

Flexible Manufacturing of Vaccines

Millipore®

Preparation, Separation,
Filtration & Monitoring Products

Landscape of Vaccine Manufacturing

Diverse and Constantly Evolving

Market growth drivers

> 8%

Global growth rate of vaccine market



Human and veterinary vaccine needs are growing



Emerging & re-emerging diseases



Decentralization of vaccine manufacturing & tech transfers



New vaccine & manufacturing technologies

Challenges



Strong diversity in vaccine types, manufacturing processes & cost models



Old manufacturing processes & facilities



Funding processes



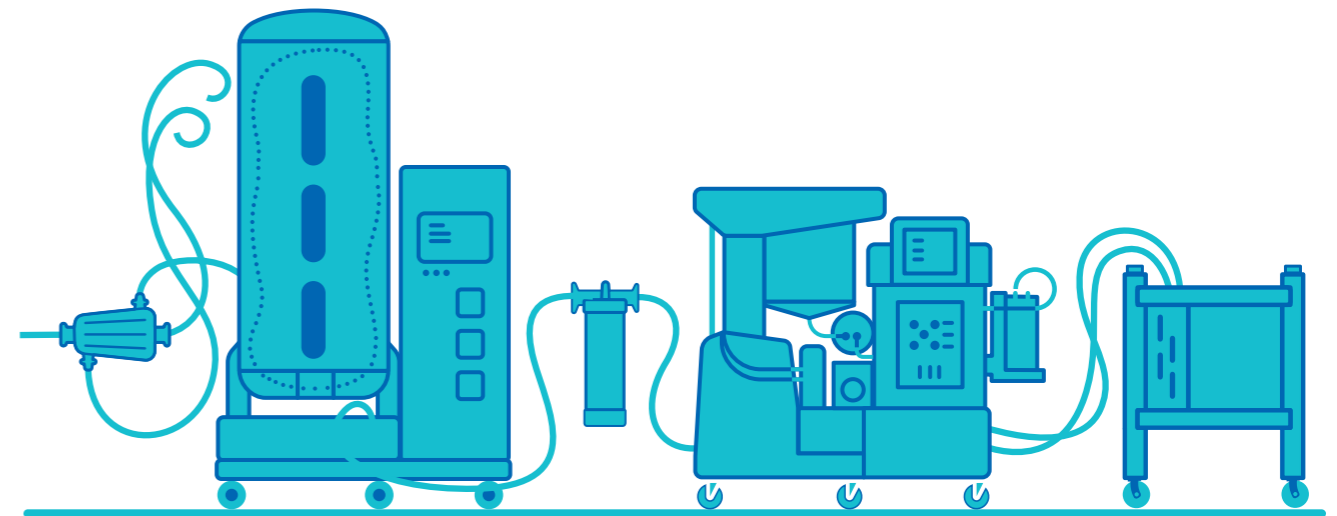
Pandemics and outbreaks are inevitable



What is Flexible Manufacturing?

Flexible Manufacturing: A production method that features single-use technologies that can adapt to changes and market demands.

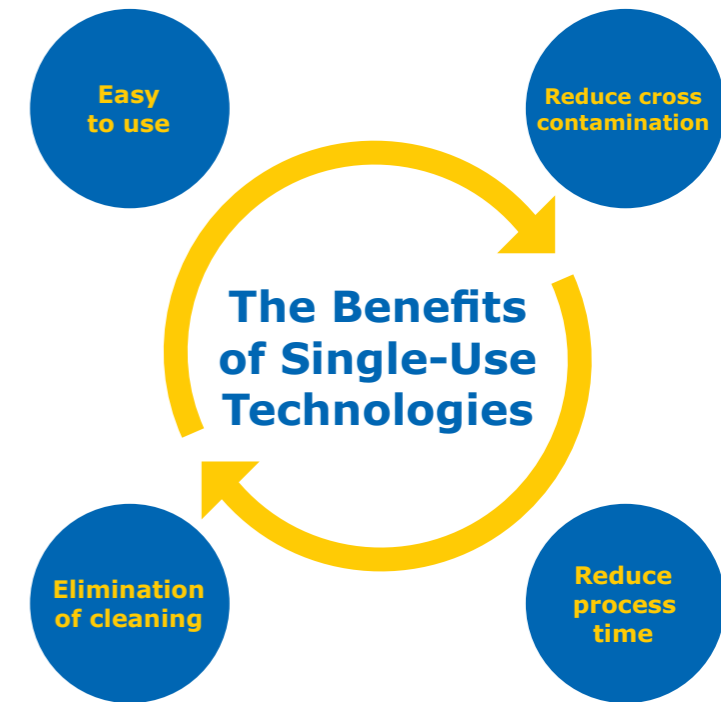
- Integration of single-use products in an existing facility
- Single-use components used in the final filling of vaccine product
- Full single-use manufacturing facility



