ADVANCED APPLICATIONS for Digital Twins in Pharma

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With the help of Digital Twins, companies can achieve greater certainty and precision in making informed decisions at various stages of the product lifecycle, driven by a deep understanding of underlying Critical Business Parameters (CBPs).

We present a novel, holistic approach to utilizing Digital Twins (DTs) and AI Agents throughout the pharmaceutical product lifecycle by focusing on CBPs that influence both product and company performance. Our approach involves the development and operation of multiple Digital Twins, each targeting a specific parameter and collectively forming a network of interconnected models—referred to as a federated Digital Twin, herein called "Twin of Twins."

We also explore the role of AI Agents as assistants throughout the DT lifecycle, including conception, development, validation, operation, and maintenance. Additionally, we propose a modular approach that simplifies complex process flows and cost models into standardized building blocks, enabling the creation of efficient and scalable Digital Twins. Considerations around cost, validation, and ethical implications are also addressed.

INTRODUCTION: WHAT ARE DIGITAL TWINS?

Decisions often must be made without fully knowing the outcomes. The use of "safe spaces" to test scenarios, understand potential effects, and make informed decisions is therefore nothing new. Throughout history, architects and engineers have used scale models and mock-ups to visualize and test structures and concepts before implementation, thus mitigating construction errors and operational risks. Similarly, mathematical models that simulate real-world aspects have been used for decades in engineering and finance to improve decision-making and predict outcomes prior to implementation.

Key differentiators of current approaches include the integration of connected devices, the Industrial Internet of Things (IIoT), High-Performance Computing (HPC), and advances in artificial intelligence (AI). Together, these digital innovations enable the simultaneous inclusion of numerous adjustable variables in simulation models, providing a more comprehensive understanding of real-world events and enabling real-time simulations.

At the forefront of this transformation is the concept of DTs, which are defined as precise digital replicas of physical systems [1]. By leveraging the aforementioned digital enablers, DTs are continuously updated with real-time data from the physical world, enabling highly accurate simulations and predictive insights. This empowers organizations to test, optimize, and accelerate data-driven decisions, all while minimizing risk and enhancing operational efficiency.

DIGITAL TWINS IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is expected to provide society with a reliable supply of safe, effective, and affordable medicines of high quality that reflect the current state of science and technology. These and other Critical Business Aspects (CBAs) must be considered throughout the pharmaceutical product lifecycle [4]. DTs can be used to assess these interacting CBAs and are increasingly becoming important tools for accelerating decision-making and minimizing business risks [5]. They are particularly useful when evaluating change projects that may impact CBPs—the specific metrics and factors used to measure and control the respective CBAs.

For example, a CBP such as annual output depends on numerous other factors, including the supply chain, production scale, process flexibility, product yield, plant utilization, external and operational

Figure 1: Example of a ToT to with CBPs, CBAs, and DTs

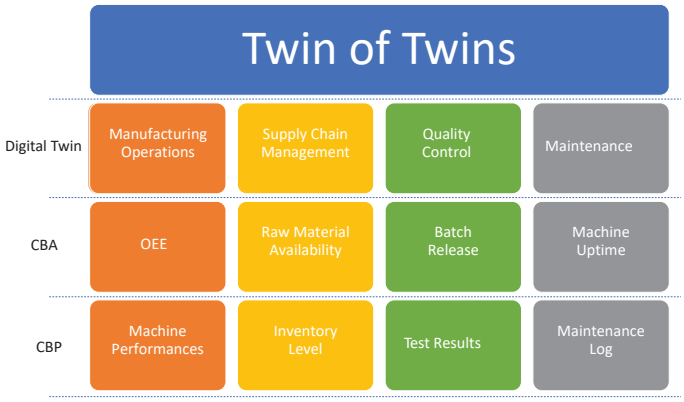


Table 1: Directly applicable use cases for DTs in the pharmaceutical sector, some of which have already been implemented

