EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Quality Innovation Group (QIG):

Two years experience in regulatory support of Innovation in pharmaceutical manufacturing

CASSS Strategy Forum

8&9 December 2025

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Outline

- Quality Innovation Group : Role, activities
- Listen & Learn Focus Groups: e.g. Continuous Manufacturing (CM), Platforms
- Innovative technology seen and guidance developed
- Guidance CM, Modelling, Decentralised Manufacturing

QIG: EU catalyst for advanced manufacturing

EMRN

European medicines regulatory network

Predictable reg framework
Support EU innovation efforts

Training, guidance

Support

International regulatory convergence

Assessment support tailored to technology novelty

Rapporteurs and Assessment Teams

QIG

Quality Innovation Group

8 Core experts

(Chemical, Biological, ATMP & GMP)

+ ad hoc experts

Academic expertise
Research projects

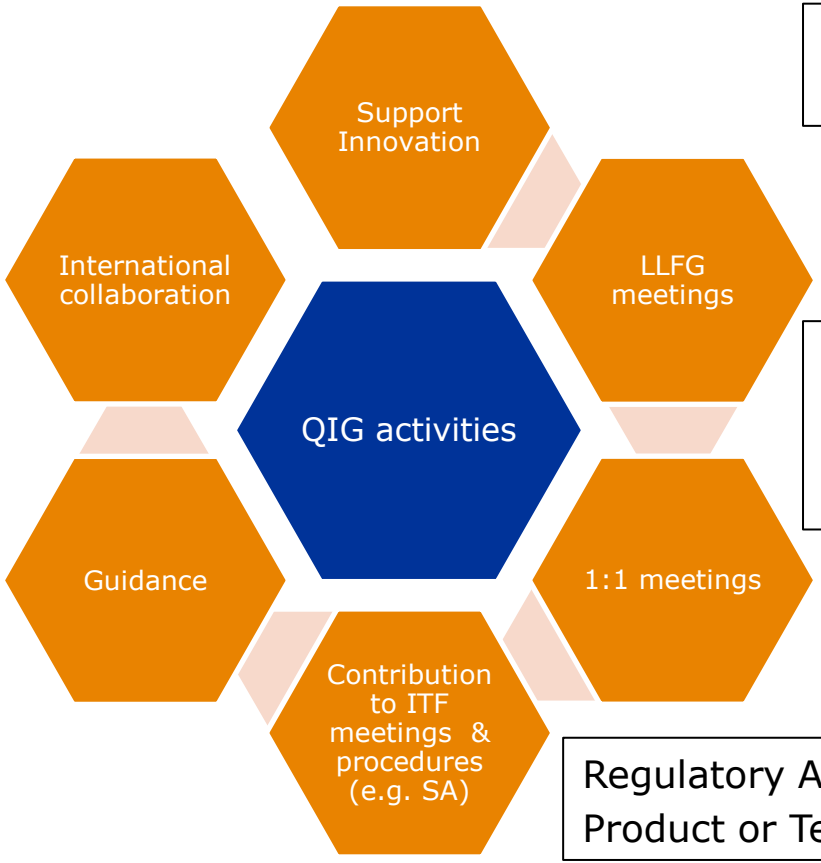
Support from development throughout lifecycle

Point of entry to EMRN
Informed open discussions

Links

EU Innovation network, ITF, National IOs

Quality Innovation Group -Activities



Entry point for interaction with EU regulators on Advanced Manufacturing

LLFG: Listen & Learn Focus Groups

Stakeholders with expertise/experience, Academics, Learned societies

Upon invitation, after expressing interest

Regulatory Advice on Novel Product or Technology

QIG priority topics discussed at Listen & Learn Focus Groups

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Close to Patient
POD, QP

Decentralised manufacturing

Continuous manufacturing
(Biologicals or End-to-End)

1st LLFG (13 March 2023)

Digitalisation and Automation of manufacturing and control

2nd LLFG (12 October 2023)

What to document and How?