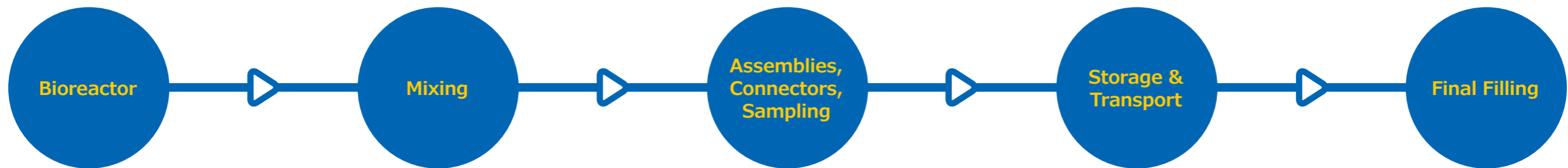
What are Single-Use Technologies?

Single-Use Technologies: May consist of bioreactors, mixers, connectors, storage bags, and tubing

- 1 Disposable** products intended for one-time use and then discarded
- Usually made from **plastic** materials that can be **presterilized** via gamma irradiation and are ready-to-use straight from packaging
- May be **rigid** (e.g., molded parts like connectors) or **flexible** (e.g., storage bags)

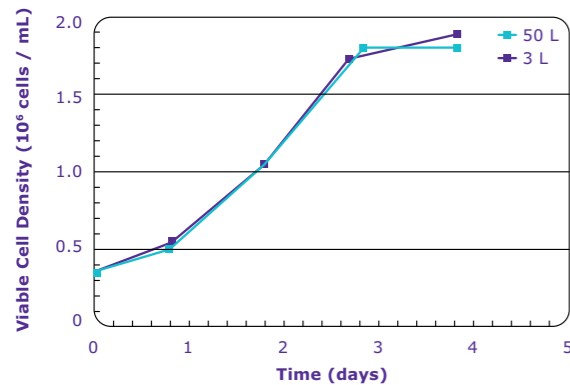


Single-Use Technologies in a Stainless Steel Process Upstream through Final Filling

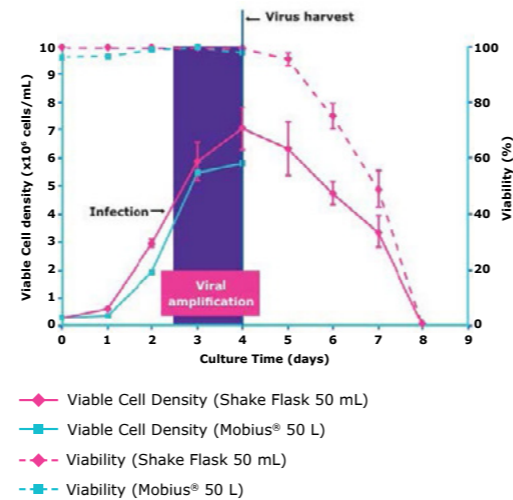


Scalable Mobius® Bioreactors Case Studies

MDCK 3 L to 200 L Scale-up



BHK21 3 L to 50 L Scale up



Proof of concept for scalable mammalian cell culture and virus production in Mobius® bioreactors



Mobius® 3L
Bioreactor



Mobius® 50L
Bioreactor



Mobius® 200L
Bioreactor



Mobius® 1000L
Bioreactor



Mobius® 2000L
Bioreactor

Advantages

- Easy scale up & process optimization
- Proven performance in virus production
- Provides 3 L to 2000 L full scale capability

