Recombinant Protein Vaccine Platform Based on Hybrid Technology

A Comparison of Full Stainless Steel, Full Single-Use, and Hybrid Systems

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EXPERTISE IN BIOPHARMACEUTICAL

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Contents

1 Introduction

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1.1 Tofflon Global

Experts in Biopharmaceutical Company

Leading Brand in China Pharmaceutical Equipment Market

Top 3

USD 800 Million Revenue (FY 2023)

800

5,800+

5800+ Professionals
805+ Engineers

Since 1993 Shanghai

Over 15 Manufacturing Plants all around the world (11 in China, 4 Overseas)

15+

2,000+

3,000 +

Serving **over 3000** pharmaceutical companies worldwide

2000+ Patented Technologies
200 Software Copyrights

25+ Local Representative
Build local capability with

380+ Local Employees
Localized team with

45+ Countries
Products delivered to

Top Customers

World Top 20

NOVARTIS, Roche, AstraZeneca 阿斯利康, Boehringer Ingelheim, Takeda, MSD, sanofi, AMGEN, Lilly

Top Brands

LESAFFRE, Yakult, DANISCO, SACCO, Pharmathen, VIANEX, ANFARM, 第一三共ヘルスケア, Otsuka 大塚製薬

Diagnosis

Roche, Abbott, DiaSorin, BRACCO, mindray 迈瑞

CDMO

Lonza, WuXi Biologics, Recipharm, CASYMCHEM, PORTON 博腾生物

Animal Health

zoetis, Boehringer Ingelheim, MSD, Elanco, Ceva

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1.2 Tofflon In Southeast Asia

20+ Years in Southeast Asia Market

The 2nd Priority International Market in Tofflon Group

12 Million USD in 2022

25+ Local Employees

3 Companies in Singapore, Indonesia and Vietnam
4 Local Service Team in Different Countries

50+ Sets of Equipment

Delivered to **30+** Customers

Sales and service offices in Southeast Asia

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1.3 Tofflon Integrated Solutions

Bio Process → **Bio Tech** → **Bio Pharma**

DS

- Cryopreservation — LN2 Storage System
- Seed Cultivation — CES System(10L-200L)
- Cultivation — Bioreaction System
  - Bio-Vessel and Pipe System
    - SS Bioreactor/ Fermenter (50L-20KL)
    - Single Use Bioreactor (50L-2000L)
- Filtration — Deep-filtration System
  - Hollow Fiber
- Purification — Chromatography System
  - Chromatography System
  - Chromatograph System(Lab-Scale)
  - Chromatography Colum(Manual)
  - Chromatography Colum(Auto)
- Virus Removal — Virus Removal Filtration
- Concentrate Replacement — Ultrafiltration
- Solution Frozen — Freeze & Thaw
  - Inactivation System

DC

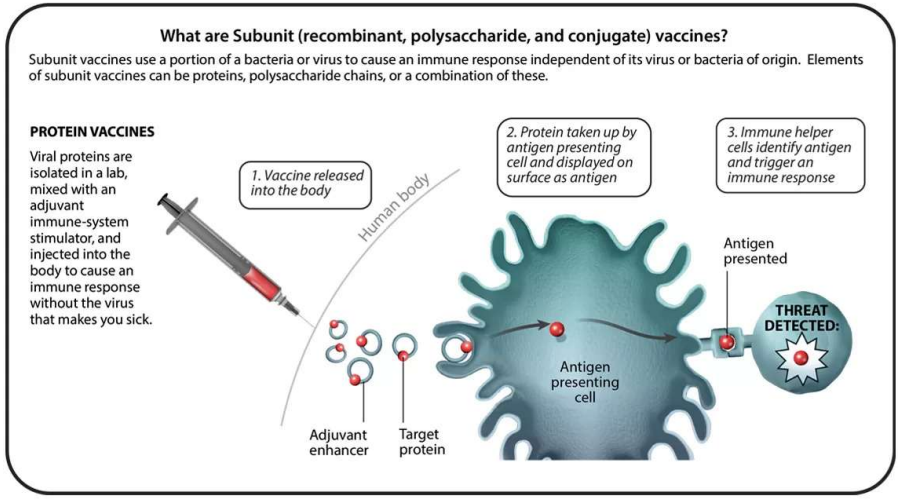
- Cell preservation solution
- Cryopreservation tubes
- Culture Media
- Disposable cell culture bags
- SUB Bag
- Culture Media
- Chromatography Resin
- Fixture
- Membrane
- Freeze & Thaw Bag
  - Bag Mouth
  - C-FLEX Pipe

