

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



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

Merck 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 Merck 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 Merck 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®

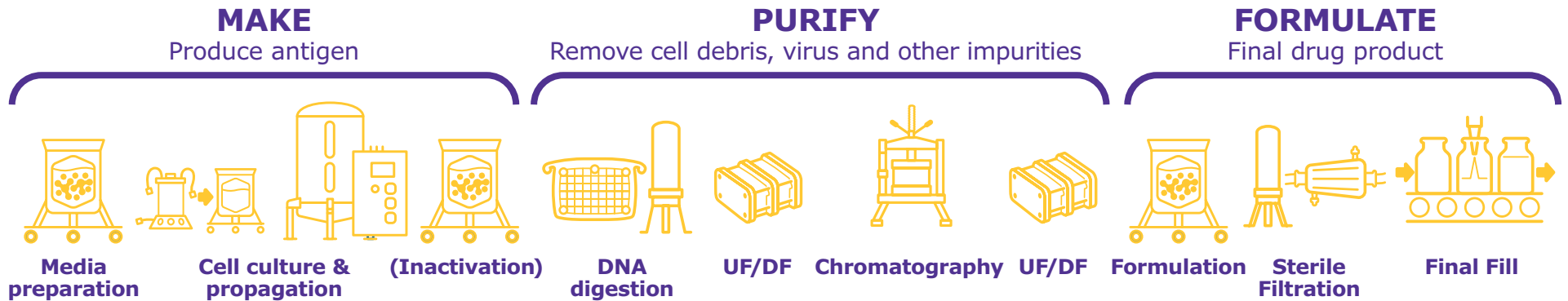
The BioReliance® portfolio from Merck encompasses biopharmaceutical characterization, safety testing and process development, as well as clinical and commercial biomanufacturing. Our experienced teams and operational expertise make us the partner who supports you all the way and always has your vital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

Comprehensive Products & Services Portfolio

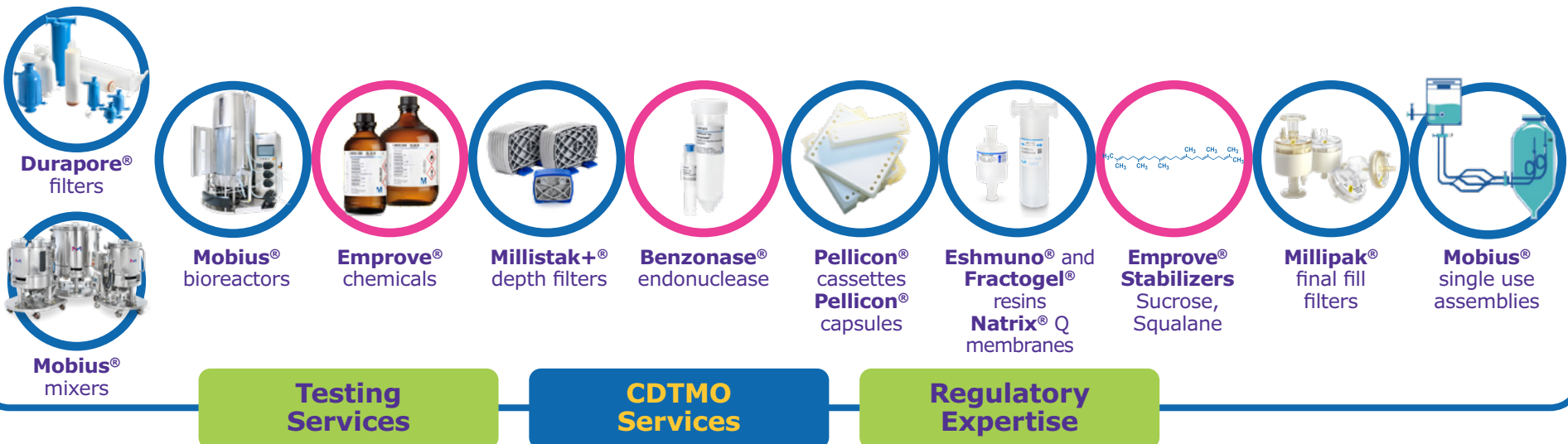
Key Capabilities to Increase Efficiency and Safety of Vaccines

