The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the EMA Draft “Reflection Paper on the Use of Artificial Intelligence in the Lifecycle of Medicines”. ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 21,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

Instead of line-by-line comments, ISPE is providing general comments in 3 sections:

(1) technical and regulatory concepts in the reflection paper that are supported by ISPE,

(2) technical and regulatory aspects that are missing in the reflection paper but should be considered for future documents,

(3) considerations for international harmonization and collaboration

1. Technical and Regulatory Concepts for AI/ML supported by ISPE

* ISPE agrees that the use of AI/ML for the pharma industry should follow specific principles consistent with EU legal requirements.
* ISPE supports the use of risk management and risk-based implementation in AI/ML applications, from early development throughout the product lifecycle, and through decommissioning.
* ISPE agrees with the importance of transparency and ethical considerations for AI/ML technologies and further recommends technical and scientific standards to reduce potential issues, such as the introduction of bias in algorithms and AI development.

1. Aspects missing from Reflection Paper.

* The reflection paper has very little information about pharmaceutical manufacturing; principles laid out for product development are equally applicable to manufacturing and product quality.
* The application of AI to the production of specific ATMPs, such as autologous products, must include ethical and patient privacy considerations.
* Initial applications of AI in pharmaceutical manufacturing will likely be in supporting Quality Assurance activities (e.g., deviation or complaint processing, tracking, and trending) and not directly in the higher-risk areas of manufacturing process control or batch release.
* Validation considerations should be flexible to incorporate incremental approaches, such as the use of agile development methodologies; validation and release could be done subsection by subsection until complete. Technologies such as Natural Language Processing (NLP) could be amenable to such an approach.
* Principles of ICH Q9(R1) risk management should be incorporated into AI/ML development and deployment. ICH Q12 tools could be used to simplify change management of AI/ML for manufacturing process improvement and allow model adjustment without submission of variations.
* To support industry in understanding and applying emerging AI technology, it may be of greater value to provide regulatory examples for AI in pharmaceutical manufacturing rather than prescriptive regulatory requirements.

1. Considerations for International Collaboration & Harmonization

* Several other health authorities are working on AI/ML and have released similar communications. We suggest collaboration globally to move toward global harmonized guidelines for AI/ML development and validation.
* Future guidelines for AI should focus on principles rather than “red lines”. This approach will provide industry flexibility to advance the technology. Regulation should be sufficiently flexible to allow innovation in AI/ML development.
* Regulators worldwide should be aware that advanced technologies, including AI/ML, will lead to greatly increased data generated. The complete data generated may or may not be used for product quality-related decision-making.