European Federation of Pharmaceutical Industries and Associations

Agile Manufacturing Concepts and the Role of the QP in the Draft EU General Pharma Legislation

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on behalf of the
EFPIA MQEG/Mobile Agile Manufacturing Team

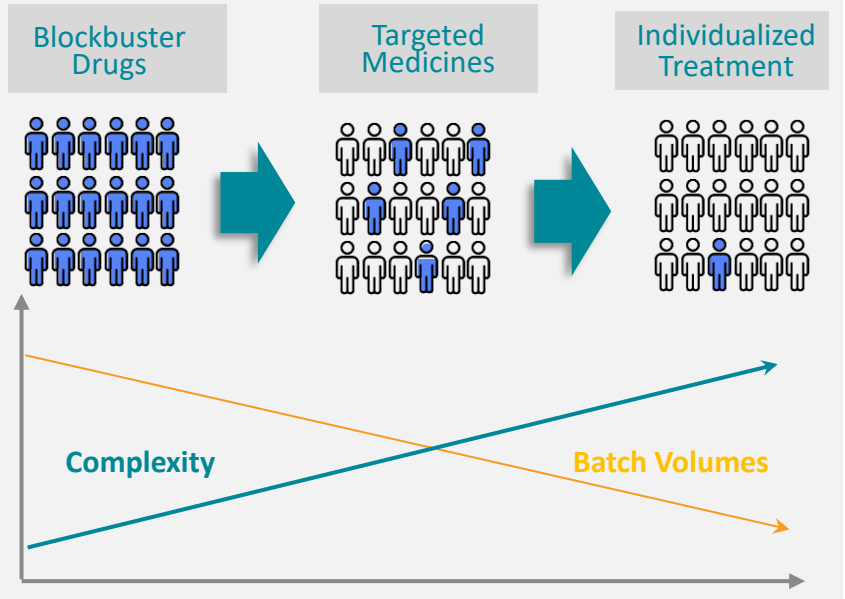
TABLE OF CONTENT

Overview

INTRODUCTION

Advances in science lead to new drugs with challenges to manufacturing and supply chain

Patient population shrinks
Product complexity increases



driving

Need to adapt manufacturing assets and supply chain set-up

Modular equipment design and automation

- Fast changeover times
- Dose form flexibility
- Standardization

Enables agile supply chain

- Fast to patient
- Seamless tech transfers

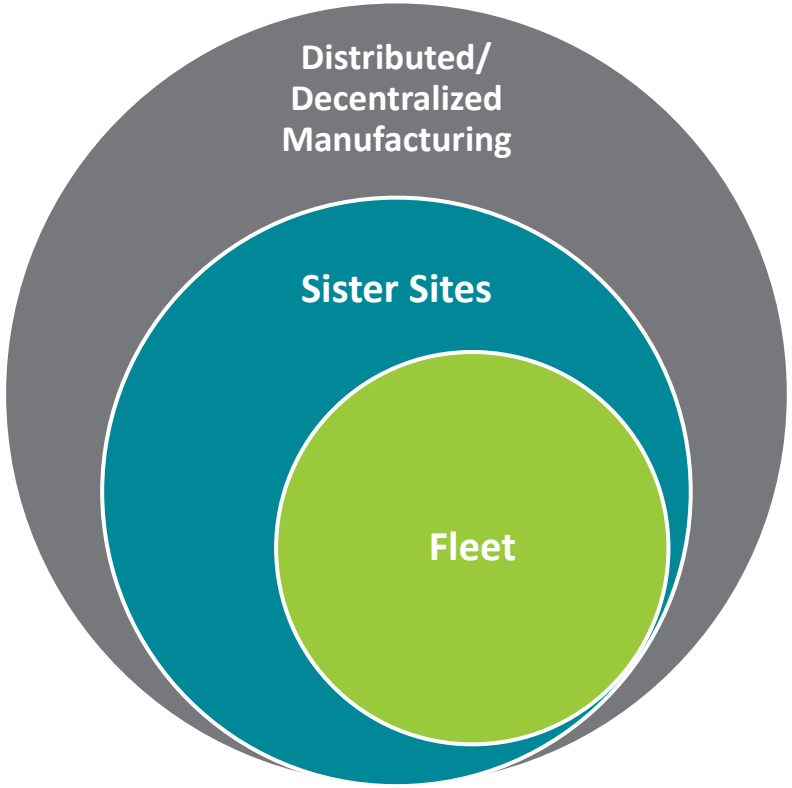
Solutions needed to optimally serve patients with targeted and individual medicines

