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4.0 WHITE PAPERS: AN EDUCATIONAL SERIES

Why Life Science Manufacturing Needs Industry 4.0

In the first of a series of whitepapers exploring the implementation of Industry 4.0 principles within the Life Sciences industry, we introduce the evolution of Life Sciences manufacturing through the industrial revolutions, highlighting the limitations of Industry 3.0. The solution to overcoming some of the major challenges facing the Life Sciences industry may be found in the adoption of Industry 4.0 principles, yet implementation of 4.0 is only in its infancy.

ABOUT THE AUTHORS

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The Industry 3.0 Stack Continues to Dominate Life Sciences Manufacturing

Amplified by the COVID-19 pandemic, managing the struggle within Life Sciences to rapidly bring drugs to market, increase production, and navigate turbulent supply chains has become much more difficult. There is a need for the Life Sciences industry to simultaneously "do more with less" while also complying with 21 CFR Part 11 and/or an equivalent standard. In support, the FDA invested millions of dollars into research to understand why these challenges are plaguing Life Sciences and develop solutions to overcome them.[1] The overwhelming consensus emerging is that technologies from the third industrial revolution—Industry 3.0—alone are not sufficient for meeting today's needs or traversing unexpected disruptions, from all-too-common natural disasters to the ongoing global pandemic.[2]

The evolution of manufacturing is commonly referred to as a series of "Industrial Revolutions." The first Industrial Revolution began with mechanization, the second revolution featured mass production, and most recently, the third leveraged automation and technology.

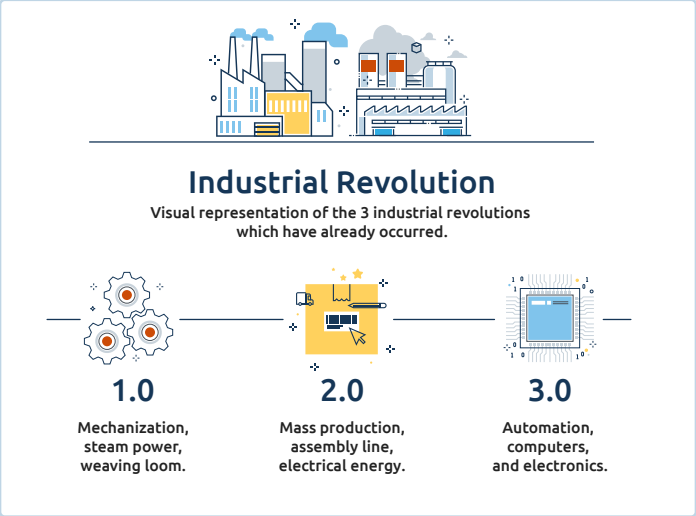

Figure 1: Industrial Revolutions 1-3

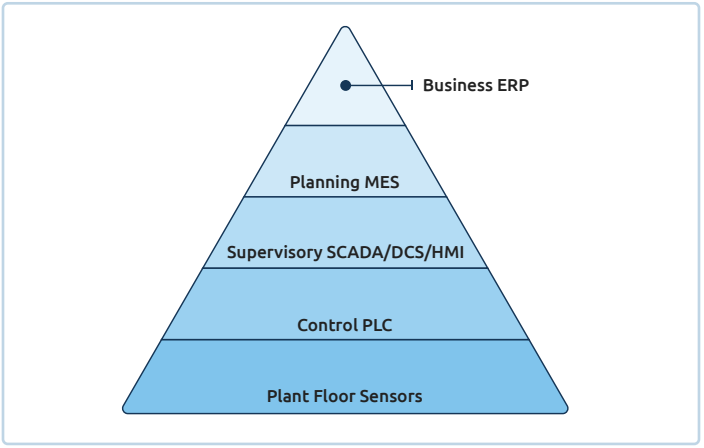

Figure 2: Traditional 3.0 Automation Stack

During the third revolution, many pharmaceutical companies successfully implemented automation while meeting the regulations unique to Life Sciences. Industry 3.0 focused on applying automation systems to every layer of the business in a discrete fashion. Each layer builds upon the one below, creating what is commonly referred to as an "automation stack." This detailed structure is specified by industry standards such as ISA-88.

