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Accelerate Life Sciences Innovation with Operations Digital Twin

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Support for Accelerating Operations is Crucial

Digital Twin for Life Sciences Manufacturing

Life Sciences companies always need to innovate quickly to get to approved products, but the operations to get the drugs and medical devices to patients after that are just as crucial. Fortunately, today marrying planning, scheduling, S&OP, and a virtual view or digital twin of the production process can enable manufacturing to help accelerate innovation and make it sustainable.

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Rapid Life Sciences Innovation

Speed to Market

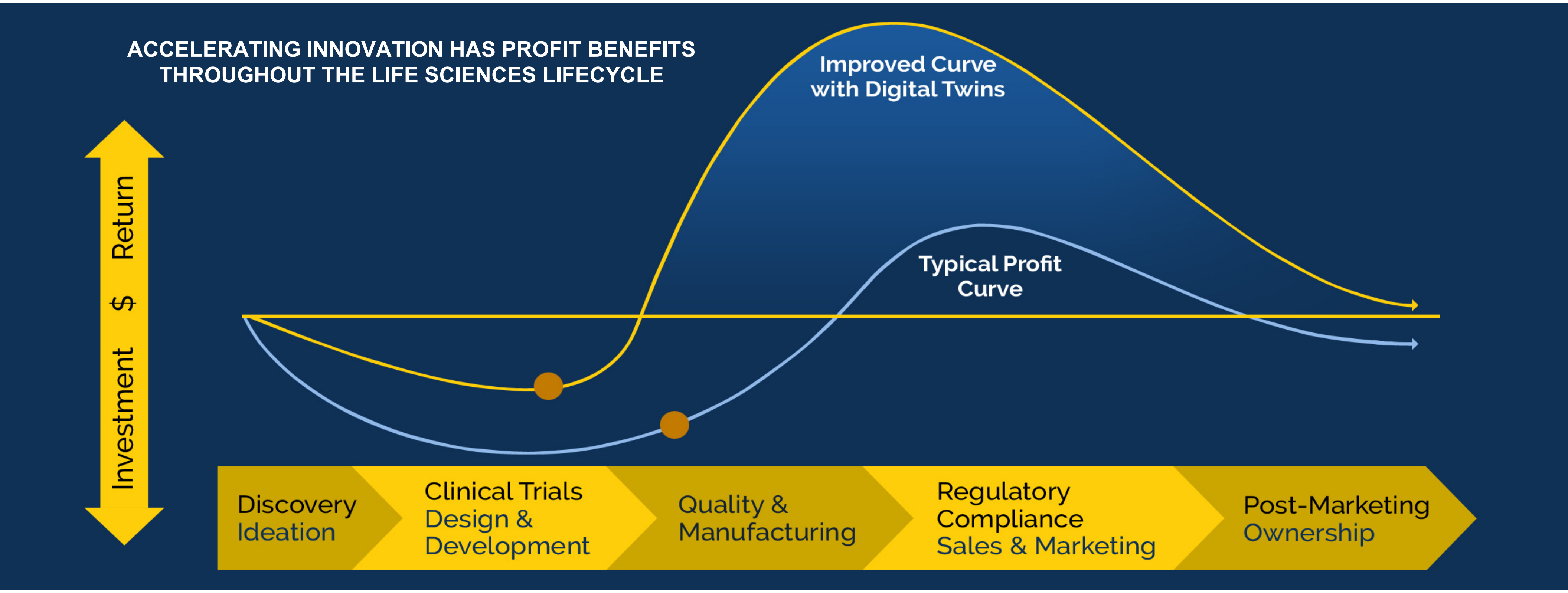
Innovation has always been at the heart of life sciences companies' success. Being quick to market helps both profits and patients. Of course, fast is relative, with most drugs and biologics taking 10-15 years[1] from Phase I to approval, and medical devices taking three to seven years from concept to approval.[2]

The question is: Can life sciences companies accelerate this innovation process and make it more reliable? We have seen that they can by using current software and methods. It's important to remember that innovation and supporting software serve not only R&D but also operations.

Quality by Design

Every aspect of innovation must increasingly aim for Quality by Design (QbD). For drugs, the EMA website defines it: "Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development, and manufacturing of medicines." Modeling and simulation allow a virtual test of a design against quality and regulatory requirements. This can result in improved product quality and patient safety before physical prototypes are built.

In short, **ensuring data-driven approaches early on can generate better outcomes** at every stage of the product lifecycle. The chart below shows that concept.



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New Realities and Opportunities

Data for Agility

A tiny percentage of drugs and devices in discovery phases finally gain agency approval. For those that do, industry changes and pressures include personalized medicine, stricter guidelines for reimbursement, and responsiveness to pandemics and other situations. So, data must always be current and in context for QbD analysis. Current data also supports good decisions at every step along the way.

