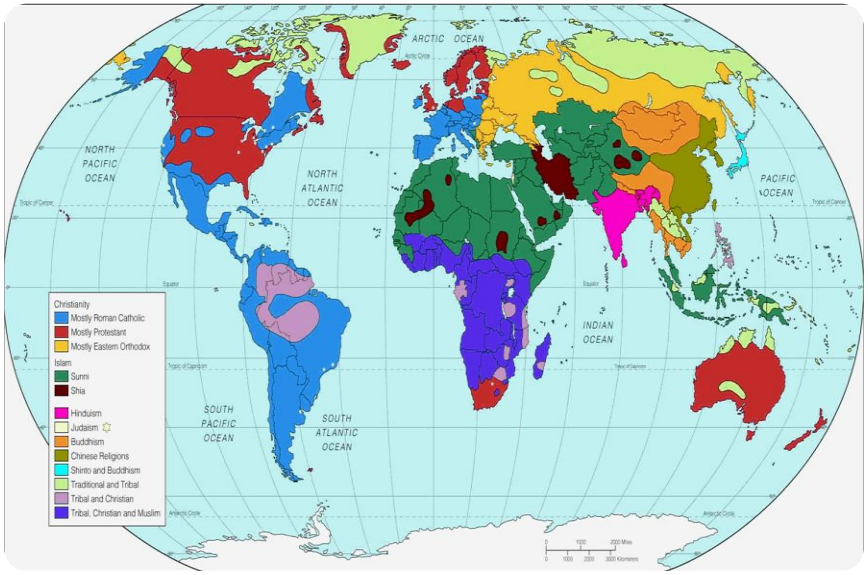

Challenges in Getting Global Approvals for Post-approval Changes

FDA/PQRI Conference on Evolving Product Quality

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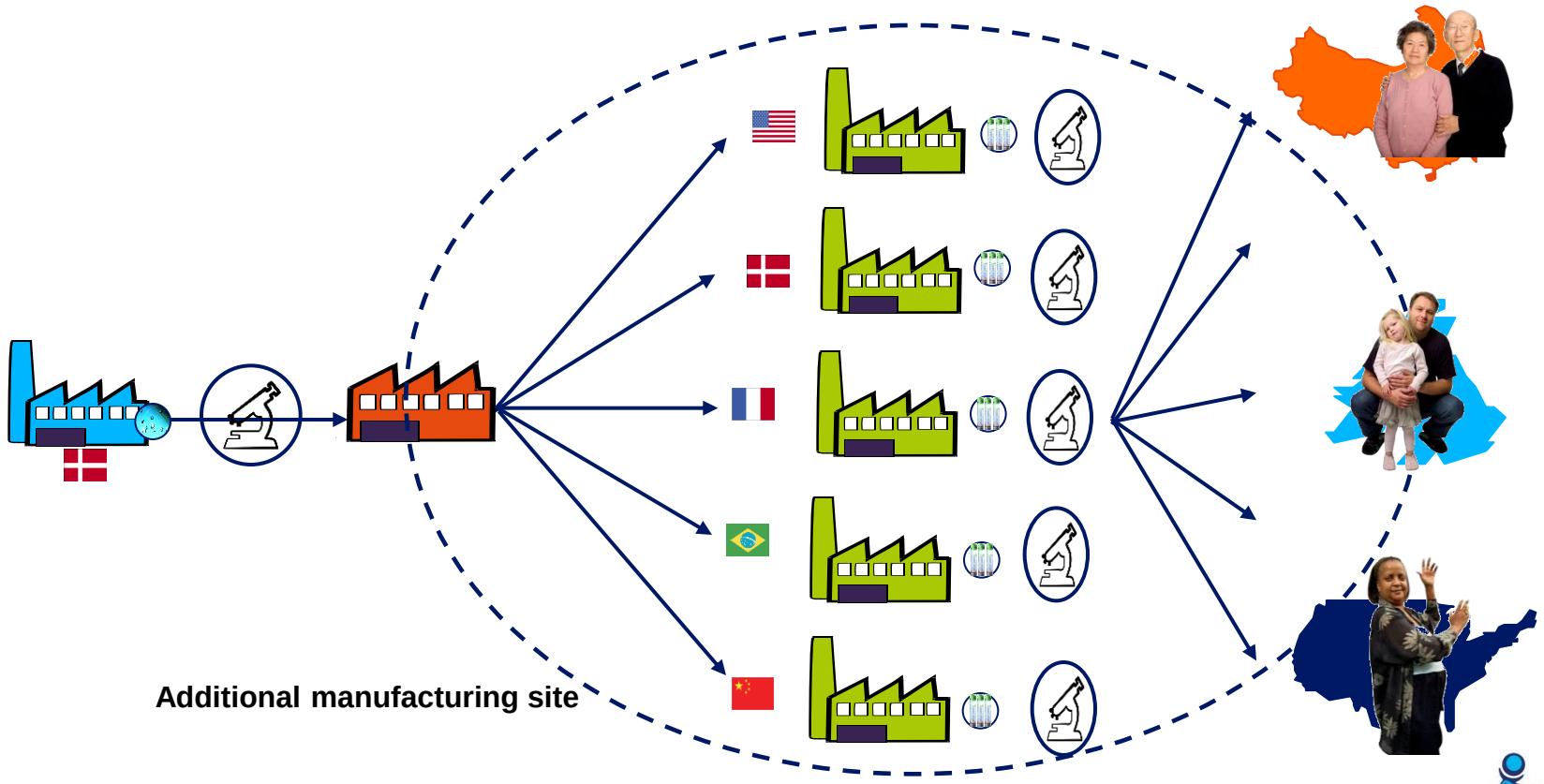
Agenda

