European Federation of Pharmaceutical Industries and Associations

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Autonomous & Portable Manufacturing

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Reflection Paper


Executive Summary

- Technologies are evolving at a rapid pace, and innovative pharmaceutical companies invest significantly in the modernisation of their manufacturing and supply operations towards more agile processes and methods that includes 'Autonomous & Portable' solutions.
- These provide unique opportunities to enhance consistency, in relation to traditional scale up, especially when moving from clinical to initial commercial supply or subsequent transfer/addition of manufacturing sites due to the consistency of equipment, procedures and Quality systems. Higher production volumes can more easily be reached through scale-out, in comparison to a traditional scale-up approach, and can overall enable more rapid response to patients' demands.
- This reflection paper will serve to initiate a dialogue with Regulators to introduce the concept in a way that ensures regulatory standards continue to be met, and products' Quality preserved, as these remain the innovative industry driving manufacturing principles. In Europe, such considerations are especially timely to address the EU Pharmaceuticals Strategy that will consider the "*impact of emerging new manufacturing methods such as decentralised or continuous manufacturing. These methods create new manufacturing models, with a shift from industrial to 'bedside' manufacturing. While speeding up production times, they create new challenges in terms of appropriate quality, inspection and oversight*", and building on the EFPIA initiated dialogue with the EMA Quality office to engage in discussions on emerging technologies.

1. Introduction

- The innovative pharmaceutical industry's key objective remains to ensure that medicines to save and improve lives are available to patients globally, and that their safety, efficacy and quality is preserved.
- As manufacturing technologies evolve, innovative pharmaceutical companies invest significantly in the modernisation of manufacturing and supply operations and in the effectiveness of their quality management system; this includes implementing more agile approaches to the ways they manufacture medicinal products. Such innovative trend is accelerated by several factors, including the development of digital technologies (see EFPIA paper on Digitalization in pharmaceutical manufacturing), 3D printing, and of more specialised or personalised medicines, and which may require dispensing closer to patients.
- Agile manufacturing is becoming more and more critical to address the increasing number in natural disasters, the 'green agenda', and global pandemics, such as Covid-19 and future crisis. All require enhanced flexibility and speed in manufacturing operations to deliver critical medicines to patients globally. With regard to Covid-19, hundreds of vaccines and therapies are being developed at a record pace and evaluated worldwide; every company with a potential candidate needs to be ready with the capacity to produce these at a commercial scale, requiring immediate investment in process and facilities accelerated execution.
- To this effect, it is critical for regulatory frameworks to evolve and prepare for such scenario, and EFPIA welcomes some elements of the EU Pharmaceutical Strategy[1] to:
    - Support competitiveness, innovation and sustainability of the EU pharmaceutical industry and the development of high quality, safe, effective and green medicines;
    - Ensure preparedness for new manufacturing technologies;
    - Ensure a strong EU voice in the world, by promoting a high level of quality, efficacy and safety standards, and advance international harmonisation by proactively proposing topics in line with the latest scientific developments, at e.g. ICH[2] and/or PIC/S[3].
- All above elements can support the introduction of new manufacturing technologies, including 'Autonomous & Portable' units such as Portable On Demands (PODs), and which this paper focuses on.

2. The concept of 'Autonomous & Portable' manufacturing & Benefits

- Where applicable, the industry is looking to introduce 'Autonomous & Portable' manufacturing facilities such as prefabricated modular constructions, or Portable On Demands (PODs), and that would encompass the following scenarios:
    - One or multiple units that house a defined set of pharmaceutical operations,
    - Unit(s) that can be placed within an existing facility or be fully autonomous,
    - A same unit that can be replicated in an equivalent manner, or
    - Unit(s) that can be moved within a same territory, or to a different region of the world.
- The concept of 'Autonomous & Portable' manufacturing can address the industry ability and commitment to innovate.

[1] Communication from Commission to European Parlimanet, the Council, the European Economic and Social Committee and the Committee of the Regions - Pharmaceutical Strategy for Europe, 25th November 2020.

