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Technical requirements for digital twins in advanced pharmaceutical manufacturing

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Contents

Foreword

the Shanghai Pharmaceutical Profession Association is in charge of this English translation. In case of any doubt about the contents of English translation, the Chinese original shall be considered authoritative.

This document is drafted in accordance with the rules given in the GB/T 1.1-2020 *Directives for standardization - Part 1: Rules for the structure and drafting of standardizing documents.*

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Introduction

The concept of the digital twin represents an innovative confluence of digital technology with the physical realm, whereby physical entities are digitally modeled to create corresponding virtual counterparts, thereby mapping the physical world into a digital framework.

This document, incorporating the Quality by Design (QbD) concept, delineates the requirements for implementing digital twin technology within advanced pharmaceutical manufacturing processes. By simulation and optimizing production lines in terms of yield, robustness, and asset utilization, this document seeks to clarify objectives and values, guiding the industry toward the adoption of automated techniques such as Process Analysis Technology (PAT). The aim is to enhance production efficiency, minimize variability, reduce production cycles, and improve the controllability of product quality and timeliness of QC release testing. This, in turn, will lead to safer and more effective pharmaceutical products for the patients, thus fostering the high-quality development of the biopharmaceutical industry.

Technical requirements for digital twins in advanced pharmaceutical manufacturing

1 Scope

This document specifies the relevant requirements for the use of digital twin technology in advanced pharmaceutical manufacturing, encompassing system architecture, system construction elements, functional requirements, and safety requirements.

This document is applicable to the design and execution of activities related to digital twins in the realm of advanced pharmaceutical manufacturing.

2 Normative references

The following documents, cited through normative references, constitute essential provisions of this document. Only the versions corresponding to the dates provided apply; for documents without dates, the latest versions (including all amendments) apply.

GB/T 43709-2024 *Asset management informationization-Requirements for data quality management*

Good manufacturing practice for drugs (GMP) (revised in 2010)

T/SHPPA 010-2021 *Technical requirements for digital quality assurance in pharmaceutical manufacturing*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
digital twin

a hybrid model comprising a tangible physical system of biological or non-biological entities, a virtual image based on real-time data coupling, and foundational models established through digital technology and a user interface

Note: In the field of biopharmaceuticals, the physical entity of a tangible physical system can be a biological cell, a reactor, or a complete factory or supply chain.

3.2
virtual model of physical asset

a digital virtual model constructed for the tangible physical system object of the digital twin, characterized by deep system understanding and the capability of synchronizing with the physical system independently

Note: It is characterized by having a deep understanding of the system, being self-sufficient, and being able to synchronize with the physical system without the need for direct access to the physical world.

3.3
advanced pharmaceutical manufacturing

the employment of modern technologies and methods for pharmaceutical production, including digital manufacturing, real-time process control, continuous manufacturing, artificial intelligence, rapid prototyping, etc

Note: Including but not limited to digital manufacturing, real-time process control, continuous manufacturing, artificial intelligence, rapid prototyping technology (such as 3D printing technology), etc.

4 Technical requirements

4.1 System architecture

4.1.1 General requirements

4.1.1.1 In order to establish robust connections between physical entities and their corresponding virtual models, an overall management strategy must be considered to accommodate the introduction of the new sensors and the iteration of various systems and models. The system architecture should oversee the entire factory and asset hierarchy, necessitating the creation of an abstraction layer that bridges physical reality, sensors, and virtual models.

4.1.1.2 As a hierarchical, scenario-based digital framework, the system architecture must be capable of describing all physical entities and their relationships within the system, including sensors. This architecture should facilitate the mapping and interpretation of system components while maintaining adaptability and resilience in response to changes in physical entities.

4.1.1.3 When integrating the system architecture into industrial control databases, Enterprise Resource Planning (ERP) systems, Manufacturing Execution Systems (MES), the Internet of Things (IoT), or other platforms utilizing diverse standards, proactive measures are essential to prevent inconsistencies across these systems. Furthermore, the system architecture should be managed as a Master Data Management (MDM) solution, serving as a single reference source for other systems, ensuring coherence and consistency across the enterprise.

4.1.2 Basic architectural requirements

Data from physical entities must be transmitted in real-time to the virtual model for visualization, analysis, and experimental design. When a fixed virtual model is implemented, the data and parameters within the virtual model should be updated in real time as per the real status of the physical entities .