The foundational layer of the traditional automation stack is the Plant Floor, which contains sensors that document the process raw data. Typically, this includes the process value (PV) readings from equipment such as temperature probes, valves (open/closed), flow meters, etc.

The layer above is Control, which automates a specific piece of equipment. Programmable Logic Controllers (PLCs) are often used to control the actions of individual machines on the plant floor, such as a single centrifuge.

Above Control is the Supervisory layer, which contains the Human Machine Interface (HMI) and either a Supervisory Control and Data Acquisition (SCADA) system or a Distributed Control System (DCS). Though SCADA and DCS are not identical, for the purposes of this paper we will identify both in the Supervisory layer. Both system types are utilized to visualize and coordinate equipment across the manufacturing plant.

The Batch Engine, which loads processing phases as part of recipe infrastructure on multiple pieces of equipment, resides in the Supervisory layer. In addition, this layer focuses on coordinating alarms and events across the process.

The central element of the next layer of the automation stack is the Manufacturing Execution System (MES). In Life Sciences, MES is typically used to digitize operator instructions (SOPs, Batch Records, logbooks, etc.). MES leverages the benefits of digitization to help ensure consistency and quality are met throughout the manufacturing process. MES can track and validate data inputs provided by operators. It can also help identify outliers or exceptions.

At the top of the stack is Enterprise Resource Planning (ERP), software used to manage business decisions. An ERP centralizes data from across the organization, including finance, inventory, and logistics.

Data transfer and coordination between these systems is critical to successfully manufacture drug therapies.

However, these systems are not intrinsically connected in a 3.0 stack because they use different namespaces

In computing, every data point must have a unique ID. The collection of these IDs within a system is known as a namespace. Each layer in a 3.0 factory typically has a unique namespace, with potentially unique structure (that is, not standardized across different layers). Therefore, to allow data communication, a discrete connection must be engineered to link the two different namespaces. This structure generates many challenges.

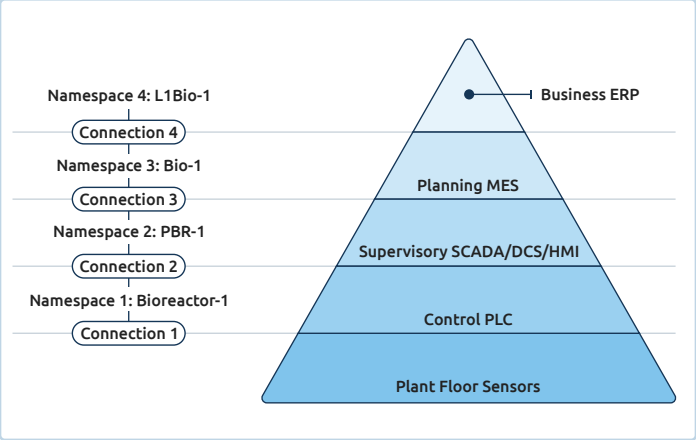

Figure 3: Traditional 3.0 automation stack with multiple namespaces visualized. **Note:** The image shows an example of the same bioreactor having four different names across four unique namespaces, requiring connections to be configured four times.

Legacy 3.0 technologies implemented across Life Sciences are inefficient and expensive because they require discrete connections

The inherent nature of the traditional automation stack makes scaling a 3.0 factory expensive. Adding new equipment comes with numerous new data points that must be manually added and mapped across the different namespaces.

