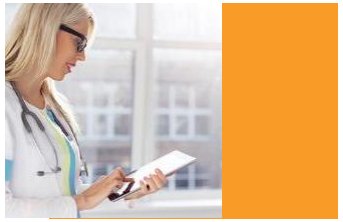
European Federation of Pharmaceutical Industries and Associations

Agile (Innovative) Manufacturing and Decentralized Manufacturing in latest regulatory environment including new EU Pharma Legislation

Colin Cox on behalf of EFPIA MQEG Agile Manufacturing Team

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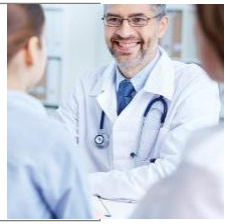


Why Innovative Manufacturing Matters

Manufacturing flexibility is becoming a strategic requirement for resilient medicines supply.

- The need for agile and mobile manufacturing goes beyond personalised medicine.
- It is also relevant for all product types, including conventional biologics.
- Key drivers:
  - **drug shortages**
  - **geopolitical instability, wars and tariffs, blocked transport routes and fragile supply chains**
  - **pandemics and sudden demand shifts**
  - **enabling more affordable and cost-efficient medication**
  - **sustainability and CO_2 footprint reduction**
- Local or distributed manufacturing can improve supply resilience

Regulatory Frameworks Can Enable or Block Innovation

Whether innovative manufacturing becomes feasible depends strongly on how legislation and guidance are designed.

- Enabling regulation can:
  - **recognise decentralised and distributed manufacturing models**
  - **leveraging global PQS to allow more efficient transfers between authorised manufacturing sites**
  - **support mobile or modular manufacturing units**
  - **apply risk-based change and variation procedures**
  - **focus on quality systems, control strategy and data integrity**
- Restrictive regulation can:
  - **limit use to narrow product categories**
  - **create lengthy approval pathways for site transfers**
  - **make alternative manufacturing sites difficult to activate**
  - **reduce Europe's ability to respond to shortages and crises**
- The goal is not lower standards, but smarter and more adaptive regulation.

EFPIA Interpretation of «The Council final recommendation on the **Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC** »

Centralised manufacturing remains the core regulatory model, but decentralised manufacturing is now explicitly recognised as an acceptable manufacturing paradigm. Decentralised manufacturing within the Directive is defined as a set of manufacturing activities carried out under the control of an authorised central site that supervises one or more decentralised sites located in sufficient proximity to patients, **particularly where justified by product characteristics such as short shelf life, time-critical release, personalisation, or advanced therapies. The key constraint, however, is the justification.**

EFPIA Interpretation of «The Council final recommendation on the **Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC** », cont.

- Decentralised manufacturing must be justified based on the nature of the manufacturing process, patient proximity needs, time-critical handling, safety, quality, or efficacy considerations, and the ability to ensure robust central oversight: **"When justified by the specific properties of the manufactured medicinal product and consideration related to the quality, safety and efficacy of a medicinal product, such as short shelf life, or (where) proximity to the treated patient or customisation for an individual patient to their benefit, the marketing authorisation applicant may request the competent authority to approve the use of a decentralised manufacturing…"** (Recital 109, Article 26b). If a decentralised setup is not justified, competent authorities may require a return to centralised manufacture.

Justification for decentralised manufacturing of conventional Drug Products – a collection of arguments by the EFPIA Agile Manufacturing Team

Rationale to enable Decentralised Manufacturing of conventional Drug Products

- No compromise on quality: Maintained through a Global PQS, central process ownership, and a central site Qualified Person with full batch release responsibility.
- Improved supply security in the EU: addresses existing shortages of biologics by increasing redundancy and regional availability.
- Typically, more robust manufacturing processes, and less 'sensitive' molecules
- Scale-out instead of scale-up: Enables faster capacity expansion and replenishment compared to large central plants.
- Cost-neutral manufacturing model: Reduced logistics, lower inventory risk, and avoidance of major facility expansions prevent cost inflation.
- Reduced dependency on long-distance transport and energy-intensive cold chains, supporting sustainability goals.
- Greater resilience to geopolitical disruption (wars, pandemics, trade and transport blockages).
- Essential for future biologics: Particularly relevant for short-shelf-life products, conjugates, and cold-chain-sensitive modalities.
- Strategic importance for Europe: Enables innovative modular manufacturing and supports the shift toward local production without restricting applicability to ATMPs.

Conclusion: Decentralised manufacturing is a robust, quality-equivalent, and future-proof alternative for conventional drug products —well aligned with current geopolitical, sustainability, and supply-security needs.