Pandemic Lessons

What we learned from COVID:

- Switching to new products can be quick and business-saving
- Regulators are ready to respond and approve life sciences products rapidly when needed
- Front-line employees matter – attracting, training, re-training, and keeping them safe and able to work with remote support
- Agility is possible with new data-driven approaches to setting up or making changes to validated processes

Manufacturing Must Keep Pace

Adopt New Production Approaches

Life sciences manufacturers across the board are adopting new production approaches. Examples include:

- Continuous processing in pharma
- Modular manufacturing facilities that can reconfigure quickly
- Personalized cell and gene therapy in which each batch must be perfect for the patient to get treated and the company to be reimbursed
- Quality by Design – shifting responsibility left to plan for success
- Research shows that top performers are finding issues earlier[3]

Not Only Post-Market

Manufacturing runs throughout the lifecycle of life sciences products. Manufacturing issues to shorten the time from approval to full production volume and quality are clear. Even in early-stage concept, discovery, and pre-clinical phases, companies must make samples to evaluate. Manufacturing for clinical trials must be flawless for valid results.

Simulation for Speed

Historically, companies made "cardboard city" sets of plant equipment to simulate flow through a production line. These approaches to factory modeling are not competitive. They are not fast or easy to change. Nor can they show all impacts – such as sustainability, ergonomics, and changes in mix or throughput. Thus, the **virtual production line or digital twin is crucial**.

Protect Resources

Virtual versions enable agility for the plant to add, switch, and handle different mixes of products confidently. **This leverages the equipment and facility resources more effectively**. People are crucial resources, and a twin can help attract, **train, maintain knowledge, and keep scarce skilled employees safe**. The virtual version reflecting the real at all times can guide employees and empower them to report issues rapidly.

Digital Twins: Marrying Virtual and Real

Varieties of Digital Twins

As the definition suggests, many physical items or sets of items can have a twin. There are several varieties of digital twin relevant to life sciences manufacturers.

- **Product digital twin** can focus on as-designed or the entire lifecycle of a medical device or biopharmaceutical product and its structure
- **Operations digital twin** is a virtual model of the production process and how it ideally operates to create as-built products to match the as-designed
- **Equipment or Maintenance digital twin** can be used to monitor status and ensure production plant assets are maintained to keep the plant running
- **Supply Chain digital twin** can model interactions between multiple plants, warehouses, and companies that procure and ship parts from and to each other

There may also be other twins for specific purposes, but these are the main ones.

Twins are Related

These twins are related. You can see how an operations digital twin could work with a product digital twin to make it, and generate all of the parameters, work instructions, and procedures needed. The operational and maintenance twins may use many of the same core equipment models, but the operational twin may focus on the flows between them, while maintenance will focus on keeping each asset running. And the supply chain twin can benefit from multiple operations twins showing capabilities for each "link in the chain." **These twins can benefit each other, but do not all need to be in place to be effective.**

Tech-Clarity definition of digital twin:

The digital twin is a **virtual model of a physical item**. The model represents a specific product, configuration, pieces of equipment, plant, city, or other physical asset with enough fidelity to predict, validate, and optimize performance and behavior. It's connected and kept in sync with its physical twin over its lifecycle to collect, aggregate, and analyze actual field data to monitor performance, gain intelligence, and close the loop between designs and the real world.