Slide 6

KY4 Is there better way to stylish this page? The Tofflon logo in middle looks terrible.
Karl Yu, 11/10/2024

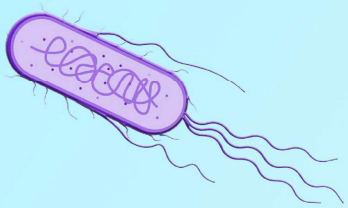
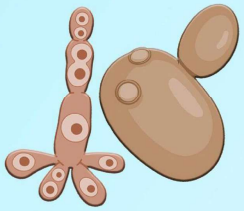
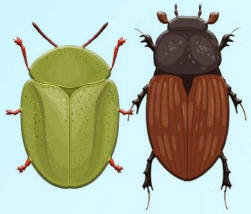
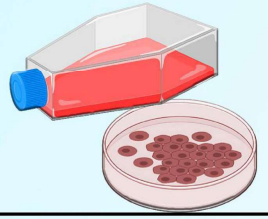
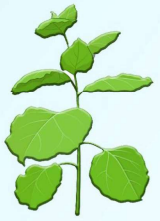
1.4 What Are Recombinant Protein Vaccines?

- **Definition:**
  - Vaccines that use a specific protein from a pathogen (***antigen***) to induce an immune response.
  - Produced by inserting the gene for the antigen into a host cell, such as yeast or mammalian cells, which then express the protein**.**
- **Mechanism of Action:**
  - The purified protein is administered, prompting the immune system to recognize and respond to the pathogen if encountered in the future.
  - Often combined with adjuvants to boost immune response.



Source: Pfizer, https://www.pfizer.com/news/articles/understanding_six_types_of_vaccine_technologies

1.5 Comparison of Expression Systems for Recombinant Protein Production

Expression systems	Bacteria	Yeast	Insect cells	Mammalian cells	Plant cells
					
Advantages	• Cost-effective • Scalable • Rapid growth • Easy manipulation • High-level expression • Genetic stability	• Low production cost • No endotoxins contamination • High-density fermentation • Support most protein folding	• Carry and deliver large amount of DNA • High protein expression • Support eukaryotic protein PTMs • Proper protein folding and assembly	• Perform proper folding, assembly, and PTMs of proteins	• Highly scalable • Cost-effective • Carry out N-glycosylation • High expression • Correct folding and assembly
Limitations	• Poor immunogenicity • Recombinant proteins lack PTMs • Protein solubility issues • Contamination by bacterial endotoxins • Inability to create di-sulfide bonds	• Vlp yield lower than E. coli • High mannose modification • Lack mammalian like PTMs	• Difficult to scale up • High production cost • Baculoviruse contamination • Simpler N-glycosylation than mammalian cells • Incomplete modification of proteins	• Require large-scale production facilities • Lengthy expression time • Low yield • Contamination by mammalian pathogens	• Low yield than mammalian cells • Technical and regulatory issues

Source: https://www.researchgate.net/publication/357553767_Virus-Like_Particles_Revolutionary_Platforms_for_Developing_Vaccines_Against_Emerging_Infectious_Diseases

1.6 Benefits and Examples of Recombinant Protein Vaccines

- **Key Benefits:**
  - **Safety:** Does not use live or whole pathogens, reducing the risk of side effects.
  - **Precision:** Targets specific antigens for a tailored immune response.
  - **Scalability:** Suitable for large-scale production, with stable storage conditions.
- **Examples:**
  - **Hepatitis B Vaccine:** Prevents hepatitis B infection using yeast-expressed antigen.
  - **HPV Vaccine:** Targets HPV to prevent cervical and other cancers.
  - **Novavax COVID-19 Vaccine**: Uses SARS-CoV-2 spike protein for COVID-19 prevention.