1. Complexity and current challenges of global life-cycle management
2. A case study to illustrate the issues
3. Summary

Global Manufacturing Set-up - Example

- Similar production sites world-wide



Global Manufacturing Set-up - Example

'Same-same' Transfer Concept

- Similar factories
- Similar equipment
- Same raw materials
- Same processes and standards
- Same quality system
- Same quality standards

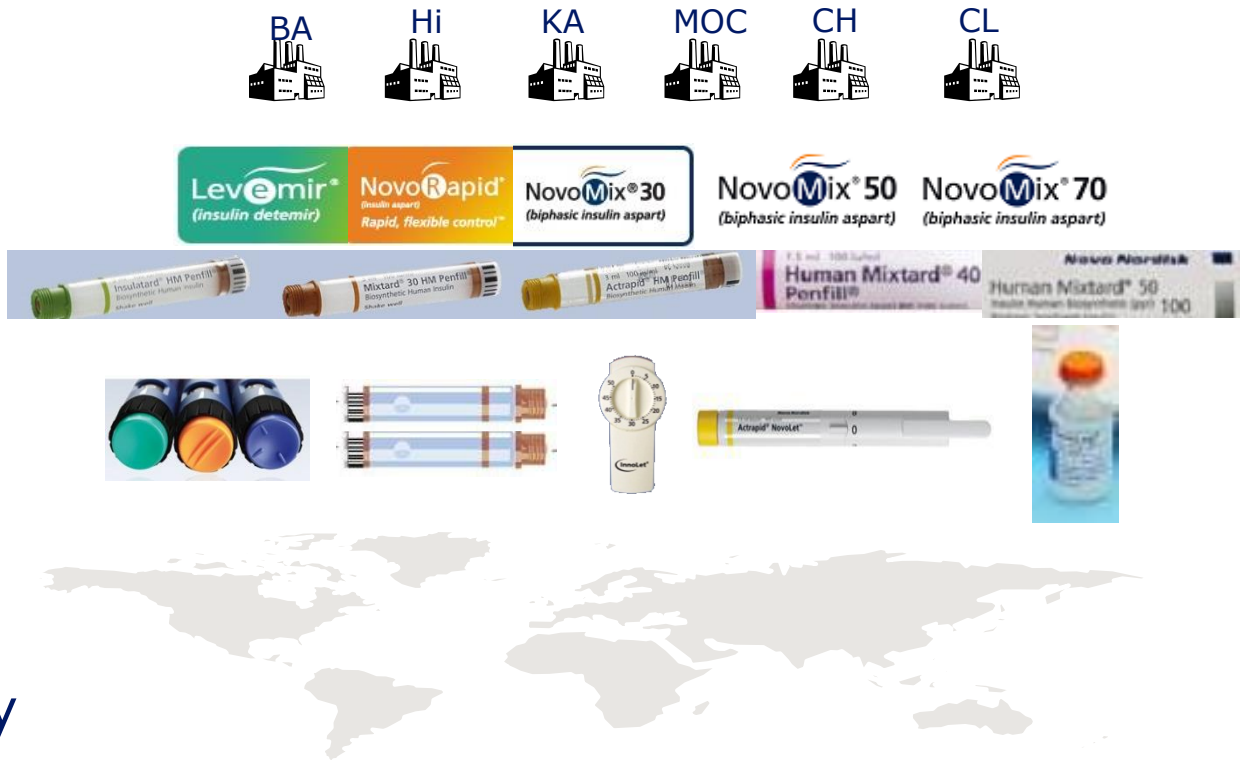
Reasons for Making Post-approval Changes