Use Case	Description
Drug Discovery and Development	DTs can accelerate drug discovery and reduce research and development (R&D) costs in the company's innovation pipeline (the CBA, in this case) by simulating experimental systems, thereby optimizing resources, accelerating timelines, and improving success rates of R&D efforts [8, 9].
Clinical Studies	As a critical aspect of clinical trial management, DTs simulate patient responses in order to measurably optimize study design, ensure protocol compliance, limit the number of subjects required, and ultimately ensure data quality [10, 11].
Facility Design and Modification	With facility management as the CBA, the DTs evaluate the intended design changes in terms of their impact on process performance, product quality, assets and equipment, space utilization, and environmental control [12].
Environmental Impact Reduction	DTs optimize manufacturing processes and logistics to reduce waste, energy consumption, and environmental impact, supporting the critical aspect of environmental sustainability. Important metrics include energy consumption, waste volume, resource consumption, environmental impact, maturity of sustainable development, and ecological footprint in an industrial comparison [13, 14].
Manufacturing and Supply Chain	For DT management, the same as the CBA, the overall process is to identify bottlenecks, optimize efficiency, and ensure availability and quality [15, 16].
Predictive Maintenance of Equipment	DTs driven by sensors and IIoT reduce downtime and safeguard product quality, ensuring the CBA of equipment availability. Key metrics are asset health, maintenance schedules, performance efficiency, downtime reduction, and quality impact [17, 18].
Training and Education	DTs allow staff to be safely trained on new equipment and for new processes, guaranteeing product quality and patient safety while ensuring the CBA of staff development. Key CBPs are progress in learning, risk reduction, competence, and performance improvement [19].
Continuous Improvement	Under the critical aspect of optimized processes, DTs assess and refine changes to operational workflows and measurably improve their impact, performance, efficiency, cost, and quality [20].
Regulatory Compliance and Reporting	This is an emerging application where DTs maintain real-time records of drug development and manufacturing, facilitate regulatory compliance, prepare for audits and inspections, and ensure the critical aspect of inspection readiness. Key metrics include compliance status, documentation quality, inspection performance, risk assessment, and reporting efficiency [19].
Collaboration and Data Sharing	Under the critical aspect of knowledge management, DTs improve the collaboration between researchers, industrial companies, and healthcare institutions by providing standardized real-time data. The key metrics are the efficiency of collaboration, data sharing, quality of communication, access control, and level of integration [21, 22].
Personalized Medicine	Another goal of DTs is to simulate patient behavior and predict individual drug responses, enabling personalized treatment plans and tailor-made medicine that improves the patient's well-being, viewing it as a critical aspect, with optimized treatment success and minimum risks and side effects [10, 23–25].
Treatment Adherence	Another pioneering project is when DTs are based on synthetic patient data that provides insights into treatment adherence, enables timely intervention, and improves the critical aspect of treatment compliance. Important CBPs here are treatment adherence, treatment response, patient behavior, timing of intervention, and outcome assessment [26, 27].

constraints [1], and market demand. A DT capable of simulating such relationships with a high degree of accuracy enables informed and rapid decision-making, thereby reducing both operational costs and business risks.

With the help of high-performance computing (HPC) and modularization, DTs gain the ability to interconnect and simulate multiple CBPs simultaneously. DTs are now overcoming past limitations to become powerful tools that provide direct, unbiased,

Table 2: Non-exhaustive list of CBAs

CBA	Important Metrics
Regulatory Compliance	Regulatory approvals, adherence to regulations, and post-market surveillance (pharmacovigilance)
Quality Control (QC) and Quality Assurance (QA)	Product quality, stability testing, documentation, and traceability
Supply Chain Management	Global supply chain, supply chain resilience, risk management, and inventory management
R&D	Innovation and discovery, clinical trials, pipeline management, intellectual property (IP), process optimization, and scaling up
Financial Performance	Revenue and revenue growth, cost control, and financial sustainability
Sales and Marketing	Market access, product differentiation, pricing strategy, and brand management
Risk Management	Compliance risks, product liability, and financial risks
Patient Safety and Ethical Considerations	Patient safety, drug accessibility, ethical conduct, and social responsibility

Table 3: Non-exhaustive list of CBPs

CBP	Important Metrics
Production Capacity	Yield and throughput
Quality Metrics	Batch failure rate, out-of-specification (OOS) results, and deviation rate
Cost Metrics	Cost per batch, cost of goods sold (COGS), and inventory turnover rate
Production Time and Efficiency	Cycle time, overall equipment effectiveness (OEE), and manufacturing capacity
Supply Chain Metrics	Lead time, supplier reliability, and quality
Compliance and Regulatory	Regulatory approval timelines, regulatory compliance costs, audit findings, training compliance rate, documentation accuracy, and completeness
R&D and Innovation	Program pipeline, pipeline depth, pipeline value, time to market, R&D cost efficiency, clinical trial success rate, regulatory approval rate, patent strength, and expiry
Commercial Performance	Market share, sales growth, profit margins, and product revenue mix
Sales and Financial Performance	Revenue per batch or unit, profit margin, cash flow, return on investment (ROI), market share, and demand forecasting
Patient Safety and Efficacy	Adverse event rates, product recalls, and patient satisfaction

real-time information on CBAs and the likely impact of planned changes—supporting engineers, scientists, and decision-makers across product development, production, and management. CBAs and CBPs will be discussed in more detail later.

