Ensuring Supply Chain Security and Continuity in Global Vaccine Manufacturing

Zhaoli (Jolie) Zhou, Ph.D.
Rajkumar Gaikwad, Product Director
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Overview of Vaccines Products and Processes

Supply Chain Topics and Challenges

Truking Bioengineering BU & Products
Vaccines are the most powerful way to protect billions of people worldwide and have transformed public health. The WHO estimates that 2–3 million lives are saved each year by current immunization programs.

A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen.

Vaccines can be classified as live-attenuated vaccines, or non-live vaccines, also, whole-organism vaccines, subunit vaccines, and nucleic acid vaccines.

The global vaccines market is projected to grow from $61.04 billion in 2021 to $125.49 billion in 2028 at a CAGR of 10.8%.

North America is the dominant in the global vaccine market, while Asia-pacific is the fastest growing region.
A typical process that FDA expects vaccine developers to follow:

- **Technical Approach**
  - Protection mechanism information
  - Target antigen identification

- **Preclinical Development**
  - Antigen characterization & purification
  - Formulation & adjuvant selection
  - Immune studies in animals
  - Investigation of immune mechanisms
  - Initial toxicity evaluation
  - Production of batches by GMP for Phase I/II clinical trials

- **Clinical Development**
  - Phase I: Safety, immunogenicity & dose ranging in small numbers
  - Phase II: Safety, immunogenicity in 100s-1000s volunteers with dose ranging & possibly efficacy evaluation
  - Phase III: Large multi-center efficacy, immunogenicity & safety trials in large numbers of subjects

- **Approval & Licensure**
  - Cost-effectiveness assessment for reimbursement
  - Immunization implementation
  - Post-licensure pharmacovigilance with sustained monitoring of AEs
  - Phase IV studies on new indications

- **Investigational New Drug (IND) submission**
- **Clinical Submission**
- **Regulatory Submission Filing**
- **BLA Submission**

- **Medical Need**
  - Epidemiology
  - Target population
  - Disease burden
  - Health economics

- **Vaccine Development**

- Traditionally, the preclinical, clinical and post-licensure phases can take a long time (10-30 years).

- New type of vaccines and technologies can speed up the development and improve safety, tolerability, and potency.

- Covid-19 vaccine proved that when stakeholders make a concerted efforts, “a vaccine development process that takes an average of 10 years and has never taken less than 4 years was compressed to 11 months”.

- Vaccination is only one component of disease prevention, it also requires the medical infrastructure, public education, for successful implementation.

- The challenge is coordinating the diverse agendas of political, corporate, and individual stakeholders.

References:
- Vaccine development, FDA website.
- Key steps in vaccine development, Ann Allergy Asthma Immunol, 2020, Jul, 125(1), 17-27
- WHO global vaccine market report, 2022, a shared understanding for equitable access to vaccine
To reach the population-scale effects, a key goal is to provide protection as widely as possible to have sufficient coverage in all countries at risk, this can only be achieved by global cooperation.

Mass production of vaccine can be a daunting task, it requires the vaccine manufacturers to achieve large-scale production at rapid pace. Scale-up and supply chain strategies have to be established from earlier phases.

To accelerate vaccine production, it is essential to collaborate with multiple supply partners and testing providers.

“A herd immunity” or “herd protection”
If enough individuals are vaccinated, and if vaccination prevents not only the development of disease but also infection itself, transmission of the pathogen can be interrupted and the incidence of disease can fall further than would be expected, as a result of the indirect protection of individual who would otherwise be susceptible.
Manufacturing and Materials

21CFR 210 & 211: Component of the quality System

- Vaccines have to be manufactured according to the relevant cGMP guidelines.
- Scaling up and expanding manufacturing capacity by adding sites all need to have secure access to enough GMP materials.
- Typically, more than 200 individual materials are required for production of a vaccine. Many of the materials are often produced in different counties and need global support.