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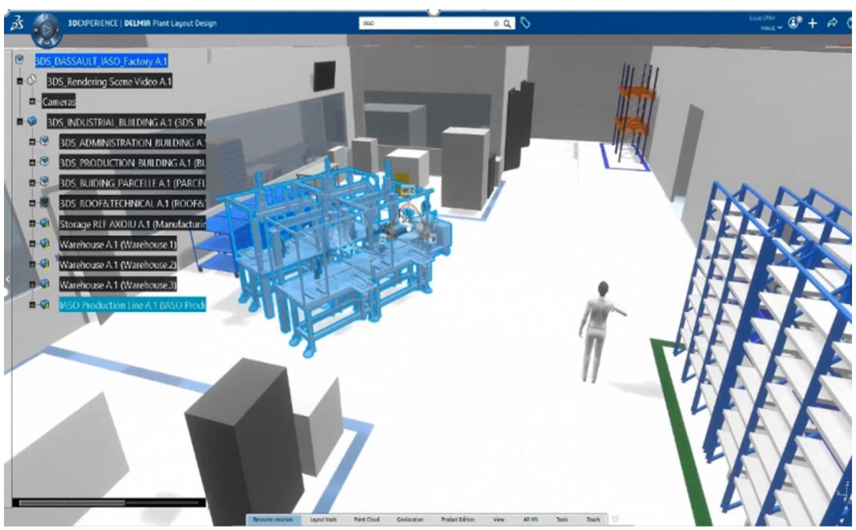
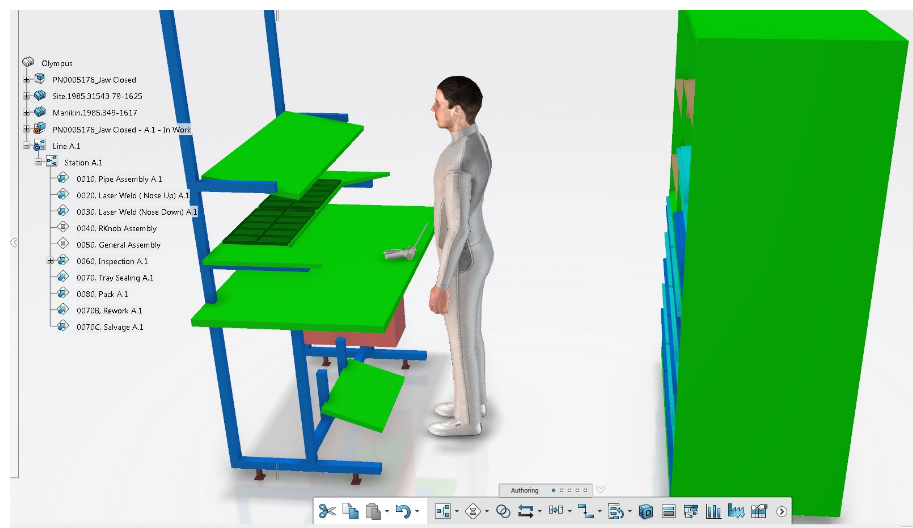
Operations Digital Twin Examples

VIRTUAL AND REAL PRODUCTION PROCESSES IN BIOPHARMA

VIRTUAL PLANT LAYOUT CAN ENSURE SOUND OPERATIONS ACROSS LINES



DIGITAL TWIN OF PROCESSES AND ERGONOMICS SUPPORTS RESOURCE AND WORKFLOW PLANNING



Digital Twin of Operations Accelerates Progress

Digital Plant Maturity

Biopharmaceutical companies and their top suppliers have banded together to create the BioPhorum Digital Plant Maturity Model.[4] "The model describes maturity levels that range from manual paper-based, i.e., 'pre-digital' plants, through to the fully automated 'adaptive' plant of the future. The model is designed to help companies transform their manufacturing capability and address questions that were previously difficult to answer…." Companies are aiming to be connected, then predictive, and finally adaptive or self-optimizing.

Twinning for Adaptive

At the core of an adaptive plant – whether medical device, pharmaceutical, or biotech, is a twin that enables self-optimization as conditions change. Digitally simulating a production process has been around for decades. Simulation models have helped accelerate innovation in life sciences. However, twinning a process takes this to the next several levels. A digital twin is a fuller, more dynamic model designed to stay in sync and not only run occasionally. It is this always-on optimization that enables predictive and adaptive operations.

Product Twins

Modeling the product plus the process of creating it has power. Again, this can start early in the innovation cycle. Examples of a digital twin of products:

- A device's digital twin includes configuration/variant management for a meta-specification, then tailored per country, site, batch, or unit.
- A drug or biologic's digital twin includes ingredients, recipe, process, and acceptance criteria specifications.

Combining the product and process twins is the foundation of a more mature and sustainable digital plant.

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BIOPHORUM DIGITAL PLANT MATURITY MODEL LEVELS

Maturity level	Level name	Description
1	pre-digital plant	manual, paper-based processes
2	digital silos	'islands of automation'
3	connected plant	high level of automation, integration and systems standardization
4	predictive plant	integrated plant network, pervasive real-time predictive analytics
5	adaptive plant	'plant of the future', autonomous, self-optimizing, plug-and-play

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Twin Benefits in Operations

Validating manufacturing with 3D and virtual simulation in the Life Sciences industry leads to:

38%
reduction in time to market

35%
fewer prototypes

34%
less ECOs

Operations Digital Twin

Production is inherently physical – materials, equipment, products, etc. Yet virtual planning and what-ifs in a digital twin can radically improve real results. An operations digital twin can be used for dynamic process definition, setup, commissioning, production planning, and execution.

Innovation Benefits

Research shows substantial business benefits to the twin approach in life sciences to manufacturing engineering alone.[5] Imagine stacking up benefits in production planning and execution as well as engineering and commissioning. This is possible by keeping virtual and real in sync, dynamically feeding each other for continuous improvement and success.

Like a GPS

The analogy to a GPS for driving is apt – you use it to plan your route, but as you drive, it will also update you on traffic issues that might lead you to change the plan. The result is faster, cheaper, lower-energy-use, lower-stress navigation – which a twin can provide for production.