Learn more about
vaccine production

Mobius® Single-Use Mixing Solutions Case Study

Comparison of stainless steel and single-use Mobius® Power MIX for the formulation of inactivated Poliovirus vaccine (50 L)

Total hard cost (USD)



Total soft cost (USD)



Total labor hours (h)



Cycle time (h/run)



Overall capacity (L/h)



Stainless Steel



Single-Use Mobius®
Power MIX

Mobius® single-use mixing solutions increase formulation mixing capacity by two-fold at a reduced cost compared to stainless steel



Single-Use Membrane Chromatography Case Study

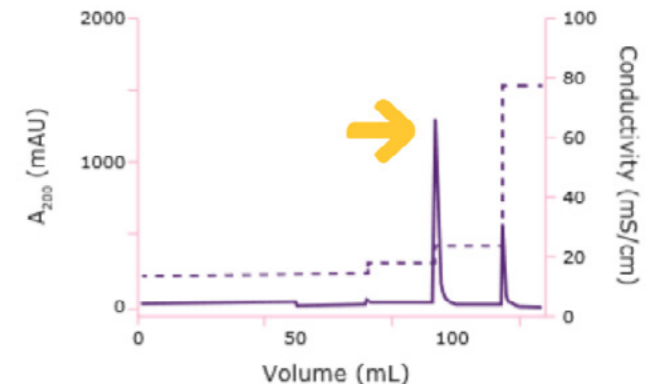
Natrix® membrane chromatography for cost-effective, single step purification

- Three-dimensional macroporous hydrogel structure provides high binding capacities and flow rates
- Natrix® HD-Q Membrane Adsorber: AEX with Quaternary amine functional group



NatriFlo® HD-Q
Membrane Adsorber

Adenovirus vector based Rabies vaccines purification with Natrix® HD-Q Membrane Adsorber



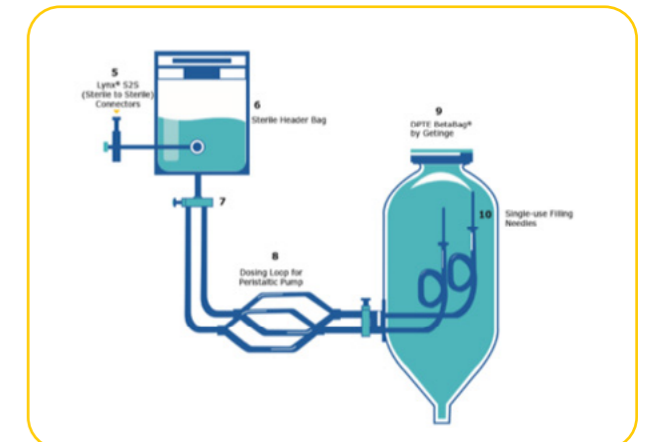
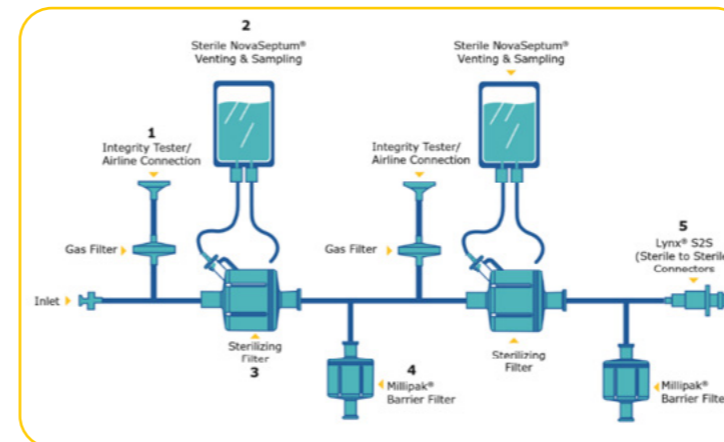
Separation of the adenovirus based rabies vaccine from impurities with 75-80% recovery

Single Use Within Final Filling

A Critical Step in Vaccine Manufacturing

Final filling is one of the most critical steps in the manufacturing of biologicals