Most engineers working in Industry 3.0-born models specialize in a single layer of the automation stack. Rarely would an engineer familiar with ERP software have in-depth knowledge of the PLC or MES software it connects to. Multiple groups of engineers are required to configure these connections. Furthermore, every discrete connection must be validated. Thus, a typical 3.0 project necessitates budget for engineering and validating connectivity in addition to process functionality.

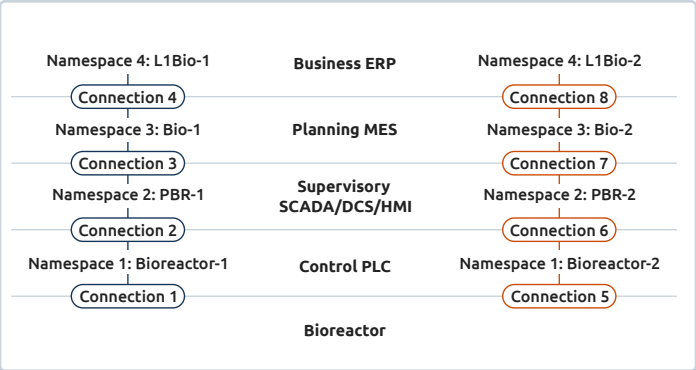

Figure 4: Visual representation of adding an identical second bioreactor in a 3.0 factory. **Note:** The pathways configured for the first bioreactor only account for Bioreactor-1 data points. Adding an identical Bioreactor-2 would still require the same engineering effort to configure connections for Bioreactor-2 data points between each system. Each connection depicted in Figure 4 represents hundreds of discrete connections between the data points associated with each bioreactor.

Between licensing, hardware, loading limitations, engineering, and validation costs to maintain these connections, it is only feasible to discretely connect a fraction of the total data produced. A survey conducted by Forrester of 1,805 business intelligence data users estimates that up to 73% of available data created by a system is not used.[3] A major contributing factor for data waste is the prohibitive expense of connecting every data point for analysis. As a result, 3.0 factories connect the minimum number of points required to operate the plant, leaving behind a wealth of uncontextualized data with no value or knowledge created from its information.

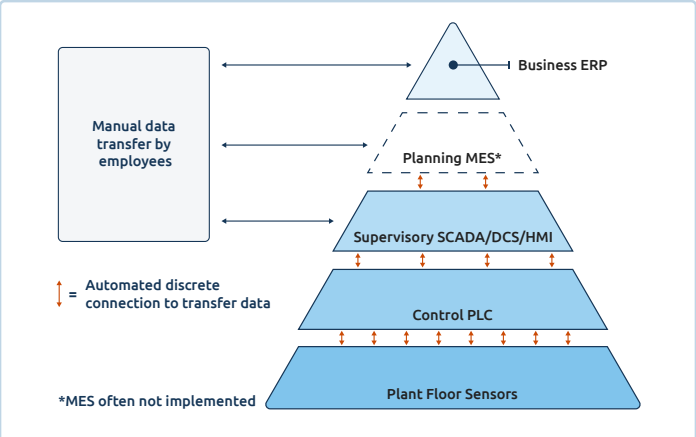

Figure 5: Visual representation of data connections decreasing across 3.0 automation stack

A common example of industry reluctance to digitize data connections is manufacturer refusal to implement MES software. Operators must use paper SOPs, MBRs, and logbooks, which cannot provide the depth of Data Integrity offered by digitization.

Such reluctance poses a major issue:

as data connectivity decreases, so does data context.

In the Life Sciences industry, transparency cannot be sacrificed. Retrieving missing context for investigations or CAPAs becomes time-consuming and expensive. Multiple groups (e.g. Manufacturing, QA, QC, Engineering, and MSAT) are required to manually retrieve data from their respective systems to gain all necessary information with context and perspective.

Another consequence is that employees are often required to manually transfer data across the stack, elevating risk for Data Integrity associated with human intervention. Symptoms include: paper pushing, excessive emails, sending Excel attachments, and whiteboard meetings. As a result, employees spend time transferring data instead of analyzing it to make GxP decisions.

