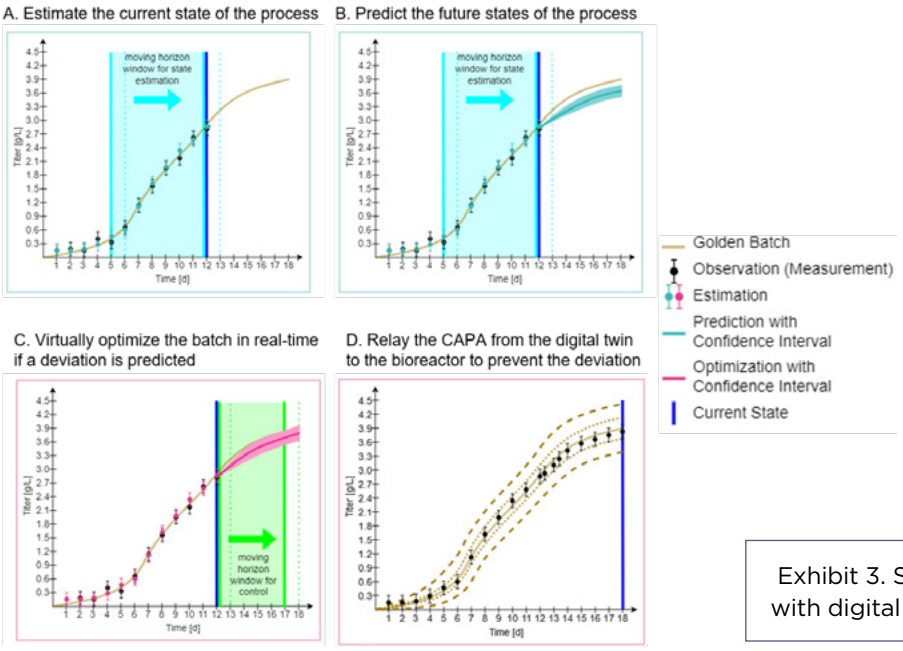


Exhibit 3. Steps in communication with digital twin

VALIDATING A DIGITAL TWIN

When deploying a digital twin for real-time model predictive control of the cell culture process, it needs to be validated. The regulatory guidelines on validation of machine learning based models are not yet finalized. However, we expect that the following approach would be suitable. The validation must be carried out in two steps. In the first step we aim to establish the accuracy of the digital twin and, in the second step, we aim to continuously verify the robustness of the twin.

To build an accurate digital twin, it is necessary to train it with cell culture data that has variability. This helps the twin learn the dynamics of good and bad cell culture processes and improves its ability to extrapolate from the known knowledge space. Since such variability is best achieved during the early stages of process development, it is necessary to train the digital twin using data from these stages. The rewards of building the digital twin at the earlier stages are also higher. We estimate that a company can save between eight and 15 months of Chemistry, Manufacturing and Controls (CMC) time by iteratively developing and using the digital twins through the stages of clone selection, process development, scale-up, and process characterization. The twin retains the knowledge from data acquired at each stage to compound its accuracy. Thus, the first step of the validation is achieved before deploying the twin for model-predictive control of manufacturing processes.

In the second step of validation, the digital twin is continuously verified for robustness. This does not mean that the validation