- Stainless steel systems are robust, but not as flexible and responsive to adapt to the growing demand
- Certain vaccines require the maintenance of cold chain supply
- Multiproduct handling can be difficult
- Regulatory scrutiny
- Final filling validation and qualification increases complexity



Advantages of Single-Use Technology in Final Filling Capacity Increase and Time Reduction vs Stainless Steel

| | Traditional | Single use |
|-----------------------|---------------|---------------|
| Clean and set-up | 14 Hrs | <1 Hr |
| Cleaning validation | Extensive | Zero |
| Filling time | 24 hrs | 10 hrs |
| Average vials/hr | 3,000 | 10,000 |
| Aseptic connections | 50 | 0 |
| Operator training | 2 weeks | 2 days |
| Equipment utilization | 35% | 82% |
| Total time | 38 hrs | 12 hrs |

Single-use
final filling can
increase capacity
>40% and reduce
filling time
requirements

Final filling
assemblies
can be designed
to fit process
requirements

Establishing a New Manufacturing Facility

Challenges and Points to Consider

Challenges

- Initial budget might be limited
- Uncertainty when entering a new market
- Different vaccines have different processes
- Importance of creating an affordable vaccine product with profit margins
- Embracing the external landscape and potential unexpected demands and outbreaks

Points to consider when establishing a manufacturing facility

Budget

How to assess financial impact and gains of different options?
Cost impact in case of relocation/ repurposing?

Location

Is there an existing building?
Is “duplication” desired for other locations?
Possibility of relocation?

Vaccine Production Forecast

Single-product or multi-product plant?
How to match current production scale?
Capacity/scalability needs (up and down)?
Possibility to repurpose facility/eqpt?

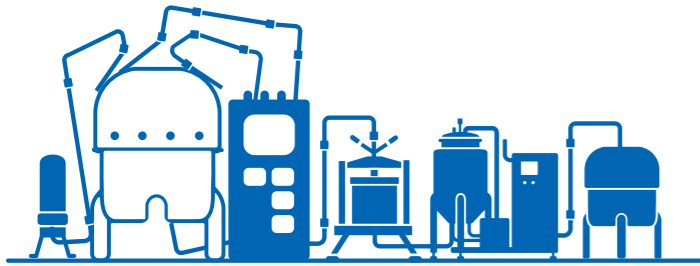
Time

Need for rapid deployment?
Expedited timing/constraints?

