MERCK

Flexible Manufacturing of Vaccines

Get Started

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

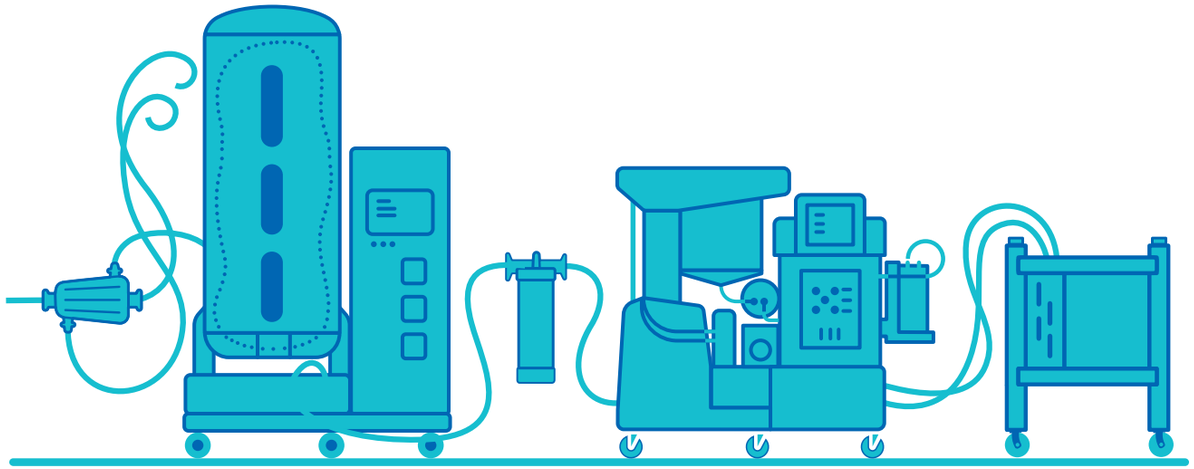
Funding processes

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.

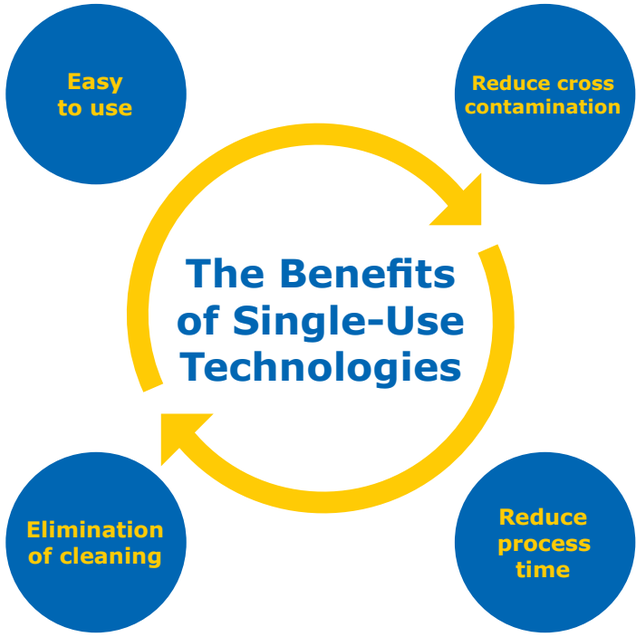
- Integration of single-use products in an existing facility
- Single-use components used in the final filling of vaccine product
- Full single-use manufacturing facility



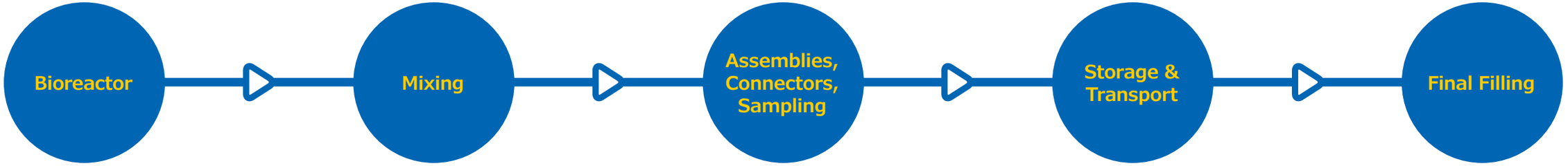
What are Single-Use Technologies?