Why Standardization? - within and across companies/industry

- **Innovation and Adaptability:** Standardization supports the adoption of new technologies such as gloveless, fully automated, and autonomous systems. This allows for continuous improvement and adaptation to new modalities and patient needs.
- **Speed and Flexibility:** Standardized and modular equipment designs allow for faster changeover times and seamless technology transfers.
- **Reduced Transfer Risk:** By using standardized units, the risk associated with process transfers gets minimized; ensuring consistency and reliability throughout the product lifecycle.
- **Efficiency:** Standardization helps in minimizing upfront investments, when commercial volumes are still volatile.
- **Enhanced Supply Chain Agility:** Modular and automated equipment designs enable a more agile supply chain, which can respond quickly to market events. This supports a reliable supply of products to patients.
- **Enhanced Quality and Compliance:** Standardized processes and equipment contribute to maintaining high-quality standards and compliance with regulatory requirements. More direct comparable process data contribute to process robustness.

Examples of Standardization

- **Sister Sites**
  Functionally equivalent manufacturing facilities with differences carrying a low risk to impact product quality and with an established change process to maintain functional equivalence through the product lifecycle using a centralized PQS.
- **Fleet**
  A population of identical or equivalent systems operating across multiple manufacturing facilities across different countries, operated throughout the lifecycle under the same PQS.



Decentralized Production with Standardized Units - Opportunities

Modular standardized systems

Modular strategy: scaled to the batch sizes, adding parallel activity of the same to increase capacity ('scale-out')

- Flexibility and agility over the asset and product life cycle
- Support enhanced product quality by increasing process robustness
- Support less human interactions and error

Opportunities

- Increased efficiency: scale out enables an adapted batch and sampling strategy
- Use risk based approach to audit the units (be it mobile or fixed) - making use of their sameness under a global PQS
- Use of matrixing for validation and re-validation

Sister Sites - Scope & Assumptions

- Well characterized Biological Medicinal Products
- Multiple GMP regulated manufacturing sites with only facility-fit differences in equipment or process
- Facility-fit only (low risk) = like-for-like; highly similar
- Sister manufacturing sites may span geographies
  (NB environmental considerations)
- Same/similar standard operating procedures and personnel training
- CMOs can be in scope, based on risk evaluation
- Same raw materials suppliers
- Sister sites are managed under the same PQS (centralised)

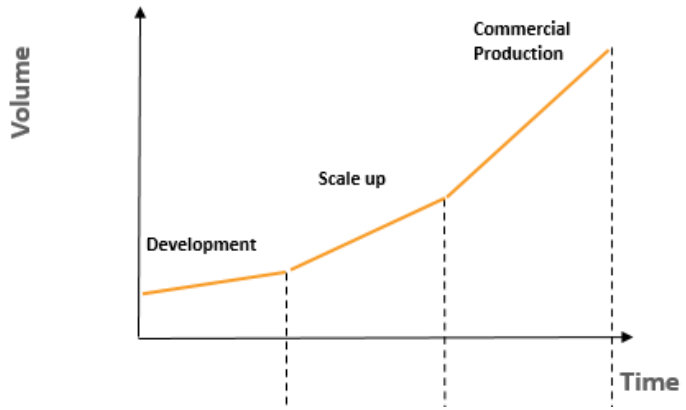
The Concept of a Fleet

The Fleet is the population of units of a production system that meet equivalency standards to:

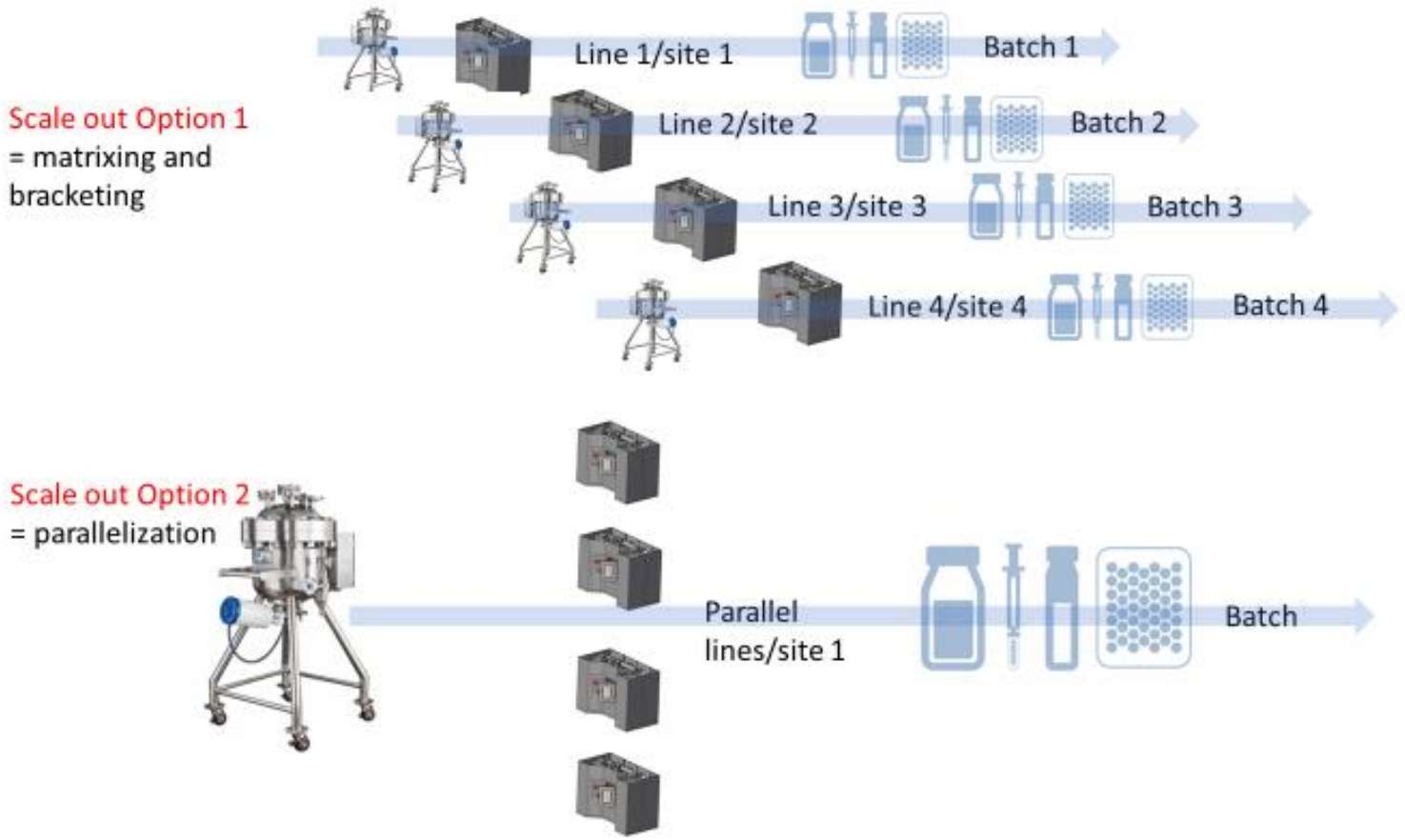
- Accelerate ordering, delivery and start up of additional equipment within a fleet
- Accelerate transfers and improve robustness due to standardization of systems and processes
- React agile and flexible to varying market demands (e.g. in pandemic cases, supply chain issues) due to availability of equivalent equipment across the network
- Strengthen quality and compliance due to aligned training (Augmented/Virtual Reality), standardization in calibration, qualification, validation and maintenance, consistent improvement actions and change management

Scale-out options leading to a fleet of similar machines

- Capacity “grows” with the volume
- Same fill technology over entire product life cycle = lean tech transfer
- Investment adjusted to demand needs
- Standardized module enables short lead-time and easy “like for like” installation & startup