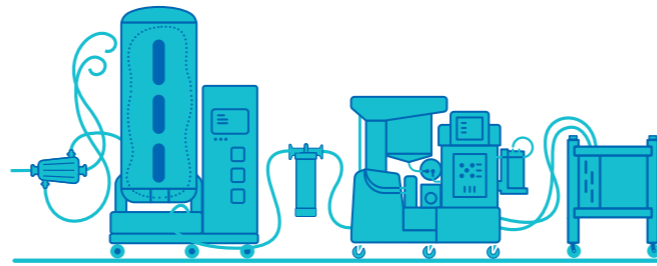
Benefits of a Single-Use Facility

Decreased Overall Expenditure, Time & Footprint

Traditional large vaccine manufacturing facilities



Manufacturing facility using single-use technologies



Traditional stainless facility

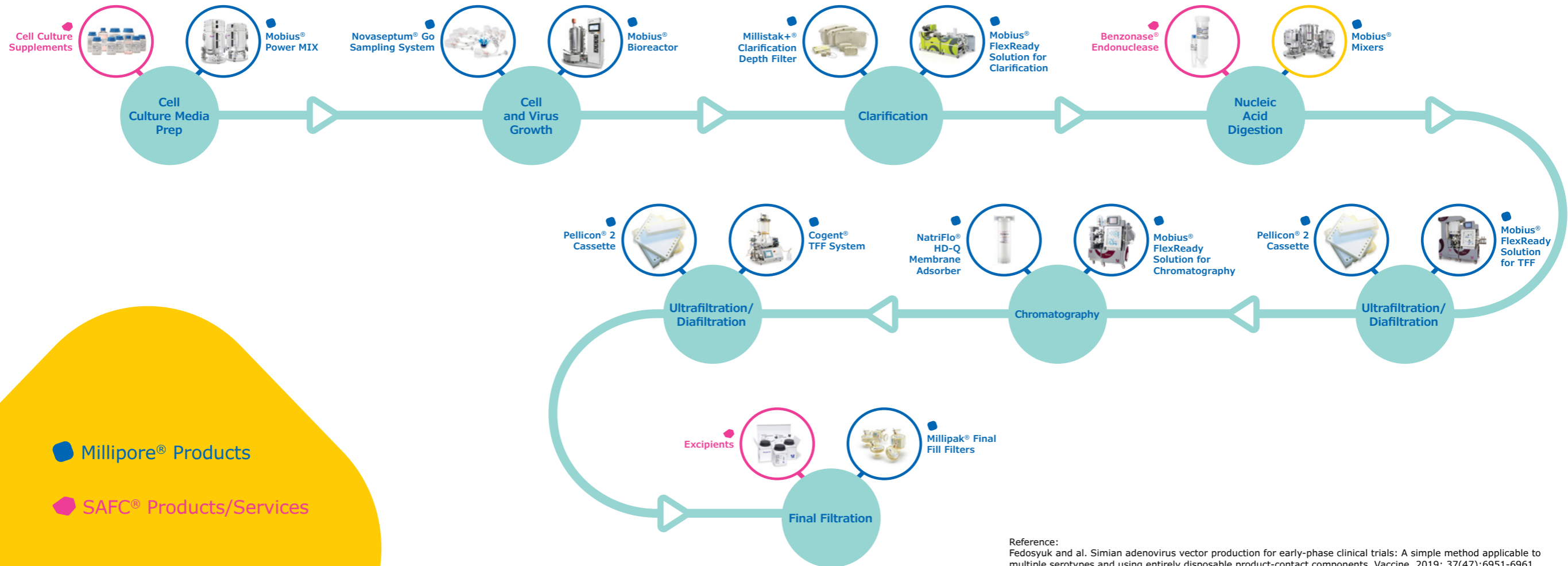
Single-use facility

| | Traditional stainless facility | Single-use facility |
|-------------------|--------------------------------|------------------------|
| Capex required | ~\$500M to \$1B | \$20-100M |
| Time to construct | 5-10 years | 1.5 years |
| Change over time | 4 weeks | 0.5 days |
| Footprint | ~>70,000 m ² | ~11,000 m ² |

Advantages of Single-Use Platforms

- Reduces capital
- Easy to use
- Reduces cross-contamination risk
- Faster production
- Reduces cleaning costs
- Flexibility to change scale or process
- Reduces time to market

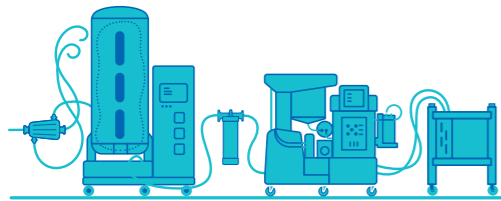
Single-Use Platform for Adenovirus Vector-Based Vaccine Manufacturing



Reference:
Fedosyuk and al. Simian adenovirus vector production for early-phase clinical trials: A simple method applicable to multiple serotypes and using entirely disposable product-contact components. Vaccine. 2019; 37(47):6951-6961