2 Production Process Overview

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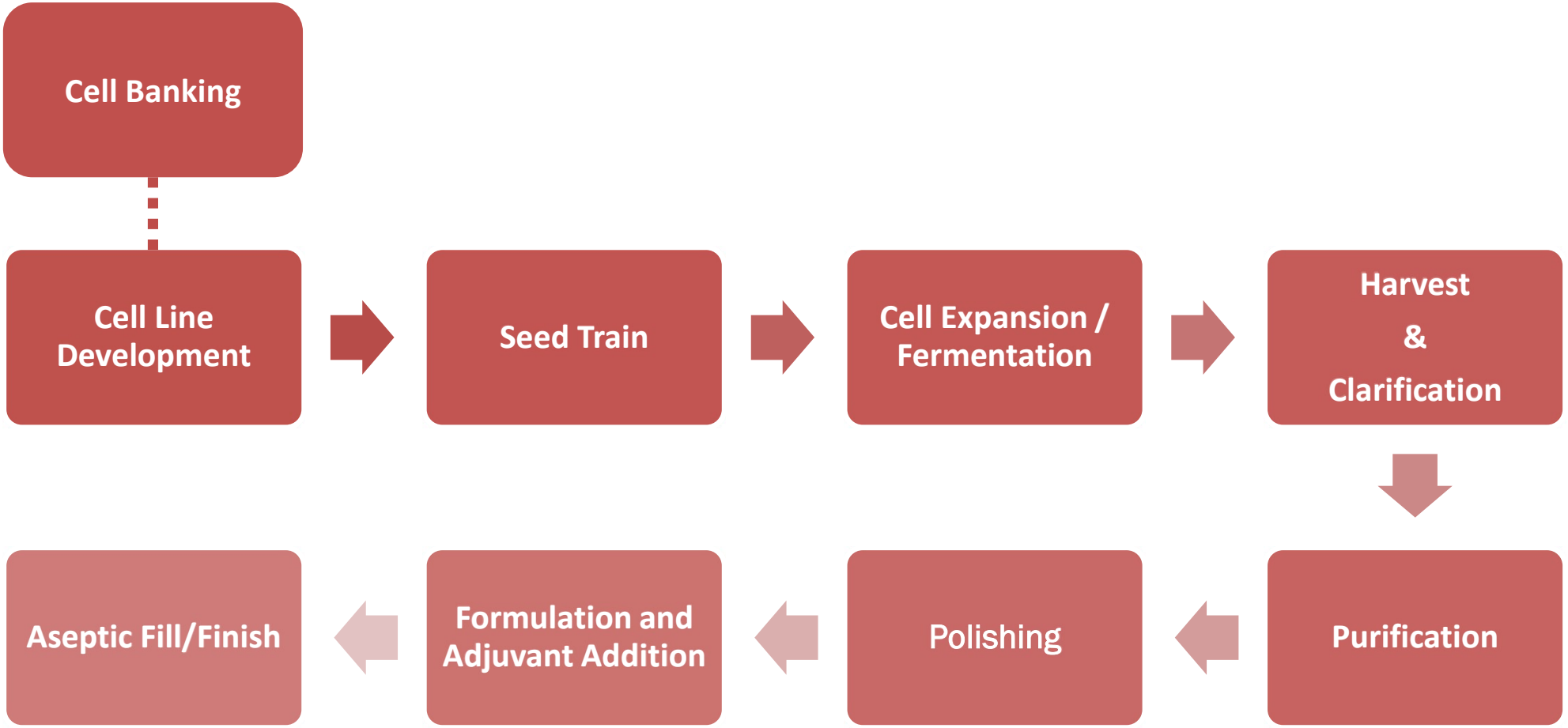
2.1 Process Flow for Recombinant Protein Vaccine Production



Slide 11

KY6 I think we can add a few more from Watson's slides
Karl Yu, 11/10/2024

3 Manufacturing Platforms Overview

3.1 Full Stainless Steel System Overview

Definition: *Traditional setup for biopharmaceutical manufacturing where all major components (bioreactors, tanks, piping) are made from stainless steel.*

