U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Artificial Intelligence in Drug Manufacturing

Discussion Paper | 2023

Disclaimer: This paper is for discussion purposes only and is not a draft or final guidance. It is meant to facilitate early input from stakeholders outside the Agency. The Agency intends to consider such input in developing a future regulatory framework. As such, this document is not intended to convey any current regulation or policy related to artificial intelligence manufacturing technologies.

Introduction

CDER's mission is to ensure that human drugs are safe and effective, meet established quality standards, and are available to patients. To advance this mission, FDA's Pharmaceutical Quality for the 21st Century Initiative promotes an efficient, agile, and flexible pharmaceutical manufacturing sector that reliably produces quality drugs without excessive regulatory oversight. Trends in drug development highlight a need for more flexibility in manufacturing.

Advanced manufacturing is a term that describes an innovative pharmaceutical manufacturing technology or approach that has the potential to improve the reliability and robustness of the manufacturing process and resilience of the supply chain. Advanced manufacturing can: (a) integrate novel technological approaches, (b) use established techniques in an innovative way, or (c) apply production methods in a new domain where there are no defined best practices. Advanced manufacturing can be used for new or currently marketed large or small molecule drug products.

FDA has recognized and embraced the potential of advanced manufacturing. In 2014, CDER established the Emerging Technology Program (ETP) to work collaboratively with companies to support the use of advanced manufacturing. CDER observed a rapid emergence of advanced manufacturing technologies through the ETP and recognized that regulatory policies and programs may need to evolve to enable timely technological adoption.

The National Academies of Sciences, Engineering, and Medicine issued a 2021 report titled *Innovation in Pharmaceutical Manufacturing on the Horizon: Technical Challenge, Regulatory Issues, and Recommendations*, highlighting innovations in integrated pharmaceutical manufacturing processes. These innovations could have implications for measurement, modeling, and control technologies used in pharmaceutical manufacturing. Artificial intelligence (AI) may play a significant role in monitoring and controlling advanced manufacturing processes.

Scope

As FDA considers the application of its risk-based regulatory framework to the use of AI technologies in drug manufacturing, the Agency has identified in this discussion paper areas for which public feedback would be valuable. CDER scientific and policy experts identified these areas from a comprehensive analysis of existing regulatory requirements applicable to the approval of drugs manufactured using AI technologies.[1] The areas of consideration in this discussion paper are those for which FDA would like public feedback. There are additional areas of consideration not covered within this document; for example, difficulties that could result from potential ambiguity on how to apply existing Current Good Manufacturing Practice (CGMP) regulations to AI or lack of Agency guidance or experience.[2] The areas of consideration presented in this discussion paper focus on the manufacture of drug products that would be marketed under a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA).

Public feedback will help inform CDER's evaluation of our existing regulatory framework. While the initial analysis focused on products regulated by CDER, FDA's Center for Biologics Evaluation and Research (CBER) has also encountered a rapid emergence of advanced manufacturing technologies associated with AI. As such, both CDER and CBER stakeholders are invited to provide feedback on the discussion questions.[3]

[1] This analysis included a review of applicable statutory provisions, regulations, and guidance related to quality assessment and inspections to determine whether an application presenting an advanced manufacturing technology implementing AI can fit within our current regulatory framework. The analysis did not extend to applications of AI in supply chain management of drugs.

[2] The areas of consideration and policy development identified in the discussion paper are not exhaustive of all application and current good manufacturing practice (CGMP) considerations. The determination of critical areas is based on CDER's analysis of the regulatory framework and stakeholder engagements through the ETP.

[3] For the purposes of this discussion paper, all references to drugs include both human drugs and biological products (including those regulated by CBER), unless otherwise specified. CBER is also seeking early input from stakeholders outside the Agency on how the considerations outlined for AI may be further tailored to CBER-regulated products, many for which there is limited manufacturing experience or undefined critical quality attributes. We also note that some developers may be interested in exploring the use of AI in the bioinformatics pipelines as part of the upstream manufacturing process to generate and select candidates for precision medicine complex biological products, e.g., cancer vaccines, cellular and gene therapies, and we are interested in hearing from stakeholders on this topic.