Cost Modeling of Vaccine Manufacturing

Single Use vs Traditional Stainless Steel, 40M Doses



Single-Use Process



Reduction in capital %



Capital charge



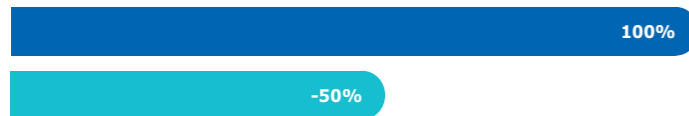
Increase in number of doses



Consumables



Labor



Total impact on cost/dose

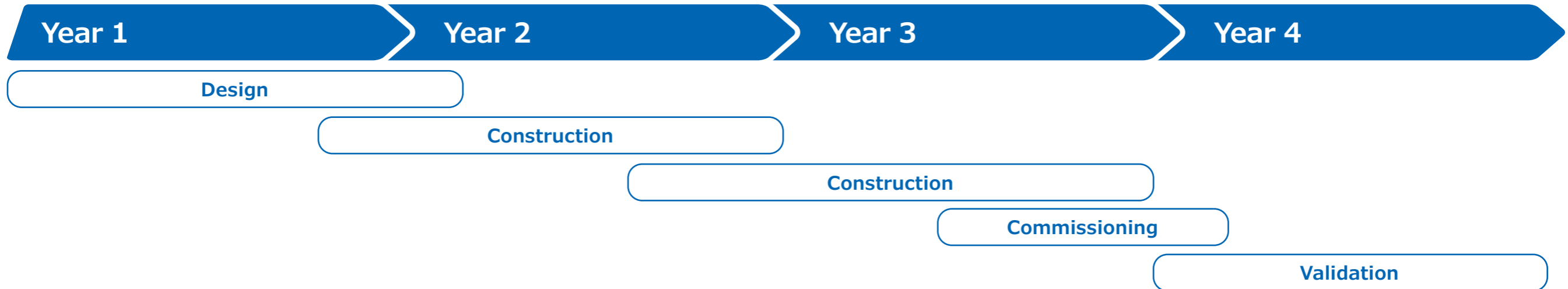


9M USD reduction in CAPEX and a 36% reduction on the cost of a single dose

Single-Use Facility Construction Steps

Facility Timeline

Stainless Steel Timeline



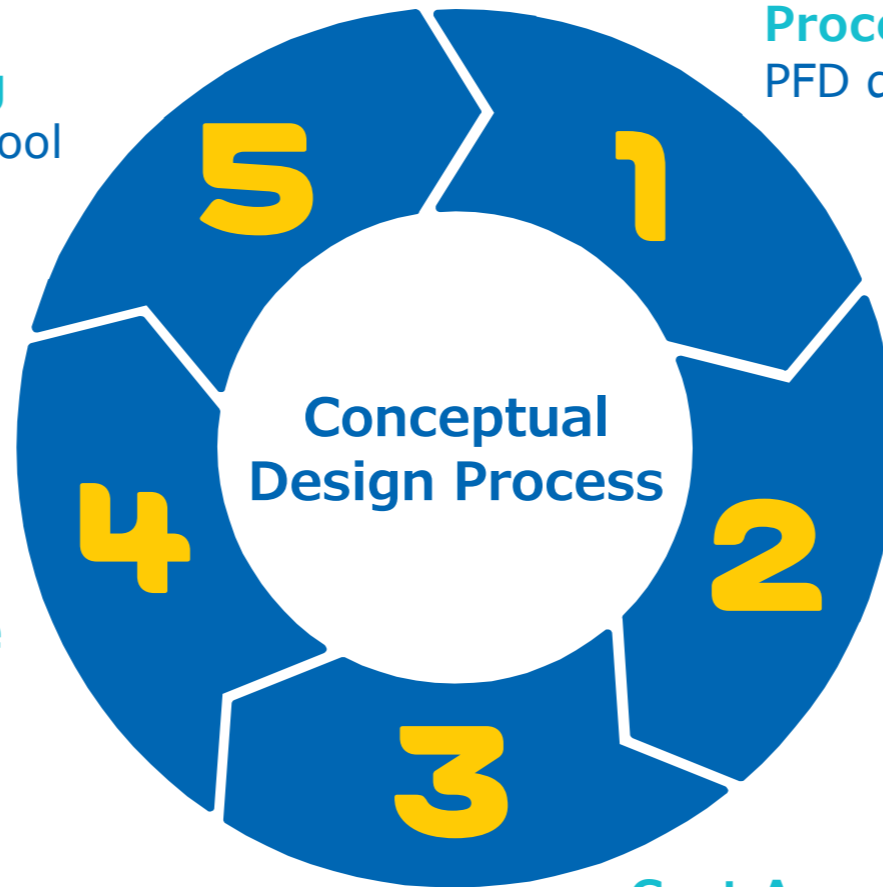
Single-Use Timeline



Conceptual Design Approach Single-Use Factory

Virtual Tour, 3D Modeling
Partnership with HAKOBIO tool

**Time Assessment of
the Conceptual Phase**
Detailed scheduling



Process Modeling & Design
PFD definition based on production modeling

Facility Layout
Product, personnel, process flows

Cost Assessment
CAPEX & OPEX assessment

Single-Use Facility Construction Prefabricated and Mobile Concept

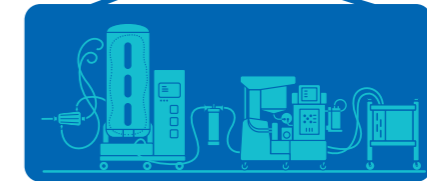
Demand for prefabricated modules

- Manufacturing site construction projects need to be expedited
- On-site validation can be complex and will require external resources