Applicati

- **La** high
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- **Hi** quirir
- **Lo** stab
  pro
- **St** ntinu
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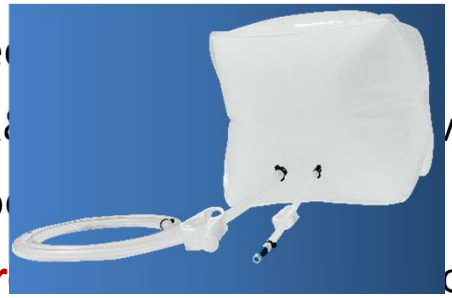
3.2 Stainless Steel: Pros and Cons

Pros	Cons
Durability: Long-lasting and withstands high temperatures and pressures.	**High Initial Cost**: Requires significant capital investment for setup.
Efficient Cleaning & Sterilization: CIP and SIP systems ensure thorough cleaning and maintain aseptic conditions.	**Complex Setup and Validation**: Installation and validation are time-consuming and costly.
Cost-Effective for Large Scale: Reusable for long product lifecycles, which reduces per-unit costs over time.	**Limited Flexibility**: Challenging for multi-product facilities due to lengthy changeover times.
Environmental Benefits: Lower waste compared to single-use systems, reducing environmental impact.	**Maintenance Needs**: Requires regular maintenance to prevent corrosion and avoid downtime.

3.3 Full Single-Use System Overview

Definition: *A manufacturing setup that utilizes disposable components such as bioreactors, tubing, bags, and filters, which are discarded after each batch or use.*



extensive containment is unnecessary, making waste disposal simpler.

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3.4 Single-Use: Pros and Cons

Pros	Cons
Flexibility: Quick setup and changeover make it ideal for multi-product facilities and small batches.	**Waste Generation**: High levels of plastic waste from disposable components, raising environmental concerns.
Lower Initial Capital Investment: Reduced need for stainless steel infrastructure, lowering initial setup costs.	**Limited Scale**: Not as suitable for very large-scale production due to the limitations in single-use bioreactor sizes.
Reduced Risk of Cross-Contamination: Disposable components eliminate the need for extensive cleaning and reduce contamination risk.	**Costly Consumables**: High ongoing costs for single-use bags, tubing, and filters, which must be replaced for each batch.
Simplified Validation and Cleaning Requirements: No CIP/SIP needed, saving time and reducing operational complexity.	**Material Compatibility Issues**: Some biopharmaceuticals may interact with plastic components, potentially affecting product quality.

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3.5 Hybrid System Overview

Definition: *Combines single-use and stainless steel components for a flexible and scalable manufacturing platform.*

Applications:

- **Multi-Product Facilities:** Ideal for facilities producing various recombinant vaccines, allowing quick changeovers between products with minimal downtime.
- **Transition from Clinical to Commercial Production:** Supports scalability by using single-use components for early-stage production and stainless steel for larger, commercial batches.
- **Seasonal or Variable Demand:** Suited for facilities handling vaccines with fluctuating demand, like flu vaccines, by enabling rapid scale-up with single-use and stable production with stainless steel.
- **Tech Transfer and Process Optimization:** Facilitates easier tech transfer by allowing new products to be integrated into existing workflows with minimal disruption.