Plans to Submit

Manufacturing plans are a crucial aspect of innovation for life sciences companies since the manufacturing plan is submitted along with product information to regulators for approval. Today's personalized medicine also makes each production run more critical than ever.

Virtual Uses through Validation

Pre-approval

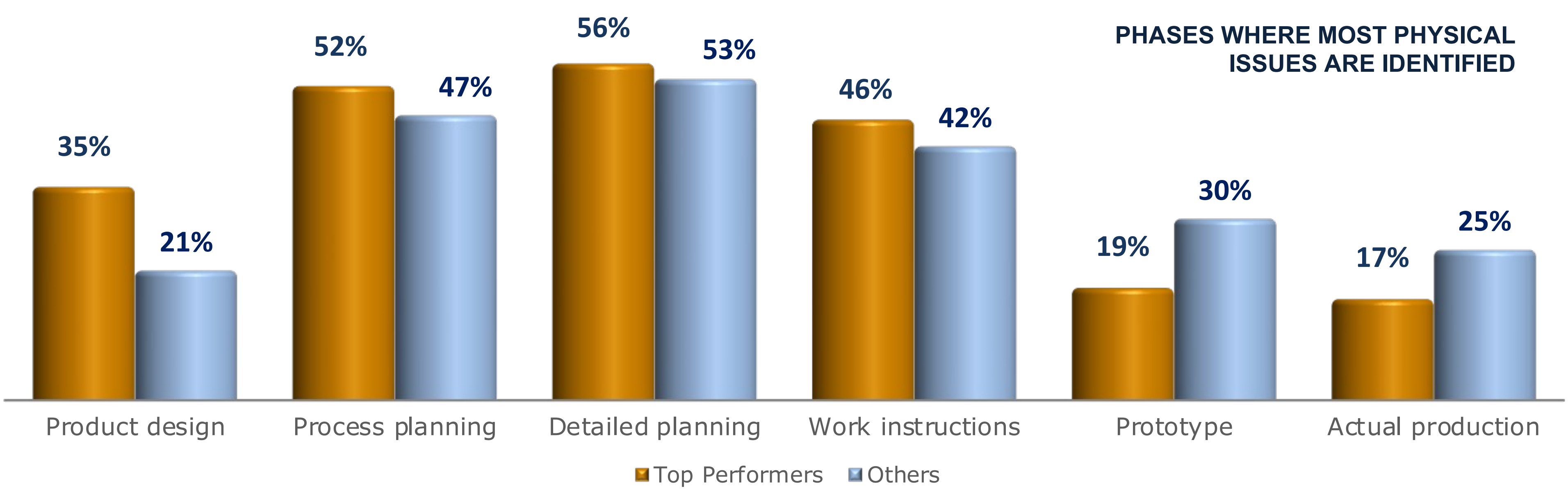
As we mentioned, manufacturing happens early, and manufacturing planning can benefit from a twin even before approval. At the least, starting with a digital twin in clinical engineering can help improve and gauge clinical trial production runs. This early optimization may avoid the need to overproduce to account for uncertainty.

Manufacturing Engineering

Manufacturing Engineering clearly can benefit from a digital twin. This includes plant layout and upgrades; exploring new production methods, equipment, and robotics; and keeping employees safe with social distancing, ergonomics studies, and automation simulation. A twin of the process is the most efficient way for manufacturing engineers to work.

Commissioning and Validation

Commissioning a new line or process using a digital twin, you can find problems before prototyping and production.[6] Virtual commissioning may leave only 10-20% of the work for go-live time. Imagine the savings of time, energy, effort, and stress by fully modeling the product through the validation process.