Summary

- **Decentralised manufacturing can address situations where conventional centralised manufacturing is not optimal for patient access, product characteristics, or supply resilience, and should be enabled as a regulatory pathway for innovation, while maintaining the same expectation of product quality and patient safety.**
- **Current regulatory interpretation may limit implementation; dialogue is needed to enable appropriate GMP-compliant agile/mobile manufacturing models.**
- **The justification for decentralised manufacturing should be complemented by implementing provisions that:** (1) explicitly include biologics and standard products with supply-chain risks, (2) enable agile transfers between authorised manufacturing sites, (3) support mobile, modular and local manufacturing capacity (4) allow faster activation of alternative sites during shortages, crises or geopolitical disruption (5) recognise equivalent control strategies under a harmonised Pharmaceutical Quality System (6) EU should aim for a level playing field with other regions advancing in the field.
- **For discussion / future options:**
  - Consider the use of **Delegated Acts** to establish and maintain a future-proof regulatory framework for decentralised manufacturing, enabling timely adaptation to technological innovation without requiring repeated legislative amendments.
  - Other opportunities: new **Regulatory Sandbox** tool (Art. 113-115) to allow more flexible implementation of decentralised manufacturing for **conventional drug products (however product-specific) or** Upcoming **Biotech Act** as a way for the EU to act and revisit scope?

Backup

EFPIA Interpreation of «The Council final recommendation on the **Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC** »

- Decentralised sites do not require separate manufacturing authorisations but must be **registered** with, supervised by, and subject to inspection by the competent authority of the Member State in which they are located. “Manufacturing or testing steps of medicinal products may be carried out at decentralised sites under the responsibility of the qualified person of an authorised central site, provided that such sites are registered with the competent authority of the Member State in which they are located.” (Article 112(2)) and “Decentralised sites shall not be required to hold a separate manufacturing authorisation where they operate under the manufacturing authorisation of the authorised central site.” (Article 112(3)).

EFPIA Interpreation of «The Council final recommendation on the **Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC** », cont.

- Decentralised manufacturing may include individual or multiple steps of the manufacturing and/or testing process, while final batch certification and release remain under central responsibility. The **Qualified Person** remains the central guarantor of manufacturing compliance and is responsible for certifying that each batch is manufactured and checked in accordance with EU law and the marketing authorisation before release. Where manufacturing is decentralised, the Qualified Person at the central site bears formal responsibility for oversight of all decentralised sites, ensuring consistent GMP application, appropriate audits, quality agreements, documentation, and effective control of outsourced or distributed manufacturing steps, and acts as the single point of accountability vis-à-vis competent authorities.
- Marketing authorisation holders retain full lifecycle responsibility for the quality, safety, efficacy, and continuous availability of their medicinal products across all Member States where they are placed on the market.

Presentation by DG Sante
at DIA 2026

DECENTRALISED MANUFACTURING (DCM)

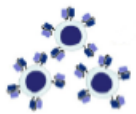
New manufacturing framework

Central manufacturing site
- supervision and control, coordination
- manufacturing authorisation,
- Qualified person

Decentralised manufacturing (DC) sites
- full or partial manufacturing performed in compliance with GMPs
- located in sufficient proximity to patients (e.g. hospital)
- can be located in different Member States
- registration process

Specific products (short shelf life, customisation for an individual patient…)

- ATMPs
- 3D printing...



Use of DCM justified and approved through the marketing authorisation or clinical trial authorisation

- Implementing Act on DCM principles
- Delegated act on exchange of information and cooperation between the competent authorities
- Delegated act on DCM for IMPs

Global Status of Regulatory Frameworks for Decentralised Manufacturing

UK (MHRA)

- First region to issue legally binding regulation on decentralized manufacturing *'Human medicines Modular Manufacture and Point of Care regulations 2025.'*
- Employs a hub-and-spoke model, where a single Control Site holds the manufacturing licence and oversees all distributed manufacturing activities (subordinate sites) with one Master File per product.
- Point of Care Model
  - producing medicines directly at or near the site of patient care—such as hospitals, surgical theatres, mobile units, or even patient homes
- Modular Manufacturing
  - relocatable, self-contained production units that can be deployed flexibly across different sites. These units may be used for personalized cancer vaccines, pandemic response, or regional manufacturing hubs

Global Status of Regulatory Frameworks for Decentralised Manufacturing, cont.

US (FDA)

- Advanced manufacturing is essential for future pharmaceutical supply, but the current regulatory framework is fundamentally misaligned; FDA has set up with the FRAME initiative a strategic program to transition pharmaceutical regulation, in close collaboration with stakeholders and global partners.
- FDA supports distributed manufacturing, but only within a fundamentally redesigned regulatory framework shifting from site-based control to platform-, data-, and lifecycle-based oversight.

ICH

- ICH Reflection Paper (endorsed by ICH Assembly October 2025)
  - With respect to DM, the paper describes emerging networked manufacturing paradigms in which smaller-scale, equivalent manufacturing units operate across multiple locations and are often supported by centralized oversight, advanced automation, and real-time data exchange
  - Whilst these approaches can improve responsiveness and reduce supply risk, they also raise novel regulatory questions related to pharmaceutical quality system (PQS) distribution, remote oversight, model-based control strategies, product release, stability testing, and process validation
  - Proposes a stepwise path toward future ICH guidance that would build first on harmonized principles for process models and continuous process verification, enabling their use across decentralized networks for quality decision-making