# Application of AI in a GMP / Manufacturing environment- an Industry approach

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## Executive Summary

The pharma industry is continuing to seek opportunities to embrace the advances in new technology and computerized systems in GMP manufacturing and to adopt novel methods applied to other industries with the aim to bring medicines to patients faster. The integration of AI across pharmaceutical operations is transforming traditional practices, from drug discovery to patient care, enabling more efficient research, development, and manufacturing processes.
Artificial Intelligence (AI) refers to the simulation of human intelligence in machines. In the pharmaceutical manufacturing context, AI encompasses technologies and applications called machine learning (ML), natural language processing, and robotics. These AI-tools can analyze data, perform tasks enabled by rule-based decisions with human oversight with potential for eventual minimal intervention. AI presents new potential risks to the GMP environment but risks that can nevertheless be assessed and mitigated using current methods well practiced in the GMP environment.

As a principle: AI is a new and digital way to run established processes more efficiently. However, EFPIA recognize that there are new potential risks associated with the use of AI in pharmaceutical manufacturing regulated by GMPs. However, principles laid down in the existing GMPs including the Computerized System Validation framework, already provide a well-established procedure to conduct risk assessment to manage and mitigate these potential new risks. Therefore, these well-established frameworks and processes should strongly assist in mitigating any potential risks presented by “High Risk” systems as defined in the context of the EU AI Act and if used in the GMP environment.

This position paper presents at high level an industry approach on how to utilise the existing GMP framework to embrace AI/ML solutions in GMP regulated biopharmaceutical manufacturing, outlining the general principles and considerations for applying this and conducting validation where necessary. A risk-based approach should be applied and needs to consider the context of use of AI in manufacturing, the extent of control by the AI and extent of ‘human in the loop’ in any GMP decision making. In addition, the importance of workforce capability builds to support protection of patient safety, product quality and ensure data integrity.

# Background

AI has an immense potential to enable and augment the way manufacturing of APIs and medicinal products can be developed and commercialised by enabling efficiencies and improved data insights to bring medicinal products to market. Industry must ensure it continues to act responsibly and that its use of AI/ML remains trustworthy and compliant with current and evolving regulatory expectations to maintain its license to operate. The application and the use of AI/ML in all areas is evolving rapidly. There are perceived uncertainties about the application of AI and sometimes this has led to calls for the need to develop additional regulations for AI/ML applications used in a GMP regulated pharmaceutical manufacturing environment. However, (EU-GMP Annex 11) [5] on Computerised system Validation is undergoing a process of review by EMA [8] to update and introduce considerations for the use of AI/ML. Industry has commented on suggested enhancements to the existing framework to provide the necessary oversight and avoid the creation of additional regulatory burden.

### Innovation linking to Quality Management Systems

Given the speed and rapid evolution of benefits that AI applications can bring, industry is proactively using and adapting existing GMP frameworks and guidance to establish a risk-based approach to the use of AI and embedding this within their Quality Management Systems (QMS). This position paper aims to support the concept, that although it recognised that there are additional risks to be identified and respective risk control measures to be implemented, the overall risks associated with the use of AI in GMP regulated applications in Manufacturing is controlled. The existing GMP frameworks already provide a well-established process to conduct risk assessment and to mitigate potential risk. Using these frameworks with the new set of risks to be considered when implementing AI will enable industry to utilise the unique benefits AI can offer to support the goal of efficiently and effectively supplying medicines to patients.

### Considerations for industry in the use of AI in GMP regulated manufacturing

Industry recognises that there is the need to identify and assess risks and control them in the use of AI applications as an emerging technology in a GMP regulated manufacturing environment. The industry is at a critical point in supporting response to the pull for knowledge from regulators on this topic. Pharmaceutical companies through trade associations such as EFPIA are open to support regulators developing a more concrete position and clearer understanding to form appropriate regulatory expectations for AI use, whilst enhancing the highest standards of product quality, data integrity and patient safety. It will continue to contribute to the development of future guidance to enable the benefits and efficiencies AI can bring to the GMP manufacturing environment. After the achieved milestone of approving the AI Act in the EU, the pharmaceutical industry will potentially likely receive some revisions to regulatory expectations and examples as part of the ICH guidance process and enhancement of GMPs in the future (e.g., (EU-GMP Annex 11) [5]). This contrasts with the voluntarily applied standards (e.g., GAMP [7]) where the compliance should not be enforced in inspections.