- Ensure market access and **continuous supply of live-saving medicines to patients** by reacting to supply demands
- Support **continuous improvement** and optimization of manufacturing process and ensure the quality of the medicinal products
- **Remain state of the art** with manufacturing methods and analytical techniques
- Fulfill regulatory **agency requirements**

Making post-approval changes, however, is very complicated and challenging with current global diverse regulatory environment.

Supply Flexibility – the complexity

- 6 production sites
- 10 products
- 5 presentations
- 180 Countries with different product demand and different regulatory constraints



Total: 54.000 different combinations

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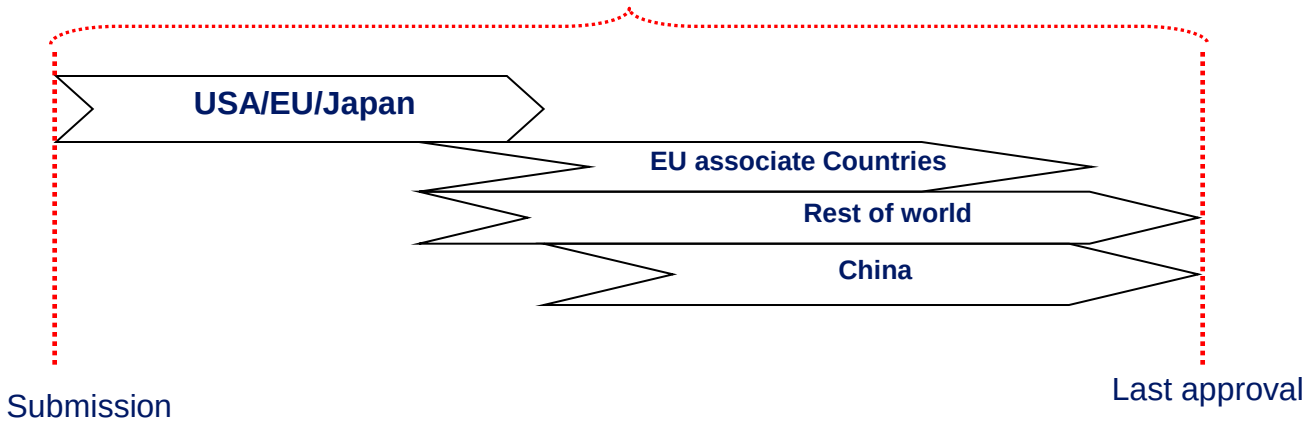
Consequence in Product Supply

Result:

- For a new filling site, long and different approval time lines => some countries will have to be supplied from the old filling factory for four years.
- Company must be able to produce different variants of the same product

Example of 1 change: introduce a new filling site

Total expected approval lead time for a world wide approval



A Case Study: *Regulatory complexity to add a new filling plant in China for a licensed biotech product*

Global Manufacturing Set-up: Why China?