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Virtual Uses Post-Approval

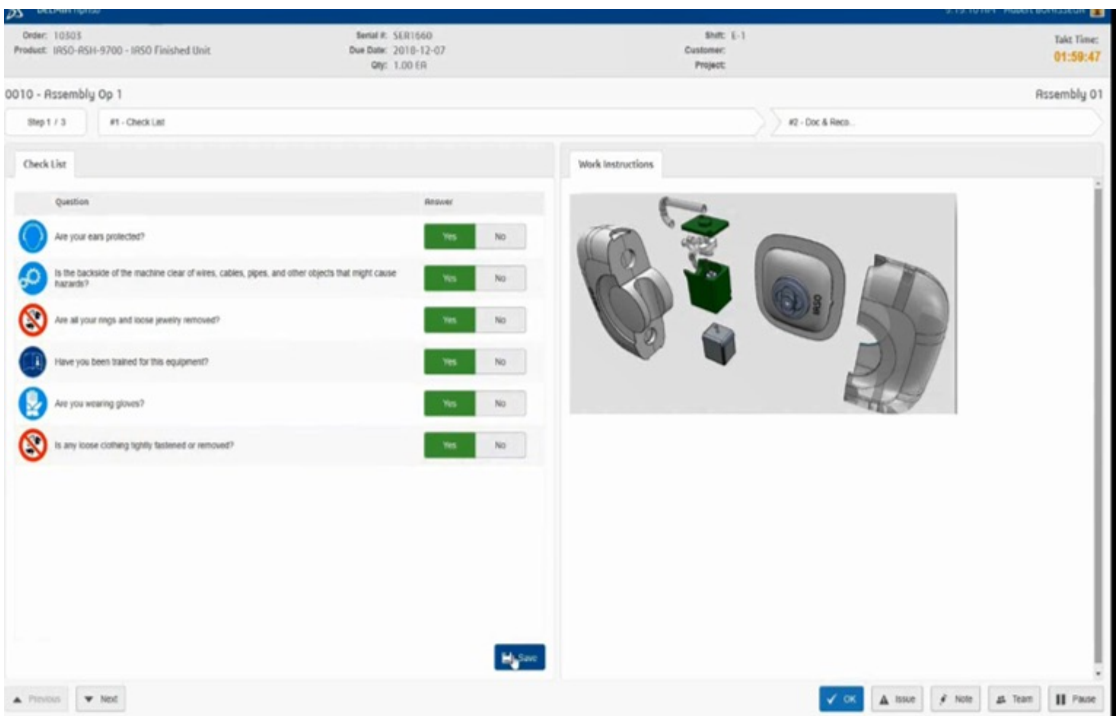
Planning

Once a product is approved and the line commissioned and process validated, **the digital twin can support production planning at all levels**. Sales and operations planning (S&OP) to coordinate across the enterprise, plus production planning to ensure all resources are ordered in a timely fashion. Going further, detailed production scheduling helps utilize current capacity in the most beneficial way.

Production

Once a plan is in place, **the twin enables the plant to make what's needed at high yield and quality.** The operations team can troubleshoot in the twin, then improve on the floor. This includes optimization of changeovers, exploring best practices for product changes, and continuous improvement.

DIGITAL WORK INSTRUCTIONS INTEGRATED WITH MES FOR EXECUTION AND QUALITY MANAGEMENT



Training and Quality Validation

Training and quality are two of the most common use cases for digital twins. Training examples include guiding workers to ensure assembly processes and validating steps are completed in the proper sequence and training new workers or current employees on new processes and procedures. This training also supports Quality needs for consistent production and testing processes with sign-offs. Life sciences companies can get to a validated process more rapidly using the twin that reflects and is connected to the actual process.

Ongoing Changes

Of course, a mix of planning and production uses for the digital twin can model and predict the best way to respond to demand shifts, supply disruptions, or regulatory changes. Life sciences manufacturers will always need to improve how they handle product changes, mix changes, disruptions, new needs, and shifts in regulatory focus, and **the twin is ideally suited to those what-if scenarios**.

Benefits of Virtual to and from Real

VIRTUAL TO REAL	BENEFIT AREA	REAL TO VIRTUAL
Virtual products and processes simulating	**Innovation Speed & Time to Market**	Actual data ensures the twin is correctly engineered
Scan the factory and capture the process and product model to accelerate	**Time to Market**	Ramp up to full volume rapidly by showing results of materials, workflow, mix, and decisions
Design quality into the process from early twin to ensure product quality and efficacy	**Quality**	Show actual issues with product design, materials, or work processes – gauge CAPA effectiveness and support Quality by Design (ObD)
Simulate a product and its process in advance, allow production to train early	**Speed of Tech Transfer**	Instant feedback to engineering from early trial runs
Optimize workflows, mix, automation prior to real product on the line	**Time to Manufacture**	Actual throughput, speed, and discrepancies from expected
Model and evaluate possible carbon, materials, and energy decisions in product process design	**Sustainability**	Actually available materials and energy prices as they fluctuate feed improved ESG results
Simulate workspaces and processes to check clearances and ergonomics	**Safety**	Operator and MES training and feedback on actual situations
Model various changeover sequences, mixes, shift staffing, and equipment settings	**Efficient Agility**	Always-on operations data about efficiency in various conditions, time to changeover, takt time
Clear up-front documentation of planned process to validate	**Validation & Regulatory**	Data to prove compliance with planned and validated process
Examining all aspects in the virtual model to identify the root cause more quickly	**Troubleshooting**	Send actual issue data to the model as problems arise and fixes and attempted
Virtual runs with various possible approaches to select the best to optimize production	**Optimizing**	Actual data to gauge how new way is working and what next issue is to address

Closing the Virtual-to-Real Loop

Software Elements

Keeping the digital twin in sync with actual operations is a crucial differentiator for today's virtual models. This means that the virtual or digital twin of the process must get actual signals from the real world it represents. This comes in the form of operations software.

