CMC Strategy Forum China 2022

Multiple manufacturing sites

Executive Summary

The standard industry practice of registering multiple manufacturing sites is a key element of any comprehensive supply strategy aimed at ensuring the availability of critical medicines for patients.

The registration of multiple manufacturing suites and/or lines within one facility helps secure additional capacity and reduces the risk of patient supply disruption in the event of regional disruption (natural disaster, conflict, etc.).

The registration of additional manufacturing sites located in different geographical regions is currently accepted by most Health Authorities as it is recognized as providing additional assurance of supply continuity for patients.

Successful applications are supported by prospective risk-based tech transfer aligned with regulatory expectations, guidance and best practice, including appropriate process validation and comparability data packages.

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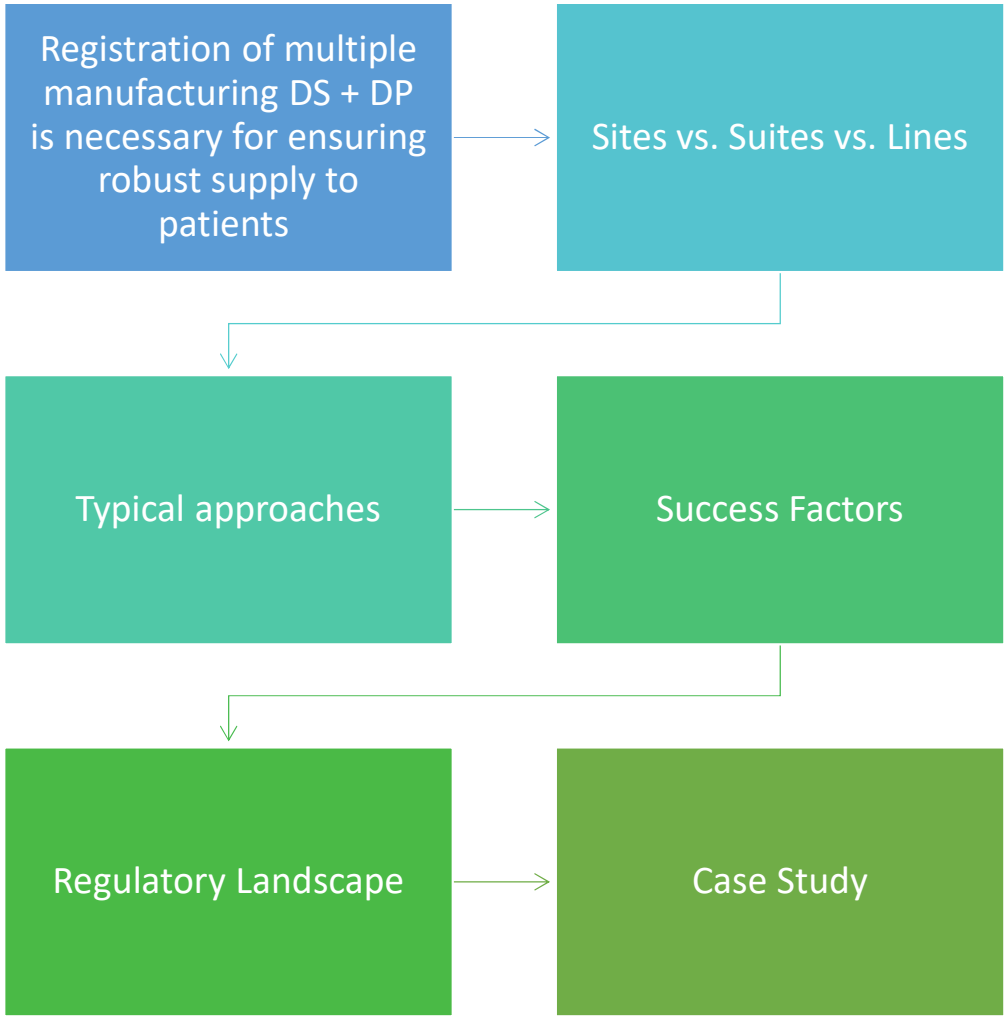
Overview: Multiple Manufacturing Sites