4.1.3 Intelligent Architectural Requirements

The virtual model should be optimized using Artificial Intelligence (AI) techniques., employing the supervised or unsupervised equipment to learn algorithms of diverse datasets processing, in order to monitor, simulate and optimally manage the physical entities, as well as the prediction of their status. The digital twin system should be maintained in a continuous self-learning condition to ensure real-time data coupling, thereby enabling dynamic synchronization between the physical entity and its virtual model. This approach will enhance the quality of product and efficiency of pharmaceutical manufacturing.

4.2 System construction elements

The digital twin system is composed of physical entities, virtual models, and bidirectional data exchange. It should maintain real-time connectivity and be capable of evolving to encompass multiple levels of mirroring, depending on the required precision. Typically, the system is divided into five levels based on the depth of mirroring:

a) Digital construction of pharmaceutical factory facilities and equipment: Realizing a virtual framework;

b) Real-time transmission of information data: Reflecting critical process parameters and key quality attributes of materials in drug manufacturing, thereby creating a business framework;

c) Simulation of mechanisms: For scenarios where the physical, chemical, and biological mechanisms of active pharmaceutical ingredients (APIs) or formulations are well-defined, the system should enable simulation and issue identification within the virtual environment, based on explicit mathematical models;

d) AI-driven predictions: In cases where the physical, chemical, and biological mechanisms are unclear, the system should leverage big data and AI models to predict and resolve process-related issues;

e) Collaborative intelligence among multiple twins: Enabling mutual iteration and optimization between physical entities and virtual models across global factories within a group.

4.3 Functional requirements

4.3.1 Sensors

4.3.1.1 Sensors play a critical role in this system. They encompass both hardware sensors, which capture the physical environment (e.g., temperature, pressure, pH, velocity, and flow rate), and software sensors, which analyze basic physical parameters and convert them into higher-level measurements. Sensors should accurately measure the state of physical entities and generate the synchronized status between the physical entity and the virtual model.

4.3.1.2 Legacy sensors that provide with analog outputs must be converted to digital signals. When sensors are managed by Programmable Logic Controllers (PLCs), it is essential that they can utilize data, thereby preventing data lock-in within the PLC.

4.3.1.3 Defective products should be clearly marked and rejected to avoid confusion with released products.

4.3.1.4 Data generated by sensors must be consistent and maintained in robust traceability with the factory digital platforms, including Manufacturing Execution Systems (MES), Laboratory Information Management Systems (LIMS), Electronic Lab Notebooks (ELN), and others. Manual intervention or data transfer between measurement systems and data capture should be avoided, in compliance with the specifications outlined in T/SHPPA 010-2021, Section 4.1.2.

4.3.2 Virtual models of physical entities

4.3.2.1 Modeling

4.3.2.1.1 The digital twin system for advanced pharmaceutical manufacturing should collect data information from multiple domains—such as production, transportation, and processing—to enable multidimensional modeling. The virtual model within the digital twin system is more than a traditional IT solution. In addition to capturing process data at the logical level, it must also represent the actual real physical factories and manufacturing equipment. Figure 1 illustrates the framework of the virtual model for advanced pharmaceutical manufacturing.