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

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

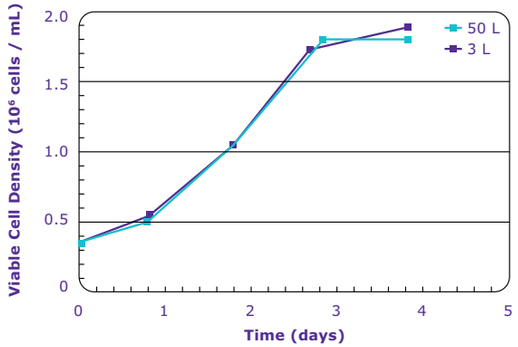


Single-Use Technologies in a Stainless Steel Process
Upstream through Final Filling

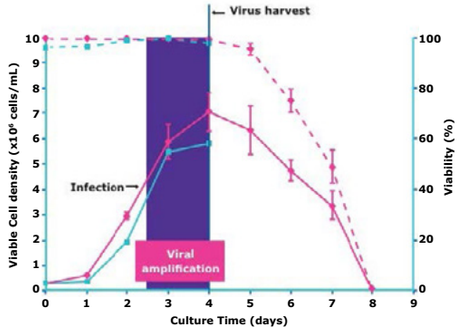


Scalable Mobius® Bioreactors
Case Studies

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

Scaling Influenza Vaccine Production

FMDV 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)

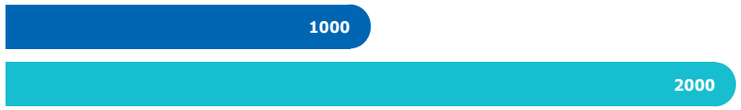
Mobius® single-use mixing solutions increase formulation mixing capacity by two-fold at a reduced cost compared to stainless steel

Total hard cost (USD)

Cycle time (h/run)

Total soft cost (USD)

Overall capacity (L/h)



Total labor hours (h)

Stainless Steel

Single-Use Mobius® Power MIX

Assumptions: 0.5mL/dose & cost of formulated bulk of 1.98$/mL, 20 batches/year, labor rate 5.50 USD/h

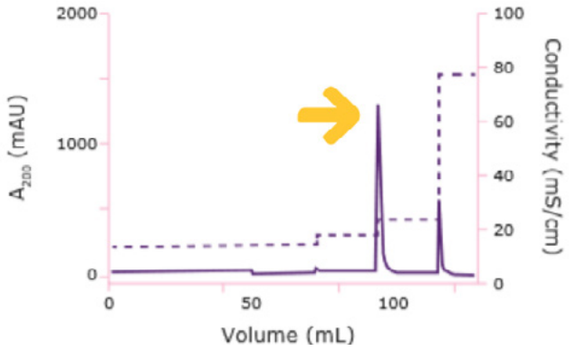
Mobius® Single-use Mixers

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

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



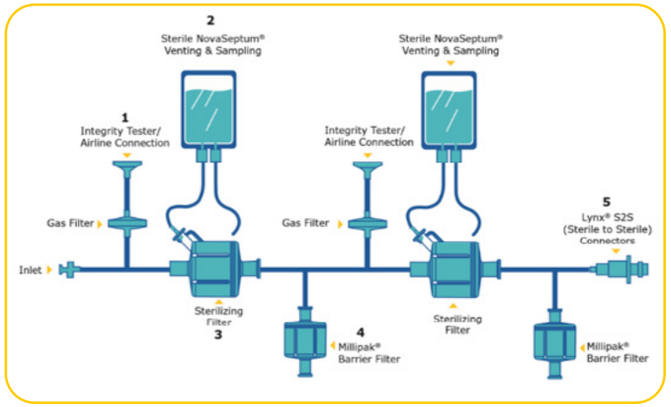
Separation of the adenovirus based rabies vaccine from impurities with 75-80% recovery

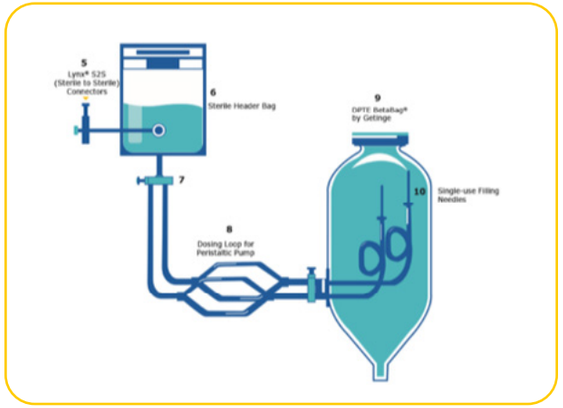
NatriFlo® HD-Q Membrane Adsorber

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





Mobius® Formulation and Final Fill

Final Filling Process Design Considerations

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

Reference: Jenness E, Gupta V (2011) Implementing a Single Use Solution for Fill–Finish Manufacturing Operations, BioProcess International Supplement, May 2011: 22-26.

