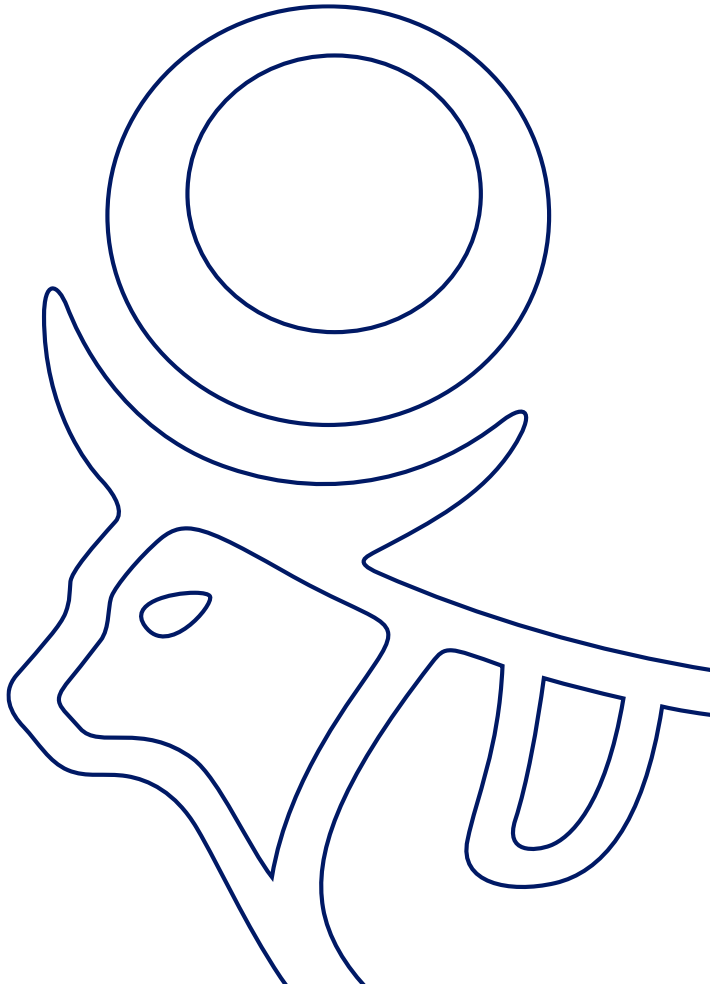
# Accelerating US Manufacturing Onshoring

EU Landscape Insights And Innovative Approaches.