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



example products



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

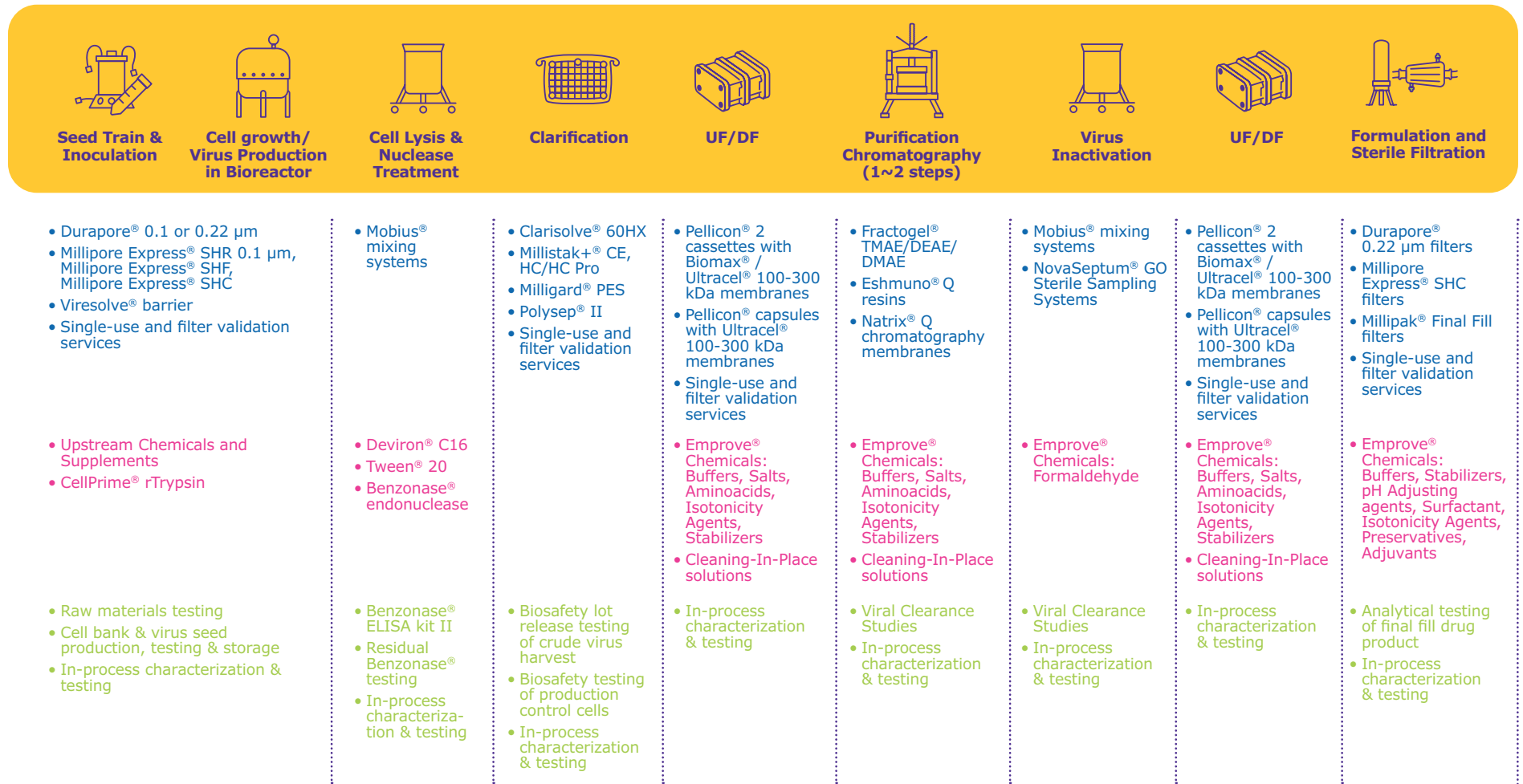
3

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.