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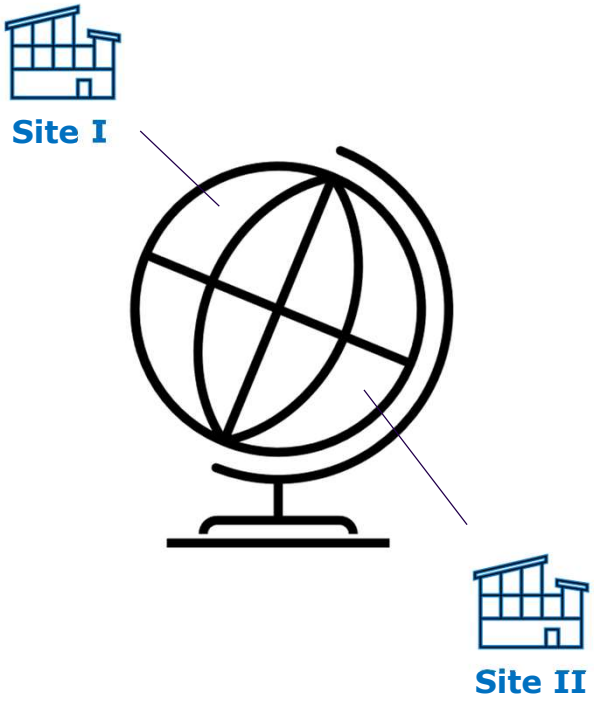
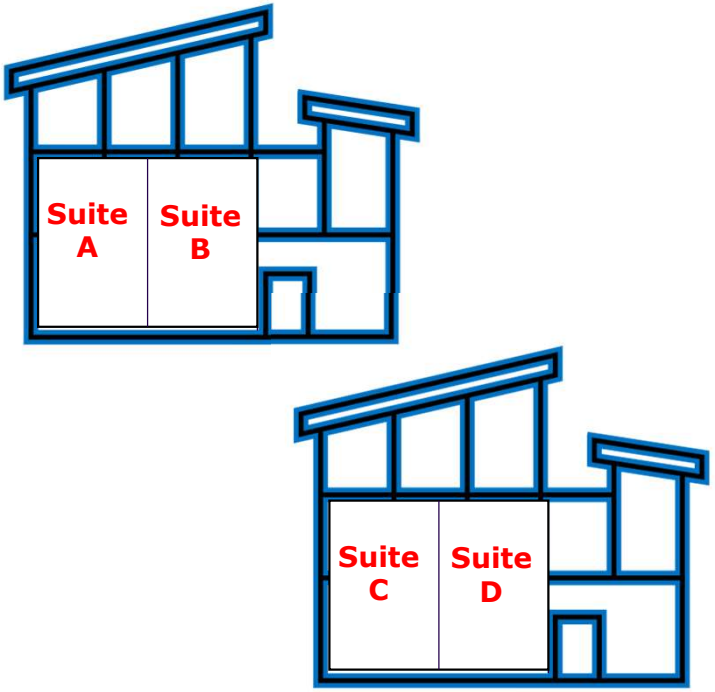
Supply Security: Multiple Sites, Suites & Lines

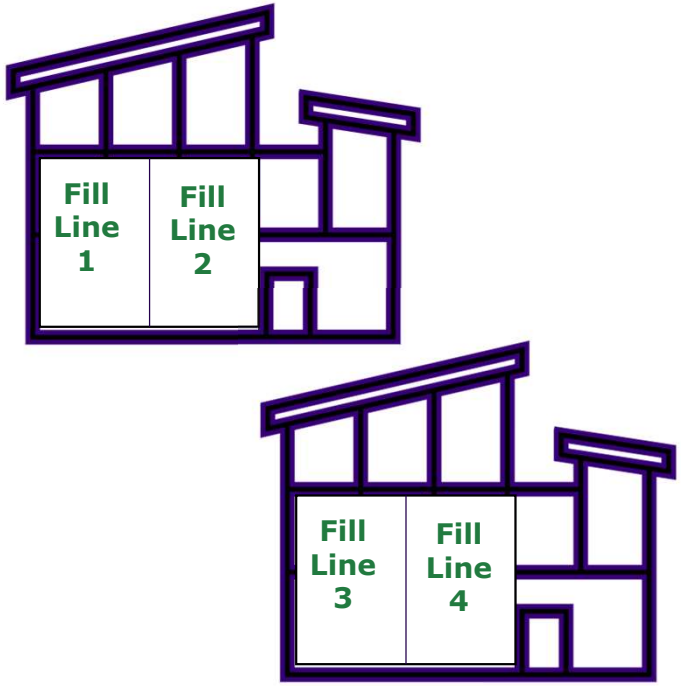
Multiple Manufacturing Sites
Located in different regions



Multiple Manufacturing Suites
Located within the same Manufacturing Site (one or more buildings)



Multiple Fill Lines
Located within the same Manufacturing Site (one or more buildings)



Multiple Manufacturing Sites – Standard Industry Practice

- Establishment of multiple, alternative manufacturing facilities is a key strategy employed by the pharmaceutical industry to ensure robust patient supply continuity.
  - Mitigates risk to the product from local disruption or catastrophic events that may ultimately negatively impact the movement of materials and/or supply chain activities leading to shortage of product (weather events, conflict, endemics, pandemics, etc.)
  - Provides flexibility in product allocation and supply chain logistics
  - Secures commercial supply for high demand products that require additional manufacturing capacity.
- Manufacturing facilities are commonly designed with several identical manufacturing areas within the same manufacturing facility (Slide 4).
- In certain cases, registration of additional manufacturing sites in different geographical locations further mitigates site-wide and regional risks.