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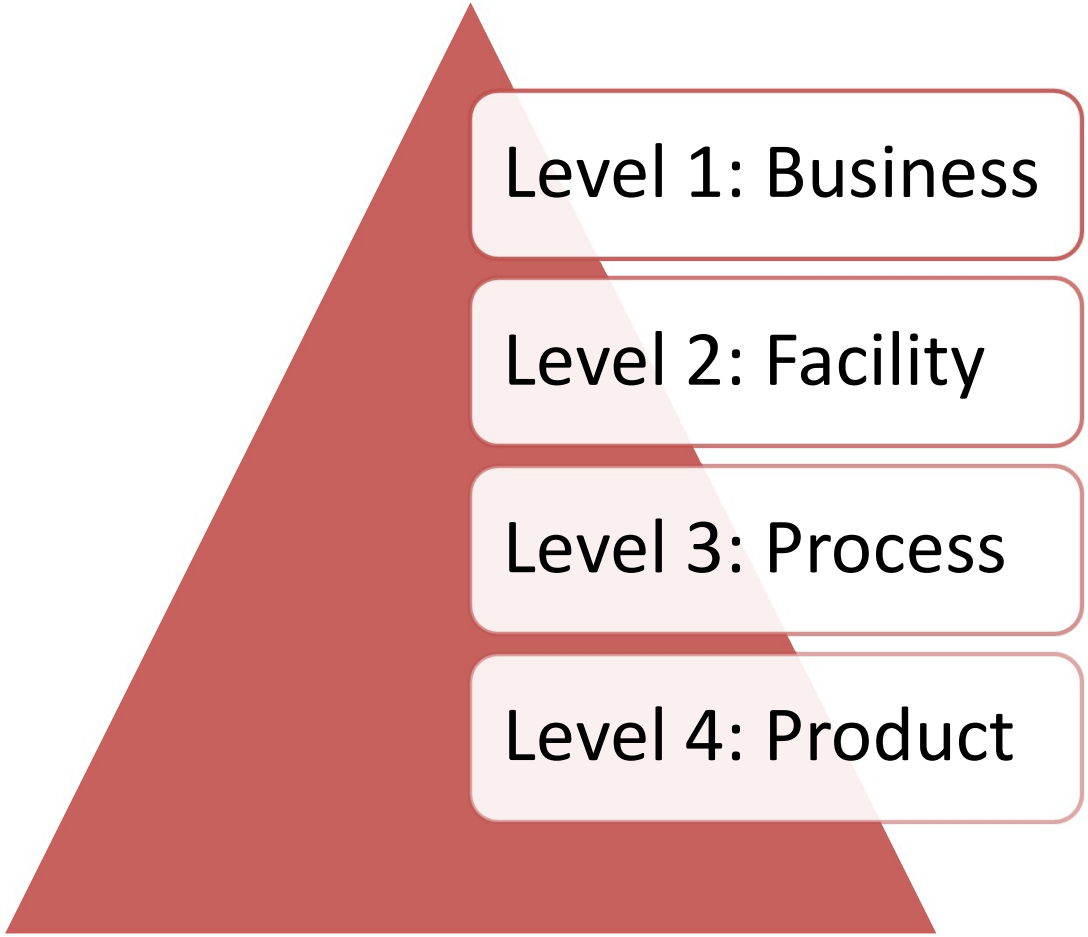
3.6 Hybrid Systems: Pros and Cons

Pros	Considerations/Challenges
Scalability and Flexibility: Easily adapts to different production scales, from clinical to commercial.	**Complex Integration**: Requires careful design and validation for compatibility between components.
Adaptability to New Technologies: Supports integration of advanced sensors, automation, and digital tools.	**Operational Complexity**: Staff need expertise in both single-use and stainless steel systems.
Optimized Space Usage: Efficient use of space with single-use in constrained areas and stainless steel for stable infrastructure.	**Supply Chain and Logistics**: Managing consumable and maintenance supply chains can be challenging.
Environmental Benefits: Reduces plastic waste by combining reusable components with disposables where needed.	**Cost Balance**: Requires thorough analysis to balance upfront and ongoing costs (CapEx vs. OpEx).