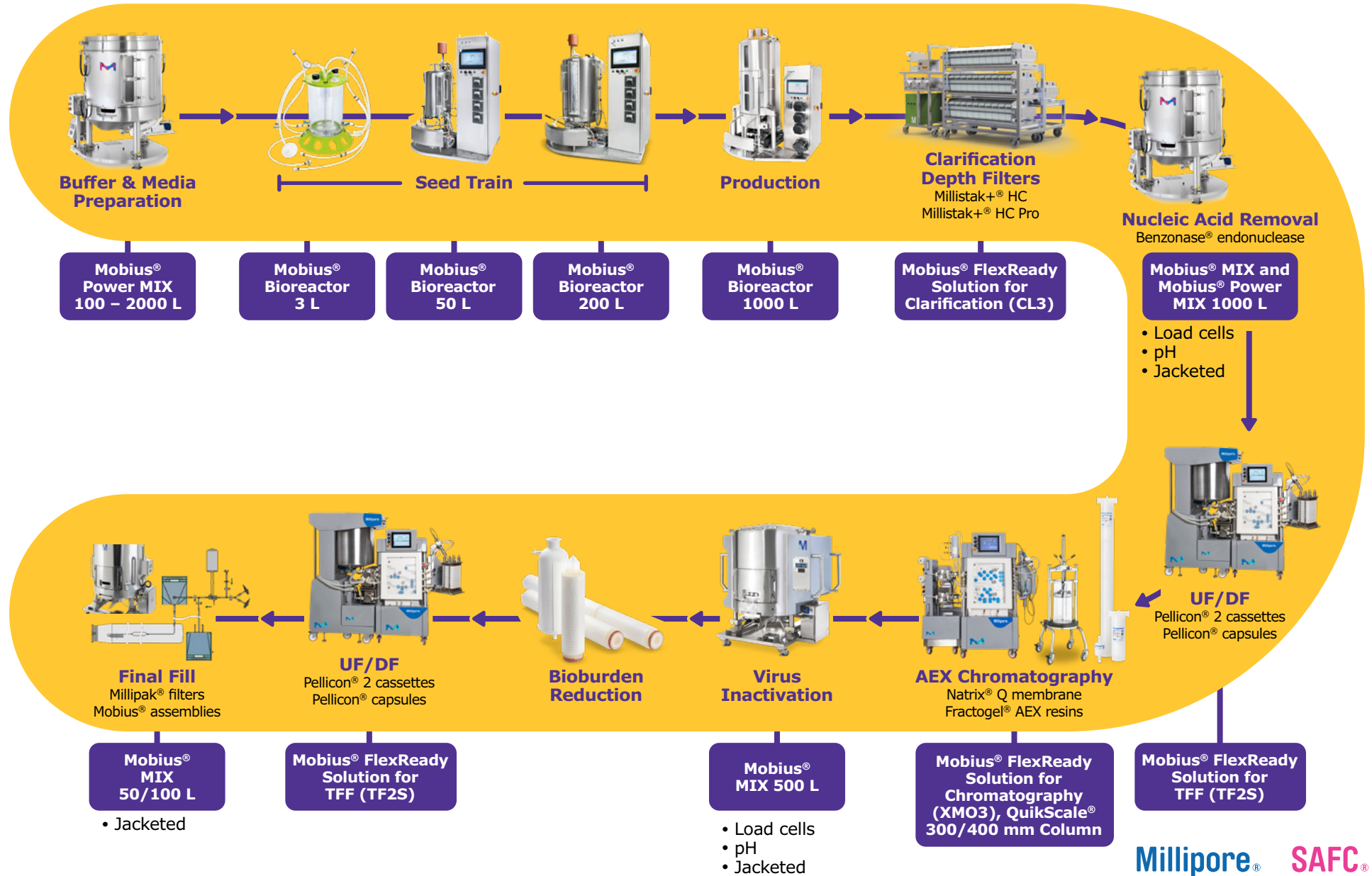
Production & Purification of Virus Based Vaccines