Fast adjustment of production by adding further machines of same features



ENABLER

A robust Global PQS system spanning equivalent control over the lifecyle

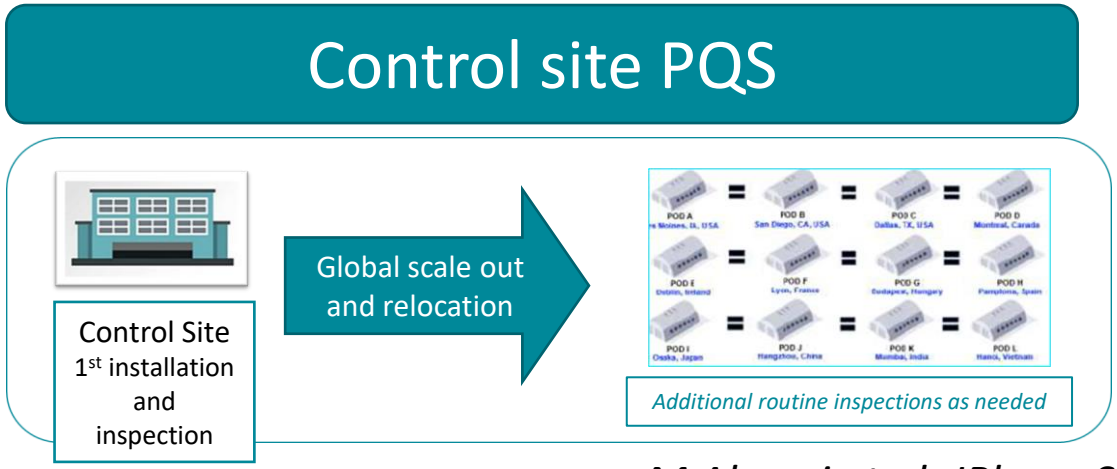
Compliance with regulatory expectations

Oversight of decentralized sites

Control across the euqipment and product lifecycle

HOW A CONTROL SITE CONCEPT CAN LOOK LIKE

Controlling the additional capacity (i.e. the fleet) under a Control Site concept



M Algorri et al, JPharmSci, 2022

The control site would be responsible for:

- **compliance of the global PQS and a procedure to add a new location, via a notification**
- **overseeing the PQS implementation and execution across all sites**

Control site concept managing a “fleet of machines”

Demonstration of Equivalency during Life-Cycle

Qualification risk assessment may allow for streamlined performance of qualification

Validation Master Plan (Control Site Concept / Fleet Master Plan)

- Qualification master plan
- Validation master plan

Could also be a (re-)validation matrix (e.g. rolling validation over fleet of units)

Changes are handled via Global change control under the responsibility of the Control Site

Test protocol templates

Site/Unit A | Site/Unit B | Site/Unit C | Site/Unit D | Site/Unit E | Site/Unit E

May be a matrix of clinical manufacturing and commercial manufacturing

Validation Master Summary Report (lead by Control Site)

- Qualification summary report
- Validation summary report

Regulatory Concepts for Decentralized Production

EC - FDA - MHRA

MHRA proposal in drafting - broader scope?
FDA FRAME refers to 'units' (rather than site)

Proposal for Directive of EP&EC, 26. April 2023

Conventional

Decentralised Manufacturing (sites)

Distributed Manufacturing (units)

Autonomous and/or Mobile units

Point of Care
(hospital / home setting)
Limited products scope

Sites vs units Same/different?

Central site

DRAFT EU DIRECTIVE*

Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

The draft EU General Pharma Legislation supports a fleet (of distributed units) concept under a central control site

✱ Provisions on decentralized manufacturing

…'in cases where manufacturing or testing steps of medicinal products need to take place in sites close to patients, such as advanced therapy medicinal products with short shelf-life, these steps may need to be decentralized to multiple sites to reach patients across the Union. When the manufacturing or testing steps are decentralized, they should be carried out **under the responsibility of the qualified person of an authorized central site.** The decentralised sites should not require a separate manufacturing authorization from the one granted to the relevant central site but should be registered by the competent authority of the Member State in which the decentralised site is established. *Page 38, (109)*

✱ Control of decentralized sites

Decentralized sites are controlled through registration and supervision by the competent authority of the Member State in which the decentralised site is established**. The manufacturing authorization holder of the central site must register all of its decentralized sites** ….and request the competent authority of the Member State in which the decentralized site is established to register the decentralized site. The marketing authorization holder may commence the activity in the decentralized site in connection with the central site only when the decentralized site is registered in the Union database referred to in Article 188(15) and the link is made in the database with the authorization of the corresponding central site by the competent authority of the Member state where the decentralized site is located. The competent authority of the Member State supervising the decentralized site may decide to carry out an inspection as referred to in Article 188(1), first subparagraph, point (a), and shall cooperate with the competent authority of the Member State responsible for the supervision of the central site. *Chapter XI Manufacturing and import, Articles 142 - 153*

* "Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC", published on 26 April, 2023

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Concept of Decentralised Manufacturing Sites