Given the diversity of activities involved, it is clear that different types of DTs must be applied across disciplines to achieve relevant results. Some are based on multiphysics, others on tangible relationships, and still others on intangible processes, systems, and workflow dynamics. Connecting these various DTs to generate high-level insights requires a modularly connected network of DTs—referred to as a "Twin of Twins" (ToT)—where each DT specializes in a specific task [6].

Some applications of DTs in the pharmaceutical industry, where multiple CBPs must be managed simultaneously to assess associated CBAs, are illustrated in Figure 1. To create a digital ToT, a digital maturity level of 5—according to the BioPhorum Digital Plant Maturity Model (DPMM) [7]—is required for the business processes involved. This level pertains to autonomous, self-optimizing, plug-and-play facilities.

POTENTIAL USE CASES FOR DTS

In addition to the envisaged control of interdependent CBAs via ToTs, a growing number of directly applicable and partially realized use cases should also be considered, as shown in Table 1.

KEY CHALLENGES

Key challenges include protecting data privacy and security due to the large amount of information shared, integrating DTs into commonly used legacy systems, and the high initial implementation costs, which, however, are outweighed by substantial advantages in the long term.

CBAS AND CBPS

Tables 2 and 3 outline non-exhaustive lists of the CBAs and CBPs, respectively, of business-critical disciplines such as process control, production and supply chain management, quality control, and finance. CBAs help pharmaceutical companies drive innovation, improve patient outcomes, and achieve long-term success. Each of these aspects requires detailed planning, monitoring, and

Figure 2: An example of a decision sequence in an autonomous system consisting of DTs and AI agents. Simplified core equations of the steps have been added [29, 30].

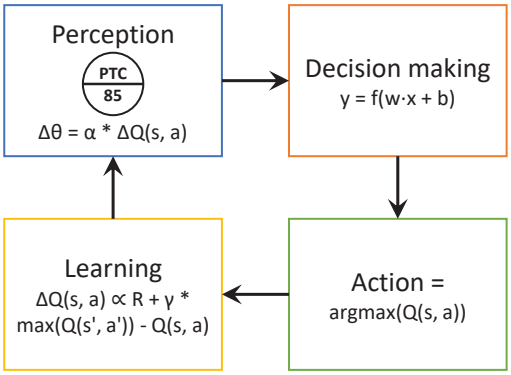
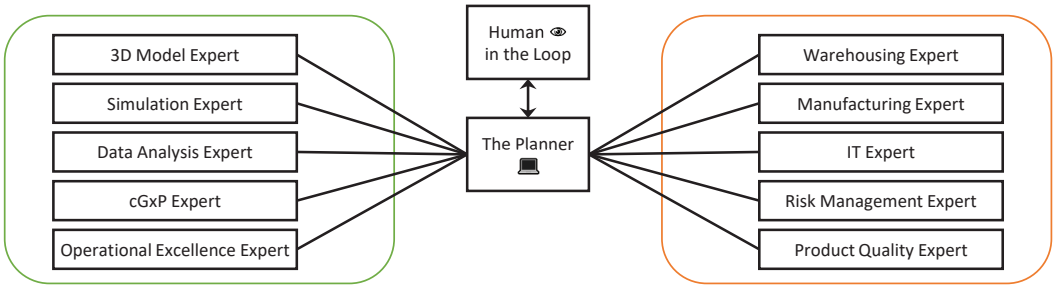


Figure 3: Diagram of how the planner agent orchestrates other AI agents with different capabilities. The green box is more useful in the creation of a DT, while the orange box is more useful in the subsequent operational phase.



resources to ensure that pharmaceutical manufacturing operations are successful, sustainable, and in compliance with regulatory standards. CBPs enable pharmaceutical manufacturers to measure and control quality, efficiency, and profitability while staying compliant and competitive. Monitoring these metrics closely can help identify opportunities for process improvements and cost savings, while maintaining rigorous quality and regulatory standards.

AGENTIC AI-POWERED TOT ENVIRONMENTS

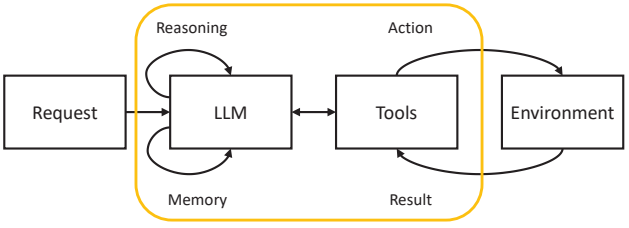
Agentic AI refers to AI systems designed to operate autonomously, make decisions, and execute requests with minimal human intervention [28]. A large language model (LLM) is used to understand a request and then executes the needed tasks with software-defined tools. This is a shift from passive AI that, for example, informs the user that stock is low, to an active AI that also asks the user to reorder the material if necessary.