- One aspect is **supply chain planning and detailed scheduling**, which factors in the movement and availability of materials and other resources such as equipment and people.
- Another is the manufacturing operations management (**MOM**) or manufacturing execution system (**MES**), which delivers in-context information to employees to execute to the plan and schedule but also returns data about actuals. Actuals include achieved quantities, quality, yield, throughput, and related product and process performance, often spanning multiple plants.

Data Continuity

Manufacturers need accurate, timely data AND strong data continuity between virtual and real. The dynamic nature of a functional digital twin requires both real and virtual to be agile. So operations should easily update when the virtual twin creates a better option, and the digital twin should update and re-optimize based on actual data from the process. Quality and compliance are better assured with this closed-loop data flow between virtual and real.

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Tech-Clarity definition of Manufacturing Execution System

Systems that deliver information to optimize production activities from order launch to finished goods. **MES guides, initiates, responds to, and reports on plant activities as they occur.** To do so, MES puts into context a wide array of current and accurate data from both operations technology (OT) and information technology (IT). MES can deliver mission critical-information about production activities across the product lifecycle, enterprise, and supply chain via bi-directional communications.

Considerations for Useful Virtual

Diverse Twin Foundation

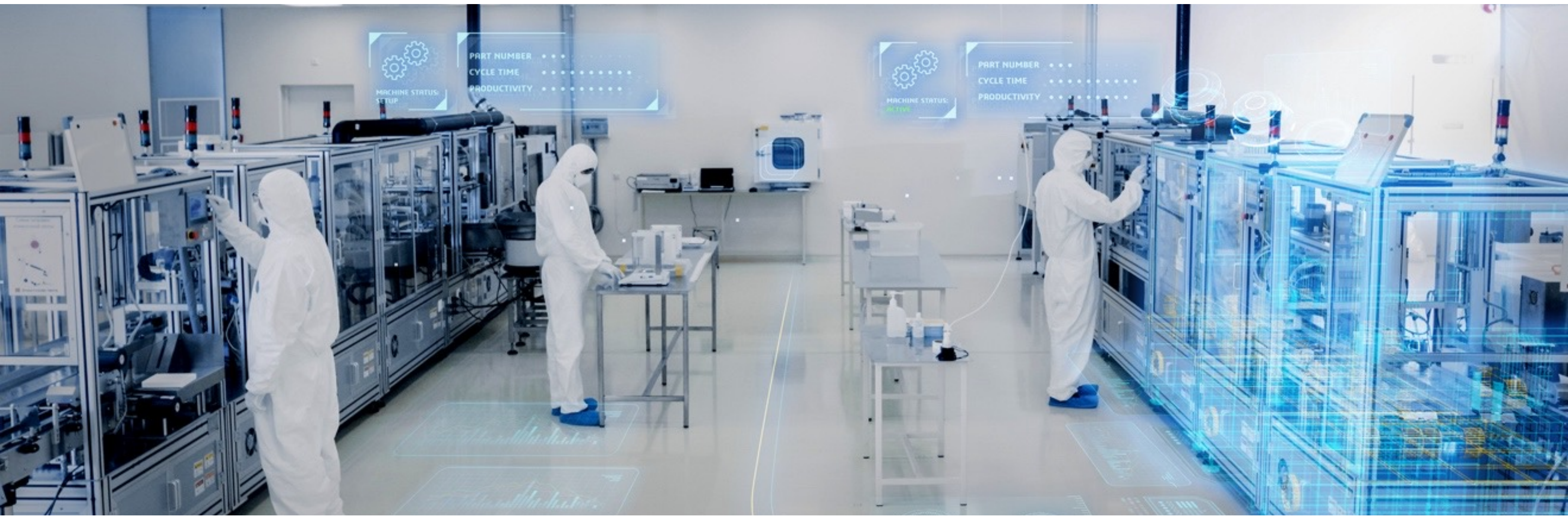
The question is, how to create your digital twin? A solution that takes a systems engineering approach can deliver substantial benefits. The process or plant model of the digital twin must be decomposed into requirements as a starting point to align all disciplines. Ideally, it balances all aspects and coordinates domains to reduce risk. In systems engineering, for a twin, **the overall process or plant breaks down into objects you can run**.

Dynamic and Integrated

The digital twin must be dynamic and designed to take new data into account constantly. So, while a 3D model can be a starting point, it cannot be static in any dimension. It must also be designed for collaboration, connection, and continuous closed-loop data flows with SCP, MES/MOM, and other operations data. **This closed-loop data flow between virtual and real** is what will make it so valuable to life sciences manufacturers.