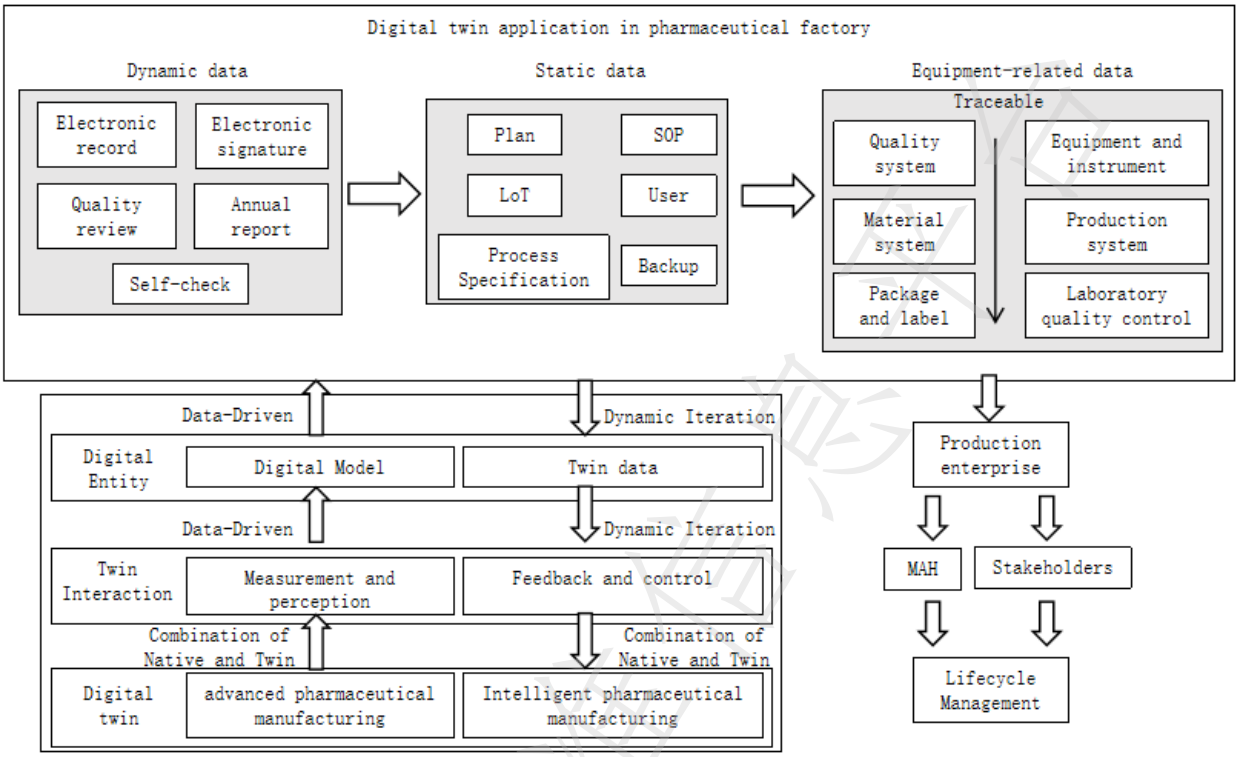

Figure 1 The framework of the virtual model for advanced pharmaceutical manufacturing

4.3.2.1.2 Typically, a standard 3D Computer-Aided Design (CAD) model is used based on the research objectives and practical needs of the process. However, in biological Drug Substance (DS) production, 3D models may not be the most effective representation, selection of the virtual models should be based on appropriate chemometric mechanisms, such as whole-cell simulations, reactor physical behavior, mass transfer factors, and other multi-scale biological reaction processes.

4.3.2.1.3 To ensure compliance with Good Manufacturing Practices (GMP), Quality Assurance (QA) for digital elements, such as electronic deviation management, change management, and quality reviews, should be also considered in the digital way and fully integrated into the system.

4.3.2.2 Availability

Sub-models from equipment suppliers should be integrated as components of physical entities wherever possible. If the virtual model is originated from the supplier, it is essential to ensure its appropriate availability and use. The virtual model should be an open, programmable system. it is recommended that suppliers should enhance the transparency of the standards they followed, clearly define the naming conventions and hierarchical structures in both software and hardware development.

4.3.2.3 Intelligent architecture model

In an intelligent architecture, virtual models should have the capability to evolve autonomously and influence the physical world in reverse. This includes the following functionalities:

a) Simulated system behavior: Without input from the physical environment, system behavior can be simulated using a combination of mechanism and data models. These models could cover the dynamic characteristics of facilities, equipment, personnel, materials, environment, and biopharmaceuticals.

b) Process simulation: The system should simulate changes in physical entities-such as biological fermentation, chemical reactions, material mixing, packaging performance, or drug delivery device functions-based on key process parameters and quality attributes. This includes complex process control strategies and models that reflect dynamic material and parameter transfers, monitor potential deviation risks, and clarify interaction methods with physical entities.

4.3.2.4 Professionalism

4.3.2.4.1 Integration across disciplines-including pharmacy, statistics, computer science, engineering mechanics, materials science, communication science, and integrated circuits-is essential to avoid leaving process characterization, understanding, and control at a purely formal level. Instead, these should be automatically utilized by digital simulations.

4.3.2.4.2 Virtual model can be used to explain the operation of pharmaceutical production . Meanwhile, the physical causal relationships and correlations should be clearly defined. Data information produced by the model should be consistent with accumulated data from small-scale, pilot-scale, or commercial production of physical entities.

4.3.3 Connectivity

4.3.3.1 The system must also effectively transmit data from physical entities to virtual models, whether through Supervisory Control and Data Acquisition (SCADA) systems, industrial Ethernet, standard mobile networks, or edge computing methods.

4.3.3.2 Plans and measures must be developed to mitigate confusion and inconsistencies arising from the complexity of communication protocols. When using compressed datasets for virtual models, the digital infrastructure should meet the corresponding requirements and confirm the algorithms used for data conversion and simplification.

