ISPE Response to the EMA Quality Innovation Survey 9 February 2022

1a. Which **novel manufacturing technologies**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

(1) Continuous manufacturing- both small and large molecule
(2) Automated sterile fill/finish (e.g., gloveless robotic isolators)
(3) Digitization of manufacturing and facilities
(4) Standardized single use systems

1b. What are the potential barriers in the legislation or current guidance that could slow down or prevent implementation of these novel manufacturing technologies?

(1) Large molecule continuous manufacturing lacks experience and regulatory precedence. Unresolved issues remain for small molecule products to have both batch and continuous in the same dossier, especially when using slightly different formulations and/or control strategies.
(2) Unclear or inconsistent expectations about how current regulations will be applied to new systems (e.g., horizontal vs vertical air flow). Applying current environmental monitoring approaches to these systems actually adds risk to the system due to handling of the monitors in and out of the otherwise closed system.
(3) Current regulations might not allow decision making by computers (e.g., automated batch release); requirements related to complete data retention are unclear and could be highly burdensome if strictly interpreted; lack of standardized terminology and approaches
(4) No current standard for interchangeability of single use systems that could result in reduced qualification activities

1c. What would be needed in the legislation or current guidance to facilitate the introduction of these **novel manufacturing technologies**?

(1) Recommend a workshop on remaining gaps to continuous manufacturing for both small and large molecules – could be tied to ICH Q13 examples. Additionally, a guideline for batch and continuous manufacturing in the same dossier is needed.
(2) Guidance may be needed related to expectations for the automated sterile fill/finish technology
(3) Guidance or potential changes in regulations to account for automated quality decisions; guidance for standardized terminology on digitization in a GMP environment
(4) Consider a regulatory pathway for interchangeable single use systems, based on technical standards established through standards development organizations

2a. Which **novel analytical technologies**, are you working on that will be used ofr testing medicinal products (e.g., QC, IPCs, process monitoring) in the next 5-10 years?

(1) Multiattribute methods for proteins (i.e., LC-MS)
(2) Computer based analytics for analytical method development and predictive analysis

(3) Rapid microbiological testing
(4) Artificial intelligence for visual inspection

2b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **novel analytical technologies**?

(1) Lack of regulatory experience and guidelines
(2) Lack of regulatory experience and guidelines
(3) Lack of regulatory experience and guidelines
(4) Lack of guidelines for artificial intelligence/machine learning models and potential reporting requirements for post approval change

2c. What would be needed in the legislation or current guidance to facilitate the introduction of these **novel analytical technologies**?

(1) Publish a guideline or examples of regulatory submissions containing multiattribute methods
(2) Publish a guideline or examples of regulatory submissions describing how to include predict analytical method development information in a dossier
(3) Publish a guideline or examples of regulatory submissions containing rapid microbiological testing
(4) Publish a guideline describing how performance-based approaches (aligned with ICH Q12) or analytical target profiles (aligned with ICH Q2(R2)/Q14) for models, including AI/ML, to manage changes and validation/verification of the models

3a. Which **novel control strategy approaches**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

(1) Models for process control including artificial intelligence & machine learning
(2) Real time release testing
(3) Continuous process verification
(4) We would like to propose a concept of an interim PACMP or other pre-agreed upon regulatory flexibility for limited time changes in controls, operations, facilities or labeling that could be used to avert disruptions in drug supply. Such a pathway could reduce time to reconfigure manufacture sites or suppliers and decrease recovery time from a disruption event.

3b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **novel control strategy approaches**?

(1) It is currently unclear what model elements should be submitted in the dossier or solely maintained within the quality system. Registering model inputs and algorithms is burdensome and the subsequent requirements for filing variations disincentivizes the technology
(2) Regulators have expressed a desire to demonstrate failure of RTRT limits (e.g., for dissolution and/or new technologies like continuous manufacturing) which is impractical and sometimes dangerous for the equipment
(3) Increased data collection requires burdensome increased data storage under current regulatory expectations. Additional clarity is needed that continuous process verification data can be managed solely within the quality system without inclusion in regulatory filings or subsequent variations

(4) No existing mechanism for conditional, limited time PACMPs

3c. What would be needed in the legislation or current guidance to facilitate the introduction of these **novel control strategy approaches**?