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Typical Approaches: Addition of New Manufacturing Site

Sending site performs knowledge transfer of production details to receiving site

- *Major steps of validated production process at sending site are unchanged*
  - Minor modifications are acceptable due to site specificities if justified
  - In-process controls may be identical or within a scientifically justified proven range
- *Inputs to the process are identical or same grade*
  - For example, the master cell bank is identical, but a reagent used in the process may come from a different supply provided it is of the same pharmacopeial grade.
- *Appropriate Risk-based Process Validation*
  - Follow industry standards and guidelines with robust protocols and pre-defined acceptance criteria
  - In some instances, identical/functionally equivalent suites, lines, equipment may allow for matrix/family validation approaches to be considered (HA consultation may be needed).
- *Analytical Testing and Analysis*
  - Release specifications for the DS/FDS and DP are unchanged and must meet the same criteria
  - Robust analytical comparability program that includes extended characterization and comparable stability profiles is common
- *Clinical data is not required based on successful completion of analytical comparability*

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Success Factors – Ensuring no impact to Quality

- ***Key Considerations***
  - Risk-based approach, including evaluation of all similarities/differences and potential impact of differences
  - Analytical Comparability – robust protocols with pre-defined acceptance criteria
  - GMP status + Inspection history
  - Batch numbering/traceability
  - Routine trending of data across sites and Quality oversight
  - Follow-up/completion of all commitments to HA's
  - Health Authority approval prior to country allocation/distribution

Regulatory Landscape

Registration of Multiple Sites, Suites and/or Lines

- Typically allowed in most countries/regions, including EU, US, Japan, Canada, Brazil, China, Australia, etc.
- For most major markets - No limitations on number of sites (as many as 4 sites registered for larger products)
- A few countries only allow one site/product

Standard data packages

- Data requirements will depend on exact nature of site transfer
- Samples/in-country testing – Not required for EU, US, Japan, Brazil, Canada
- Site qualification based on analytical comparability (no clinical data)
- Case Study (slides 9-10)

Regulatory activities/pathways

- Prior consultation with Health Authorities
- Post approval timelines
- Use of PACMPs
- Use of mutual recognition for GMP aspects

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Case Study: Registration of Second FDS Manufacturing Site for Recombinant Biologic

Manufacturing, control, and release of FDS

Background

- Post-approval transfer of recombinant biologic to additional manufacturing site in a different geographical region
  - Needed to ensure robust global supply

Approach

- Standard tech transfer/validation approaches and data packages were employed (next slide)

Regulatory Considerations

- Prior consultation was conducted with multiple HA's, including CDE, to ensure alignment
- Regulatory Pathway = Prior approval variation/submission was required in all markets
- Standard approval timelines expected for a major change
  - Initial HA Approvals: 6-12 months
  - Global HA Approval (all countries): 24-36 months

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Case Study: Registration of Second FDS Manufacturing Site for Recombinant Biologic

Manufacturing, control, and release of FDS

Key Considerations	EU	China
Standard Validation Approach: Transfer of Validated Manufacturing Process (Sending site → Receiving Site) • Normal processing parameters, no extended hold times. Adaptations only if required due to site specificities. • Qualification of Laboratory-Scale Models cell culture and purification steps • Determination of operating parameters Proven Acceptable Ranges (PAR) • Hold times • LIVCA – Limit *of in vitro* cell age • Column/Filter Sanitization and Storage • Resin lifetime • Filter lifetime • Leachates from contact surfaces • Medium, buffer and solution validation • Shipping	✓	✓
Standard Full-scale Validation Studies: • 3 consecutive full-scale PPQ bioreactor runs • Executed per industry best practice/regulatory guidance for design of process validation studies; Parameters and quality attributes selected for evaluation based on the PPQ studies used for approved site. Impurity levels were evaluated for processing consistency across PPQ batches	✓	✓
Standard Comparability Approach • In-process + release data • Stability (real-time + accelerated) • Extended characterization	✓	✓
Standard FDS Stability Package: • Typically 3-6 months on 3 x full-scale/representative • Long-term + Accelerated	✓	✓
DP Stability	Not required at time of submission	1-3 x DP batches per strength 3-6 months data mandatory
Current Storage Condition and Shelf-life Maintained (approved)	✓	✓
In-country Registration testing to support change	Not required	3 DS + 3 FP/strength
HA Approval Within 6-18 months	✓ (Type II, 6 mo.)	✓ (Major change submission; 12 -18 mo.)

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