**Kacimi Karim**

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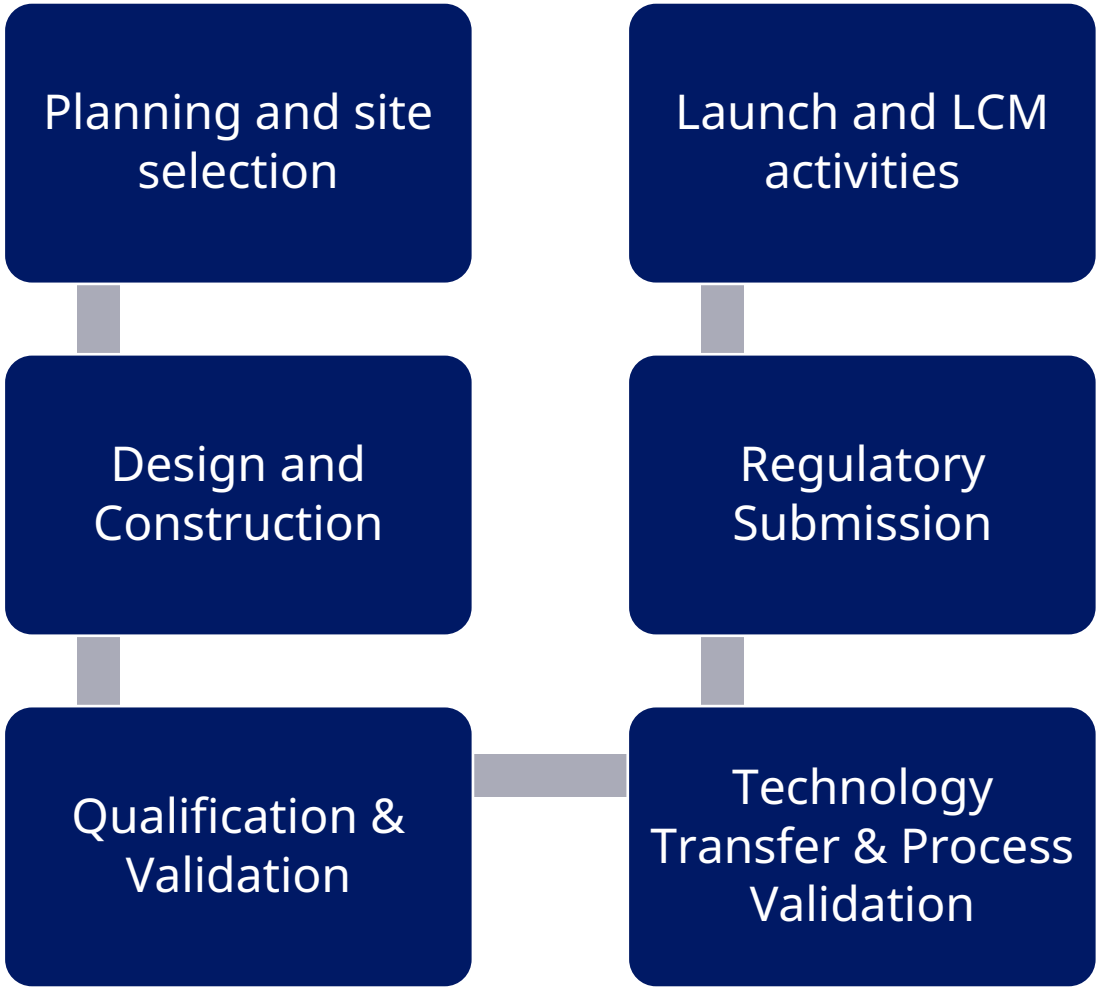
# The Current Landscape.

# High-level End to end process




**Common Practice of Regulators**

- It usually a multi-administration/jurisdiction process.
- Favor early engagement and discussion.
- It is Risk based approach.
- Demonstrate GMP compliance is key.
- A Pharmaceutical quality system  should be in line with ICH.

As each project is unique. No data available on the average time to launch. A realistic estimate would be:

5 years → 7 years

**Fastest known project 2 years in Singapour.**

# US vs EU comparison.



## In the EU

- Facility approval (MIA + GMP certificate) is structurally **separable from product approval** and is **recognized across multiple products**; post-authorization site changes are handled through codified variation types.
- Inspections may occur during MIA issuance and/or during MAA or variation assessment, with **the outcome codified as a GMP certificate of defined validity**.
- **QP declarations** and **QP batch certification** are central regulatory elements for both site launch and ongoing release.

## In the US

- **Site assessment and approval are intrinsically tied** to each product's NDA/BLA and its supplements; there is no stand-alone GMP certificate or site authorization.
- Inspections (PAI/PLI) are typically performed late in the product-review cycle and are a **gating step for approval**; late-stage findings can directly delay launch.
- **No QP role is described**; responsibility rests within the company's quality system and is not codified in a single named regulatory role in the available information.

# Inspection Model

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## In the EU

- Inspections are performed by national competent authorities within a **coordinated EMA framework.** The model is codified around "**distinct inspections" defined by site**, product, activity group and operation group.
- Planning is **explicitly risk-based and supported by a multi-authority network** that shares inspection plans, conducts joint/concurrent inspections, and records outcomes in the EU-wide EudraGMDP database.

## In the US

- The FDA is the **single federal authority** conducting GMP inspections under U.S. law and CGMP regulations. The FDA employs a **risk-based model** to determine whether inspections are pre- or post-approval, generally pre-announces routine inspections, and reserves unannounced "mission-critical" inspections for high-priority cases.

# Eudralex Vol 4 vs 21 CFR 210-211.

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**The two regulation are very similar:**

Core GMP expectations for ensuring quality, safety, and consistency of drug products are **essentially the same.**

**In the EU**

- EudraLex Volume 4 integrates GMP expectations into **a single, more detailed and comprehensive GMP guideline.**
- Additional detail and broader coverage of manufacturing activities

**In the US**

- 21 CFR 210 (general) and 211 (finished product) **separate high-level and detailed requirements.**
- 21 CFR 210 separates **general cGMP requirements** from the more specific **finished-product requirements** in 21 CFR 211.