Background

AI offers many possibilities in the pharmaceutical industry, including but not limited to optimizing process design and process control, smart monitoring and maintenance, and trend monitoring to drive continuous improvement. The use of AI to support pharmaceutical manufacturing can be deployed with other advanced manufacturing technologies to achieve desired benefits. AI is an enabler for the implementation of an Industry 4.0 paradigm that could result in a well-controlled, hyper-connected, digitized ecosystem and pharmaceutical value chain for the manufacturer.[4]

Through interactions with industry, FDA has received valuable feedback, including potential AI use cases in pharmaceutical manufacturing. Below are examples, based on these interactions and a review of published information, that forecast how AI might be used in pharmaceutical manufacturing. These examples are not exhaustive and the potential applications of AI in pharmaceutical manufacturing may continue evolving.

- **Process Design and Scale-up:** AI models such as machine learning—generated using process development data—could be leveraged to more quickly identify optimal processing parameters or scale-up processes, reducing development time and waste.
- **Advanced Process Control (APC):** APC allows dynamic control of the manufacturing process to achieve a desired output. AI methods can also be used to develop process controls that can predict the progression of a process by using AI in combination with real-time sensor data. APC approaches that combine an understanding of the underlying chemical, physical, and biological transformations occurring in the manufacturing process with AI techniques are expected to see increasing adoption and have already been reported by several pharmaceutical manufacturers.

[4] The term "Industry 4.0" refers to the fourth industrial revolution which brings together rapidly evolving technologies to dramatically change the manufacturing landscape. Industry 4.0 is characterized by integrated, autonomous, and self-organizing production systems. See Arden S, A Fisher, K Tyner, L Yu, S Lee, M Kopcha, 2021, Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future, *International Journal of Pharmaceutics*, 602(1), https://doi.org/10.1016/j.ijpharm.2021.120554.

- **Process Monitoring and Fault Detection:** AI methods can be used to monitor equipment and detect changes from normal performance that trigger maintenance activities, reducing process downtime. AI methods can also be used to monitor product quality, including quality of packaging (e.g., vision-based quality control that uses images of packaging, labels, or glass vials that are analyzed by AI-based software to detect deviations from the requirements of a product's given quality attribute).
- **Trend Monitoring:** AI can be used to examine consumer complaints and deviation reports containing large volumes of text to identify cluster problem areas and prioritize areas for continual improvement. This offers the advantage of identifying trends in manufacturing-related deviations to support a more comprehensive root cause identification. AI methods integrated with process performance and process capability metrics can be used to proactively monitor manufacturing operations for trends. These methods can also predict thresholds for triggering corrective and preventive action effectiveness evaluations.

Terminology

The definitions below are for the purposes of this discussion paper only.

- **Artificial Intelligence (AI):** A branch of computer science, statistics, and engineering that uses algorithms or models that exhibit behaviors such as learning, making decisions, and making predictions.
- **Machine Learning (ML):** A branch of AI that provides systems with the ability to develop models through analysis of data without being explicitly programmed and to improve based on data or experience.
- **Model:** An abstract description of a physical system in any form (including mathematical, symbolic, graphical, or descriptive) that represents a certain aspect of that physical system.
- **Cloud Computing:** A model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g., networks, servers, storage, applications, services) that can be rapidly provisioned and released with minimal management effort or service provider interaction.[5]

[5] See the National Institute of Standards and Technology's definition of cloud computing at http://csrc.nist.gov/publications/PubsSPs.html#800-145.

- **Metadata:** Contextual information required to understand data.
- **Edge Computing:** A distributed form of computing done at or near a particular data source.
- **Data Management:** The processes for collecting, storing, organizing, maintaining, and securing data created by an organization.
- **Internet of Things (IOT):** A type of cyber-physical system comprising interconnected computing devices, sensors, instruments, and equipment integrated online into a cohesive network of devices that contain the hardware, software, firmware, and actuators which allow the devices to connect, interact, and exchange data and information. IOT devices include sensors, controllers, and mechanical equipment.

Areas of Consideration Associated with AI

1. **Cloud applications may affect oversight of pharmaceutical manufacturing data and records.**

   With evolving developments in cloud and edge computing, the software location involved in pharmaceutical manufacturing may change. For example, the software that controls execution may still be implemented close to the manufacturing equipment to ensure no impact on performance or security, while other software functions that are not time critical could occur in the cloud (e.g., model updates, control diagnostics, and process monitoring analytics). Third-party data management systems could be used for functions that extend beyond data storage. For example, data stored in these systems may be analyzed by AI to support models for process monitoring and APC.