Registration	How to?	Conditions	Assessment / comment
Decentralised Sites (DS) must be 'registered' (and not authorised, ie no manufacturing authorisation needed) Art. 142(3)b	Central Site manuf. auth. holder must request the authority of the MS in which the DS site is established to register the DS	Information on DS to be provided by CS: - Name or corporate name - Permanent address of the DS - Proof of establishment in the Union – Art. 148 Registration in the Union DB needed before starting operations (MS to enter certificates – Art. 188(15))	**Ok** only concept is limited to **'site' (ie limited advancement)** Unlikely we will be able to move further through GL, Implementing/Del. Acts?…
Central Site (CS) *Manufacturing Authorisation Art. 144*	*Provide explanation on whether the site is the CS responsible for the oversight of DSs - Art. 143* *Written confirmation of each DS GMP compliance by conducting regular audits - Art. 144*	*Request for change by manuf. Auth. Holder => MS has 30 (up to 90) days to update the DB - Art 145*	*Manuf. Authorisation to be updated accordingly (e.g. if other DSs are added): process relies on MS* **CS -> EU Located**

*'Poposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC', published on 26 April, 2023

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Concept of Decentralised Manufacturing Sites

Other DSs provisions	How to?	Conditions	Assessment / comment
Supervision Art. 148(8)	DSs supervised by authority where located	Local authority to cooperate with the authority of the MS responsible for supervision of the CS	**Ok**
QP Art. 151, 153	1 Central Site QP	DSs manufacturing or testing steps carried out under the responsibility of the QP of a CS	**Ok** provided delegation possible and further clarification – see details on next page

*'Poposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC', published on 26 April, 2023

What‘s New - Definition of a ‚Qualified Person of an authorized central site’

Opportunities for this new role

- **Central site QP operating as supervisor**
  - Education: Different experience may be needed, details to clarify
  - ‚Responsible persons‘ (RP) located locally incl. outside EU territory
  - RPs perform delegated duties and report back as defined in the PQS
- **Change control managed centrally**
  - Ensuring (local) changes do not affect concept of fleet of decentralized sites
- **Authorised by the PQS**
  - describing roles, resposibilities and further details
  - PQR reports on all sites (centralized and decentralized)

EFPIA - Further considerations

EFPIA suggets to clarify the necessary details on how the QP may fulfill the duties for the central site such as:

- **Opportunites for delegation of tasks**
  - QP of the central site can delegate tasks to individuals at local sites (not necessarily in the EU/EEA territory) as assigned in the PQS. The delegation will allow interacting with the competent authorities in local language.
  - The representative at the local site should be a person within or reporting to a QA function (e.g., in case of contracted work) but not necessarily named as 'QP' in the manufacturing authorization.
- **Remote certification by the centralized QP**
  - Following the applicable requirements in the MS where the QP is registered

CONCLUSION

Modular Standardized Units for Decentralized Manufacturing and the Role of the QP in the draft EU Pharma Legislation

Existing principles apply

- We welcome the suggested oversight for decentralised manufacturing sites in the EU-GPL
- Advances in science lead to new drugs with challenges to manufacturing and supply chain
- Obvious adoptions for ‘sister sites’ and ‘fleed’ concepts

Standardisation as chance

- Central PQS to manage compliance, oversight and controls
- Validation master plan including all sites
- The QP of the central site can delegate tasks to local ‘responsible person’

Regulatory guidance

- Same approaches - different terminologies
- Regulators and industry to continue to exchange on best practices

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Back-Up slides

ABSTRACT

Agile Manufacturing Concepts and the Role of the QP in the Draft EU Pharma Legislation

- The EFPIA Mobile Agile Manufacturing Team, along with its Agile Aseptic Manufacturing topic team has made significant progress in developing approaches to decentralized manufacturing with standardized units.
- These advancements are facilitated by the European Commission's proposal for the Revision of the General EU Pharmaceutical Legislation, particularly the introduction of decentralized manufacturing sites under control of a centralized site.
- The presented approaches to standardization (Fleet Concept and Sister Site Concept) enable rapid, agile transfers for scale-out and are based on a robust global PQS system. Another important aspect is the role of the Qualified Person in such a PQS system and in the draft EU General Pharma Legislation. Opportunities and further considerations for this role are also subject to this presentation.

A DECISION TREE APPROACH TO SISTER MANUFACTURING SITES

When sister site approach is valid vs traditional