AI applications require vast amounts of data, ensuring the privacy and security of patient and proprietary information has been highlighted as a major challenge. However, in a GMP environment, the privacy and security of patient and proprietary information are not typically applicable to the GMP Manufacturing

environment. Unless associated with AI Device manufacturing in which case Notify Body opinion is required or in circumstances in cell and gene therapy applications, where there may be a convolution of patient medical/biological and manufacturing action data.
To address the new risks AI application may bring, industry suggest these controls to be covered by the updated Computerized System validation (EU-GMP Annex 11) [5] and documentation (EU-GMP Chapter 4) [6] guidelines. These may include e.g.,

- Identify if the AI application must be managed under a GMP framework.
- Include additional consideration for hazards with AI where risk needs to be managed.
- Adopt relevant processes in the QMS (e.g., Change control, data management incl. data integrity)
- Define 'human in the loop' concepts.
- Use the established terms from the traditional computerised system validation framework.
- Define context of use, data requirements, performance verification
- Cyber security consideration

## Current GMP Framework in use to support AI:

**Potential use cases and benefits of AI/ML in a manufacturing environment**

AI can significantly optimize pharmaceutical manufacturing processes by enhancing quality control, predicting equipment failures, optimizing production schedules, and reducing downtime.
Examples of applications may include:

- **Quality Control**:
  Through advanced image recognition and data analysis, AI improves quality control in manufacturing, detecting and pre-empting deviations in real-time and ensuring products meet stringent regulatory standards.
- **Quality assurance**:
  AI supports identifying root causes of deviations and suggesting effective CAPAs by recognizing deviation patterns.
- **Process Monitoring and Fault Detection**:
  AI enhances process monitoring and fault detection by using sophisticated algorithms to analyse real-time data from manufacturing equipment. This allows for the early identification of potential issues, thereby reducing downtime and maintaining production efficiency.
- **Flexible manufacturing**:
  AI enhances supply chain transparency and efficiency by forecasting demand and optimizing inventory.
- **Yield and output optimization**:
  Predictive process monitoring on yield allowing to perform correction online and improve the batch yield predictive process performance monitoring on Critical Quality Attributes (CQA) and Critical Process Parameter (CPP).
- **Predictive maintenance practices**:
  Improve production lead times by reducing / optimizing unavailability of manufacturing equipment and utilities: temperature monitoring, anomaly detection in equipment performance.

## Validation Framework

Industry consider that existing validation methodology provided in the e.g., (EU-GMP Annex 11) [5] is suitable to manage risk and the validation activities in the use of AI solutions in development, manufacturing and related processes. These frameworks that cover risk assessment including GMP determination assessments or equivalent, validation planning approach, design review, testing, ongoing verification, periodic review. The training of users can be supplemented by ensuring consideration is given to include additional potential risks that need to be managed when using AI. EFPIA and its member companies agree that the established structures, processes, and systems (GMP, QMS) already provide a robust framework to assess, mitigate and control the risks of its use.

Potential new/additional risks to be mitigated in the context of the validation framework may include e.g.,

- Context of use
    - How much human intervention use / human control is established.
    - Acceptance criteria to be part of the requirement specifications and design qualification.
- Data requirements for the different stages of the lifecycle
    - Model training data to have appropriate quality and procedural controls i.e., to ensure that a robust model can be developed.
- Design of AI self-control and risk factors (Context)
- Performance verification/Testing data considerations
    - Independence of the training data by restricting access of data scientist to these data at any time (risk of overfitting)
    - Executed representing all aspects of the intended use.
    - Verification of AI system outcomes and risks
- Verification of model, data input and output quality and training / retraining
- Documentation of the design of the model, data input and output, quality and training / re training needs.
- Periodic retesting of AI application and re-testing to ensure it continues to meet the business performance acceptance criteria.
- Additional considerations for AI applications that are fully automated and learn under a quantifiable optimization range,
    - Design of thresholds and notifications, human factor intervention
    - Verification of thresholds, notifications, and human factor intervention

**Using GMP Risk Assessment approaches to identify and mitigate risk in AI use.**

The QMS describes the control processes for supporting compliant pharmaceutical manufacture to support patient protection. These can be used and adapted to assess and to manage risks of using AI. The EU-GMP Annex 11 [5] provides the principles for risk management, which has to be translated into policies and procedures by a company's QMS." The first step in risk assessment is to identify whether an AI application needs to be managed under GMP control or not. Considerations for the risk assessment may include 1) evaluating the intended use and potential impact of the AI on patient safety/product quality and data integrity, 2) understanding the level of autonomy of the AI model i.e., is it simply providing insights by bringing data into one place for information only, has it fixed training boundaries where the system is trained once before use vs Learning independently, where the system continues to train itself

while being operational and 3) the extent of human intervention in the process .In all cases of use of AI 'Human in the loop' (HITL) is a key criterion to integrate that judgment supporting risk-based decision making into AI applications. Human expertise is used to supervise, guide, interrupt or enhance the performance of AI applications ensuring greater accuracy and control of risk related to patient safety, product quality and related data integrity. It should always be the case to consider the extent of a 'Human in the Loop' (HITL) required to provide oversight on critical process steps. The overall risk assessment considering all these factors will determine the level of validation required.

