MilliporeSigma

Comprehensive solutions for your vaccine platforms

Process Development & Manufacturing

Millipore®
Expert Pharm/BioPharm
Products & CTDMO Services

SAFC®
Pharma & Biopharma
Raw Material Solutions

BioReliance®
Pharma & Biopharma
Manufacturing &
Testing Services

MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany.

Our Mission

vaccines, empowered

You want to scale and deliver your vaccine to the world quickly. Our collaborative global vaccine capabilities will take your innovation from pre-clinical to full-scale GMP-manufacturing efficiently, safely, and cost-effectively.

Discover how expertise—empowered by collaboration—can refine and overcome manufacturing challenges in all vaccine modalities/platforms.

Our Portfolio of Brands

MilliporeSigma has brought together the world's leading Life Science brands, so whatever your life science problem, you can benefit from our expert products and services.

Millipore®

The Millipore® portfolio from MilliporeSigma offers an ecosystem of industry-leading products and services, spanning preparation, separation, filtration and monitoring – all of which are deeply rooted in quality, reliability and time-tested processes. Our proven products, regulatory and application expertise are a strong foundation you can rely on to consistently perform at the highest level.

SAFC®

The SAFC® portfolio from MilliporeSigma offers customized and ready-to-use raw material solutions, backed by deep regulatory expertise. Our high-quality products and services are supported by an experienced and responsive team of raw material and regulatory experts who are committed to understand your requirements and provide tailored solutions that meet your exact needs.

BioReliance®

The BioReliance® portfolio from MilliporeSigma encompasses biopharmaceutical characterization, safety testing and process development, as well as clinical and commercial biomanufacturing. Our experienced teams and operational expertise make us the partner who supports you all the way and always has your vital goal in mind.

MilliporeSigma

Comprehensive Products & Services Portfolio

Key Capabilities to Increase Efficiency and Safety of Vaccines

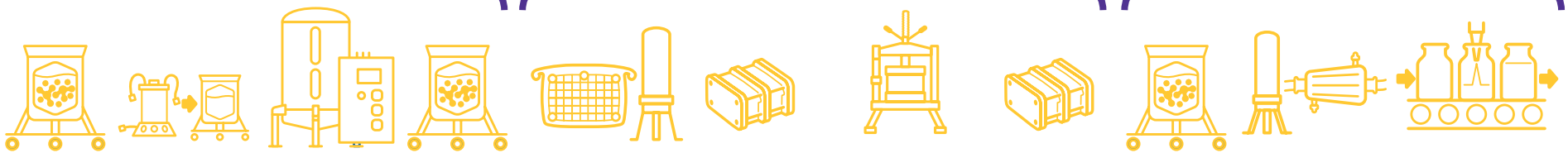
This document describes a range of products most commonly used for vaccine process development and manufacturing. Because each vaccine workflow is unique, however, selection of products most appropriate for your specific workflow requires testing and confirmation through MSAT support.

steps

MAKE
Produce antigen

PURIFY
Remove cell debris, virus and other impurities

FORMULATE
Final drug product



Media preparation | **Cell culture & propagation** | **(Inactivation)** | **DNA digestion** | **UF/DF** | **Chromatography** | **UF/DF** | **Formulation** | **Sterile Filtration** | **Final Fill**

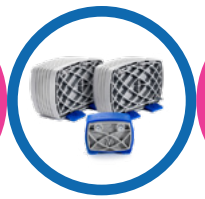
example products

Durapore® filters

Mobius® mixers

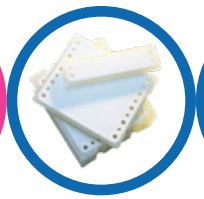
Mobius® bioreactors

Emprove® chemicals



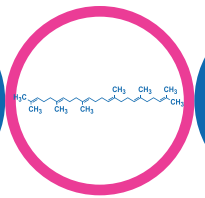
Millistak+® depth filters

Benzonase® endonuclease



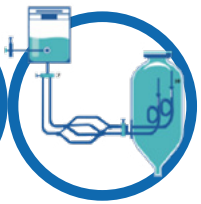
Pellicon® cassettes **Pellicon®** capsules

Eshmuno® and **Fractogel®** resins **Natrix®** Q membranes



Emprove® Stabilizers Sucrose, Squalane

Millipak® final fill filters



Mobius® single use assemblies

Testing Services | **CDTMO Services** | **Regulatory Expertise**

Millipore® SAFC® BioReliance®

Inactivated/Live-attenuated Vaccines

1

An **inactivated vaccine** (or killed vaccine) consists of **virus** particles that have been grown in culture and lose disease producing capacity but remain capable of raising immunogenicity.

2

The virus is either in the supernatant or cell lysis is required, followed by Benzonase® endonuclease. Formaldehyde/beta propiono lactone is used for inactivation, followed by purification of the virus using chromatography and TFF.

Process Challenges:
1. Virus purity
2. HCP, DNA clearance
3. Virus recovery

3

Examples of live-attenuated vaccine: VARIVAX® (MSD); examples of inactivated vaccines including: BBIBP-CorV (Sinopharm), Fluzone® (Sanofi).

Virus propagation is cell-culture based and common cell lines used are VERO, Per.c6, MDCK.

Production & Purification of Virus Based Vaccines

Inactivated/Live-attenuated Production Platform

Seed Train & Inoculation

- Durapore® 0.1 or 0.22 µm
- Millipore Express® SHR 0.1 µm, Millipore Express® SHF, Millipore Express® SHC
- Viresolve® barrier
- Single-use and filter validation services

- Upstream Chemicals and Supplements
- CellPrime® rTrypsin

- Raw materials testing
- Cell bank & virus seed production, testing & storage
- In-process characterization & testing

Cell growth/ Virus Production in Bioreactor

Cell Lysis & Nuclease Treatment

- Mobius® mixing systems

- Deviron® C16
- Tween® 20
- Benzonase® endonuclease

- Benzonase® ELISA kit II
- Residual Benzonase® testing
- In-process characterization & testing

Clarification

- Clarisolve® 60HX
- Millistak+® CE, HC/HC Pro
- Milligard® PES
- Polysep® II
- Single-use and filter validation services

- Biosafety lot release testing of crude virus harvest
- Biosafety testing of production control cells
- In-process characterization & testing

UF/DF

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing

Purification Chromatography (1~2 steps)

- Fractogel® TMAE/DEAE/ DMAE
- Eshmuno® Q resins
- Natrix® Q chromatography membranes

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- Viral Clearance Studies
- In-process characterization & testing

Virus Inactivation

- Mobius® mixing systems
- NovaSeptum® GO Sterile Sampling Systems

- Emprove® Chemicals: Formaldehyde

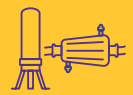
- Viral Clearance Studies
- In-process characterization & testing