   Data integrity and data quality must be ensured in these environments. While FDA allows the use of third parties for CGMP functions under appropriate oversight by the manufacturer, existing quality agreements between the manufacturer and a third party (e.g., for cloud data management) may have gaps with respect to managing the risks of AI in the context of manufacturing monitoring and control. During inspections, this may lead to challenges in ensuring that the third-party creates and updates AI software with appropriate safeguards for data safety and security.

Further, FDA inspection approaches for evidence gathering of records management may need to expand due to the complexity of managing third-party cloud data and models. For example, the ongoing interactions between cloud applications and process controls could complicate the ability to establish data traceability, create potential cybersecurity vulnerabilities, and require evaluation of the procedures in place to monitor data integrity vulnerabilities during an inspection.

Some Potentially Associated Requirements and Policies

- Regulations:
  - 21 CFR 11, 211.180, 211.184, 211.194, 600.12
- Draft Guidance for Industry:
  - Data Integrity and Compliance with CGMP (April 2016)[6]
- Guidance for Industry:
  - Contract Manufacturing Arrangements for Drugs: Quality Agreements (November 2016)
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)

2. **The IOT may increase the amount of data generated during pharmaceutical manufacturing, affecting existing data management practices.**

Digitization of manufacturing controls may generate more information about a process and product. The increase in data may be in terms of both the frequency and the types of data recorded. There are regulations and guidance addressing the amount of data and metadata to be stored for each batch of drug product manufactured; however, if the raw data collected during the manufacturing process increases significantly, there may be a need to balance data integrity and retention with the logistics of data management.

Applicants may need clarity regarding regulatory compliance for generated data (e.g., which data needs to be stored and/or reviewed and how loss of these data would impact future quality decisions such as product recalls). Further, applicants may need additional clarity for data sampling rates, data compression, or other data management approaches to ensure that an accurate record of the drug manufacturing process is maintained.

[6] When final, this guidance will represent the agency's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Also, there may be challenges in storing the data in a structured manner that enables retrieval and analysis to support an applicant's decision-making. Moreover, as manufacturing equipment becomes interconnected into a network, maintaining stewardship, privacy, and security of such data generated by the equipment may pose a challenge to preserving product quality or maintaining pharmaceutical manufacturing.

Some Potentially Associated Requirements and Policies

- Regulations:
  - 21 CFR 211 Subparts D and J
- Draft Guidance for Industry:
  - Data Integrity and Compliance with CGMP (April 2016)[7]
- Guidance for Industry:
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)

3. **Applicants may need clarity about whether and how the application of AI in pharmaceutical manufacturing is subject to regulatory oversight.**

AI could be used in various manufacturing operations such as monitoring and maintaining equipment, identifying areas for continuous improvement, scheduling and supply chain logistics, and characterizing raw materials. Applicants will need to understand the applications of AI in manufacturing operations that are subject to regulatory oversight (e.g., CGMP compliance, new drug or biologics license applications).

Some Potentially Associated Requirements and Policies

- Regulations:
  - 21 CFR 11, 211.68, 211.84, 211.180, 211.184, 314.50, 314.94, 601.20
- Draft Guidance for Industry:
  - ICH Q9(R1) Quality Risk Management (June 2022)[8]
  - ICH Q12 Implementation Considerations for FDA-Regulated Products (May 2021)[9]
  - Data Integrity and Compliance with CGMP (April 2016)[10]

[7] When final, this guidance will represent the agency's current thinking on this topic.

[8] When final, this guidance will represent the agency's current thinking on this topic.

[9] When final, this guidance will represent the agency's current thinking on this topic.

[10] When final, this guidance will represent the agency's current thinking on this topic.

- Guidance for Industry:
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)
  - ICH Q8(R2) Pharmaceutical Development (November 2009)
  - ICH Q10 Pharmaceutical Quality System (April 2009)
  - ICH Q11 Development and Manufacture of Drug Substances (November 2012)
  - ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (May 2021)
  - Q8, Q9, & Q10 Questions and Answers — Appendix: Q&As from Training Sessions (July 2012)
  - Process Validation: General Principles and Practices (January 2011)
- Compliance Program:
  - 7346.832 — Preapproval Inspections (October 2022)
  - 7356.002 — Drug Manufacturing Inspections (October 2022)
  - 7356.002M — Surveillance Inspections of Protein Drug Substance Manufacturers (October 2021)

4. **Applicants may need standards for developing and validating AI models used for process control and to support release testing.**

   AI can be used in APC applications to control manufacturing processes by adapting process parameters based on real-time data. Additionally, AI models can be used in conjunction with interrogation of in-process material or the final product to: (1) support analytical procedures for in-process or final product testing, (2) support real-time release testing, or (3) predict in-process product quality attributes. There are limited industry standards and FDA guidance available for the development and validation of models that impact product quality, which can create challenges in establishing the credibility of a model for a specific use.

