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Human Medicines Division

2023 work plan for the Quality Innovation Group (QIG)

Consolidated workplan

Name of Operational Expert Group:	**Quality Innovation Group (QIG)**
Chairperson:	Marcel Hoefnagel

Work plan period: January 2023 – December 2023

1. Strategic goals:

Pharmaceutical manufacturing is undergoing profound changes supported by latest advances in novel technologies (e.g. continuous manufacturing, personalised medicines, 3D printing), analytics and data processing including digitalisation and increased automation ('Industry 4.0').

The need for more agile manufacturing approaches and supply chains aims to bring new therapies to patients more rapidly and/or to improve supply and resilience in pharmaceutical manufacturing.

Adopting these innovative technologies may present both technical and regulatory challenges to industry and regulators.

The QIG serves as a forum to support the development, implementation, assessment and inspection of novel manufacturing approaches and technologies for the benefit of patients in Europe. The QIG comprises expertise in quality for chemicals and biologics, including ATMPs and GMP. It will focus and help expand the EU regulatory network expertise necessary to support and assess medicinal products using such innovative materials and technologies in order to ensure preparedness of the EU regulatory network and EMA and its scientific committees to regulate these.

1.1. ***Work plan period: January 2023 – December 2023***

Taking into account the background information available (i.e. EMA Regulatory Science Strategy to 2025, stakeholders responses to the QIG survey published in December 2021, an overview of ITF meetings with CMC discussions between 2019-2021, and relevant information from the NCAs), the following priority topics for QIG for 2023 are proposed and listed together with their Focus area and challenges.

Challenges have been identified from interactions with industry and literature review; further dialogue with stakeholders is required to fully understand the CMC and GMP challenges faced, discuss which could be addressed by the QIG.

1. Continuous manufacturing (CM)

CM offers the potential to enhance process and product understanding, reduce production times and accommodate supply needs to demand, and therefore facilitate the availability of medicines to patients.

Regulators have some experience with this technology and international guidance is being developed (i.e. ICH Q13).

Justification for topic selection:

Regulators are gaining experience with this manufacturing approach, however so far, all applications received in EU pertain to chemical molecules. The uptake of CM for biologics in EU is lagging behind.

Moreover, according to the responses to the QIG survey launched in December 2021 (advertised on **SME Office Newsletter - November 2021 - Issue 54 (europa.eu)**) this may be due to the perceived lack of flexibility in EU to have both batch and CM processes, and potentially alternative compositions, within the same MA. It is noted that this concern may also apply to other new manufacturing technologies.

Focus-area:

The QIG together with stakeholders shall explore regulatory challenges from developers and try to address those in order to remove or minimise existing or perceived barriers and support the increased registration of CM processes for biologics in the EU.

The regulatory concepts that may require consideration to fully embrace CM into the EU regulatory framework include, e.g. the impact of end-to-end approach on current GMP requirements, and the implementation of full performance-based control strategies, and general aspects related to alternate manufacturing.

2. Decentralized manufacturing (DCM) including manufacturing at point of care (POC)

The advent of new therapeutic approaches that have features such as very short shelf-lives and may be highly personalised (e.g., advanced therapy medicinal products (ATMPs); blood derivative products;) may need a "decentralised" manufacture (local to the patient) at different locations, such as hospitals, pharmacies or even mobile units.

Bringing manufacture closer to the patients can facilitate supply and some applicants are starting to develop portable manufacturing plants (e.g. Portable Continuous Miniature Modular (PCMM)

manufacturing platform for solid oral dose medicines). This may also be applicable to techniques such as 3D printing.

This new paradigm of decentralised manufacturing presents new challenges since it requires a shift away from existing regulatory frameworks that are designed to meet the regulatory expectations for large-scale centralised manufacture.

Justification for topic selection:

The current legislation does not address the details associated with the decentralised paradigm in terms of supervision system of decentralised sites and lifecycle management.

Few identified barriers are the lack of flexibility in introducing facilities and adaptability of current GMP requirements. Clarity is needed on regulatory expectations (dossiers and inspections) regarding moving manufacturing units/hubs (e.g., how decentralised (remote) sites should be registered in the Marketing Authorisation (MA) or clinical trial authorisation (CTA), whether a MIA is required for each remote site, whether a QP is required for each remote site) and data requirements to demonstrate consistency and comparability between decentralised sites and the suitability of an overall control strategy.