UF/DF

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing



Formulation and Sterile Filtration

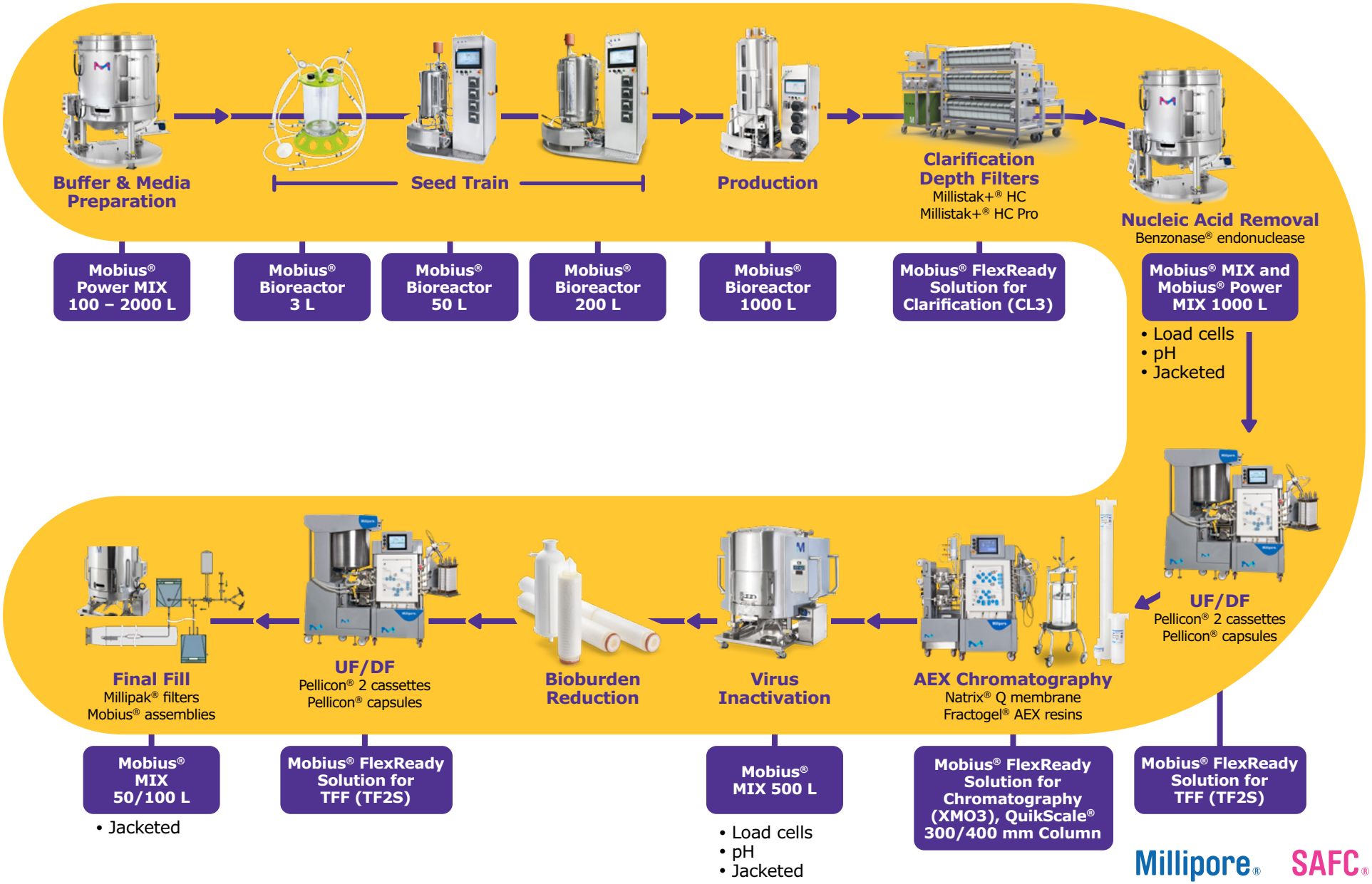
- Durapore® 0.22 µm filters
- Millipore Express® SHC filters
- Millipak® Final Fill filters
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Stabilizers, pH Adjusting agents, Surfactant, Isotonicity Agents, Preservatives, Adjuvants

- Analytical testing of final fill drug product
- In-process characterization & testing

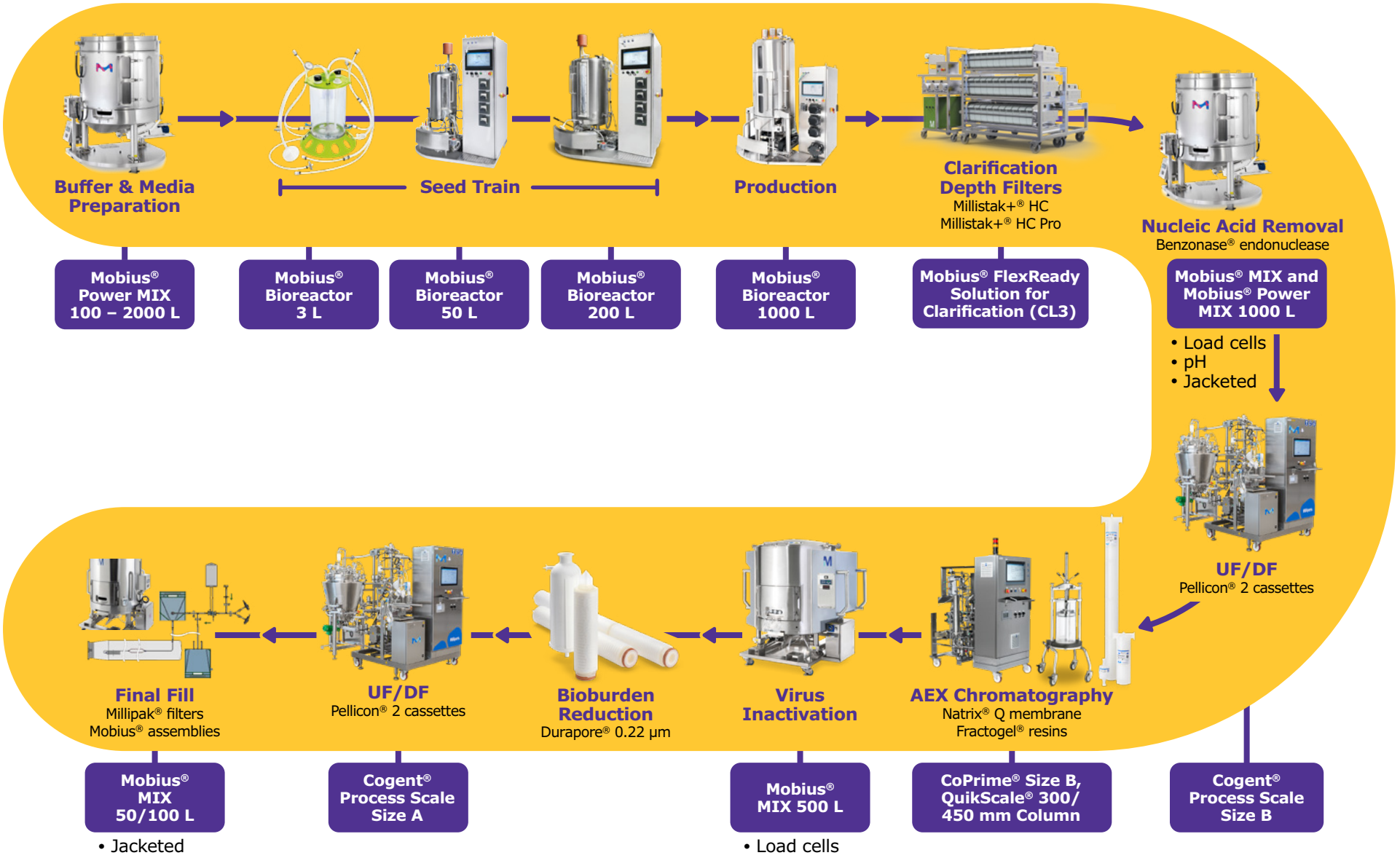
Assurance & Regulatory Compliance

Virus-Based Vaccines (Cell based) – 1000 L Single-Use



Millipore® SAFC®

Virus-Based Vaccines (Cell based) – 1000 L Hybrid*



*Mix of Single-Use & Multi-Use systems

Millipore® SAFC®

Subunit Vaccines

1

Subunit vaccines contain fragments of protein and/or polysaccharide from the pathogen, which are likely to produce a strong and effective immune response. By restricting the immune system's access to the pathogen in this way, the risk of side effects is minimized.

Depending on the characteristics of the protein to be expressed, cell lines such as mammalian, yeast, bacteria or insect cells can be used.

2

Following production of the antigen, purification includes clarification, IEX and/or HIC chromatography and TFF followed by sterile filtration.

3

Examples of subunit vaccines include: Acellular pertussis, Meningitis, Shingles, cell-based Influenza, and many COVID vaccines under development by some top sellers including FluBlok® (Sanofi), Shingrix® (GSK), Nuvaxovid (Novavax), ZifiVax™ (Longcom), etc.