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?

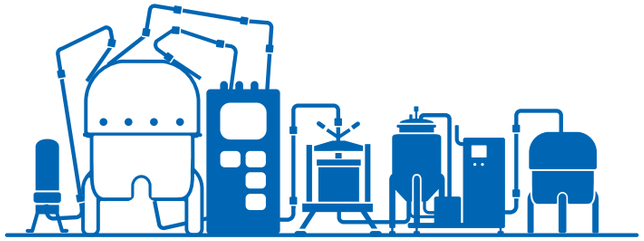
Time

Need for rapid deployment?

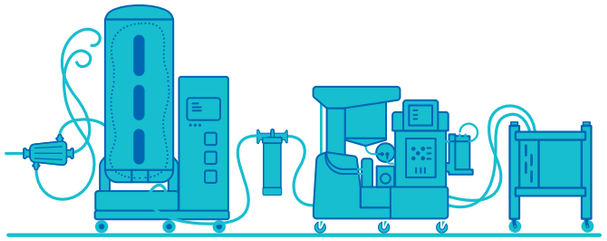
Expedited timing/constraints?

Benefits of a Single-Use Facility
Decreased Overall Expenditure, Time & Footprint

Traditional large vaccine manufacturing facilities



Manufacturing facility using single-use technologies

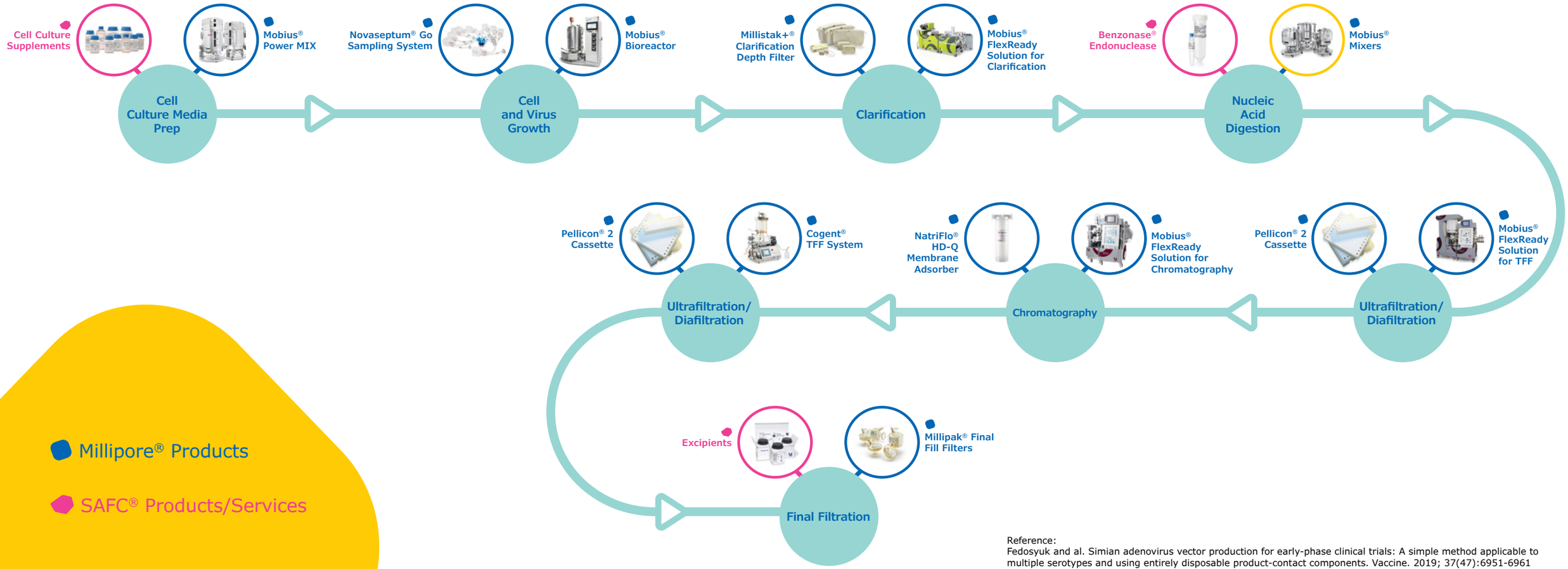


	Traditional stainless facility	Single-use facility
Capex required	**~$500M to $1B**	**$20-100M**
Time to construct	**5-10 years**	**1.5 years**
Change over time	**4 weeks**	**0.5 days**
Footprint	**~>70,000 m²**	**~11,000 m²**