   The robustness of the underlying data shapes decisions made by the AI model. This can create challenges in avoiding unintended biases during model development and validation. AI models can also store knowledge gained during development for a specific use case and then apply it to a different but related use case to accelerate model development. Applicants and manufacturers may need clarity regarding how the potential to transfer learning from one AI model to another can be factored into model development and validation.

As AI methods become more complex, it becomes more challenging to explain how changes in model inputs impact model outputs. In these cases, applicants may be challenged to define standards that validate the model and sustain the explainability[11] of the model's output and impact on product quality.

Some Potentially Associated Requirements and Policies

- Regulations:
  - 21 CFR 11, 211.68, 211.110, 211.165, 211.180
- Draft Guidance for Industry:
  - ICH Q14 Analytical Procedure Development (August 2022)[12]
- Guidance for Industry:
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)
  - ICH Q8(R2) Pharmaceutical Development (November 2009)
  - ICH Q9 Quality Risk Management (June 2006)
  - ICH Q10 Pharmaceutical Quality System (April 2009)
  - ICH Q11 Development and Manufacture of Drug Substances (November 2012)
  - Process Validation: General Principles and Practices (January 2011)
  - Development and Submission of Near Infrared Analytical Procedures (August 2021)
- Compliance Program:
  - 7346.832 — Preapproval Inspections (October 2022)
  - 7356.002 — Drug Manufacturing Inspections (October 2022)
  - 7356.002M — Surveillance inspections of Protein Drug Substance Manufacturers (October 2021)

5. **Continuously learning AI systems that adapt to real-time data may challenge regulatory assessment and oversight.**

In the current paradigm, models deployed in manufacturing (e.g., in-process controls, real-time release testing) are developed, validated, implemented, and updated as needed through the change control process within the pharmaceutical quality system. AI models (e.g., machine learning-based models) can involve continuous learning wherein the model evolves over time as new information becomes available.

[11] Explainable AI models provide accompanying evidence or reasons for the model outputs. The provided explanations are understandable to the user and accurately reflect the model's process for generating the outputs. Explainable AI models only operate under conditions for which they were designed. See https://nvlpubs.nist.gov/nistpubs/ir/2020/NIST.IR.8312-draft.pdf.

[12] When final, this guidance will represent the agency's current thinking on this topic.

It may be challenging to determine when an AI model can be considered an established condition of a process. It may also be challenging to determine the criteria for regulatory notification of changes to the model as a part of model maintenance over the product lifecycle. Applicants may need clarity on: (a) the expectations for verification of model lifecycle strategy and the approach for FDA's examination of continuously updated AI control models during a site inspection, and (b) expectations for establishing product comparability after changes to manufacturing conditions introduced by the AI model, especially for biological products.

Some Potentially Associated Requirements and Policies

- Regulations:
  - 21 CFR 11, 211.68, 211.180, 314.70, 314.97, 601.12
- Draft Guidance for Industry:
  - ICH Q12 Implementation Considerations for FDA-Regulated Products (May 2021)[13]
- Guidance for Industry:
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)
  - Q8, Q9, & Q10 Questions and Answers — Appendix: Q&As from Training Sessions (July 2012)
  - ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (May 2021)
  - Development and Submission of Near Infrared Analytical Procedures (August 2021)
  - Changes to an Approved NDA or ANDA (April 2004)
  - Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)
  - SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation: Guidance for Industry (October 1997)
  - SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)

[13] When final, this guidance will represent the agency's current thinking on this topic.