Without access to real-time data, a business is left making reactive decisions. For example, many ERP systems in charge of scheduling do not have access to the real-time status of the equipment on the plant floor. The scheduler is forced to rely on Manufacturing to relay status before publishing a static schedule, which can't be updated until Manufacturing manually notifies management of the daily progress. This results in a perpetually outdated schedule, making it difficult to maximize uptime by coordinating installs or repairs. Furthermore, batch releases can be delayed solely due to time required to release paper records.

Compounded across multiple factories, these issues result in a weak supply chain, where information travels in a linear fashion.

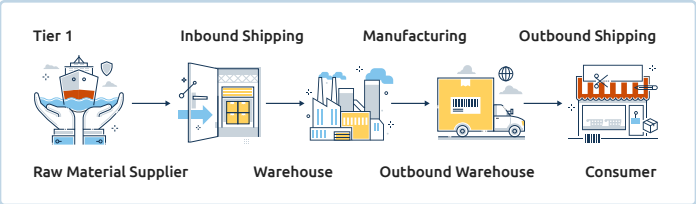

Figure 6: Visual representation of traditional supply

Most 3.0 factories are built upon such discrete and manual connections. As mentioned earlier, discrete connections require time, effort, and money to maintain, so they end up being minimized. This causes two main issues.

First, factories only closely monitor their first-tier suppliers—the ones directly linked to them in the supply chain. If there is a disturbance upstream at 2nd or 3rd tier suppliers, the factory won't know until it hits their tier 1 partner. This cuts into reaction time, putting the factory at risk of experiencing a material shortage.

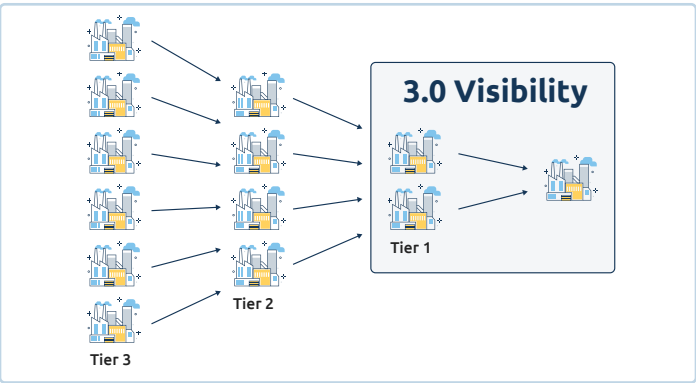

Figure 7: Supply Tiers

Second, many 3.0 factories have a conservative list of first tier suppliers with which they coordinate. To maintain discrete awareness of all possible suppliers in the industry would require enormous effort and is not financially feasible. However, this reduces the factory's flexibility to avoid disturbances when they occur.

Fundamentally, these challenges stem from a lack of data visibility. Data is how one gains information to make decisions. If data is difficult to access, decisions become inefficient and expensive to make. This underlying data inefficiency explains why many 3.0 factories struggled to scale and respond quickly during the pandemic.

Industry 4.0 is the response to the challenges faced in Industry 3.0

Industry 4.0 technologies can be broken down into 9 key pillars. Each pillar is a tool aimed at using data-driven technology to overcome the limitations identified from Industry 3.0.

1. ROBOTS

Robots can automate repetitive tasks without human interaction to increase productivity. This allows operators to focus on more complex tasks and decision-making.

2. 3D PRINTING

3D printing allows for product personalization. In the manufacturing space, it might be used to print replacement parts locally, reducing potential downtime waiting for a part to ship from a tier 1 supplier.

3. AUGMENTED REALITY

Augmented reality provides easily accessible visual data. One application could be to utilize virtual reality headsets for training operators to handle hazardous scenarios without any of the associated risk.