Production & Purification of Protein Subunit Vaccines

Insect Cell Expression System

Media and Inoculum Preparation	Cell growth in Bioreactor and Virus Inoculation	Nucleic Acid Removal	Clarification	CEX Chromatography	UF/DF	AEX Chromatography	Virus Removal	UF/DF Formulation	Formulation and Sterile Filtration
• Durapore® 0.1 or 0.22 µm • Millipore Express® SHR 0.1 µm, Millipore Express® SHC or Millipore Express® SHF • Viresolve® barrier • Single-use and filter validation services	• Mobius® mixing systems • NovaSeptum® GO Sterile Sampling Systems	• Millistak+® C0HC/C0SP • Clarisolve® filters • Milligard® PES • Polysep® II • Single-use and filter validation services	• Eshmuno® CMX resin • Eshmuno® CPX resin	• Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes • Pellicon® capsules with Ultracel® 100-300 kDa membranes • Single-use and filter validation services	• Eshmuno® Q resins • Natrix® Q chromatography membranes	• Viresolve® NFR, Viresolve® Pro	• Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes • Pellicon® capsules with Ultracel® 100-300 kDa membranes • Single-use and filter validation services	• Durapore® 0.22 µm filters • Millipore Express® SHC filters • Millipak® Final Fill filters • Single-use and filter validation services
• Sf-RVN® Insect Cell Line • EX-CELL® CD Insect Cell Media • Upstream Chemicals and Supplements	• Benzonase® endonuclease		• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions		• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers, pH Adjusting agents, adjuvants
• Raw materials testing • Cell bank & virus seed production, testing & storage • In-process characterization & testing	• Benzonase® ELISA kit II • Residual Benzonase® testing • In-process characterization & testing	• Biosafety lot release testing of bulk harvest • In-process characterization & testing	• In-process characteriza-tion & testing	• In-process characteriza-tion & testing	• In-process characterization & testing	• Viral Clearance Studies • In-process character-ization & testing	• Biosafety, Analytical and Stability testing of purified bulk drug substance • In-process characteriza-tion & testing	• Analytical testing of final fill drug product • In-process characteriza-tion & testing

Assurance & Regulatory Compliance

Production & Purification of Protein Subunit Vaccines

CHO Cell Expression System

Media and Inoculum Preparation

- Durapore® 0.1 or 0.22 µm
- Millipore Express® SHR 0.1 µm, Millipore Express® SHC or Millipore Express® SHF
- Viresolve® barrier
- Single-use and filter validation services

- CHOZN® cell line
- Cellvento® CHO media
- EX-CELL® CHO media
- Upstream Chemicals and Supplements

- Raw materials testing
- Cell bank production, testing & storage
- In-process characterization & testing

Cell growth in Bioreactor

- Millistak+® HC/HC Pro
- Millistak+® Pod
- Clarisolve® filters
- Milligard® PES
- Polysep® II
- Single-use and filter validation services

- Biosafety lot release testing of bulk harvest
- In-process characterization & testing

Clarification

Capture Chromatography

- Eshmuno® S resins
- Fractogel® SO3 resins

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing

Virus Inactivation

- Mobius® mixing systems
- NovaSeptum® GO Sterile Sampling Systems

- Emprove® Chemicals: Surfactants (PS-80, TnBP)

- Viral Clearance Studies
- In-process characteriza-tion & testing

Polishing Chromatography

- Fractogel® TMAE/DEAE/DMAE
- Eshmuno® Q resins
- Natrix® Q chromatography membranes

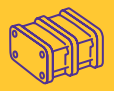
- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing

Virus Removal

- Viresolve® NFR, Viresolve® Pro

- Viral Clearance Studies
- In-process characterization & testing



UF/DF

- Pellicon® 3 cassettes with Biomax® / Ultracel® 10-50 kDa membranes
- Pellicon® capsules with Ultracel® 30 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- Biosafety, Analytical and Stability testing of purified bulk drug substance
- In-process characterization & testing

Formulation and Sterile Filtration

- Durapore® 0.22 µm filters
- Millipore Express® SHC filters
- Millipak® Final Fill filters
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers, pH Adjusting agents, adjuvants

- Analytical testing of final fill drug product
- In-process characteriza-tion & testing

Assurance & Regulatory Compliance

Protein Subunit Vaccines (CHO Cell-Based) – 1000 L Single-Use

Buffer & Media Preparation

Mobius® Power MIX 100 – 2000 L

Seed Train

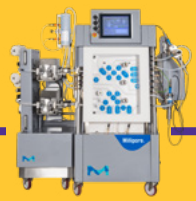
Mobius® Bioreactor 50 L

Production

Mobius® Bioreactor 1000 L

Clarification Depth Filters
Millistak+® HC
Millistak+® HC Pro

Mobius® FlexReady Solution for Clarification (CL3)



CEX Chromatography

Mobius® FlexReady Solution for Chromatography (XMO3), QuikScale® 300/400 mm Column

UF/DF
Pellicon® 3 cassettes
Pellicon® capsules

Mobius® FlexReady Solution for TFF (TF2S/TF3S)

AEX Chromatography
Natrix® Q membrane
Fractogel® EMD DEAE

Mobius® FlexReady Solution for Chromatography (XMO3), QuikScale® 300/400 mm Column

Virus Filtration
Viresolve® NFR
Viresolve® Magnus Vpro

Mobius® FlexReady Solution for Virus Filtration (VF3)

UF/DF
Pellicon® 3 cassettes
Pellicon® capsules

Mobius® FlexReady Solution for TFF (TF2S)

Sterile Filtration
Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF

Final Fill
Millipak® filters
Mobius® assemblies

Mobius® MIX 50/100 L

- Jacketed

Millipore®

Protein Subunit Vaccines (CHO Cell-Based) – 1000 L Hybrid*

Buffer & Media Preparation

Mobius® Power MIX 100 – 2000 L

Seed Train

Mobius® Bioreactor 50 L

Production

Mobius® Bioreactor 1000 L

Clarification Depth Filters
Millistak+® HC
Millistak+® HC Pro

Mobius® FlexReady Solution for Clarification (CL3)

CEX Chromatography

CoPrime® Size B, QuikScale® 300/ 450 mm Column

UF/DF
Pellicon® 3 cassettes

Cogent® Process Scale Size A

AEX Chromatography
Natrix® Q membrane
Fractogel® EMD DEAE

Virus Filtration
Viresolve® NFR
Viresolve® Magnus Vpro

Mobius® FlexReady Solution for Virus Filtration (VF3)

UF/DF
Pellicon® 3 cassettes

Cogent® Process Scale Size A

Sterile Filtration
Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF

Final Fill
Millipak® filters
Mobius® assemblies

Mobius® MIX 50/100 L
- Jacketed

CoPrime® Size B, QuikScale® 300/ 450mm Column

*Mix of Single-Use & Multi-Use systems

Millipore®

Virus-Like-Particle Vaccines (VLP)

1

VLPs contain repetitive, high density displays of viral surface proteins that present conformational viral epitopes able to elicit strong cell and B cell immune responses.

VLPs self assemble into structures morphologically resembling viruses.

Since VLPs cannot replicate, they provide a safer vaccine methodology and can be produced in a variety of cell culture systems (yeast, insect, bacteria) against different strains.

2

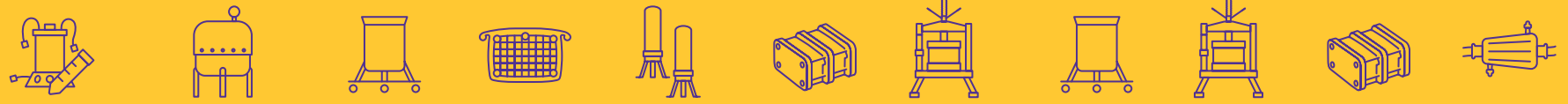
After VLP production, cells are harvested and separated into a pellet prior to being disrupted/lysed for the release of VLPs. The lysate is subsequently clarified. Further purification involves the use of UF/DF, chromatography, inactivation/removal VLP, final formulation and final sterilizing filtration.