AI Questions & Feedback Section

1. ***What types of AI applications do you envision being used in pharmaceutical manufacturing?***
2. ***Are there additional aspects of the current regulatory framework (e.g., aspects not listed above) that may affect the implementation of AI in drug manufacturing and should be considered by FDA?***
3. ***Would guidance in the area of AI in drug manufacturing be beneficial? If so, what aspects of AI technology should be considered?***
4. ***What are the necessary elements for a manufacturer to implement AI-based models in a CGMP environment?***
5. ***What are common practices for validating and maintaining self-learning AI models and what steps need to be considered to establish best practices?***
6. ***What are the necessary mechanisms for managing the data used to generate AI models in pharmaceutical manufacturing?***
7. ***Are there other aspects of implementing models (including AI-based models) for pharmaceutical manufacturing where further guidance would be helpful?***
8. ***Are there aspects of the application of AI in pharmaceutical manufacturing not covered in this document that FDA should consider?***

Conclusion

This discussion paper presents areas for consideration and potential policy development that CDER identified based on evaluating the application of the existing regulatory framework to use of AI in pharmaceutical manufacturing. A regulatory framework for advanced manufacturing evaluation will address these areas while also considering how potential changes could affect existing technologies and facilities. CDER will use feedback submitted to the docket to inform future policy development. Please submit your comments regarding this discussion paper to https://www.regulations.gov, Docket No. FDA-2023-N-0487.

Appendix A: Related Guidance, Policy, and Regulations

FDA Draft Guidance for Industry
Data Integrity and Compliance with CGMP (April 2016)[14]
ICH Q9(R1) Quality Risk Management (June 2022)[15]
ICH Q12 Implementation Considerations for FDA-Regulated Products (May 2021)[16]
ICH Q14 Analytical Procedure Development (August 2022)[17]
FDA Guidance for Industry
Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)
Changes to an Approved NDA or ANDA (April 2004)
Development and Submission of Near Infrared Analytical Procedures (August 2021)
ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)
ICH Q8 (R2) Pharmaceutical Development (November 2009)
ICH Q10 Pharmaceutical Quality System (April 2009)
ICH Q11 Development and Manufacture of Drug Substances (November 2012)
ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (May 2021)
Process Validation: General Principles and Practices (January 2011)
Q8, Q9, & Q10 Questions and Answers — Appendix: Q&As from Training Sessions (July 2012)
SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation: Guidance for Industry (October 1997)
SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)
Compliance Program
7346.832 — *Preapproval Inspections* (October 2022)
7356.002 — *Drug Manufacturing Inspections* (October 2022)
7356.002M — *Surveillance inspections of Protein Drug Substance Manufacturers* (October 2021)
Code of Federal Regulations, Chapter 21
PART 11 — ELECTRONIC RECORDS; ELECTRONIC SIGNATURES
PART 211 — CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
§ 211.68 Automatic, mechanical, and electronic equipment
§ 211.84 Testing and approval or rejection of components, drug product containers, and closures
§ 211.110 Sampling and testing of in-process materials and drug products
§ 211.165 Testing and release for distribution
§ 211.180 General requirements
§ 211.184 Component, drug product container, closure, and labeling records
§ 211.194 Laboratory records
PART 314 — APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

[14] When final, this guidance will represent the agency's current thinking on this topic.

