Strategies for management of manufacturing process for Blood Products

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Agenda

1. Manufacturing Network Overview
2. Blood Products Manufacturing
3. Supply Chain of Blood Products
4. Life Cycle Management Strategy
5. Case Study: Contract Manufacturing
6. Summary and Conclusions
Manufacturing Network Overview
## Manufacturing Sites

<table>
<thead>
<tr>
<th>Location</th>
<th>Employees</th>
<th>Core Products</th>
</tr>
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</table>
| Marburg, (MRB) Germany          | 3,000+    | • Coagulation factors  
|                                 |           | • Critical care                                      |
| Bern, (BRN) Switzerland         | 1,700+    | • Immunoglobulins  
|                                 |           | • Albumin                                            |
| Kankakee, (KAN) USA             | 1,700+    | • Albumin  
|                                 |           | • Intermediate pastes                               |
| Broadmeadows, (BMW) Australia   | 1,200+    | • Coagulation factors  
|                                 |           | • Critical care  
|                                 |           | • Immunoglobulins                                    |
| Wuhan, China                    | 210+      | • Albumin  
|                                 |           | • Immunoglobulins                                    |
Blood Products Manufacturing
From Blood to Plasma Products
Used % of Blood to Products: ~2%

Modified from: PPTA, 2021
Blood Products Manufacturing
Principles for one Final Drug Product

Starting Material “Plasma”

Plasma Fractionation

Intermediates (Starting material of the Bulk Process)

Bulk Process Fill & Finish

Final Drug Product

Plasma Fractionation provides starting material for purification and bulk manufacturing of the final product

→ May be obtained from Different Manufacturers

→ Different Process Schemes (Variants) may be used as starting materials for bulk process

Bulk process largely defines the characteristics of plasma-derived final product

→ Different Manufacturers are usually accepted

Flexibility is required to best exploit precious plasma to meet patient demands
Alternative Fractionation Schemes are used to obtain Plasma Products:

- Interchange of Intermediates
- Varying cold alcohol fractionation conditions like: pH, temperature, alcohol %
- Combining of fractionation steps
- Various adsorption steps can be used

Alternative Fractionation Schemes are needed to address the demands for high and low volume products.

(Scheme for illustration of the principles only, not representing actual figures)
Supply Chain of Blood Products
Plasma Intermediates from single manufacturing site

Inflexible supply approach

Modified from: https://www.mapchart.net/world.html
Plasma Intermediates from multiple manufacturing sites

Flexible supply approach

Modified from: https://www.mapchart.net/world.html
Life Cycle Management Strategy
Complexity of lifecycle activities
Mitigation through various approaches

Streamlined Approaches for LCM are necessary:

- Regulatory Submission Strategies through Post Approval Change Management Protocols (PACMPs)
- Science-Based approaches aligned with ICH Q12 i.e. definition and proposal of EC
- Risk-Based classifications of Post Approval Changes (PACs) with collaboration between Regulatory, R&D and Operations
- Continuous Optimization of information in Dossier
Complexity of lifecycle activities
Mitigation through Annual Report

Solution:
• Extensive and extended use of Annual Reports
• Risk based approach for lifecycle

Result:
• Increase in the lifecycle efficiency
• Better access to the quality products for the patients
Case Study: Contract Manufacturing
Case Study: Contract Manufacturing
Responsibilities for MAH and CMO: Intermediates and Final Product

CONTRACT MANUFACTURER
- Plasma Fractionation
- Intermediates

- Contract Manufacturer subject to GMP inspections
- Comply with all applicable regulations
- Provides all relevant information to licensed manufacturer (manufacturing process, proposed changes, deviations, inspections etc.)

LICENSED MANUFACTURER/MAH
- Bulk Process
- Fill & Finish
- Final Drug Product

- Overall Responsible for:
  - Quality, Safety, Purity and Potency of the Product
  - Product dossier
  - Reporting of changes and deviations
  - Compliance with approved dossier and the required standards and legislations

Manufacturing Contract/Quality Agreement:
Responsibilities of the participating entities, traceability and specifications of the plasma and the intermediates, storage and transport of the intermediates etc.
Summary and Conclusions
Blood Products Manufacturing, Supply and Control

**Manufacturing**
- Network of Manufacturing Sites to utilize precious plasma in most effective and efficient way
- Alternative Fractionation Schemes to optimize range of products derived from plasma
- ICH and risk based approaches for Lifecycle Management to accommodate its complexity

**Supply**
- Exchange of Intermediates from different fractionation sites to reduce drug shortage risk and increase product availability to the patients

**Control**
- Use of international standards, regulations and agreements assures Quality of the product on each manufacturing step including operations at CMOs

Thank You for your attention!