Focus-area:

Issues requiring discussion include QP release and certification and the regulatory oversight of multiple decentralised facilities located in different EU member States (GMP inspection, MIA), comparability assessment, which may be challenging for medicinal product manufactured via DCM especially for biological products and ATMPs, MA and CTA registration, clarity around the criteria when a product will be eligible for DCM and the different modes to decentralised manufacture (e.g., personalised medicines, point of care (POC) medicines and mobile manufacturing modes) and regulatory oversight towards post-approval changes.

In addition to the change of the legal framework for decentralised manufacturing in the context of EC's Pharma strategy, GMP and quality guidance have to be developed in line with potentially novel legal requirements established.

Related topics also include but are not limited to: modular/ single use/ portable/ fully closed manufacturing equipment qualification, scale out approaches, and platform technologies.

3. Digitalization and automation

Digitalisation and automation are modernizing pharmaceutical manufacturing and have the potential to optimize manufacturing processes and product quality and accelerate the development of new therapies for patients.

This is an evolving topic which represents a shift away from production using fixed process parameter settings by using a system of real-time monitoring, simulation and self-control. This topic is connected to novel manufacturing technologies, analytical technologies, control strategies, drug delivery systems, devices, and facilities.

It encompasses the use of adaptive process models, automation, robotics, machine learning, artificial intelligence, and augmented reality in the manufacturing, testing and release of pharmaceutical products. Many definitions and terminologies need to be unequivocally established. Additional skills beyond the traditional biology, chemistry, and process engineering will be needed to adopt AI (Artificial Intelligence) in pharmaceutical manufacturing (e.g. IT and AI experts).

In order for manufacturers and developers to make operational decisions based on the new and increased sources of data across the enterprise and their supply chain and for regulators to make product approval decisions based on the data contained in the marketing authorisation application, there has to be a high level of trust in the data and so data integrity guidance covering data integration, data quality and governance, location intelligence, and data enrichment will underpin the successful take up of digitalisation and automation.

Justification for topic selection:

In order to support modernization of manufacturing, regulatory expectations, reinterpretation or adaption of current regulations, and development of guidance needs to be clarified.

Focus-area:

New terminology associated with digitisation and automation, including wider identification of parameters that are part of the control strategy, for example critical equipment attributes, critical software attributes, critical model attributes, etc. require discussion and recommendations.

The suitability of current EU GMP guidance on data integrity, covering data integration, data quality and governance, location intelligence, and data enrichment should be discussed with recommendations.

The balance between the required validation evidence of continuously evolving self-learning models and the flexibility in the regulatory documentation to allow their implementation in an agile way needs to be defined. Future revision of the EMA Guideline on Process Validation, and GMP Annex 15 Validation and Qualification, to highlight the link between data analytics/digital control strategies with on-going process validation should be discussed with recommendations.

Automated real-time review processes in quality decision-making based on 'live' data including deviations and changes and using artificial intelligence for batch QP release should be discussed with recommendations.

4. Other topics

If any other topic arises from interactions with stakeholders and is deemed to require input by the QIG, it will be examined on a case-by-case basis also considering its impact on EU supply and public health.

QIG might also decide to engage with some of these topics in 2023.

Other topics identified to be considered beyond 2023 include:

Individualized therapies (e.g. neoantigens in cancer immunotherapies).

Issues for discussion:

- Bioinformatics tools
- Scope and legal framework of manufacturing operations

Platform technologies

Novel analytical techniques

3D printing

Issues for discussion:

- Definition of starting material(s), active substance, intermediate(s) and finished product
- Flexible on-demand doses, tailored pharmaceutical form composition and shape (=customisation) and expected registration
- Batch definition in the context of production volumes based on actual patients' demand instead of mass production
- 3D printing validation and control strategy
- Traceability of the customised unit dose

Rapid microbiological methods

Issues for discussion:

- Validation
- Challenges related to the microbial identification of a potential contamination

1.2. ***5-10 year horizon***

The long-term strategic priorities for the QIG with reference to the EMRN and RSS 2025 are as follows:

1. catalyse the integration of science and technology in the quality-related aspects of medicines development and support the network in the build-up of sufficient competences to bring the regulatory responses to innovators' queries in various phases of medicines development;

2. support scientific and regulatory capacity and capability of the network and improving the scientific quality of evaluations on matters pertaining to innovation in pharmaceutical manufacturing in close collaboration with the BWP, QWP and IWG;

3. enable and leverage research and Quality innovation in regulatory science;

4. facilitate implementation of new manufacturing and analytical technologies and develop training and tools to enhance the assessment and inspection processes;

5. equip EU assessors/inspectors with the skills, training and relevant tools to regulate the new technologies;

6. develop understanding of regulatory response to nanotechnologies and new materials in pharmaceuticals;