4.3.3.3 The Internet of Things (IoT) data storage system, transmission technologies, and cloud network infrastructure should meet the connectivity requirements of digital twins, including:

a) Large-scale, high-concurrency, low-latency data storage capabilities;

b) High scalability;

c) Ensuring data availability and the continuity of business operations;

d) Data reliability in complex and diverse equipment environments;

e) The use of encryption and identity verification technologies to secure data transmission;

f) Adoption of low-power data transmission technologies;

g) Quick switching to backup devices or repair procedures in the event of equipment failure or other abnormal conditions.

4.4 Safety requirements

4.4.1 Configuration management

4.4.1.1 The digital twin system should be capable of establishing appropriate configurations and granting permissions and interface access to different departments and stakeholders within the enterprise. Configuration management should address the varying needs of different users by setting distinct usage permissions.

4.4.1.2 Furthermore, workflows should be implemented to evaluate and verify configuration-related changes when necessary. In cases involving multiple independent dynamic components, a robust configuration management mechanism is essential to ensure that configurations are automatically synchronized and comply with change management requirements.

4.4.2 Data

4.4.2.1 the virtual model should accurately reflect data related to key quality attributes, key process parameters, key material data, deviation data, release operation records, key authorization records, and data for other critical elements.

4.4.2.2 The digital twin should also encompass data from previous processes and equipment operations to accumulate sufficient information for machine learning algorithms. Pure mechanism modeling, such as that used in biopharmaceuticals, requires real-world experiments to feed as background information for the model simulation. When acquiring data, the following should be considered:

a) Data should originate from multiple experiments, including those accumulated during the early development process and those provided by suppliers;

b) Beyond the measurements themselves, a holistic understanding of the data is required,

considering multiple uses in different scenarios. During data capture, it is vital to track any changes made to the system during the experiment and adjust the dataset arrangement as necessary to ensure comparability.

4.4.2.3 Data analysis should adhere to sound data modeling practices. Existing standard taxonomies can be used to develop formal ontologies for key data domains within digital twins. In the early stages of the digital twin lifecycle, an integrated management software system for data modeling and ontology should be established to support future data model version management and the adjustment of datasets.

4.4.2.4 Confidentiality in data asset management should be maintained according to the requirements of GB/T 43709-2024. An asset management information data responsibility system should be established to control processes and generate corresponding records, while also complying with the relevant requirements of the 2010 revision of the Good Manufacturing Practice for Pharmaceutical Products and the drug approval documentation for data retention periods.

4.4.2.5 Additionally, compliance with the National Medical Products Administration's 2020 Announcement No. 74 on the trial implementation of drug record and data management requirements is necessary, as well as the electronic data requirements of Section 21, Part 11 of the US FDA's federal regulations. This includes adhering to guidelines on data reliability,electronic signatures, data management, and integrity best practices in the PIC/S GMP/GDP environment.

4.4.3 Life cycle management

4.4.3.1 During the initial design phase, the potential interactions between physical entities and virtual models must be thoroughly considered. The influence and guidance of virtual simulations on physical reality should be applied strategically. During continuous operation, it is important to fully understand the inherent physical phenomena of biopharmaceuticals to pre-formalize controllable characteristics of these phenomena and embed control strategies into the virtual models. The results of virtual model simulations can then be applied to physical entities with continuous feedback loops, thereby achieving overall continuous improvement throughout the digital twin lifecycle.

4.4.3.2 Life cycle management for digital twins should address, but is not limited to, the following stages:

a) Planning and design stage:

- Determine the application requirements of digital twins in pharmaceutical manufacturing and clearly define the expected goals;

- Design the digital twin system architecture, model structure, data integration, and interface specifications.

b) Development and implementation stage:

- Integrate production data and conduct preprocessing, cleaning, and standardization to meet the data requirements of digital twins;
- Develop digital models tailored to pharmaceutical manufacturing, including simulations of manufacturing processes and quality control models;
- Integrate digital twin systems into manufacturing processes to ensure seamless operation.

c) Operation and optimization stage:

- Monitor the digital twin system in real-time to ensure stability and accuracy;
- Continuously optimize the digital twin model and algorithms based on actual manufacturing process data and feedback, enhancing the capability of prediction and optimization.

d) Data privacy and security management:

- Develop privacy protection strategies to prevent unauthorized access to or leakage of data within the digital twin system;
- Implement security control measures, including encryption, access control, and auditing, to ensure system security.

e) Training and knowledge sharing:

- Provide training for personnel using digital twin systems to enhance their understanding and application of the system;
- Promote knowledge sharing within and beyond the team to drive continuous improvement and innovation in digital twin technology.

f) Retirement:

- Formulate a structured retirement plan and implement it in a planned manner;

- Ensure that migration, backup, or archiving of both current and historical data complies with the requirements of Section 4.4.2.5.

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