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

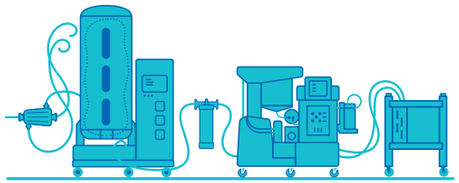


Millipore® Products

SAFC® Products/Services

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 %

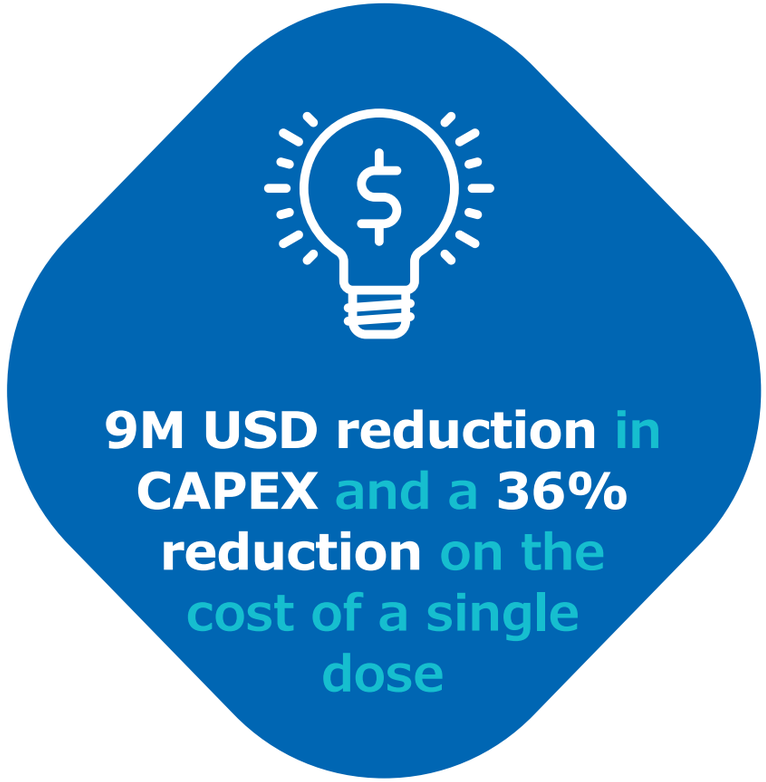
Capital charge

Increase in number of doses

Consumables

Labor

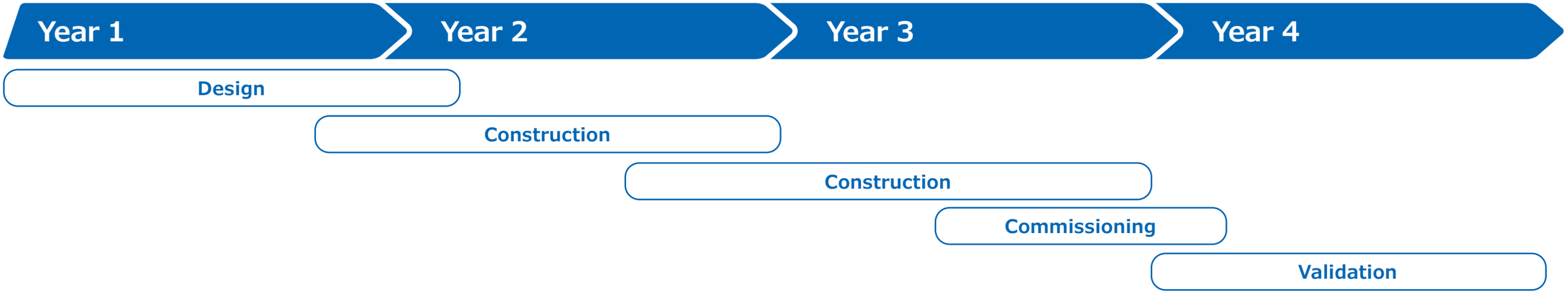
Total impact on cost/dose



The simulation was done with Merck technologies for Inactivated Polio vaccine (IPV).