7. enhance collaboration with academic groups in the area of pharmaceutical innovation and manufacturing;

8. reinforce the responsibility for product quality by harmonising and consolidating guidance to facilitate a coherent approach to the standards by regulators and industries and to address supply chain challenges;

The implementation of the above-mentioned new technologies as per the long-term strategic goals will likely require an adaptation of the legal regulatory framework in the EU. This adaptation is outside of the scope of the QIG. A revision of the legal regulatory framework is currently under

consideration as part of EC's pharmaceutical strategy (**A pharmaceutical strategy for Europe (europa.eu)**)

2. Tactical goals: activities/projects to deliver the strategic goals

2.1. Work plan period: January 2023 – December 2023

2.1.1. Meetings:

- In line with the QIG mandate, QIG plenary meetings are not expected to exceed six per year, organized (where possible) congruent to QWP, BWP and/or GMDP IWG meetings. Stakeholder interactions should be accommodated as needed.

  Ad-hoc meetings will be organized if required.

  Approximately two face-to-face meetings per year are foreseen.
- In addition, QIG will hold "Listen and Learn" focus-group meetings with relevant stakeholders to facilitate exchange of information (see section 1.5).
- Where appropriate, it is aimed to have meetings and interactions with key regulators from other regions (US and Japan, etc.) to try to achieve cross-regional alignment.

2.1.2. Guideline activities:

Develop internal position papers to share QIG considerations/positions with regards to the topics discussed.

Upon maturity of a topic develop guidance documents in consultation with relevant working parties/working groups and committees.

Support EU delegations in the development and implementation of relevant ICH guidelines within QIG's scope, including update to EU/EMA guidelines related to the implementation of ICH guidelines.

2.1.3. Product support

Supplement the assessment and inspection knowledge of the assessment team with expertise from the QIG members or QIG ad-hoc experts (see 3.3.1).

2.1.4. Training activities:

Training of the EU regulatory network on the topics within the remit of the QIG will be considered. However, since the QIG is a newly established group it may not be feasible to organize formal trainings already in 2023. Consideration will be given on the feasibility to provide informative sessions and QIG will regularly report back to BWP, QWP and IWG as appropriate.

2.1.5. Communication and Stakeholder activities:

The QIG will hold periodic Listen & Learn Focus Group meetings with external stakeholders from industry and academia in order to gather information on the latest innovations, relevant technologies and approaches and their challenges and solutions. The result of the focus group meetings will serve as a decision basis for the content of any closed one-to-one follow-up meeting with individual sponsors. Based on the input and discussion, innovative technologies/approaches that should be reviewed in more detail are identified by QIG.

Listen and Learn Focus Groups will be organised periodically, with higher frequency in the first year considering feedback from first meetings on topic progress considering in line with QIG workplan.

The first meeting is planned for Q1 2023, in virtual format, and will focus on the priority topic of the workplan (i.e. continuous manufacturing (CM) of biological active substances and/or finished products and decentralised (DM) manufacturing).

2.1.6. Cross-domain activities:

Close communication and collaboration with BWP, QWP and IWG through the members who are part of the QIG, EMA Regulatory affairs, ITF and the EU innovation office.

Identification of ad hoc experts in priority topics.

2.1.7. Any other relevant activities:

The QIG will maintain dialogue with other international regulators to identify areas of common interest and share learnings.

The QIG will strengthen the links with academia and research institutions, identifying and contacting relevant experts with the support from the EMA Research and Innovation workstream.

2.2. 5-10 year horizon (2020 – 2025/2030)

Industry and academia are consistently advancing technologies related to pharmaceutical manufacturing and analytical technologies, delivery systems, materials, devices and facility design concepts.

The QIG will monitor those advancements and work together with industry stakeholders to identify the most promising developments, define priorities, discuss the regulatory and scientific challenges encountered and propose solutions and develop guidance for assessors and/or industry/academic stakeholders.

3. Operational goals: medicinal product-specific activities

3.1. Work plan period: January 2023 – December 2023

3.1.1. Pre-Authorisation activities

QIG supports pre-submission activities on initial MAAs employing innovative materials/manufacturing technologies/facility designs as delegated by CXMP, SAWP and/or QWP/BWP/IWG and ITF briefings on in-scope developments.

Please refer to the **QIG mandate** for the mode of operation.

3.1.2. Evaluation and supervision activities

To support assessment of applications employing the above technical, manufacturing and facility design approaches as delegated by CXMP, SAWP and/or QWP/BWP/IWG***. See 3.1.1.***

Please refer to the **QIG mandate** for the mode of operation.