Prefabricated and portable PODS:

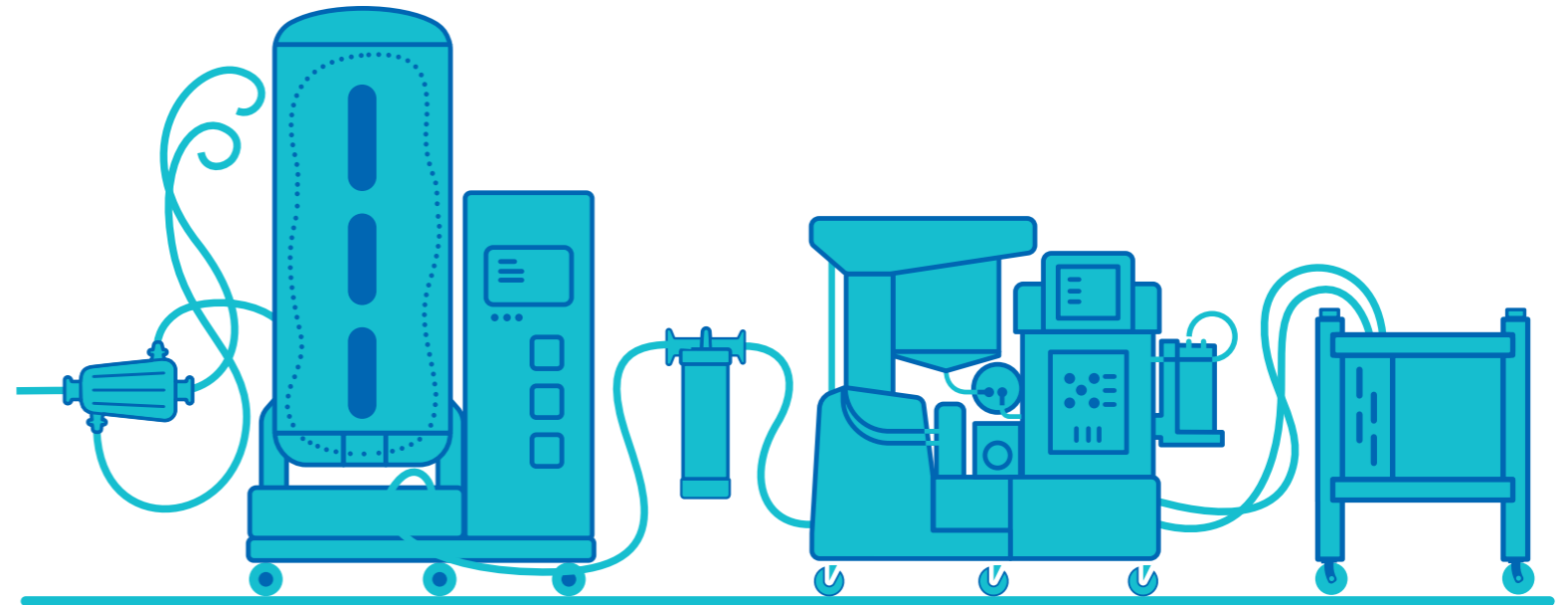
- Integrated
- Flexible
- Portable
- Scalable



Additional Resources on Flexible Manufacturing

Flexible manufacturing accelerates vaccine development and production to ensure that vaccines are available where and when they are needed most.

We can guide you through each step of your complex journey to establish a single-use facility.



For additional information, please visit
EMDMillipore.com/Vaccines

To place an order or receive technical assistance, please visit
EMDMillipore.com/contactPS