4 Choosing the Right System

4.1 Identify Key Decision Factors in Selecting the Optimal System



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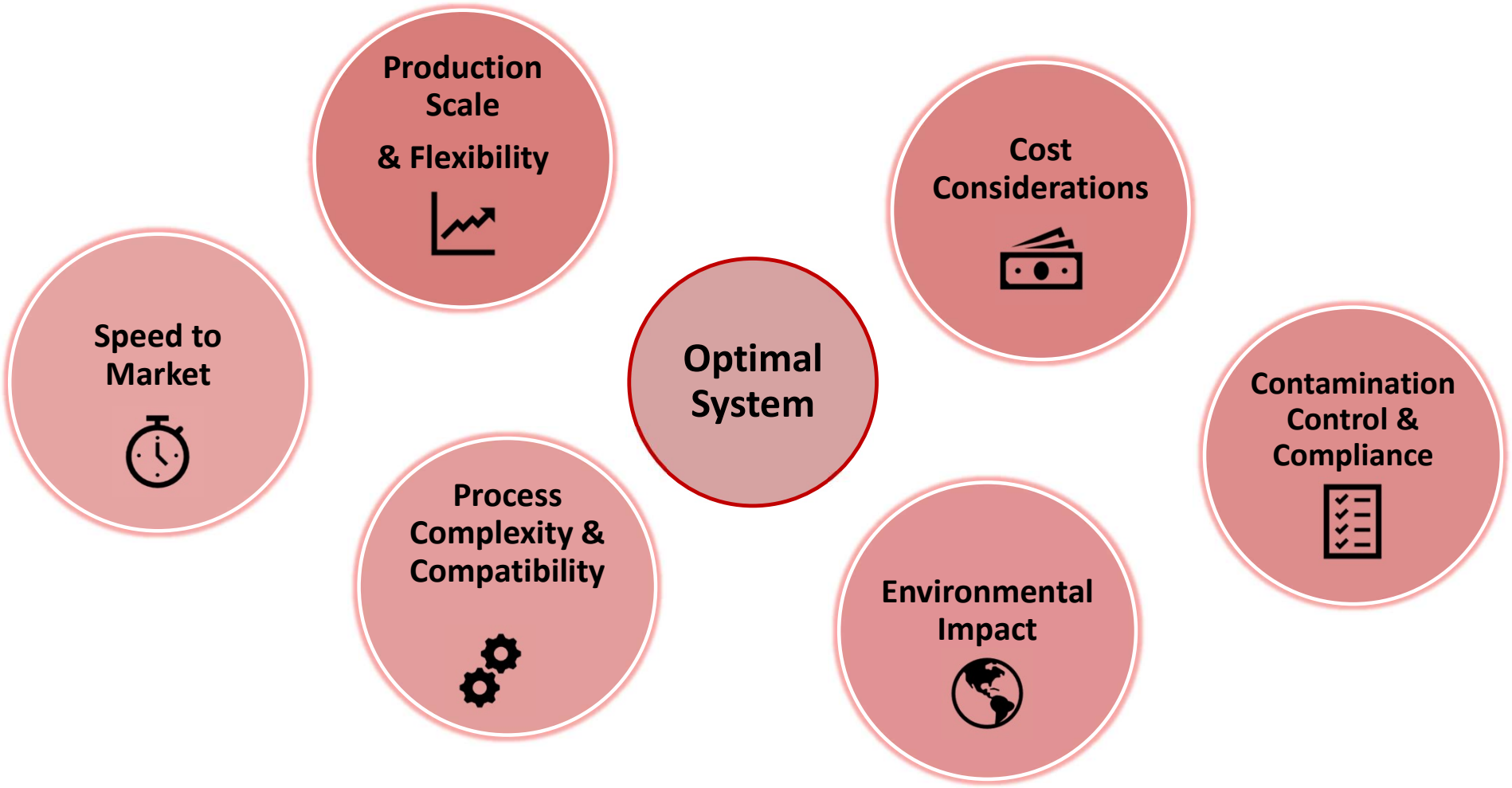
4.1 Identify Key Decision Factors in Selecting the Optimal System



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4.2 Key Decision Factors for Selecting Vaccine Manufacturing Systems

Decision Factor	Full Stainless Steel	Full Single-Use	Hybrid System
Production Scale & Flexibility	Best for large-scale, stable demand; less flexible.	Ideal for small/medium scale, quick changeovers.	Scalable; adaptable for varied batch sizes.
Cost Considerations	High initial cost, lower ongoing expenses; suits high volume.	Lower setup cost, higher consumable costs; good for short-term.	Balanced costs; lower capital with fewer consumables than single-use.
Contamination Control & Compliance	Requires CIP/SIP; good for single-product with rigorous cleaning.	Low risk; easy compliance with disposable components.	Combines disposable & reusable parts for balanced contamination control.
Environmental Impact	Less waste but high CIP/SIP resource use.	High plastic waste; sustainability concerns.	Lower waste than single-use; resource-conscious.
Process Complexity	Ideal for high pressure/temperature; broad compatibility.	Best for simpler processes; some material limitations.	Stainless steel for complex steps, single-use for simpler.
Speed to Market	Slower setup; longer validation and commissioning.	Rapid deployment; minimal setup and validation.	Balanced; fast setup with single-use, scalable with stainless steel.