Fields of application in the pharmaceutical industry are diverse, especially when used together with DTs, which can be considered advanced tools for such agents. Figure 2 shows an example of a decision sequence in an autonomous system consisting of DTs and AI agents. The signals received from the real system are processed in the DT and lead to a decision that is then executed by the AI agent. The result is finally reported back to the DT and helps improve the system parameters.

AI agents are also expected to be a valuable support both in the creation of DTs—by having agents with the different capabilities to create the different components of a DT—and in later operations, where other agents use the DT as a tool. Figure 3 illustrates how a planner agent orchestrates other AI agents with different capabilities. Its role is to receive information, make decisions, and provide feedback, but ultimately the human in the loop is still responsible for making the final decisions and taking overall responsibility.

A specific type, termed a ReAct agent (Figure 4), is designed to perceive the environment, reason, plan, and act autonomously to achieve specific goals, thereby bridging the gap between logic and action and enabling sophisticated problem-solving in the real world [31]. ReAct agents operate in a loop: receiving input, processing it with the LLM to generate a plan, executing the plan through tool

Figure 4: Diagram of how a ReAct agent (yellow box) operates



interactions (e.g., internet searches, code execution, 3D modeling, database access, DT simulations), receiving feedback, and using that feedback to improve future performance [32].

ReAct agents can leverage DT environments to safely train and experiment with virtual representations of real-world systems. Using built-in memory systems, they learn continuously from past experiences while generating synthetic data for future applications. These agents can create, validate, and optimize simulations of complex business processes, enabling thorough testing of strategies before real-world implementation. In this way, they can understand and predict CBPs and their impact on CBAs.

MODULAR ARCHITECTURE OF DTS FOR TOT ASSEMBLY

Given the different types of DTs that need to communicate and collaborate with each other to enable accurate and comprehensive simulations of business processes, standardized interfaces and reusable building blocks are necessary to ensure consistency in the development, validation, and maintenance of DTs and their associated data flows. With the Digital Twinn System Interoperability Framework [33] introduced by the Digital Twin Consortium (DTC), a modular approach has been developed to achieve interoperability between complex systems on a large scale. Seven key concepts have been defined for this purpose. These include:

1. System-centric design for cross-domain collaboration
2. Model-based standardization for reusable applications
3. Holistic information flow for comprehensive decision-making
4. State-based interactions capturing system attributes
5. Federated repositories for distributed information access
6. Actionable information beyond raw data
7. Scalable mechanisms for handling simple to complex system interactions

This standardization aims to simplify DT integration, allowing system integrators to focus on application development rather than integration work and to unify service ecosystems to enable seamless interactions when maintaining an interconnected ToTs system.

VALIDATION OF DTS AND AI AGENTS

The development, deployment, and operation of DTs and AI agents in the pharmaceutical industry present new challenges. The accuracy and safety of these systems cannot be verified using proven CSV methods and new questions arise regarding ethical aspects of accountability, bias, and safety of learning and autonomously acting systems. The challenges arise from both the inherent complexity of AI models and the stringent regulatory requirements (e.g., cGxP) to ensure patient safety and product quality.

According to ISO Standard 23247 [34], a DT should support information continuity throughout the product life cycle including design, planning, manufacturing, and maintenance. This information should be reliable, which means that the tracking of the replicated objects and the creation of updated DT models must be validated. A rational basis for the validation of AI systems for use in GxP applications has been outlined by the ISPE GAMP D/A/CH Working Group on AI Validation, which employs a maturity model to guide validation practices [35].

In addition, the US Food and Drug Administration (FDA) recently published a draft guidance document on the use of AI models in drug and biological product submissions [36], underscoring the growing importance of clear regulatory pathways. The risk-based credibility assessment described in this draft defines the risk of an AI model as a combination of the influence the model has on an outcome and the impact of the decision resulting from it. The extent to which the AI models are evaluated should then be proportionate to the model risk. This concept of "model influence" and "decision consequence" can likewise be applied equally to the risk-based validation of DTs.