3

Examples of VLP vaccines include:
Engerix® (Hepatitis B from GSK),
GARDASIL®9 (HPV from MSD)

Production & Purification of VLP-Based Vaccines

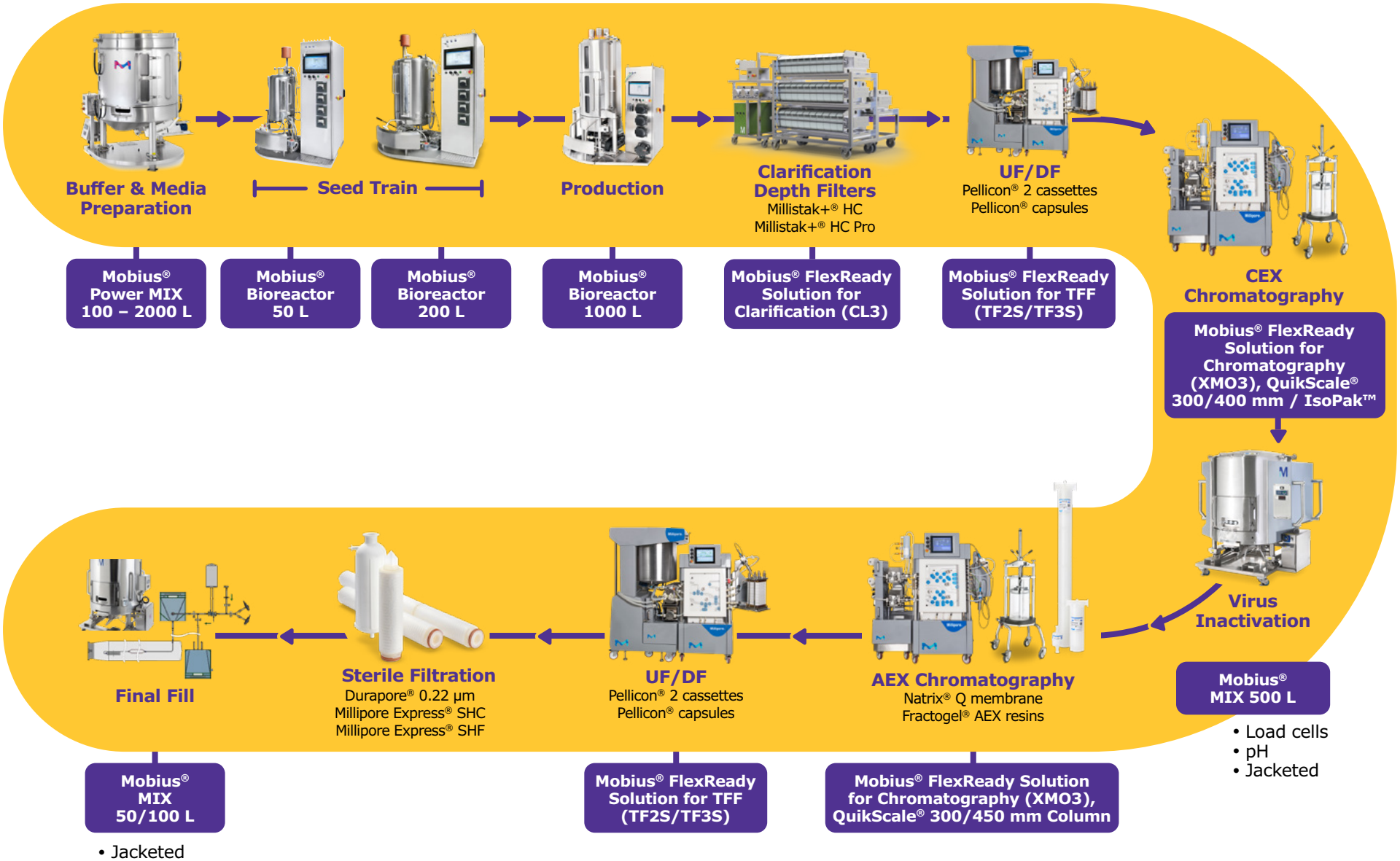
Insect Cell Expression System



Media and Inoculum Preparation	Cell growth in Bioreactor and Virus Inoculation	Nucleic Acid Removal	Clarification	Bioburden Reduction	UF/DF	Purification Chromatography	Baculovirus Inactivation	Polishing Chromatography	UF/DF	Formulation and Sterile Filtration
• Durapore® 0.1 or 0.22 µm • Millipore Express® SHR 0.1 µm • Viresolve® barrier • Single-use and filter validation services	• Mobius® Mixing systems • NovaSeptum® GO Sterile Sampling Systems	• Prostak™ Microfiltration Modules (0.1 - 0.65 µm) • Pellicon® 2 0.1-0.65 µm cassettes with Durapore® membranes • Polygard® CN, CR • Clarigard® filters • Clarisolve® depth filters • Millistak+® CE, HC/HC Pro • Single-use and filter validation services	• Millipore Express® SHC and Millipore Express® SHF • Durapore® 0.22 µm or 0.45 µm filters • Milligard® PES filters	• Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes • Pellicon® capsules with Ultracel® 100-300 kDa membranes • Single-use and filter validation services	• Fractogel® TMAE/DEAE/ DMAE • Eshmuno® Q resins • Natrix® Q chromato-graphy membranes	• Mobius® mixing systems • NovaSeptum® GO Sterile Sampling Systems	• Fractogel® TMAE/DEAE/ DMAE • Eshmuno® Q resins • Natrix® Q chromatography membranes	• Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes • Pellicon® capsules with Ultracel® 100-300 kDa membranes • Single-use and filter validation services	• Durapore® filters • Millipore Express® SHC filters • Millipak® Final Fill filters • Single-use and filter validation services
• Sf-RVN® Insect Cell Line • EX-CELL® CD Insect Cell Media • Upstream Chemicals and Supplements	• Benzonase® endonuclease			• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Surfactants (e.g. PS-80, TnBP)	• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers • Cleaning-In-Place solutions	• Emprove® Chemicals: Buffers, Stabilizers, pH, Surfactant, Isotonicity Agents, Adjuvants
• Raw materials testing • Cell bank & virus seed production, testing & storage • In-process characterization & testing	• Benzonase® ELISA kit II • Residual Benzonase® testing • In-process characteriza-tion & testing	• Biosafety lot release testing of bulk harvest • Biosafety testing of production control cells • In-process char-acterization & testing	• In-process characteriza-tion & testing	• In-process character-ization & testing	• Viral Clearance Studies • In-process characteriza-tion & testing	• Viral Clearance Studies • In-process characteriza-tion & t esting	• In-process characteriza-tion & testing	• Biosafety, Analytical and Stability testing of purified bulk drug substance • In-process characteriza-tion & testing	• Analytical testing of final fill drug product • In-process characteriza-tion & testing

Assurance & Regulatory Compliance

Virus-Like Particle Vaccines (Insect Cell-Based) – 1000 L Single-Use



Millipore®

Virus-Like Particle Vaccines (Insect Cell-Based) – 1000 L Hybrid*

Buffer & Media Preparation

Mobius® Power MIX 100 – 2000 L

Seed Train

Mobius® Bioreactor 50 L

Mobius® Bioreactor 200 L

Production

Mobius® Bioreactor 1000 L

Clarification Depth Filters
Millistak+® HC
Millistak+® HC Pro

Mobius® FlexReady Solution for Clarification (CL3)

UF/DF
Pellicon® 2 cassettes

Cogent® Process Scale Size B

Chromatography CEX

CoPrime® Size B, QuikScale® 300 mm Column

Virus Inactivation

Mobius® MIX 500 L

- Load cells
- pH
- Jacketed

AEX Chromatography
Natrix® Q membrane
Fractogel® AEX resins

CoPrime® Size B, QuikScale® 300/450 mm Column

UF/DF
Pellicon® 2 cassettes

Cogent® Process Scale Size A

Sterile Filtration
Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF

Final Fill

Mobius® MIX 50/100 L

- Jacketed

*Mix of Single-Use & Multi-Use systems

Millipore®

Viral Vector Vaccines – Adenovirus Vaccines

1

A live vector vaccine is a vaccine that uses a weakened or harmless microorganism to transport pieces of antigen to stimulate an immune response. Common viral vectors are adenovirus, canarypox, lentivirus, and alphavirus.

The vectors deliver genetic materials into human cells, and instruct them to make antigen, which then trigger an immune response. Viral vectors are genetically modified to have non-replicating viral vectors (e.g. adenovirus) and replicating viral vectors (e.g. weakened Measles).

2

Typical viral vectors purification process included cell harvest followed by cell lysis and nucleic acid treatment. Subsequent steps including UF/DF, chromatography, final sterilizing filtration may or may not be used, depending if the size of vector is too large for filtration. In this case, closed or aseptic manufacturing practices must be followed for large vectors.