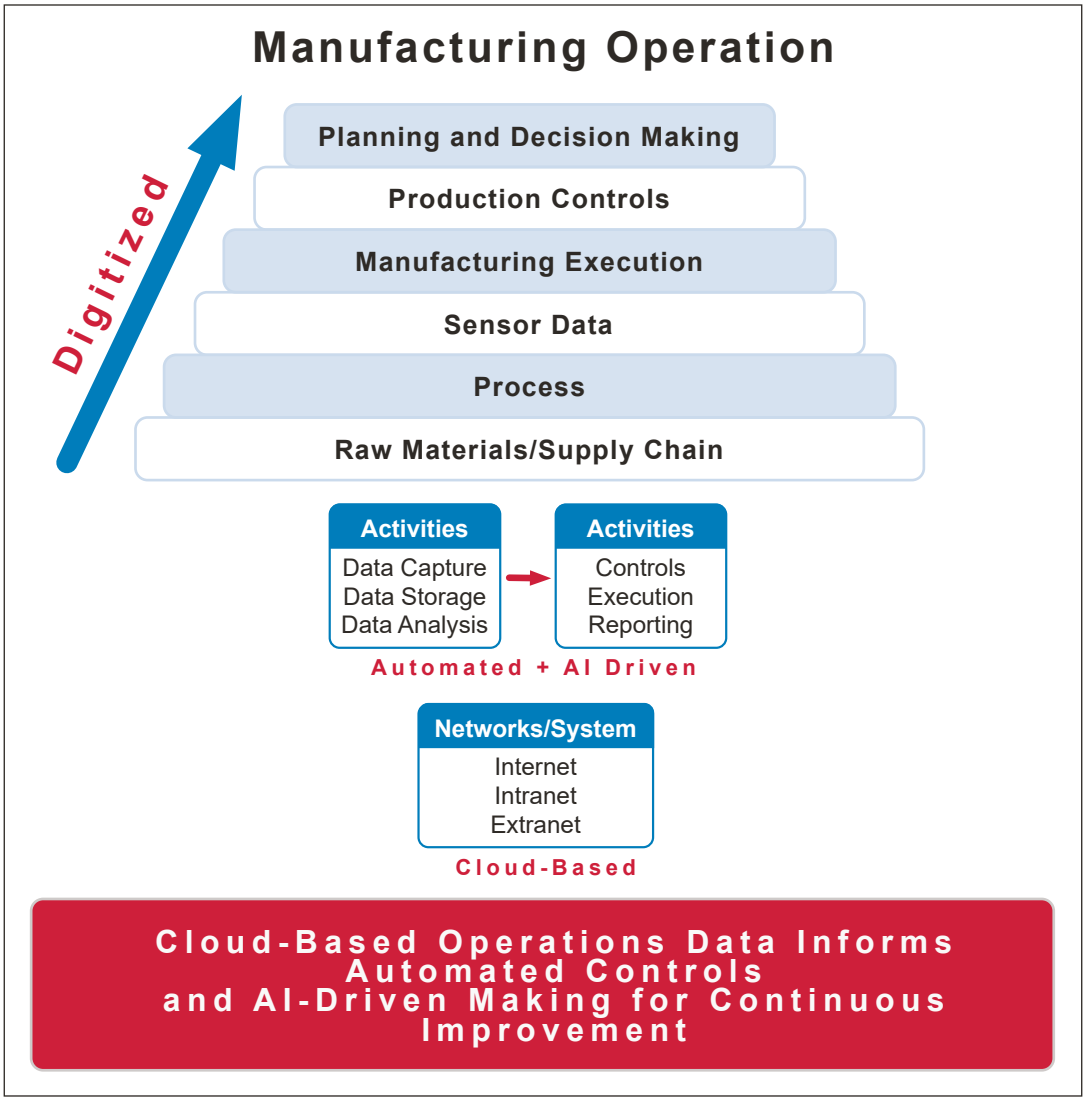
[15] When final, this guidance will represent the agency's current thinking on this topic.

[16] When final, this guidance will represent the agency's current thinking on this topic.

[17] When final, this guidance will represent the agency's current thinking on this topic.

§ 314.50 Content and format of an NDA
§ 314.70 Supplements and other changes to an approved NDA
§ 314.94 Content and format of an ANDA
§ 314.97 Supplements and other changes to an approved ANDA
PART 600 — BIOLOGICAL PRODUCTS: GENERAL
§ 600.12 Records
PART 601 — LICENSING
§ 601.12 Changes to an approved application
§ 601.20 Biologics licenses; issuance and conditions

Appendix B: Artificial Intelligence Technology Overview



Appendix C: Acronyms and Abbreviations

Acronym	Explanantion
AI	Artificial Intelligence
ANDA	Abbreviated New Drug Application
APC	Advanced Process Control
API	Active Pharmaceutical Ingredient
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDER/DLOD	Center for Drug Evaluation and Research/Division of Learning and Organizational Development
CDER/SBIA	Center for Drug Evaluation and Research/ Small Business and Industry Assistance
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
ETP	Emerging Technology Program
ETT	Emerging Technology Team
HHS	Department of Health and Human Services
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOT	Internet of Things
ISPE	International Society for Pharmaceutical Engineering
MAPP	Manual of Policies and Procedures
ML	Machine Learning
NASEM	National Academies of Science, Engineering, and Medicine
OC	Office of Compliance
OPQ	Office of Pharmaceutical Quality
OPQ/OTR	Office of Pharmaceutical Quality/Office of Testing and Research
ORA	Office of Regulatory Affairs
PAI	Pre-approval Inspection
PDA	Parenteral Drug Association
POC	Point of Care
RTRT	Real-Time Release testing
SUPAC	Scale-Up and Post-Approval Changes

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