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4.3 Additional Factors in System Selection

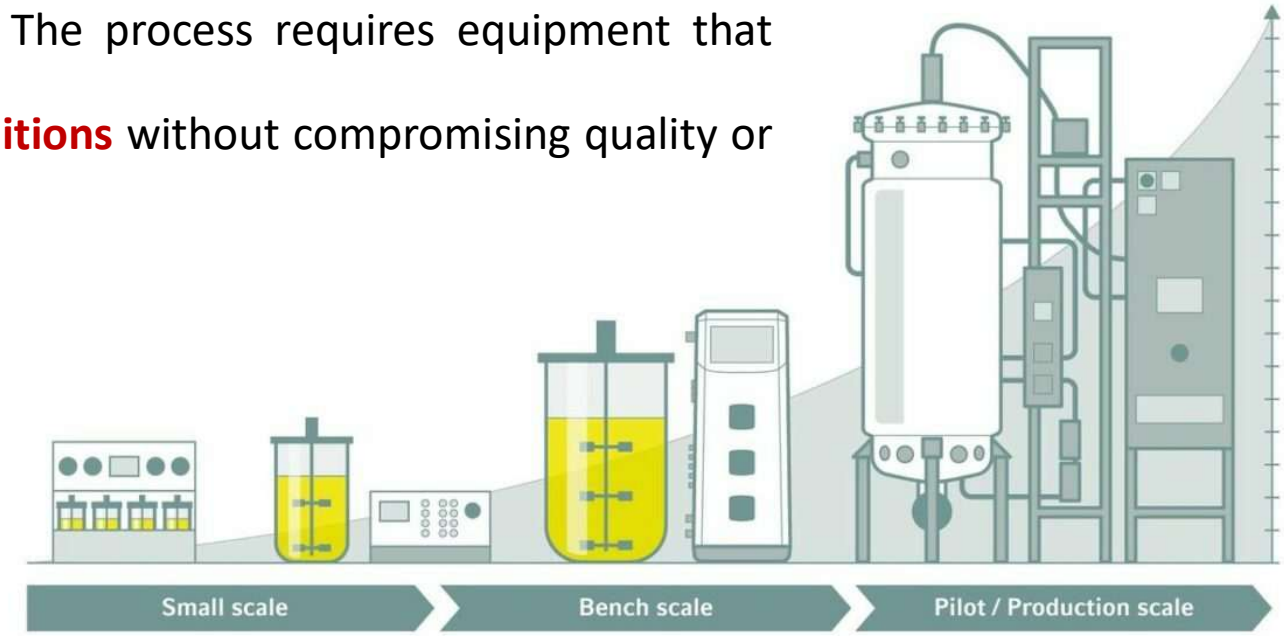
- **Product Lifecycle and Market Demand**
  - Short vs. Long Lifecycle
  - Demand Variability
- **Facility Layout and Space Constraints**
  - Physical footprint matters
- **Supply Chain & Logistics**
  - Dependence on steady component supplies affects stability
  - Robust supply chains are essential for continuity
- **Personnel Expertise & Training**
  - System complexity impacts training needs
- **Adaptability to Emerging Technologies**
  - Future-proofing is key
- **Long-Term Product Stability**
  - Consistent environmental control ensures product quality over time

5 Case Studies and Success Stories

5.1 Case Scenarios: Matching Vaccine Production Needs with the Right System

Case Scenario 1:

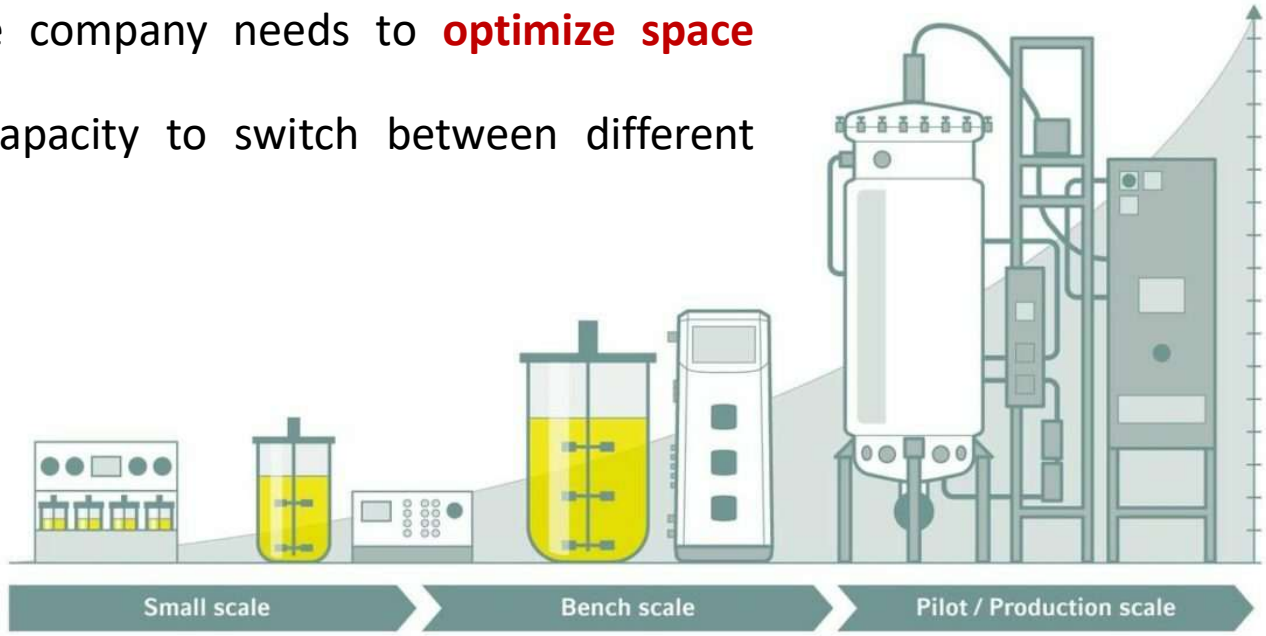
A facility is manufacturing a recombinant protein vaccine that involves **complex downstream processing**, including high-pressure chromatography and high-temperature sterilization. The process requires equipment that can **handle rigorous operating conditions** without compromising quality or sterility.



5.1 Case Scenarios: Matching Vaccine Production Needs with the Right System

Case Scenario 2:

A biopharmaceutical company produces a **wide range of vaccines**, including both recombinant protein vaccines and traditional inactivated vaccines, within a limited facility space. The company needs to **optimize space utilization** while maintaining the capacity to switch between different production scales and vaccine types.



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5.2 Success Stories: Global Projects

Customer:	Chengdu Westvac Biopharma Co., LTD
Product:	Recombination vaccine
Location:	Chengdu, Sichuan
Footprint:	8,000 m^2
Scope of Service:	CD/DD/3D, EPC, DS+DP+DPP equipment supply, AHU, inactivation, CQV, SCADA
Contract:	EPC
Feature:	Turn-key project Accelerated GMP Project Delivery

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5.2 Success Stories: Global Projects

Customer:	Uzi Ministry of Innovation Vaccine Project
Product:	Recombinant Covid-19 vaccine
Location:	Uzbekistan
Footprint:	3,000 m^2
Scope of Service:	CD/DD/3D, EPC, DS+DP+DPP equipment supply
Contract:	EPC
Feature:	Technology Transfer

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5.3 Summary of Key Points and Future Outlooks

- Each system—*stainless steel, single-use, and hybrid*—offers distinct advantages based on **specific production needs and goals**.
- It's essential to choose the process considering all aspects of the **business, facility, process, and product** perspectives.
- The primary objectives should focus on **ensuring safety, efficacy, quality, and cost-effectiveness**.
- Hybrid systems are increasingly used for **pandemic preparedness and rapid vaccine production**
- **Automation and digitalization** are set to improve future vaccine production timelines

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Tofflon Vision:

Smart Pharma Factory Builder