3

Viral vector vaccines include: ERVEBO® Ebola Vaccine (MSD), Vaxzevria™ (Oxford/AstraZeneca)

Production & Purification of Viral Vector Vaccines

Adenovirus Production Platform

Media and Inoculum Preparation

- Durapore® 0.1 or 0.22 µm
- Millipore Express® SHR 0.1 µm, Millipore Express® SHC or Millipore Express® SHF
- Viresolve® barrier
- Single-use and filter validation services

- Upstream Chemicals and Supplements

- Raw materials testing
- Cell bank & virus seed production, testing & storage
- In-process characterization & testing

Cell growth in Bioreactor and Virus Inoculation

- Millistak+® HC Pro C0SP, Millistak+® HC C0HC
- Clarisolve® filters
- Milligard® PES filters
- Single-use and filter validation services

- In-process characterization & testing

Clarification

- Mobius® Mixing systems
- NovaSeptum® GO Sterile Sampling Systems

- Emprove® Chemicals: Surfactants e.g. High Pure PS-80 and PS-20, Deviron® C-16
- Benzonase® endonuclease

- Biosafety lot release testing of crude virus harvest including Replication competent Adenovirus testing (RCA)
- Biosafety testing of production control cells
- Benzonase® ELISA kit II
- Residual Benzonase® testing
- In-process characterization & testing

Cell Lysis & Nuclease Treatment

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing

UF/DF

- Natrix® Q chromatography membranes
- Fractogel® TMAE/ DEAE/DMAE
- Eshmuno® Q resins

- Emprove® Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- Viral Clearance Studies for inactivation/ removal of enveloped virus (such as large pore filters, or low pH and solvent/detergent treatment)
- In-process characterization & testing

Virus Purification

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

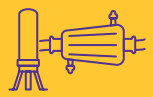
- Biosafety, analytical and stability testing of purified bulk drug substance including Replication competent Adenovirus testing (RCA)
- In-process characterization & testing

UF/DF

- Millipore Express® SHC
- Durapore® filters
- Millipak® Final Fill filters
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers

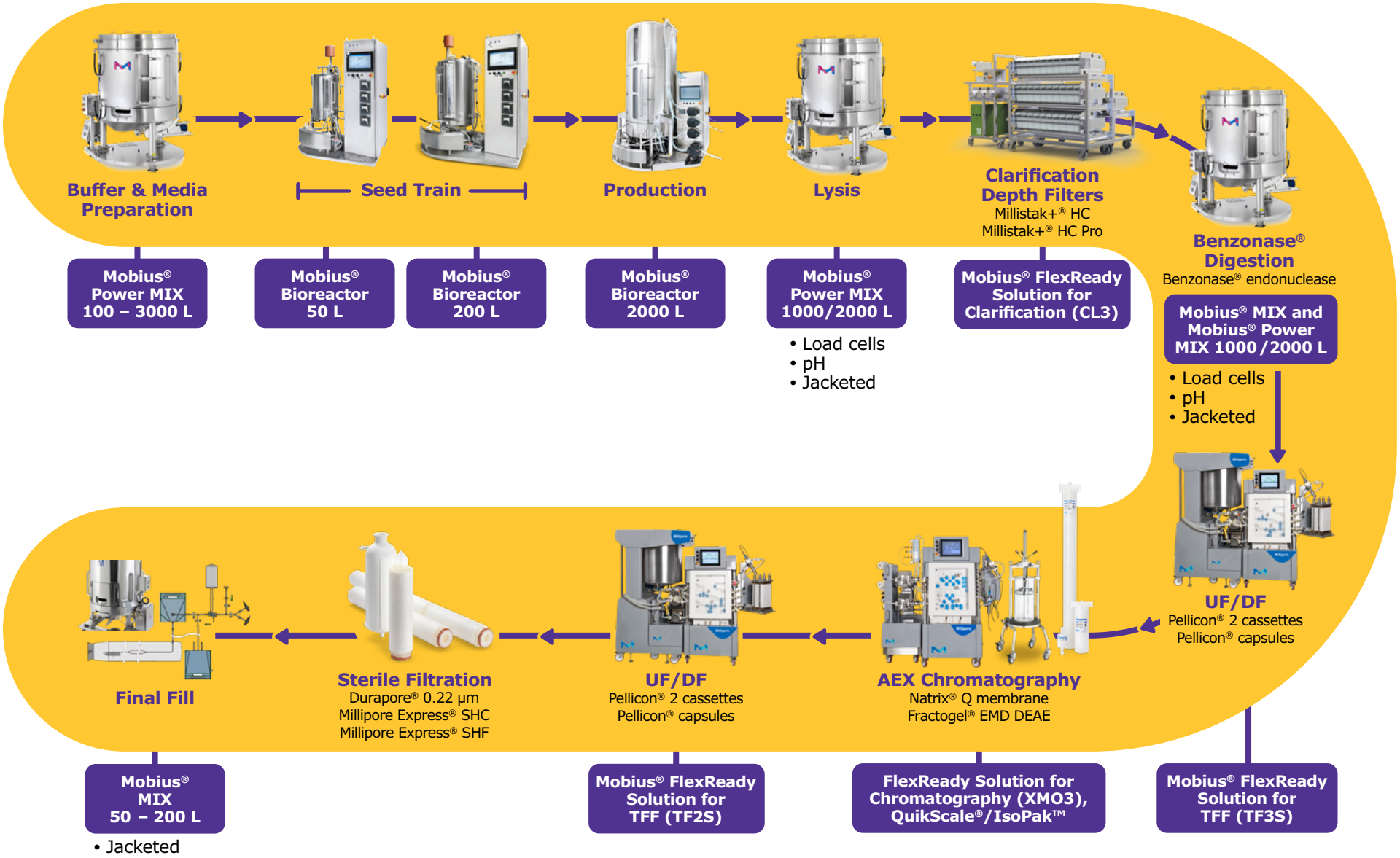
- Analytical testing of final fill drug product
- In-process characterization & testing