Lifecycle, PQS or dossier, level of detail

Actual examples, Tangible presentations

Definition, End-to-End

Process models

3rd LLFG (4 June 2024)

Platform technologies

4th LLFG (Q4 2024)

Personalised Medicines

5th LLFG (Q2 2025)

Sustainability

6th LLFG (Q1 2026)

Meeting reports incl. **challenges, possible solutions and concrete actions** that QIG will take to address the challenges

Guidance and product support

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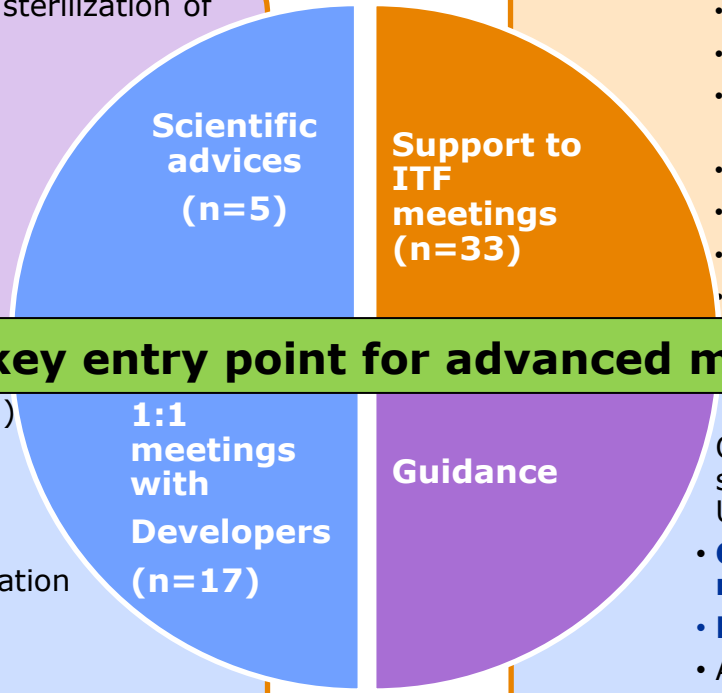
- **Helping avoid shortages**: X-ray sterilization of single use systems
- **Reduce cost**: Robotic aseptic
- **Improve supply capacity**: DCM
- Bioinformatics: NGS, Neoantigens
- Bacteriophages



- Process automation
- CM for biologics
- Decentralised Manufacturing
- Artificial Intelligence (diverse applications)
- RNA writing technology
- 3D bioprinting
- iPSCs
- Drug device

QIG: key entry point for advanced manufacturing

- Decentralised manufacturing (DCM)
- Automated cell manufacturing
- Digital twins
- Modelling DSP Control strategy
- Continuous Manufacturing: Formulation
- High Tech Facility
- 3-D printing
- Novel technology for virus detection
- **Site visits (n=3)**

Q&A on use of X-ray sterilisation processes for Single Use Systems- **published**

- **Considerations on process models (Draft)**
- **Reflections on DCM**
- AI reflection paper contrib.
- 3-D Printing (draft)

Product support by QIG

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Direct Contact
- Technology or product focused
- QIG expert assigned

Scientific Advice
- QIG expert primary assessor
- technology or product focused
- QIG Input into inspection

Initial MA application
- QIG expert input as part of assessment team
- QIG Input into inspection

Variation/line extensions
QIG expert input into review & inspection

Product and Technology support across lifecycle

Entry point to QIG
Expert advice (CMC/Inspection)
No formal assessment

Assessment activities
assigned QIG expert for primary assessment / peer review

Listen-learn Focus group meetings

Challenges & solutions gaps

+

1 – to - 1 Meetings (QIG + Applicant/Sponsor)

Support to specific Product/technology assessment

Knowledge Assessment outcomes

Guidance International convergence Training

International collaboration: FDA, Swiss Medic, PMDA & ICMRA

Knowledge sharing

- Bi-monthly meetings
- Attend & Share learnings from workshops, company meetings
- Staff/ expert exchanges