Vaccines must be manufactured at huge scale to make inroads into global populations

- Once the materials are chosen and defined in BOM, it cannot be easily changed – change control and QRM.
- Large amount of supporting data is provided by different suppliers - supplier selection and qualification are critical.
- Materials are also important for manufacturing cost and timeline planning – Tech. Transfer.

Materials ➔ Process ➔ Product

- Manufacturing, safety, and quality control of vaccines. WHO vaccines explained series.
- Vaccine production, navigating scale-up challenges, biopharma technology networks, 2021.
Incoming materials are critical components of all vaccine manufacturing processes.

Quality of incoming materials need to be tightly controlled and monitored to ensure drug product quality, efficacy and safety. Insufficient material control can lead to inconsistent performance, interruption/delay to production, and loss of expensive vaccine products.

“even one component falls short, the production of vaccine can be delayed”. Materials need to be delivered on time, with full compliance and consistency: supplier-user relationship.
## Materials Selection

- A thorough understanding of material properties and manufacturing requirements is the key to making confident and successful material choices.
- It is also critical for vaccine producer end-users to work closely with suppliers to align the requirements and share responsibilities.
- Build the materials database from start, share data and experience.

### Physicochemical Properties
- Physical properties (e.g. solubility, viscosity)
- Chemical Compatibility
- Mechanical Properties
- Thermal Properties
- Surface Characteristics (e.g., fluid interaction)
- Barrier Properties
- Optical Properties

### Safety and Quality
- Biocompatibility
- Bioburden
- Endotoxin
- Particulates
- ADCF or TSE/BSE Risk Analysis
- Extractables and Leachables
- Lot-to-lot consistency
- Certificates (COC, COA, COP, etc.)

### Application Considerations
- Design Complexity
- Available Packaging Size, Scalability
- Facility and Machine Compatibility
- Cost, Lead Time
- User Experience
- Customer Service
- Supplier Data Package
- Validation Studies

![Diagram showing alignment between communication, supplier documents, and user documents.](image-url)
Supply Chain Security

- Vaccine manufacturers need to ensure supply security to guarantee production continuity and avoid vaccine shortage.
- Suppliers also have complex supply chains.
- Any time the end-users add on products or components can increase the supply chain complexity, also increase the risks of supplier initiated changes.
- Effective supply chain management include supply chain simplification and maximize the data sharing and leverage among different products and facilities.
Standardization Consideration

- **Simplify supply chain:** build and maintain database, avoid duplications, and reduce risks.

- **Build and maintain a collection of parts and assemblies that can be used in different products and processes.** “Design once, but use many times” – Standardization.

**1. Design consideration**

- 6 fasteners required, or 2 molded junctions
- 9 fasteners required, or 3 molded junctions
- 4 fasteners required, or 1 molded junction
- 7 fasteners required, or 2 molded junctions

*Source: Design and Deployment Strategy for SUS*

**2. Component selection**

**3. New technologies**

**4. Process, Equipment and twin facilities**

- **Standardization on designs, materials, technologies, systems, and facilities** to leverage data and save time

**FDA guidance for industry:** PAT – a framework for innovative pharmaceutical development, manufacturing and quality assurance

- Benefits of single-use standardization: adopting a standard design approach. BPI, May 2021
Many biopharmaceutical end-users have experienced large amount of change notifications. Especially from “Localization” efforts.


It is typically difficult to deal with supplier changes, especially with multiple companies and multiple groups involved. Supplier changes may vary vastly, and change management should be handled differently for different types of changes.

Material changes can be categorized as “Major” changes or “Minor” changes based on risk assessment results.

Importance of “Alternative Materials and Suppliers” in the system.
Data Integrity Challenges: Many sources of data and large amount of data

Ensure supplier data integrity: supplier qualification and audit

- Data Management
  - Material/Equipment Supplier Data
  - Sub-supplier Data
  - Contract Testing Lab Data
  - Published Research Data

- External Data
  - published Research Data

- QC Lab
  - Manufacturing
  - MS&T Lab Data
  - Contract Testing Laboratories / Service Providers

Data Integrity Challenges: Many sources of data and large amount of data

- Ensure supplier data integrity: supplier qualification and audit

Data Collection, Processing, Analysis

Data Reports

- Quality and Regulatory Decisions
- Direct Manufacturing Operation and/or Continuous Improvement
Biopharmaceutical end-users and suppliers relationship is extremely important, it needs to be a **long-term formal partnership**, not stopping at purchase orders.