Formulation and Sterile Filtration

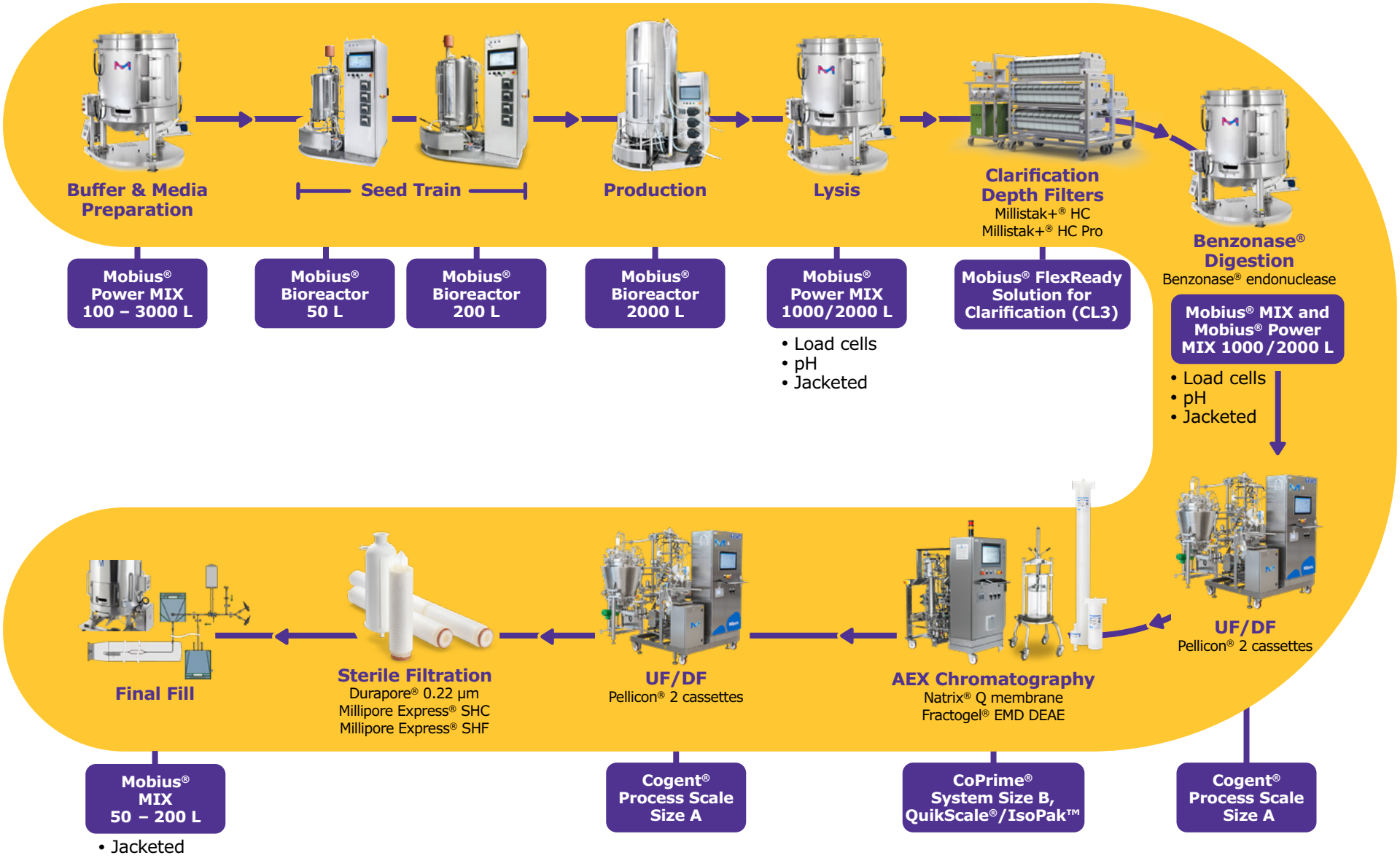
Assurance & Regulatory Compliance

Adenovirus Based Vectored Vaccines (Cell Culture-Based) – 2000 L Single-Use



Millipore® SAFC®

Adenovirus Based Vectored Vaccines (Cell Culture-Based) – 2000 L Hybrid*



*Mix of Single-Use & Multi-Use systems

Millipore® SAFC®

Plasmid DNA (pDNA) Vaccines

1

Plasmid DNA vaccines are based on purified plasmid preparations containing one or more DNA sequences capable of inducing and/or promoting an immune response against a pathogen.

E. coli-based, the purified plasmid is delivered by lipofection or gene gun. pDNA enters the nucleus of transfected local cells and plasmid-encoded genes are expressed. Foreign antigens are generated and trigger an immune response by vaccinated host.

2

After harvest, cells are lysed and clarified. Downstream purification includes TFF, chromatography, and final sterile filtration.

3

Examples of pDNA vaccines include: COVID vaccines from ZyCoV-D®.

Production & Purification of pDNA Vaccines

pDNA Production Platform

Media Preparation

- Millipore Express® SHR, Millipore Express® SHC or Millipore Express® SHF
- Single-use and filter validation services

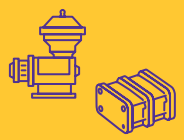
- Upstream Chemicals and Supplements

Fermentation

- Prostak™ Microfiltration Modules
- Pellicon® 2 cassettes with Durapore® 0.1, 0.22, 0.45 µm
- Pellicon® 2 cassettes with Biomax® 1000 kDa membranes or Ultracel®1000 kDa membranes
- Viresolve® barrier filters
- Filter validation services

- Emprove® Chemicals: e.g. D(+)-Glucose, IPTG

- Raw materials testing
- Prokaryotic cell bank testing and storage
- In-process characterization & testing



Cell Harvest

- Mobius® Single-use mixing systems & assemblies
- CellPrime® recombinant lysozyme
- NovaSeptum® GO Sterile Sampling Systems

- Emprove® Chemicals: e.g. Surfactants (SDS) or NaOH
- Cleaning-In-Place solutions

- Biosafety lot release testing of crude virus harvest such as host cell proteins, residual DNA, residual RNA and endotoxin, etc.
- In-process characterization & testing

Cell Lysis

Clarification

- Mobius® FlexReady solution for clarification
- Milligard® PES Filters
- Clarisolve® 60HX
- Millistak+® D0HC
- Single-use and filter validation services

- In-process characterization & testing

UF/DF

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

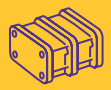
- In-process characterization & testing

Chromatography (1~2 steps)

- Fractogel® DMAE/DEAE
- Natrix® Q chromatography membranes

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Deviron® C16
- Cleaning-In-Place solutions

- In-process characterization & testing

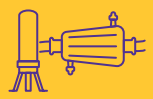


UF/DF

- Pellicon® 2 cassettes with Biomax® / Ultracel® 100-300 kDa membranes
- Pellicon® capsules with Ultracel® 100-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Buffers, Salts, Aminoacids, Isotonicity Agents, Stabilizers
- Cleaning-In-Place solutions

- In-process characterization & testing



Formulation and Sterile Filtration

- Durapore® 0.22 µm filters
- Millipore Express® SHC filters
- Millipak® Final Fill filters
- Single-use and filter validation services

- Emprove® Chemicals: Buffer, stabilizer, pH adjusting agents, surfactants, Isotonicity adjusting agents, Adjuvants

- Biosafety, Analytical and Stability testing of purified bulk drug substance
- Analytical testing of final fill drug product
- In-process characterization & testing

Assurance & Regulatory Compliance

Plasmid DNA Vaccines (*E. coli*) – 500 L Single-Use (excl. Fermenter)

Buffer & Media Preparation

Mobius® Power MIX 100 – 2000 L

Seed & Production

Stainless Steel Fermenter 500 L

Cell Harvest UF/DF

Prostak™ Microfiltration modules
Pellicon® cassettes

Mobius® FlexReady Solution for TFF (TF2S/TF3S)

Cell Lysis

Mobius® Power MIX 500 L

- Load cells
- pH
- Jacketed

Clarification Depth Filters

Millistak+® HC
Millistak+® HC Pro
Clarisolve® 60HX

Mobius® FlexReady Solution for Clarification (CL3)

UF/DF

Pellicon® 2 cassettes
Pellicon® capsules

Mobius® FlexReady Solution for TFF (TF3S)

AEX Chromatography

Natrix® Q membrane
Fractogel® EMD DEAE

Mobius® FlexReady Solution for Chromatography (Chrom 20), QuikScale® 300/450 mm Column

Sterile Filtration

Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF

Final Fill

Mobius® MIX 50 – 200 L

Millipore®

Plasmid DNA Vaccines (*E. coli*) – 500 L Hybrid*

Buffer & Media Preparation

Mobius® Power MIX 100 – 2000 L

Seed & Production

Stainless Steel Fermenter 500 L

Cell Harvest UF/DF
Prostak™ Microfiltration modules
Pellicon® 2 cassettes

Mobius® FlexReady Solution for TFF (TF2S/TF3S)

Cell Lysis

Mobius® Power MIX 500 L

- Load cells
- pH
- Jacketed

Clarification Depth Filters
Millistak+® HC
Millistak+® HC Pro
Clarisolve® 60HX

Mobius® FlexReady Solution for Clarification (CL3)

UF/DF
Pellicon® 2 cassettes

Cogent® Process Scale Size A

- 300 L tank

AEX Chromatography
Natrix® Q membrane
Fractogel® EMD DEAE

CoPrime® B, QuikScale® 300/ 450 mm Column

Sterile Filtration
Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF

Final Fill

Mobius® MIX 100 L

*Mix of Single-Use & Multi-Use systems

mRNA Vaccines

1

Delivery of an mRNA into the cytosol of a cell can induce the production of a target protein which can function as an antigen to trigger an immune response for vaccination purposes

E. coli-based, the target protein expressing gene is inserted into the plasmid DNA and the plasmid DNA acts as a precursor to the mRNA.

2

The DNA is linearized, purified and mRNA is produced through *in-vitro* transcription using enzymes. The mRNA is purified, end capped and formulated into lipids.

3

Examples of mRNA vaccines include:
COVID vaccines from Spikevax™ (Moderna) and Comirnaty® (Pfizer-BioNTech).