Quick Start Elements

Of course, building a complete twin of a production line or a factory or set of production assets might seem daunting. To enable a rapid launch, the system must have the ability to use **externally-developed twins of your equipment.** Ideally, it can also use scans of your current factory layout to get modeling started. Once data is imported, it should provide straightforward ways to add to those. Another great feature is a system with equipment libraries, including robots, AGVs, racks, conveyors, and people.



Enterprise Transformation

Interdisciplinary

As life sciences manufacturers look to speed their innovation cycles, what matters? **Collaboration across disciplines, groups, and phases of the lifecycle is essential.** Manufacturing must be a focus long before a new product is approved. Since production starts in clinical and QbD moves things left, it makes sense to start working with manufacturing early. Fortunately, the clinical group can more easily meet its goals using a digital twin of the production process.

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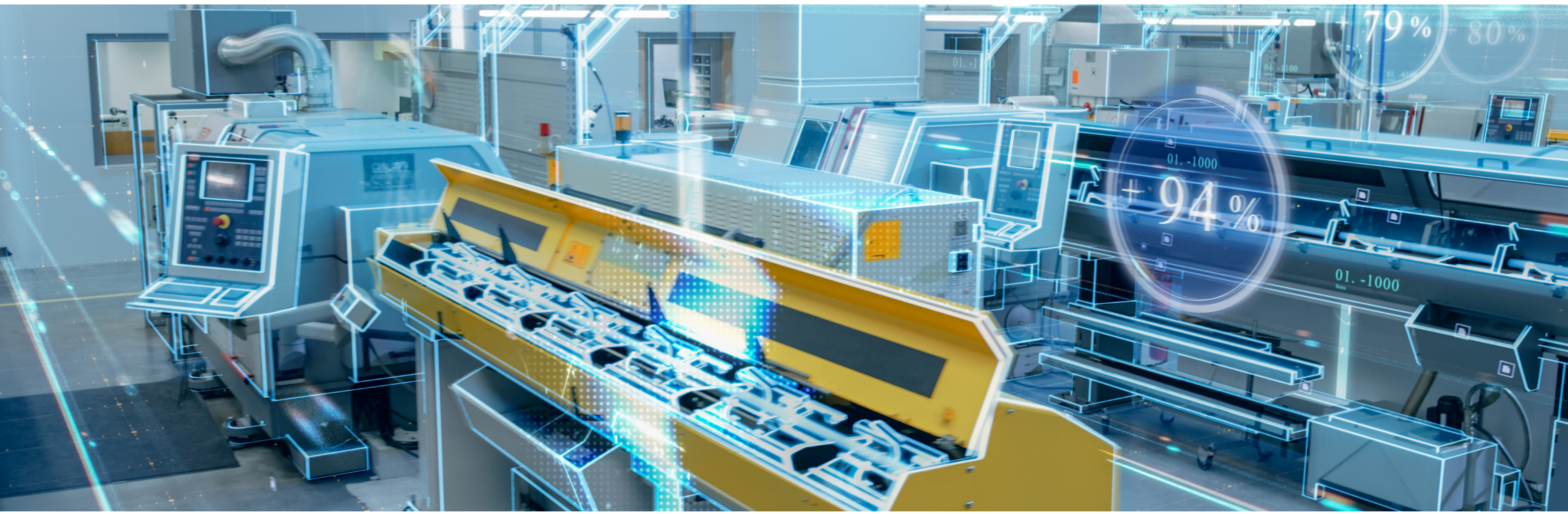
Transforming Work

The virtual-meets-real loop creates a new way of working and needs appropriate preparation. Some of the steps companies need to take include:

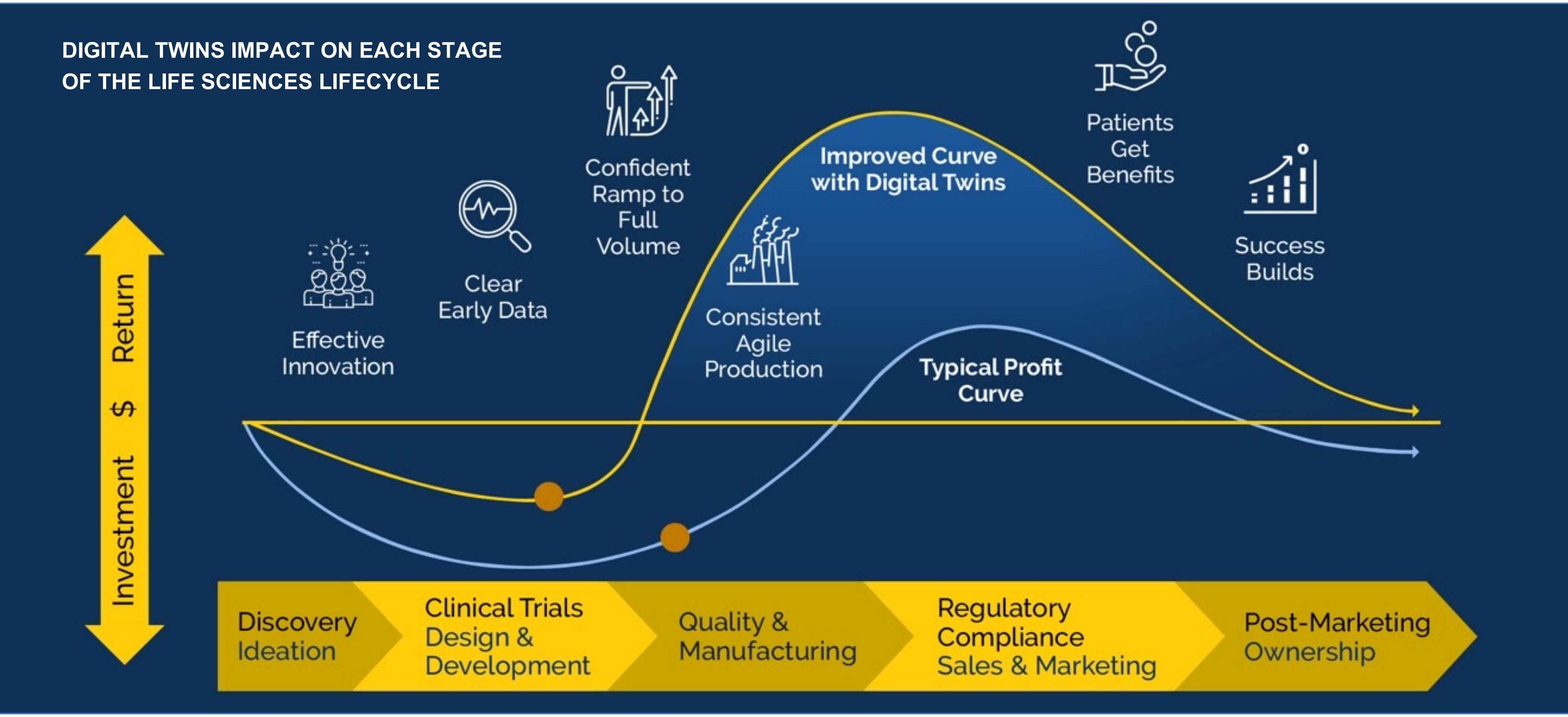
- Setting clear objectives to select the best ways of working
- Data cleansing and structuring for transparent sources of truth
- Building digital twins for the processes & areas of what-if need
- Leveraging cross-functional teams including design, engineering, manufacturing, and supply chain to collaboratively set short- and long-term objectives
- Education from the boardroom to the cleanroom production floor



Clearing the Way for Acceleration

Confidence to Change

Companies need to get to the point of confidence in their twin. This is both in creating it and in continually gathering data in the twin about product quality, production, safety, and sustainability. Every activity "moves left" to earlier in the timeline; more goes virtual, but the real operation is constantly changing. For this enterprise transformation to work, companies need high-level executive support. A production digital twin program and the ongoing new operating method it enables will typically require substantial resources and clear responsibility for the twin and its use in operations.



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Recommendations

Recommendations and Next Steps

Based on this research and our experience, we recommend that Life Sciences companies in biologics, pharmaceuticals, or medical devices:

- Treat this as a **transformational operations innovation acceleration initiative**, not an IT project.
- **Educate and create a vision** everyone shares for a more agile manufacturing operation that accelerates innovation.
- Distinguish operations twinning from a Metaverse or gaming approach: it is **for running the business**, not training or purely visual representation.
- Carefully **review your options** to ensure the digital twin platform will support the organization now and in the future.
- Get started with twinning **high-impact areas** and build on the success to get maximum value and momentum.
- If you don't have **enterprise-capable manufacturing planning, scheduling, S&OP, and execution software**, be sure those investments are in the plan.
- Be sure the top **executive team sponsors** and fully resources the program – including dedicating some of your best people and incenting everyone.
- Set an expectation that the twin will become a **crucial aspect of daily operations**: you will see what happens as things change and conduct what-ifs to gain speed and confidence in decisions.
- **Keep the end in mind:** virtual and real, constantly driving quality, innovation, improvement, and speed.

Acknowledgments

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About the Author

Julie Fraser joined Tech-Clarity in 2020 and has over 35 years of experience in the manufacturing software industry. She is an enthusiastic researcher, author, and speaker. She has a passion for manufacturing progress and performance gains through Industry 4.0 strategies and supporting software technology.

Julie is actively researching the impact of digital transformation and technology convergence in the manufacturing industries, with a focus on the plant floor and how to use manufacturing data in conjunction with data from offices, labs, and the ecosystem.

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