Suppliers can be classified into different groups based on strategic importance, performance evaluation, and supplier qualification results. Supplier classification is the basis for the company’s supplier portfolio development and QRM.

- Manufacturing needed Equipment, Instrument, Materials
- Supporting Data Packages
- Post-sale Maintenance and Services
- Troubleshooting and Investigation Support
- Industrial Information and Experience Sharing
- New Technologies for Continuous Improving

**Supplier Life-Cycle Management (SLM)**

1. Identification
2. Qualification & Selection
3. On-boarding
4. Performance Monitoring
5. Risks, Changes, & Relationship Management

SLM is based on **value, risk, and performance**. Choosing the best suppliers and then managing them in a joined-up, integrated and consistent manner.
THE R&D

- The central R&D is in Changsha with 1700 engineers & scientists,
- Europe, Italy Product Development center & R&D with 300 engineers & scientists,
- Suzhou R&D with 300 engineers & scientists
- As of August 31, 2022, a total of 4342 Chinese patent applications (1028 invention patent applications, 2876 utility model patents, 438 design patents) have been filed,
- There are 2684 valid patents (468 invention patents, 1983 utility model patents, and 233 design patents)
- Another 40 PCT international patent applications were filed and 20 patent authorizations were obtained in the United States, Russia, India, South Korea, Germany, Indonesia, Europe, and other countries.
Drug Substance

- Automatic In-line Conditioning Chromatography System
- Slurry Tank
- Truking Media
- Bioreactor
- Wave
- Depth filtration System
- Tangential Flow
- Cell Culture/Fermentation
- Clarification
- Capture
- UF/DF
- VF
- Polish
- pH adjustment
- Virus inactivation
- Production Ultrafiltration System
- Virus filtration
- Easy Chromatography Column
- Production Chromatography System
- Reservoir tank
- Magnetic stirring

Drug Product

- Washing machine
- Tunnel
- Filling and stoppering machine
- External washer
- Capping machine
- Lyophilizer + ALUS+CIP station
- Automatic inspection
- Labelling machine
- Vials feeder
- High-speed cartoning machine
- Wrapping machine
- Packing and palletizing machine
Solution Key Part: USP

- **SU Wave Bioreactor**
  - Wave bioreactor with adaptive bag provisions
  - Adaptive top tray for two-bag installation with full operational control

- **SU Bioreactor**
  - SU bioreactor with adaptive bag provisions and can retrofit to customers’ present SU setup Cylindrical or Square designs

- **SS Bioreactor**
  - SS best in class design and fully customizable as per process needs
  - Software user-friendly with a common interface for hazel-free operations

- **DF Clarification**
  - Process automation with all available DF consumables
  - CIP automation and SS-SU integrated products as per process demands
SS & SU Chromatography System / Columns
- Patented combined hybrid technology of Pack-in-place
- Axial compression packing for any resin
- Four points attachment with two-pillar top adapter movement is more reliable
- Lowest maintenance time and space requirements with NO-SWING OUT mechanisms

Multi-column continuous chromatography system
- Adaptive and dynamic control of titer concentration in perfusion-fed batch Mab platform technology
- Effective utilization of Protein A resin dynamic binding capacity without fear of losing molecules

Ultrafiltration & Diafiltration SU and SS
- Multi-cassette compatible holder
- Single Use cassette operational compatibility
- Most compact designs to avoid facility revalidation

Virus removal filtration system
- Match with different virus removal filters and filtration systems
- Single-use flow path
- Single-use sensors (all market leaders)
- Automatic operation, data management, computerization
Patented mechanical structure design

Truking Structure

- Truking Ingenuity Fully-Automatic Chromatography Column

The triangular mechanical structure strengthens the overall strength of the equipment and makes the equipment simple, lightweight, and safer.
Truking's Patented Column Disassembly Structure Adopts the hoisting method, which occupies a small area, saves space, and is convenient for transportation. It only takes 15 minutes to disassemble.