Production & Purification of mRNA Vaccines

mRNA production platform

Plasmid linearization

- Mobius® single-use mixing systems & assemblies
- Single-use and filter validation services

- Emprove® Chemicals: Mineral Salts and Buffers

- Biosafety testing
- In-process characterization & testing

- mRNA CDMO

Chromatography and/or UF/DF

- AEX resins & membranes
- Pellicon® cassettes with Biomax® / Ultracel® 30-300 kDa membranes
- Pellicon® capsules with Ultracel® 30-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Mineral Salts and Buffers
- Cleaning-In-Place solutions

- In-process characterization & testing

- mRNA CDMO

***In-vitro* transcription**

- Mobius® single-use mixing systems & assemblies
- NovaSeptum® GO Sterile Sampling Systems

- Emprove® Chemicals: Mineral Salts and Buffers, Reagents (e.g. HEPES)

- Analytical testing
- In-process characteriza-tion & testing

- mRNA CDMO

Chromatography and/or UF/DF

- AEX resins & membranes
- Pellicon® cassettes with Biomax® / Ultracel® 30-300 kDa membranes
- Pellicon® capsules with Ultracel® 30-300* kDa membranes
- Mobius® FlexReady Systems
- Single-use and filter validation services

- Emprove® Chemicals: Mineral Salts and Buffers
- Cleaning-In-Place solutions

- In-process characterization & testing

- mRNA CDMO

Enzymatic capping

- Mobius® single-use mixing systems & assemblies
- Nova-Septum® GO Sterile Sampling Systems

- Emprove® chemicals: e.g. Tris

- Analytical testing
- In-process character-ization & testing

- mRNA CDMO

Chromatography

- Natrix® Q chromatography membrane or AEX Fractogel® resins DEAE and DMAE
- Single-use and filter validation services

- Emprove® Chemicals: Mineral Salts and Buffers
- Cleaning-In-Place solutions

- Biosafety testing
- In-process characterization & testing

- mRNA CDMO

UF/DF

- Pellicon® cassettes with Biomax® / Ultracel® 30-300 kDa membranes
- Pellicon® capsules with Ultracel® 30-300 kDa membranes
- Single-use and filter validation services

- Emprove® Chemicals: Mineral Salts and Buffers
- Cleaning-In-Place solutions

- In-process characterization & testing

- mRNA CDMO

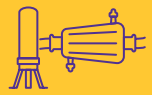
Encapsulation & Formulation

- Mobius® single-use mixing systems & assemblies
- Mobius® encapsulation assemblies
- NovaSeptum® GO Sterile Sampling Systems
- Single-use and filter validation services

- Emprove® Chemicals: solvents, salts, stabilizers
- Custom and standard Lipids: cationic Lipid, PEG Lipids, Synthetic Cholesterol, helper lipids

- Biosafety testing
- In-process characterization & testing

- Lipids CDMO
- LNP CDMO



Formulation and Sterile Filtration

- Durapore® 0.22 µm filters
- Millipore Express® SHC filters
- Millipak® Final Fill filters
- Single-use and filter validation services

- Biosafety testing
- In-process characteriza-tion & testing

- Final Fill CDMO

Assurance & Regulatory Compliance

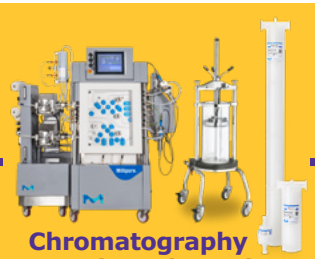
mRNA Based Vaccines – 200 L Single-Use

Plasmid DNA

***In-vitro* Transcription**

Mobius® MIX 200 L

- Load cells
- pH
- Jacketed



Chromatography AEX–Flow Through
Fractogel® resins, Eshmuno® resins, Natrix® Q membranes

Mobius® FlexReady Solution for Chromatography (XMO3), QuikScale® 300 mm Column

UF/DF
Pellicon® 2 or 3 cassettes
Pellicon® capsules

Mobius® FlexReady Solution for TFF (TF2S)

- 5 m^2 area
- 300 L tank

Enzymatic Capping

Mobius® MIX 200 L

- Load cells
- pH
- Jacketed

AEX Chromatography
Fractogel® resins, Natrix® Q membranes

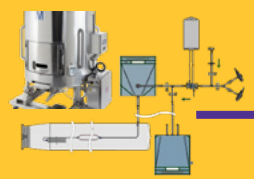
Mobius® FlexReady Solution for Chromatography (XMO3), QuikScale® 300 mm Column

Lipid Encapsulation and UF/DF
Pellicon® 2 or 3 cassettes
Pellicon® capsules

Mobius® FlexReady Solution for TFF (TF2S)

- 5 m^2 area
- 300 L tank

Sterile Filtration
Durapore® 0.22 µm
Millipore Express® SHC
Millipore Express® SHF



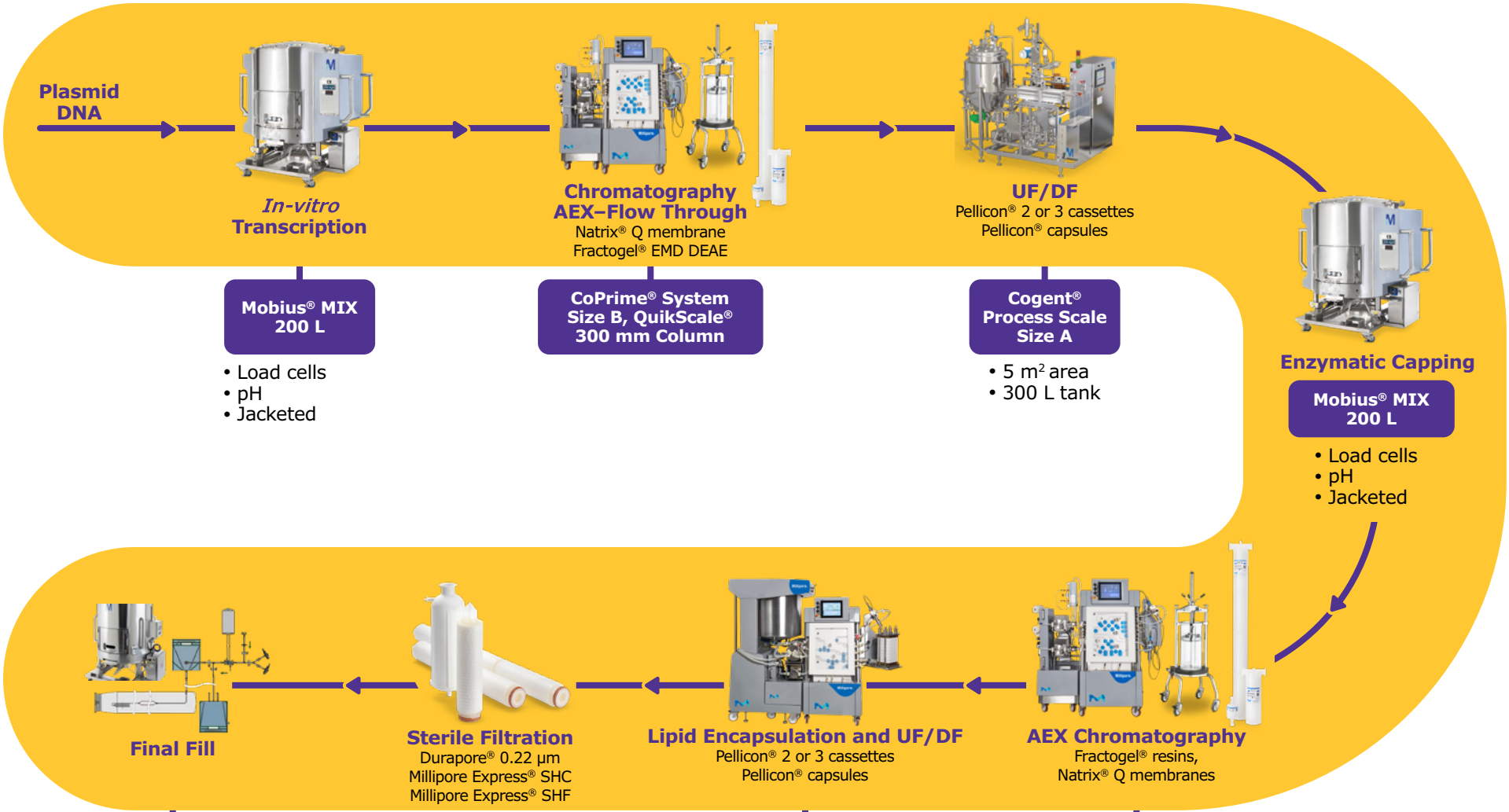
Final Fill

Mobius® MIX 100 L

- Jacketed

Millipore®

mRNA Based Vaccines – 200 L Hybrid*



*Mix of Single-Use & Multi-Use systems

Millipore®

BioReliance® Biosafety Testing Services

Patient safety and compliance

For vaccine and viral therapies, BioReliance® biosafety testing services provide a comprehensive range of assays and services to support each stage of product development. From cell banking and cell line characterization to product characterization and lot release testing, our GMP-compliant testing services and regulatory expertise can help progress your vaccine from discovery to commercialization.