- For items (1) (2) and (3), a workshop related to manufacturing data and models could be conducted, followed by guidance or examples, as appropriate
- For item (4), new guidelines and possibly regulatory changes would be needed to establish a pathway for a limited condition PACMP

4a. Which **novel drug delivery systems**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

(1) Advanced therapy medicinal products (ATMPs) and associated manufacturing sites
(2) Personalized/individualized medicines (e.g., 3D printed tablets)
(3) Digital medicine (e.g., coupled monitoring with medicinal product dosing)

4b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **novel drug delivery systems**?

(1) Inconsistent requirements within EU member states on where ATMPs can be manufactured (i.e., hospital vs. registered manufacturing site)
(2) Unclear or lacking regulations related to personalized doses manufactured in the pharmacy or home setting; also unclear expectations on regulatory expectations such as validation, batch control, stability, etc. for single batch products
(3) Inconsistent interpretation between notified bodies and inability to clarify; lack of regulatory experience and frequent confusion on device vs. drug classification

4c. What would be needed in the legislation or current guidance to facilitate the introduction of these **novel drug delivery systems**?

(1) Alignment of legislation and accompanying guidance for ATMP manufacturing sites
(2) New legislation and guidance for personalize/individualized medicine manufacturing and related manufacturing site
(3) Develop a pathway for consultation with the Medical Device Coordination Group and/or Notified Bodies

5a. Which **novel devices and/or digital solutions**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

(1) On-body delivery systems for delivery through a needle or cannula, micro projection arrays for delivery through dermis,
(2) Nanoparticles or nanomaterials for delivery of parenterals
(3) Inorganic nanoparticles for diagnostics
(4) ATMP combination products to deliver cells over extended time or to a targeted area
(5) Dose tracking devices

5b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **novel devices and/or digital solutions**?

- For items (1) through (5) there is a lack of regulatory experience and guidance and a need to harmonize regulatory approaches over multiple markets

5c. What would be needed in the legislation or current guidance to facilitate the introduction of these **novel devices and/or digital solutions**?

- For items (1) through (5), conduct workshops and develop guidance for considerations for novel devices and pathways; discuss internationally with other health authorities for alignment and convergence
- For items (2) & (3), ensure that any new legislation or regulations related to nanoparticles (including environmental and safety legislation) does not inhibit their use in pharmaceutical applications

6a. Which **novel materials**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

NO REPLY

6b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **new materials**?

NO REPLY

6c. What would be needed in the legislation or current guidance to facilitate the introduction of these **new materials**?

NO REPLY

7a. Which **novel manufacturing facility designs or design concepts**, are you working on that will be used to manufacture medicinal products in the next 5-10 years?

(1) Modular and mobile manufacturing
(2) Fully digitized and automated facility (i.e., Pharma 4.0 vision)
(3) Distributed manufacturing (i.e., network of connected geographically diverse highly similar manufacturing units)

7b. What are the potential barriers in the legislation or current guidance that could slow down or prevent the implementation of these **new manufacturing facility designs or design concepts**?

(1) Current expectation of a physical location in dossier. Lack of clarity on expectations when moving the manufacturing unit (e.g., validation, stability, regulatory submissions, facility requirements); unclear how to move manufacturing unit across inspectional jurisdictions (e.g.., between member states or in and out of EU). Potential burdensome variation fees associated with change in location when moving the manufacturing unit.
(2) Lack of regulatory experience and guidance
(3) Quality Person (QP) oversight for multiple small facilities unclear, especially when over multiple inspectional jurisdictions.

7c. What would be needed in the legislation or current guidance to facilitate the introduction of these **new manufacturing facility designs or design concepts**?

(1) Guidance on technical and regulatory expectations on moving manufacturing units; potential change in legislation related to street address requirements and fees associated with reporting changes of manufacturing location
(2) Guidance for how to meet regulatory expectations for a highly automated or fully automated manufacturing operations
(3) Guidance for how to manage distributed manufacturing from a quality systems oversight and inspectional perspective

Question 8: Other than the developments declared in responses to questions 1-7, are there any other novel CMC developments of relevance to the EMA and EU Regulatory Network, which may be of relevance to the QIG?

- Consider opportunities to incentive the use of novel technologies for approved and essential medicines
- Provide more opportunities to make changes without regulatory reporting for situations of shortages of drugs or critical material (e.g., single use systems)
- Provide a pathway for early discussions during development for innovative technologies to lower the implementation risk
- Harmonize approaches for innovative technology, for example through ICH, ICMRA, PIC/S