# PACMP vs Comparability Protocol.

## PACMP (EU)

- Scope is **broader** and **may cover one or multiple changes**, for one or several products or sites (e.g., site transfers, equipment changes, platform changes).
- **Integrates the comparability plan** (where needed) with control-strategy considerations and ongoing verification of performance.
- More **prescriptive structure**

## Comparability Protocol (US)

- **Scope is typically narrower** and change-specific.

# Emerging Tools and Concepts to speed up time to launch for manufacturing plant.

# Fleet Manufacturing

**The Concept:**

- The pharmaceutical manufacturing fleet concept consists of **equivalent systems** with the same specifications that are installed across multiple manufacturing facilities, creating a **standardized manufacturing network**.
- Regardless of site, the network shares a common manufacturing platform, equipment principles, validated processes, and QRM practices**, enabling the same product to be made at any qualified site within the network.**
- A **single comparability protocol (CP)/PACMP** defines the network wide control strategy, scope, and risk-based justification for site transfers and additions.

**The Benefit:**

- This approach **reduces the need for multiple, site-specific regulatory su** streamlines oversight, and shortens timelines for implementing post-appr manufacturing changes.
- Operationally, it **enhances flexibility and supply-chain resilience** by allo controlled redistribution of manufacturing across the fleet, helping to prev shortages and support scale-up.

Concept not yet integrated to existing law and regulations.

# AI as a catalyst.



**AI can support manufacturing plant scale-up by:**

- Providing predictive models, including digital twins, that **extrapolate pilot-scale data** to full scale, justify equipment and parameter changes, and **reduce the number of physical scale-up batches needed.**
- **Enabling real-time monitoring** through AI-driven soft sensors and analytics that verify CQAs and maintain consistent control strategies across scales.
- Optimizing operating parameters and offering decision support for adjustable process conditions, which can be embedded into master batch records and control strategies.
- **Enhancing reliability** via predictive maintenance, centralized monitoring, and automated visual inspection, thereby reducing downtime and safeguarding quality as capacity increases.
- **Facilitating knowledge transfer** from prior scale-up projects, strengthenin and regulatory justifications for new scale-up activities.
- Operating within a structured risk-management and life-cycle framework al ICH guidance and emerging AI legislation, supported by protected validatio environments and early regulatory engagement.

The regulatory status of AI driven scale up support is not yet fully determined.

# Digital Twin and Synthetic Data

**Digital twins** are virtual representations of physical systems. By integrating such models into the design and startup of a new manufacturing plant, **it can substantially reduce physical experimentation**, compress development timelines, and better align with regulatory expectations.

**Exploring process options virtually:** Different process configurations, operating conditions, and control strategies can be evaluated in the virtual environment thereby **shortening the development cycle.**

**Evaluating equipment performance:** Performance of key equipment can be assessed in silico to understand capacity, bottlenecks, and robustness before installation or full-scale trials, **reducing rework and delays during commissioning.**

# Digital Twin and Synthetic Data

**Synthetic data are:** Artificially generated data sets that mimic the statistical properties and relationships of manufacturing data, but contain no actual patient or production records.

**Why they matter :**

Provide complementary evidence for regulatory submissions when **real manufacturing data are limited** at the time of launch.

**Support modelling and simulation** (including digital twins) to design, test, and justify manufacturing processes, control strategies, and design spaces before full-s

Enable virtual bridging/comparability and scale-up assessments, **reducing d extensive early production** solely for data generation.

**Feed into quantitative risk-assessment and risk-management tools** to id steps and optimize control strategies for the new plant.

Guidance on these tools not yet mature.

# Scaling the Mountain: From Pilot to new Normal

# Conclusion

- Domestic onshoring strengthens supply resilience for critical products.

- The EU benchmark shows policy must be matched by ecosystem enablers.

- Acceleration of onshoring process will require:

➢ Reduce regulatory/administrative friction.

➢ Leveraging AI/Digital revolution at all part of the end-to-end process.