[2] ICH the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - https://www.ich.org/page/members-observers

[3] PIC/S the Pharmaceutical Inspection Co-operation Scheme https://picscheme.org/

- The concept offers many other benefits and opportunities as follows:
  - To increase manufacturing flexibility, speed and consistency when moving from small to large scale production, including from clinical to commercial supply; or when replicating a unit across countries, allowing for faster response to patients' demand through the ability to readily:
    - Duplicate equipment in a separate unit to produce larger volumes;
    - Relocate, i.e. bring closer to patients.
  - To promote 'green manufacturing' through the introduction of compact units, moving away from large traditional manufacturing plants; such fit for purpose and reduced size units can lead to an overall reduction of resources e.g. less steel, smaller buildings.
  - To enhance the consistency of equipment/facilities, including environmental controls (e.g. humidity), and associated procedures;
  - Introduce matrixing approach to the qualification of equipment, and to lower the risks related to stability, bioequivalence, process validation… when duplicating a unit or changing its location, e.g. if only water supply is changed;
  - Ensure operations such as sterility are isolated, or to avoid cross-contamination.

These are illustrated in Figure 1.

Figure 1: Opportunities provided by autonomous and portable units

	Stick-Built	Modular / Prefabricated Panels	Autonomous PODs
Cleanroom Image			
Decentralized HVAC	x	x	✓
Easily Scalable	x	x	✓
Easily Cloneable	x	x	✓
Mobile	x	x	✓
Delivery Time	2-3 years	1-3 years	3-10 months
Schedule Certainty	x	x	✓
Cost Certainty	x	x	✓

POD: Portable On Demand

Portable manufacturing can enhance consistency, in relation to traditional scale up, especially when moving from clinical to initial commercial supply or subsequent transfer/addition of manufacturing sites due to the consistency of equipment, procedures and Quality systems.

Higher production volumes can more easily be reached through scale-out, in comparison to a traditional scale-up approach.

Overall, it can enable more rapid response to patients' demand through the ability to readily relocate or replicate manufacturing units.

Scale out – more of the same

Scale-up – more resources

4. Points to Consider and Recommendations

- The introduction of the concept of 'Autonomous & Portable' manufacturing raises several considerations, including:
  - The acceptance that a unit constitutes a site when autonomous and mobile;
  - The GMP compliance status of a unit be kept when replicated or relocated in another EU-MS or a third country, through relying on the GMP compliance status of the inspectorate of the country where the equipment is originally located (e.g. where the inspectorate is a PIC/S member);
  - The registered details of an establishment (address) remain valid when changing its location by e.g. introducing a tracking system that would be referred to in the Site Master File;
  - The allowance for risk-based reporting of stability and validation studies upon change of location;
  - The insurance that the registered information be kept amenable to mobile manufacturing (3.2.S.2.1/P.3.1).

- EFPIA overall recommendations:
  - Countries' regulatory frameworks should evolve to reflect the lower risks associated with moving or replicating portable units in relation to qualification, including of personnel, and maintenance activities including e.g. bioequivalence, validation, and inspections; they should include considerations for when only the physical location is changed while keeping other elements the same.
  - This should be achieved in a globally aligned manner through building on existing inspections reliance and recognition principles, the development of ICH principles, via e.g. an addendum/Q&As to Q9 on Quality Risk Management, Q10 on Pharmaceutical Quality System or Q13 on Continuous Manufacturing[4], and inspectors training via PIC/S.
  - In the EU, building on the EFPIA initiated dialogue with the EMA Quality office to engage on emerging technologies, it is timely to pursue this dialogue with Assessors and Inspectors, especially in light of the EU Pharmaceuticals strategy that will consider the "*impact of emerging new manufacturing methods such as decentralised or continuous manufacturing. These methods create new manufacturing models, with a shift from industrial to 'bedside' manufacturing. While speeding up production times, they create new challenges in terms of appropriate quality, inspection and oversight*."
  - Note: in the US, some companies have engaged with the US FDA through its Office of Pharmaceutical Quality Emerging Technology Team (ETT[5]); the US FDA ETT has indeed received multiple submissions regarding the use of modular and mobile manufacturing facilities and processes, and FDA is engaging with stakeholders to understand the impact of PODs on product quality risk factors, and how companies' Quality Management Systems are applied.

[4] ICH Q13 provides an example of manufacturing activities that are already well-suited for such concept.

[5] FDA ETT program to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing

5. Conclusion

- To address the evolving paradigm for developing and manufacturing pharmaceuticals, this EFPIA reflection paper serves to initiate a dialogue on the concept of 'Autonomous & Portable' manufacturing towards mutual and consistent expectations from Regulators in Europe and globally.

- As for all novel approaches, EFPIA believes that knowledge and experience sharing across industry and Regulators will contribute to the successful implementation of agile manufacturing technologies in a swift and compliant manner.

- This will ultimately serve the EU agenda to foster innovation, and prepare for new manufacturing technologies, while meeting patients' needs.