COST CONSIDERATIONS

A quantitative analysis of the costs for the development of DTs and ToTs is not yet possible, as no standardized application solutions are yet available on the market in the current state of development. Some of the most important cost drivers are presented in Table 4. Essential components, AI agents, and elements that can potentially be shared in the development and maintenance of DTs and thus have a potential to reduce overall costs are listed. The estimated cost contribution is based on our experience and is only a very indicative estimate.

The initial costs for setting up a DT will strongly depend on the digital maturity level [7] of the processes to be mapped. In addition, the costs incurred by inactivity, e.g., less predictable downtimes, should be considered as well and compared to the investment costs [37]. It should also be considered that DTs are currently at an early stage of development for industrially viable applications. The more they are standardized, modularized, and commoditized, the more significant cost reductions can be expected.

CONCLUSION

DTs—empowered by connected devices, IIoT, HPC, and advances in AI—offer the potential for unparalleled accuracy in simulating complex interactions, enabling informed decision-making, and mitigating risks of the real twin. Here we have illustrated their potential in combination with agentic AI to transform the

Table 4: Critical cost drivers for building up a DT of a process system are illustrated for pharmaceutical manufacturing applications

Cost Drivers	Essential Components	AI Agents	Shared Elements	Estimated Contribution
Process DT Core	• Critical process sensors • Real-time monitoring systems • Process control interfaces • Quality monitoring equipment	• Process optimization AI • Real-time anomaly detection • Predictive maintenance • Quality prediction	• Process knowledge base • Historical data • Model libraries	20%–25% of total cost
Regulatory Compliance	• Compliance monitoring systems • Electronic batch records • Audit trail systems • Documentation tools	• Compliance verification AI • Regulatory impact analysis • Documentation generators • Validation management	• Compliance frameworks • Validation protocols • Standard procedures	15%–20% of total cost
Predictive Analytics	• HPC • Machine learning infrastructure • Model development tools • Validation environments	• Predictive modeling AI • Pattern recognition • Optimization engines • What-if analysis	• Analytics platforms • Model repositories • Training datasets	10%–15% of total cost
Data Integration and Quality	• Enterprise data lake infrastructure • Master data management systems • Data validation tools • Integration middleware	• Data quality AI • Master data governance • Real-time data synchronization • Data lineage tracking	• Data standards • Integration frameworks • Validation protocols	25%–30% of total cost
Enterprise Integration	• API management platform • Integration servers • Security infrastructure • Cross-functional dashboards	• Enterprise orchestration • Decision support systems • Cross-process optimization • Risk management	• Internal procedures • Master data • Security protocols	10%–15% of total cost

pharmaceutical industry by optimizing production and general business processes, thereby improving decision-making and product life cycle management.

One of the key innovations presented is the development of interconnected ToTs. These allow for comprehensive, modular simulations across disciplines such as process control, production, quality assurance, and regulatory compliance. A modular, standardized architecture is required for seamless integration, making DTs scalable and adaptable to a variety of relevant use cases, from drug discovery and clinical studies to predictive maintenance and supply chain management.

The integration of agentic AI extends the capabilities of DTs by enabling autonomous decision-making and active learning. AI agents that create, review, optimize, and continuously improve simulations through feedback loops can simplify operations, improve prediction of outcomes and failures, and ensure compliance with stringent regulatory requirements. Despite the immense potential, challenges such as data protection, the integration of legacy systems, and the high initial costs of DT implementation are key barriers. We believe, however, that the long-term benefits, such as increased operational efficiency, reduced downtime, and cost savings, outweigh these initial hurdles. Increasing standardization of DT technologies and AI validation frameworks, such as those proposed by the FDA and ISPE, will further facilitate adoption while ensuring safety, compliance, and ethical accountability.

DTs and agent-based AI represent a paradigm shift in the pharmaceutical industry, improving patient treatment results, driving continuous improvement, and facilitating more sustainable operations. A successful adoption of these technologies will require close collaboration between all stakeholders in the supply chain and product life cycle, continuous regulatory adaptation and investment in modular and scalable solutions. The transition to fully integrated ToTs has the potential to provide pharmaceutical manufacturers with greater control over the interacting CBPs and CBAs, leading to improved operational excellence, faster drug development, and further improvements in the quality and compliance of pharmaceutical supply to the public.

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Stefan R. Kappeler, PhD, is Senior Director of Biopharma and Regulatory at Exyte and has over 30 years of experience in the life sciences industry. He has completed a variety of projects in research, clinical development, early and late process development, technology transfer, upstream and downstream biological drug manufacturing, quality control and assurance, facility design, engineering, commissioning, and qualification. He received his PhD in molecular biotechnology from the Swiss Federal Institute of Technology in Zurich.