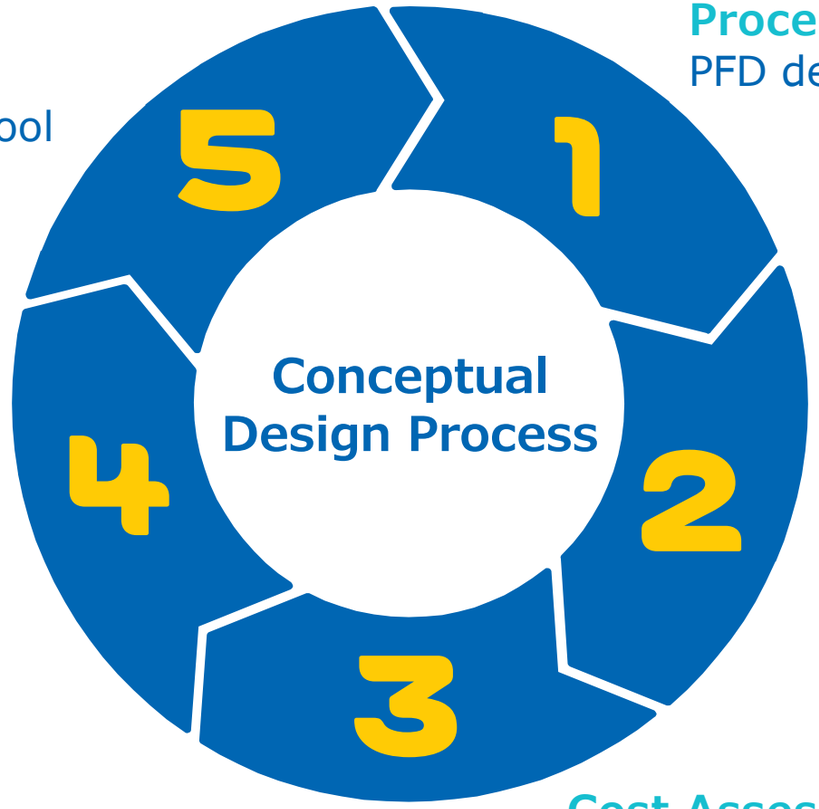
Single-Use Facility Construction Steps
Facility Timeline

Stainless Steel Timeline



Single-Use Timeline

Conceptual Design Approach
Single-Use Factory



Process Modeling & Design
PFD definition based on production modeling

Facility Layout
Product, personnel, process flows

Cost Assessment
CAPEX & OPEX assessment

Time Assessment of the Conceptual Phase
Detailed scheduling

Virtual Tour, 3D Modeling
Partnership with HAKOBIO tool

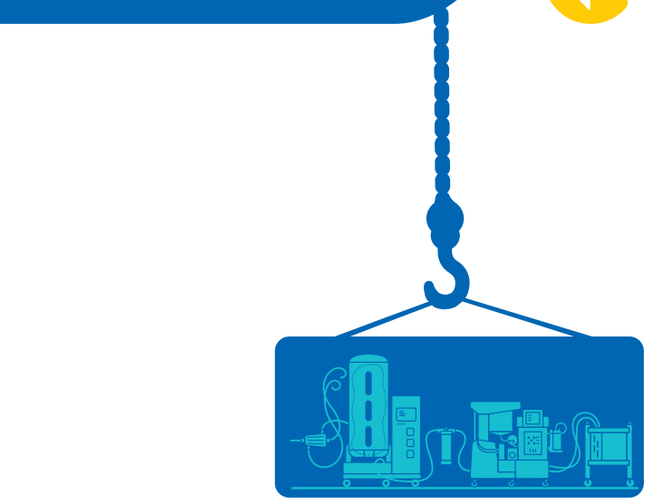
Single-Use Facility Construction
Prefabricated and Mobile Concept