4. INTERNET OF THINGS (IOT)

IOT is the implementation of sensors or probes that connect to each other and the internet to provide new data. With IOT, almost anything can become a smart device by placing a sensor on it.

5. BIG DATA

Big Data prevents data from "disappearing" as it moves up the stack. Instead, it enables all data produced by the business to be contextualized and analyzed.

6. DIGITAL TWIN

A Digital Twin is a software model of the manufacturing plant. This twin may be used with Artificial Intelligence or Machine Learning to predict problems or compare against floor data to identify optimizations.

7. CLOUD COMPUTING

Cloud computing enables the use of third parties to store data in the cloud to reduce costs and make factories easier to scale.

8. CYBERSECURITY

With interconnectivity and networking, factories can ensure compliance by protecting data across interconnected systems.

9. SYSTEMS INTEGRATION

Interconnected systems allow seamless data transfer. Data no longer need to be siloed into individual stacks.

Consider a 4.0 Factory that utilizes the 9 Pillars to facilitate data-driven decisions that drastically improve productivity and quality. Consequently:

- The factory builds efficiency and resiliency, making it more equipped to properly handle supply chain disturbances
- Visibility limitations due to discrete manual connections are eliminated
- The factory builds a connected ecosystem with 4.0 suppliers, monitored and analyzed by artificial intelligence and machine learning
- Due to expanded connectivity, materials are produced and supplied based on real-time demand
- Disturbances are identifiable in real time and appropriate personnel are alerted for immediate action

Figure 8: 4.0 Supply Chain interconnecting multiple tiers

This ecosystem includes multiple tiers and a variety of suppliers for maximum flexibility. To make this vision a reality, participating companies must first be fully digitized.

The FDA recognizes the need to transform the Life Sciences supply chain.[4] Recently, the FDA partnered with the National Institute of Standards and Technology (NIST) through Memorandum of Understanding (MOU) 225-21-006 to, "collaborate to increase U.S. medical supply chain resilience and advance domestic manufacturing of pharmaceuticals, biopharmaceuticals, and medical devices through adoption of 21st century manufacturing technologies including smart technologies, emerging manufacturing processes, and artificial intelligence and machine learning."[5]

In addition, the FDA has already funded close to 6 million dollars through the 21 Century Cures Act towards researching Industry 4.0 technology and its subsequent implementation.[1]

The fourth industrial revolution is occurring now for the Life Sciences. Those who embrace it will be the future leaders of the industry. Those who don't will be left behind.

Survey data suggests businesses with comprehensive Industry 4.0 strategies are far more successful across the board.[6] They are innovating and growing faster, successfully integrating Industry 4.0 technologies, and doing a better job of attracting and training the talent they will need in the future.

Amazon, Facebook, Google, and Tesla are all examples of companies that recognized the need to digitally transform their architecture into one that facilitated data access before their competitors. In 2013, Tesla developed its own in-house ERP called WARP instead of continuing to use a commercially-available ERP. According to the Chief Information Officer tasked with WARP's development, the reason was:

"[Tesla's vision] is to build a vertically integrated organization where information flow happens seamlessly across departments and where we have a closed feedback loop to our customers. By doing this, we can provide the best possible product, service, and overall experience to our customers in the fastest way possible, while also operating efficiently as a business"

– Jay Vijayan, CIO Tesla[7]

Most pharmaceutical companies today are facing the same challenge that Tesla faced in 2013. They have legacy systems which do not have sufficient connectivity, inhibiting their ability to quickly bring new therapies to market.

One way the Life Sciences can overcome this and accelerate the adoption of data connectivity across individual companies and the industry at large is by rethinking the way that data is connected, contextualized, and utilized. Much like Tesla and their in-house ERP, development of a data infrastructure that supports, and does not limit, the organization is the critical first step.

The next paper in our series on implementing Industry 4.0 principles across Life Sciences will introduce the Unified Namespace and its benefits in accelerating digital transformation.

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