Product specific advices / assessments

- Consultative / parallel scientific advices /collaborative assessments leading to harmonised outcomes (where possible)
- Joint (hybrid) site visits / inspections

Guidance development

- Exchanging priorities, topics of common interest
- Aligned or joined guidance/Q&As, joint ICH proposals

Continuous Biomanufacturing: Challenges

- **Lack of sufficiently rapid on-line/at-line analytical tools** to measure CQAs (e.g., HMW, LMWs, glycan, HCPs, rDNA, rPA, deamidation, oxidation, etc.)
- For upstream manufacturing: impact of process **disturbance on CQAs may last for variable period** (depending on type, intensity and duration); how to ensure separating conforming/non-conforming material
- Potential solutions:
  - Monitor process using PAT (Glucose, lactate) to detect disturbances
  - Collect fractions
  - Residence Time Distribution (RTD) modeling
- Parametric control (using a model) not in line with guidance on Control Strategy (PAR, Proven Acceptable Ranges, etc.)

Continuous Biomanufacturing (CM): Challenges (2)

- Digital Twins can support: Example of filling (inc. mixing) of Vaccine
- Parametric control (using a model) not in line with QbD guidance on Control Strategy (PAR, Proven Acceptable Ranges, etc.)
- Global Regulatory Approval & Lifecycle
- Continuous manufacturing more sustainable, lower cost, more efficient
- No CM for biopharmaceuticals in Marketing Authorisation yet
- Clinical Material is produced using CM

CM applications submitted so far in EU

Five Marketing Authorisation Applications and one Variation Application submitted and approved (all chemicals):

- Orkambi (lumacaftor/ivacaftor), Vertex Pharmaceuticals (Ireland) Limited, EMEA/H/C/003954
- Prezista (darunavir), Janssen-Cilag International NV, EMEA/H/C/000707
- Symkevi (tezacaftor/ivacaftor), Vertex Pharmaceuticals (Ireland) Limited, EMEA/H/C/004682
- Verzenios (abemaciclib), Eli Lilly Nederland B.V., EMEA/H/C/004302
- Daurismo (glasdegib maleate), Pfizer Europe MA EEIG, EMEA/H/C/004878
- Mounjaro (tirzepatide), Eli Lilly, EMEA/H/C/005620

LLFG on Machine Learning, AI & Automation

ISSUES discussed

Avoid overly prescriptive guidelines

Use of best practices and industry-applied standards (e.g. ASME V&V 40)

EU GMP Annex 11 Revision

Data experts needed for AI & model development & validation

How to store large data sets that support (AI) models?

Quality and origin of data

Human in the Loop

LLFG on Machine Learning, AI & Automation (2)

Challenges

- Uncertainty on regulatory expectations for process models
- Lack of a regulatory AI definition. No accepted harmonised standards are currently available bridging IT terminology and GMP terminology
- What information (e.g. validation or model lifecycle management) in dossier / managed under PQS
- Will AI/ML be accepted by regulators. Missing guidance on requirements for algorithms information (dossier /lifecycle management)

LLFG on Modelling issues discussed

- Provide definitions & reference to existing guidance
- Agnostic regulatory framework (to accommodate different types of models)
- Level of model risk defines dossier requirements & lifecycle management expectation
- Model maintenance protocol for lifecycle
- Classification of risk of models low, medium & high (medium is challenging)
- Consider Models deployed in GMP setting only
- Model uncertainty quantification & sensitivity analysis. (validate if model is suitable within context of use).
- Early engagement with regulators
- QIG: Models treated like any other element control strategy (Assays, Machines, Controllers):

Provide clear evidence that model is fit for purpose to give confidence to assessors & inspectors

Preliminary QIG Considerations regarding Pharmaceutical Process Models

EMA/90634/2024 (22 February 2024)

- Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification?
- Q2. What data is expected in the dossier in terms of model description and scope?
- Q3. What data is expected to be included in the dossier in terms of model validation?
- Q4. What data is expected in the dossier in terms of process model lifecycle

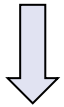
Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification?