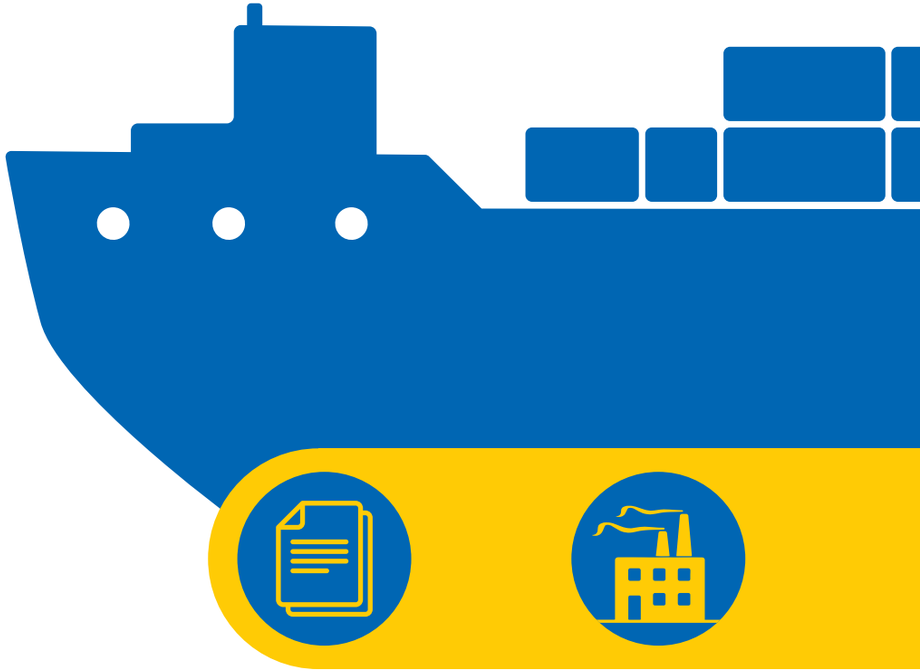
Demand for prefabricated modules

- 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





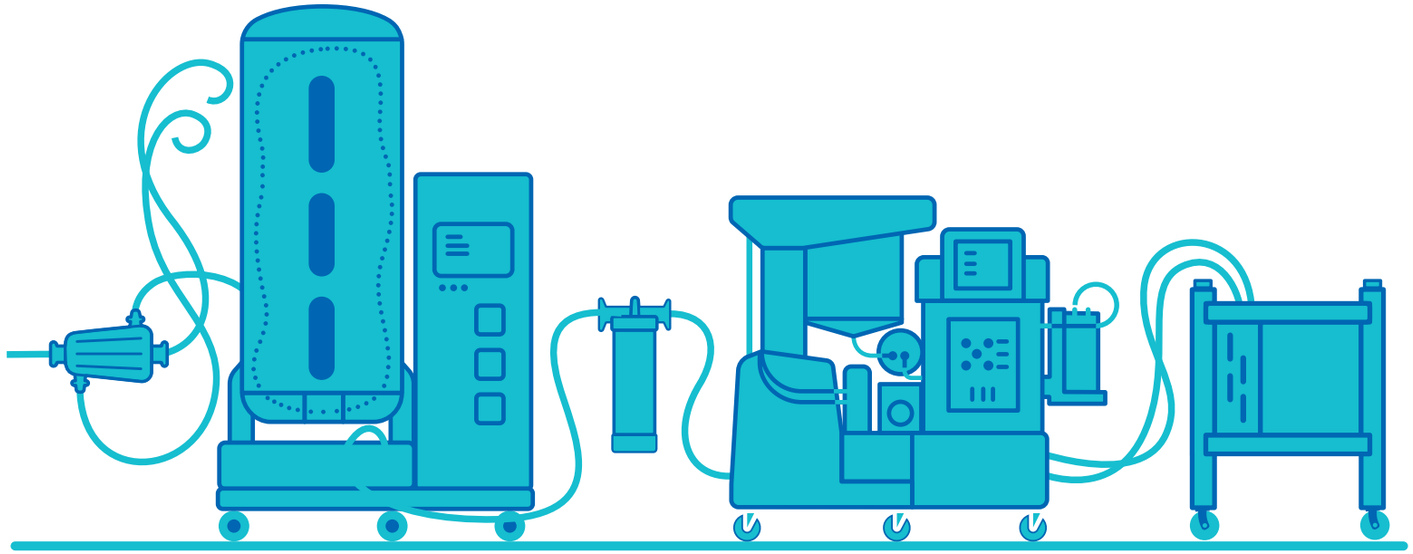
End-to-End Solutions

ICON Prefabricated Facility

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.



To learn more about Flexible Manufacturing, visit our vaccines website for more detailed information.

For additional information, please visit

MerckMillipore.com/Vaccines

To place an order or receive technical assistance, please visit

MerckMillipore.com/contactPS

Lit. No. MK_BR5360EN Ver 2.0