The hook design is cumbersome to operate. The entire operation is time-consuming.
Auto Packing Station System

- Adaptive to column sizes from **300mm to 2000mm**
- Automatic guided operation mode: instructions for column packing, unpacking, cleaning, and disassembly.
- Integrated with two Tapflo flow pumps without damaging resins slurry

<table>
<thead>
<tr>
<th>Product model</th>
<th>APS050</th>
<th>APS100</th>
<th>APS200</th>
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</thead>
<tbody>
<tr>
<td>Maximum flow (L/min)</td>
<td>50</td>
<td>100</td>
<td>200</td>
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<tr>
<td>Main piping size</td>
<td>DN20(3/4&quot;)</td>
<td>DN25(1&quot;)</td>
<td>DN40(1.5&quot;)</td>
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<td>Protection class</td>
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<tr>
<td>Wetted material</td>
<td>316L、PP、EPDM</td>
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<td>Operating Temperature Range</td>
<td>2~40°C</td>
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<tr>
<td>Operating pressure max.</td>
<td>6 bar</td>
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<tr>
<td>Adaptive Column</td>
<td>300/400/450/600</td>
<td>450/600/800/1000/1200</td>
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<td>Dimensions (L×W×H)</td>
<td>650×560×1130 mm</td>
<td>650×560×1130 mm</td>
<td>1100×740×1130 mm</td>
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<tr>
<td>Weight (kg)</td>
<td>145</td>
<td>185</td>
<td>265</td>
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</table>
Changsha plant: 6000 m², including a C+A production environment specially designed for highly clean applications, state of art facility will further expand in the National Science and Technology Industrial Park.

Quality management system meets multi-national regulations including cGMP, ICH, USP, EMA, ISO, etc. Comprehensive validation packages according to industrial guidance and best practices, including PDA, BPOG, BPSA, etc.
Final products meet ISO, USP, E.P. requirements, industry guidelines and best practices (e.g., BPOG, BPSA, PDA, etc.)

Materials management and manufacturing follow cGMP requirements. For example, biocompatibilities testing includes:

- Gamma sterilization validation
- Extractables/leachable studies
- Particulate control

Strictly testing and controlling materials to meet bioprocess application requirements, including physical, mechanical, and surface properties, chemical compatibility, barrier properties, optical properties, shelf life, etc.

High-quality management system to ensure batch-to-batch consistency of raw materials and final products
Truking Supports

Technical Support

- Automation systems, hardware manufacturing, product design, simulation modeling, and analytical techniques. Turnkey project, Tech transfer assessments

Financial Support

- Investment from cooperate to enable SUT development, from daily routine operation to facility expansion.

Manufacturing Capabilities

- Strong equipment manufacturing capabilities with large MFG capacities, can help SUT with stainless vessels and molds for various applications.
- Customized solution as per client requirement

Development Platforms

- TK AI, automation and marketing platforms can help develop unique world-leading automatic and semi-automated solutions for single-use & Multi-Use products.
Extended Support

Customer-centered, highly flexible manufacturing to ensure internal and external supply and demand balance

High-quality products based on user requirements, ensure data integrity and traceability throughout the entire production process

Assist users to assess the risks of single-use products, provide complete technical and application data packages

Provide customize, Affordable, High-Quality SU & SS Products for Biopharmaceutical Users

Plants are designed to meet FDA, EMA and NMPA standards, products range from DS to DP manufacturing

The facilities will undergo regular, comprehensive annual audits to meet the appropriate cGMP and ISO quality standards

Management team has extensive experience in both multi-national biopharma and SUS companies.
THANK YOU!

TEL: 86-731-87938283   Email: marketing@truking.com
ADD: No. 1 Xingkang road, Yutan town, Ningxiang, Changsha, Hunan, China.