- **Intended use of a model**
- Different model uses:
  - Model used to support process development
  - Model used in the control strategy in addition to other related measurements
  - Model used in the control strategy without additional related measurements
- Role of the model in the control strategy (CS), frequency of any additional monitoring, model's performance, potential consequence of an incorrect decision, criticality of the manufacturing operation(s), manufacturing mode, intrinsic risk of the medicine

Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification? *Cont'd*

Contribution of the model to a decision relative to other available evidence,

and the decision consequence



Degree of regulatory oversight

Q2. What data is expected in the dossier in terms of model description and scope?

Model description

- Low-risk: high-level description and discussion regarding model intended use
- Medium-risk: more detailed description, outline of model development
- High-risk: the above + summary of performance metrics and model validity domain

Model scope (similar concept as for NIR chemometric models)

- Low-risk: no formal scope, high-level description as stated above
- Medium- and High-risk: intended use within CS, model type, performance metrics acceptance criteria, validity domain, reference method where applicable ➔ exact content to be justified based on risk

Q3. What data is expected to be included in the dossier in terms of model validation?

- The goal of model validation is to establish the degree to which a model is an **accurate representation** of a process and can **predict** the property(ies) or material quality attribute(s) of interest.
- Focus on **model performance** (e.g., prediction accuracy) and model error, or uncertainty.
- Validation activities are expected to be designed to give confidence in the model for its intended use ➔ driven by risk

Q3. What data is expected to be included in the dossier in terms of model validation? *Cont'd*

- Illustrative examples.
- Overarching role of the manufacturing process validation to show that the process is in a state of control.
- Validity of model at commercial scale (for high-risk models, and for medium-risk on case-by-case); model verification protocol where relevant.
- Continuous model verification/protocol where relevant.

Q4. What data is expected in the dossier in terms of process model lifecycle?

- It is the MAH responsibility to ensure the model is updated as required over its lifecycle to ensure it remains fit for purpose.
- Validity of the model reviewed periodically.
- **Model maintenance protocol** (medium- and high-risk models): expected to set the conditions for changes that can be managed within the PQS or require submission of a variation.
- Extent of model maintenance activities commensurate with model type and model risk.

Decentralised Manufacturing: Challenges

- Comparability (site, product): high number sites to be installed within a short period
  - Suggested: Standardised Implementation Process + Reference Product Kit
- Quality control: Release testing using complex (biological) assays
  - Suggested: centralize release testing for assays that are complex
- Addition of new sites in timely manner (Agile)
  - Suggested: Draft guidance, Allow stability studies in parallel to implementation
- Inspections of parental site and new clonal sites
  - Suggested: Risk-based inspections

Decentralised Manufacturing for ATMP: QIG Guidance (Draft)

1. **How to register a decentralised manufacturing site and what supporting documentation should be provided?**
   - Show need to be close to patient
   - Show comparability
   - Central Site (CS) + Decentralised sites (DCS): In EU member state & All comply with GMP
2. **Will each site, involved in decentralised manufacturing of a medicinal product, need to have a MIA issued by the National Competent Authorities (NCAs) and be part of the national inspection programme?**
   - If national legislation allows, Central site MIA can cover decentralized sites
3. **Can a site involved in DCM be located outside of the European Union?**
   - No
4. **Is it necessary to have a qualified person (QP) for central and decentralised sites?**
   - QP at Central is sufficient if CS and DS in same member state
   - If DCM concerning multiple member states: QP in each member state

Take home messages

- QIG entry point for regulatory support for Innovative Pharmaceutical technologies
- Both for Technology suppliers and Pharmaceutical Manufacturers
- Agile guidance development
- International Regulatory Collaboration (e.g. ICH concept paper Advanced Manufacturing)

Acknowledgements

QIG members

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