- Patient's needs
  - Fast access to innovative drugs/biologics
  - Demand for safe, effective and high quality medicines
- Economy and market potentials
  - The 2nd largest economy
  - The domestic market is bigger for China as compared to other developing countries
- Infrastructures
  - Well educated competitive workforce
  - Strong government support

Regulatory Harmonization

- China effort
  - The GMP standards have been "upgraded" in line with WHO guidelines
  - The registration procedure has become more transparent, but the improvement is more apparent for chemical drugs than biologics
  - The Drug Technical Transfer (DTT) and Good Review Practice have been introduced
  - A substantial number of ICH guidelines have been adopted
  - Others

Regulatory Differences

- An example
  - Unlike in the major markets, e.g., USA and EU, the concept of the biologics licensure with License (US) or Marketing Authorization (EU) Holder does not exist in China

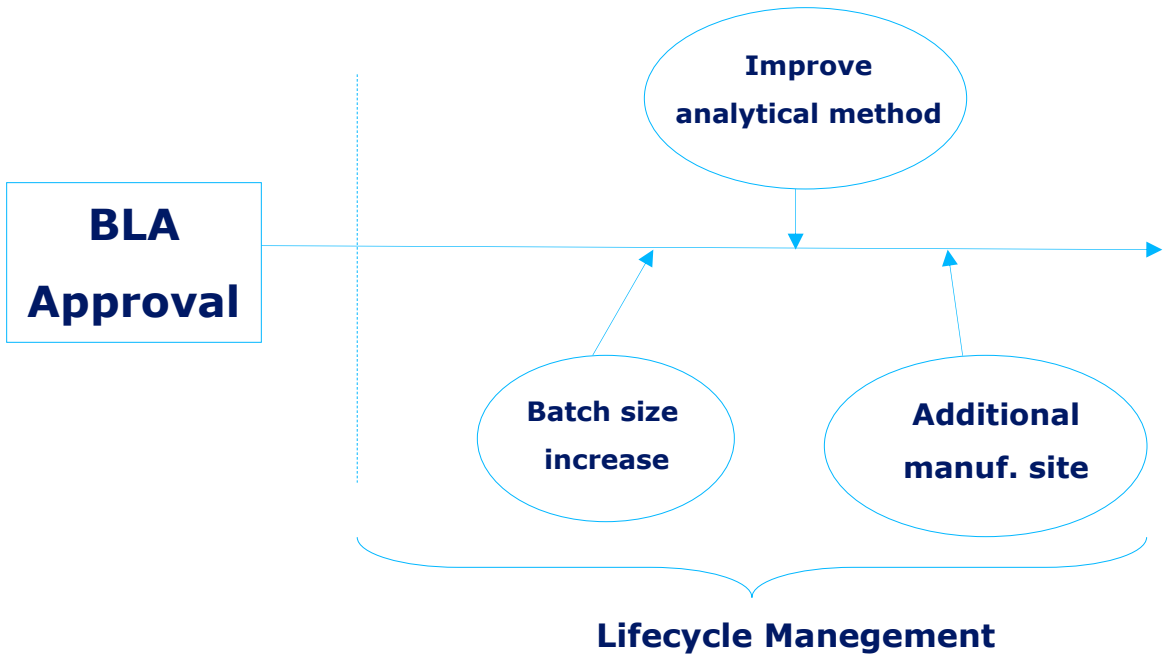
Marketing Authorization

A combined management model in China

- Marketing authorization
  - E.g., DTT/NDA
- Manufacturing authorization
  - Manufacturing permit (**one site policy for biologics**)
  - GMP certificate

Biologics License Application (BLA) in the USA

- One BLA per medicinal product
- Same BLA for the product throughout the entire lifecycle



Changes to Be Reported

- A risk-based approach
- Manufacturing Changes
  - Pre-approval supplements (PAS)
  - 30-day supplements (CBE-30)
  - Changes being effected supplements (CBE)
  - Annual reports (AR)