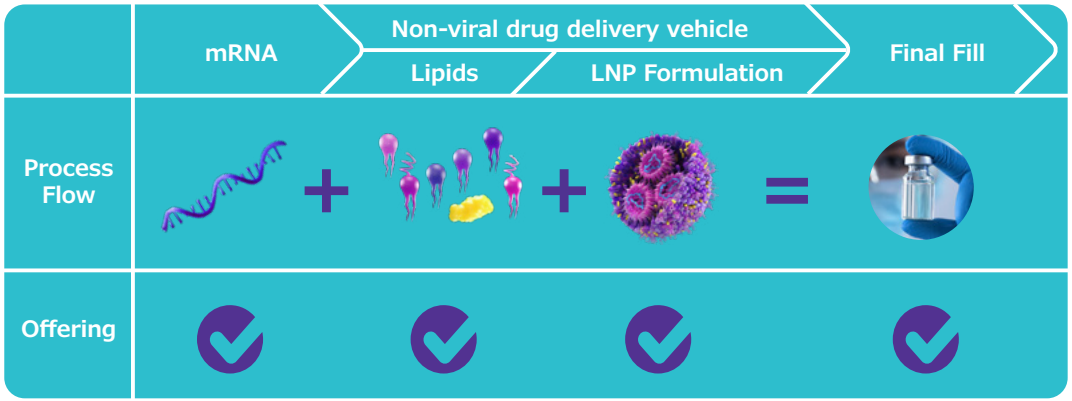
BioReliance® upstream services include:

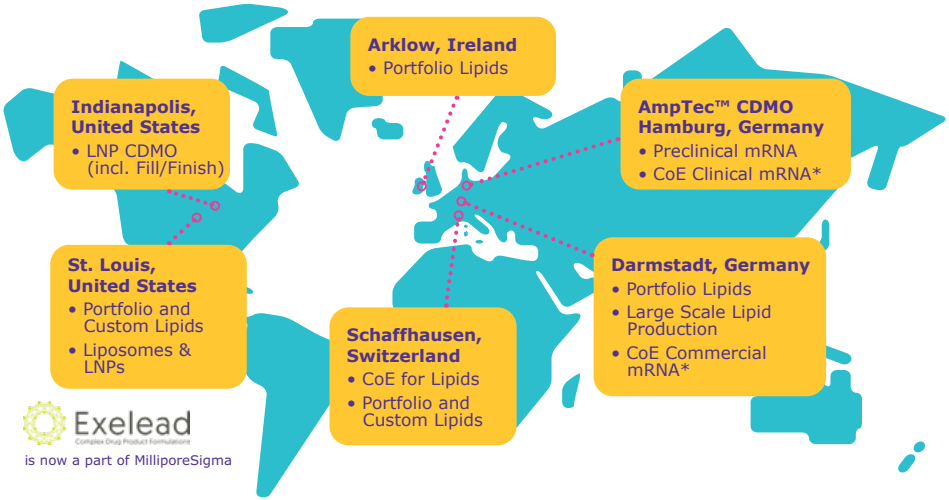
- MCB/WCB bank manufacturing
- MCB/WCB bank characterization
- Biorepository services
- Virus bank manufacturing
- Virus bank characterization
- Next generation sequencing
- Raw material testing

BioReliance® downstream services include:

- Analytical services for biologics
- Viral clearance studies
- Bulk lot release testing
- Final product release testing

Our Integrated mRNA-LNP CDMO offering





mRNA
- Preclinical Custom mRNA Manufacturing
- GMP Clinical & Commercial Custom mRNA Manufacturing*

Lipids
- Portfolio and Custom GMP Lipids

LNP/Liposomes
- Development
- cGMP Production
- Final Fill

* Availability H2 2023. Timeline Subject to change - CoE: Center of Excellence

Emprove® Chemicals

Ensure the successful process and formulation of your product

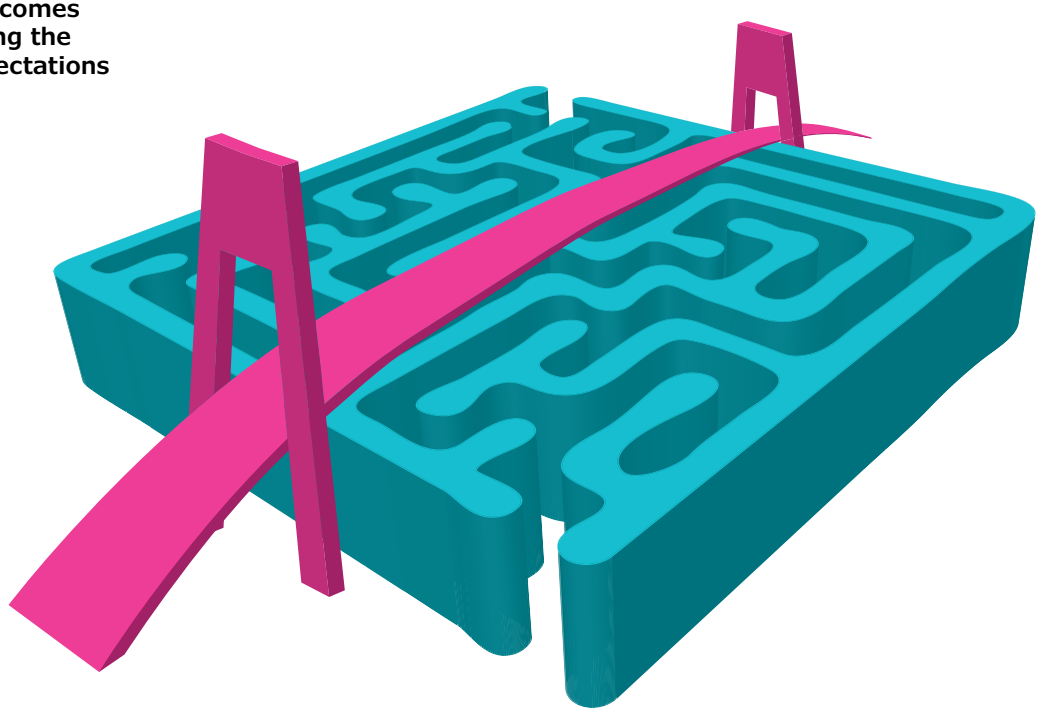
Specifically developed for high-risk applications, our buffers, salts and stabilizers are low in bioburden and endotoxins. Supported by our Emprove® program, our excipients have extensive documentation, helping minimize regulatory and quality-associated risks in your manufacturing. All this simplifies the complexity of your supplier qualification and speeds up processes, thus reducing total cost of ownership.

Our portfolio of more of more than 400 raw and starting material comes with comprehensive and thorough documentation not only covering the latest regulatory requirements, but also anticipating industry expectations not yet covered by regulation.

- Elemental impurity information according to ICH Q3D
- Multi-compendial raw materials facilitate the international drug registration procedures
- Paper-free packaging of our excipients to minimize risk

Emprove® Chemicals include:

- Buffering Agents
- Solvents & Surfactants
- Emprove® Salts & Process Specialities
- Emprove® Stabilizers & Amino-acids



M Lab™ Collaboration Centers

Our technical experts have helped biopharma/pharma manufacturers **solve over 5,000 problems** and save **13,000+ hours annually** in process troubleshooting and deviation investigations.

Industry innovators collaborate with our experts to troubleshoot existing processes, overcome barriers to single-use implementation, receive guidance for process development, learn best practices for adopting biopharma 4.0 technologies, explore applications for novel modalities, and much more.

M Lab™ Collaboration Centers are beacons of scientific leadership, producing 150+ peer-reviewed articles, technical presentations, and patent filings each year.

Expertise

M Lab™ Collaboration Centers uniquely provide the pharma/biopharma industry **access to scientific, technical, and engineering expertise** in state-of-the-art, fully equipped facilities so they can **explore ideas, learn innovative techniques, and collaborate** – whether in person or remotely – to find solutions to their toughest development and manufacturing problems.

The M Lab™ Collaboration Centers global network is comprised of **300+ technical experts** ranging from **process development scientists to bioprocess engineers supporting a variety of modalities**.

These highly qualified experts are at your disposal to **troubleshoot your process, identify efficiencies**, and **adopt innovative techniques** to help you bring life-enhancing drug therapies to market faster and more efficiently.

vaccines, empowered

To place an order or receive technical assistance

In the U.S. and Canada, call toll-free 1-800-645-5476

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EMDMillipore.com/offices

For Technical Service, please visit:
EMDMillipore.com/techservice

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

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