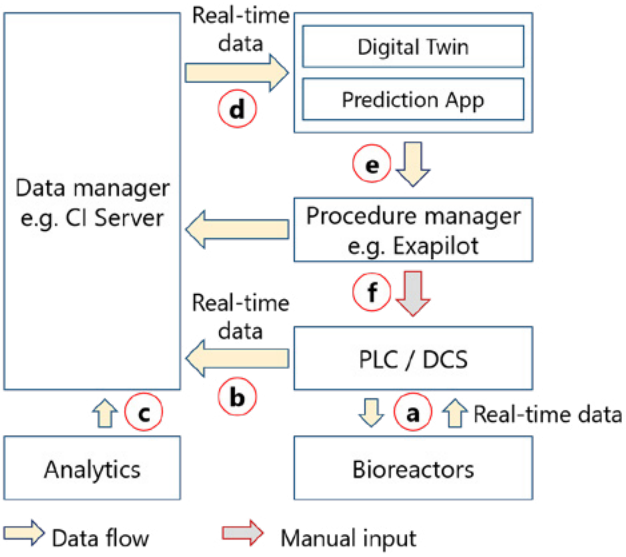


Exhibit 4. Data flow during model predictive control of a bioreactor.
a), b), c) on-line and off-line process data is transferred to the data manager. d) The data is transferred from the data manager to the Digital Twin and its Prediction App. e) The CAPA from the digital twin is relayed to the procedure manager. f) the operator reviews the CAPA and accepts or rejects it through procedure manager. f) the CAPA is sent to the PLC/DCS of the bioreactor which controls the feed valves.

must occur online or in real-time with a manufacturing batch. It means that, over the lifetime of the digital twin as data from manufacturing batches is accrued, the twin should be re-trained with it. This may be done semi-annually or annually. The re-trained twin must be validated offline for robustness. This requires development of standard tests that provide known outputs after every re-training of the digital twin. The digital twin can be updated with the re-trained twin once the offline validation is completed.

ACHIEVING COMMUNICATION BETWEEN THE BIOREACTOR AND ITS DIGITAL TWIN

To complete the 'smart' bioreactor, it must be able to communicate with its digital twin in real-time. As illustrated in Exhibit 3, this entails a few steps. The cell culture process in this example takes 18 days and is currently on day 12. The first step for the digital twin is to estimate the current state of the process using the data acquired thus far. Exhibit 3A shows the measured and simulated concentrations of product titer up to day 12. In the second step, the digital twin estimates the future states of the process (Exhibit 3B). If a deviation from the golden batch is predicted, the digital twin carries out an optimization of the process in real-time and derives a corrective action (Exhibit 3C). In this example, the product titer is predicted to be lower than the golden batch and the digital twin optimizes the feed volume to prevent the dip. Finally, this corrective action is relayed from the digital twin to the bioreactor.

Enabling communication between the bioreactor and its digital twin requires intermediary information managers. Yokogawa is building a prototype of this system using

digital solutions for data management and procedure management. Exhibit 4 shows the communication flows. A data manager provides real-time data transfers between the bioreactor and the digital twin. If the twin predicts a deviation, it relays the corrective action and preventive action (CAPA) to the procedure manager. In the current prototype, the operator has an option to accept or reject the CAPA through the procedure manager. This is the only manual step in the system. It can also be automated in the future. The procedure manager would transmit the control action to the programmable logic controller (PLC) or distributed control system (DCS) that controls the bioreactor.

SUMMARY

Smart manufacturing relies heavily on building self-adaptive processes. In practice, this means that a process should be able to detect and prevent deviations automatically. In this article, we have showcased an approach to developing a 'smart' bioreactor for manufacturing of biologics. The critical steps in achieving advanced process control include building an accurate digital twin of a bioreactor, validating it, and establishing communication between the bioreactor and its digital twin. Several of these steps are already mature and the industry is making rapid progress toward realizing 'smart' bioreactors for smart manufacturing.

ADDITIONAL RESOURCES

EBOOKS

Check out our vast library of information-rich reports that aggregate award-winning content on critical industry topics.

Here

UPCOMING AND ON-DEMAND WEBINARS

A series of live and archived events focused on presenting solutions and strategies to identifiable problems, emerging technologies and key topics that are relevant to today's pharma manufacturing professionals.

Here

PODCAST - OFF-SCRIPT

The Off Script podcast offers in-depth interviews and discussions with industry experts about hot-button topics in pharma, going behind the scenes of Pharma Manufacturing's print and online coverage.

Here

ESSENTIAL REFERENCE GUIDE

Specially designed by the editors of Pharma Manufacturing to provide the most valuable educational content for all pharma manufacturing professionals — from the 20-year veteran to the first-year employee.

Here