Tell and Wait

Tell & Do

Do & Tell

Timelines for Approval of a PAS for an Additional Manufacturing Site

Construction | Qualification | PPQ | Production

Submission | Review incl. | Approval

cGMP

Approx. 4 months

Ship products

Submission of protocol

4 months

Approval of protocol

CBE 30

to report data

Ship products

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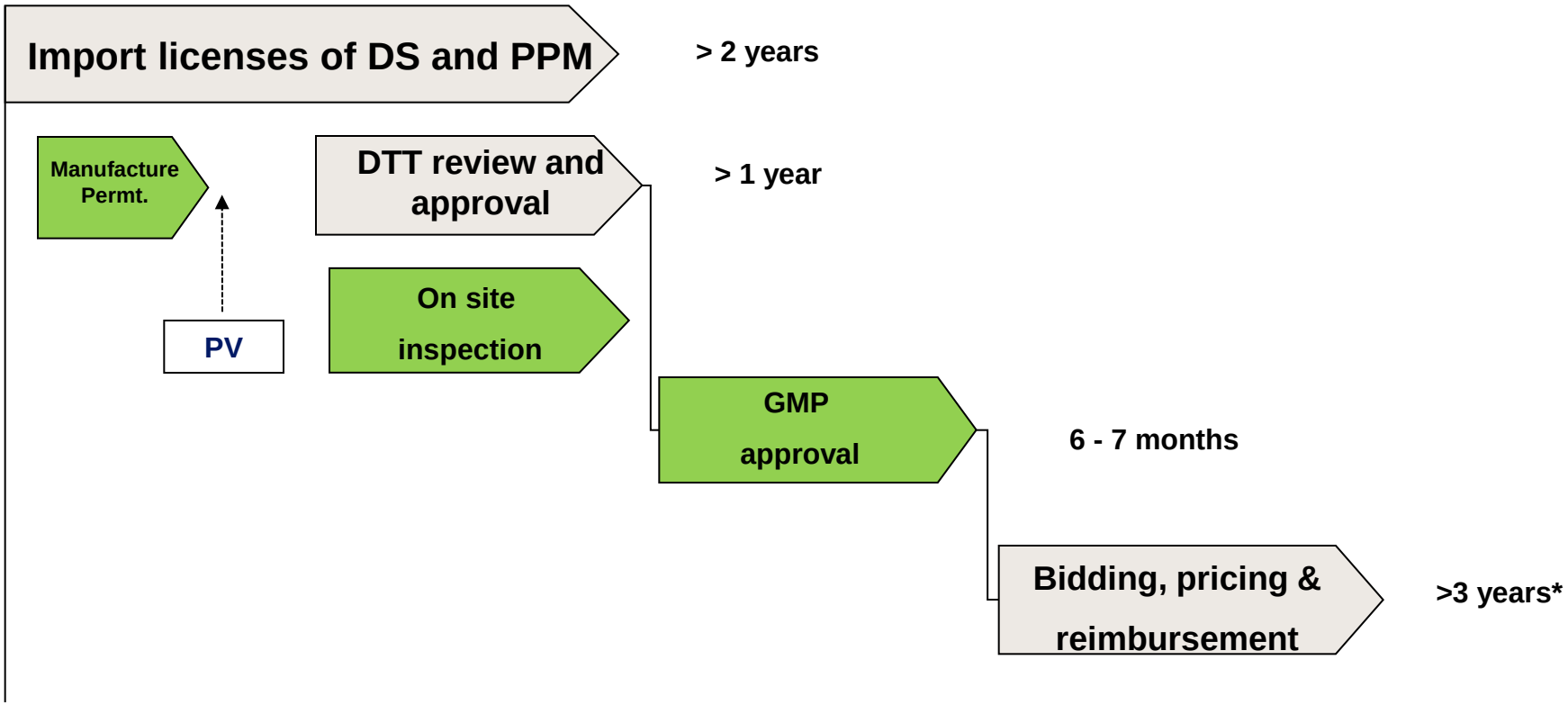
Timelines for Approval of an Additional Manufacturing Site in China for Biologics - Example



Import license for drug product is already in place

* Pay attention to 'bidding windows'

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Regulatory Pathways for Approval of a Manufacturing Site for a Licensed Biologics – Example

US System

- PAS to already approved license
- GMP inspection
  - Pre-approval inspection conduct parallel to review
  - Possible waiver
- Application review - 4 months review time

China System

- Drug technology transfer (DTT) application
- Three inspections
- Sequential process
  - No defined approval time
  - GMP certification can't be initiated without DTT approval letter
- GMP certification is product by product for biologics
- Provincial approvals required after GMP certificate obtained

Harmonized regulatory environment will facilitate global pharmaceutical development and production.

Support the Vision Statements

- One global set of CMC requirements
- One risk-based review of application for an efficient global approval
- One site inspection (or an inspection waiver based on historical GMP metrics)
- A regulatory process that enables sponsors to quickly implement continuous manufacturing and testing improvements, which would facilitate patient access to medicines and avoid drug shortages.

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Thank you