Other processes established in the Quality Management System that cover Change Control Management, Data Governance and Data Integrity controls are crucial in any case in pharmaceutical manufacturing and are part of existing GMP expectations. They also play a major role when applying AI in GMP manufacturing environments.

Consequently, EFPIA and its member companies suggest using the established, well-defined and well-understood terms from the established computerised system validation framework. Reinventing or introducing vast new terminology would be confusing because of AI is a tool to optimise established processes. Therefore, the goal must be to align these new tools to existing validation vocabulary.

## Ensuring GMP compliance and inspection readiness

Industry is in a learning mode and improving the way they can present their application of Artificial Intelligence in the GMP regulated manufacturing environment. This is guided by the existing GMP framework for validation, risk and data management, and existing inherent and well-practiced GMP competencies. Being able to reliably demonstrate to regulators that an AI application is fit for use and that a company understands and has adequately managed the risks is critical. In alignment with standard GMP concepts, they should establish the relevant controls to use AI in a GMP compliant environment so the impact on patient safety, product quality and data integrity is managed. Therefore, efforts should focus throughout the validation exercise to check the efficiency of risk control measures. This will of course facilitate good preparation for regulatory inspections.

EFPIA member companies suggest the following elements to be considered as part of inspection readiness:

**Developing the ability to explain how the GMP framework is used to support AI/ML applications.**

1. **Data Integrity**: Ensure that it can demonstrated that data used in AI/ML solutions follow the established principles (e.g., ALCOA) which is fit **for the intended use**. Ensure that it can be demonstrated that data governance measures have been implemented, such as data validation, audit trails, and data integrity checks.
2. **Risk Management**: Demonstrate that risks are managed throughout the lifecycle of the application and that the **risk of the AI/ML model** has been determined in the context of **the intended use**. GxP processes are supporting or describing established controls. They are in conjunction with the level of autonomy of the AI solution to maintain a consistent quality outcome of the processes and/or product.

3. **Computerised System Validation**: Demonstrate that the AI/ML solutions have been validated by following current GxP CSV framework. In addition, there are procedures and rationale in place to maintain the application in a validated state periodic review/retesting (operational phase).
4. **Change Management**: Implement a robust change control management process for any modifications made to the AI/ML solution. This may include evaluating the impact of changes, documenting and obtaining necessary approvals before implementation.
5. **Supplier Management**: Establish, assess and manage suppliers of AI/ML solutions. This may include conducting due diligence evaluations, monitoring performance, and maintaining supplier agreements according to EU-GMPs Chapter 7. Especially in cases where companies develop their own AI systems or also for cases where suppliers of AI systems need to be assessed. Harmonised standards by ISO/IEC [11-14] provides a few recently published informal guidance documents which can help companies to execute these elements. While these may not touch specific GxP aspects, they provide a general framework for AI development and use. Quality Agreements should be in place to set the requirements for use of AI GMP solutions in Contract Manufacturing Organizations (CMOs) and oversight should be in place as part of routine Supplier Assessments.
6. **Cyber- security:** Ensure that considerations for Cyber security are in scope of the User Requirements
7. **Training considerations:** Ensure that Data scientists and model developers are familiar with GMP requirements and related procedures. This knowledge enables them to effectively communicate the AI/ML model development within the broader software development lifecycle. Additionally, model consumers, such as SMEs, should receive training to maximize the AI/ML system's effectiveness e.g. use of optimal prompting language /phrases. Standard Quality Management System (QMS) procedures apply, ensuring that users are trained on relevant SOPs, understand proper model usage and its importance, and continue to maintain their expertise through ongoing training programs.
8. **Management Oversight:** The implementation and use of AI/ML requires thorough governance structures in the organizations. Governance for GMP related decision making is already common practice in the GMP regulated area. Companies consider that their existing oversight structures are adequate to ensure control for aspects specific to AI/ML. Although not mandated and not a baseline for regulatory inspections, reference to standards e.g., ISO/IEC [11-14] can provide useful guidance to companies on how management responsibilities associated to AI and governance structures to support.

## Conclusion

It is acknowledged that there are potential risks with use of AI in GMP manufacturing. However, the existing frameworks for risk assessment and process validation in an established Quality Management System (QMS) used by pharmaceutical companies are sufficiently robust to control and manage new technological advances, such as the use of AI/ML. Therefore, these well-established frameworks and processes should strongly assist in mitigating any potential risks presented by "High Risk" systems as defined in the context of the EU AI Act and if used in the GMP environment.

Stakeholders in industry and the regulatory authorities should not underestimate the importance of building employee knowledge, capability, understanding of the technology and its application in the GMP regulated environment on top of their existing GMP competencies and mindset so that they are in an informed position to adequately address uncertainties and assess the risks involved in an AI application in GMP regulated manufacturing areas.

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