Inactivated/Live-attenuated Production Platform

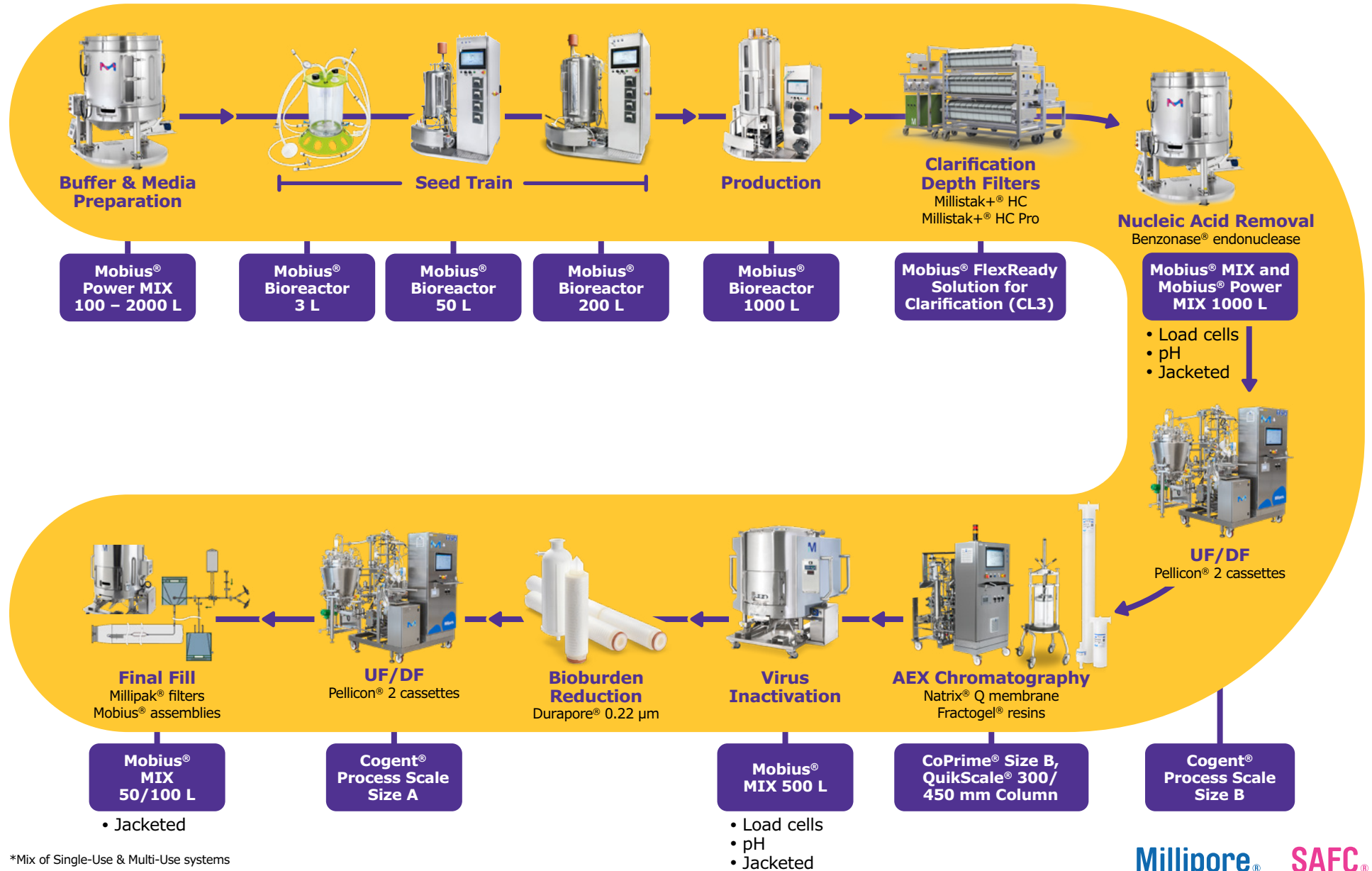


Assurance & Regulatory Compliance

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



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



*Mix of Single-Use & Multi-Use systems

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

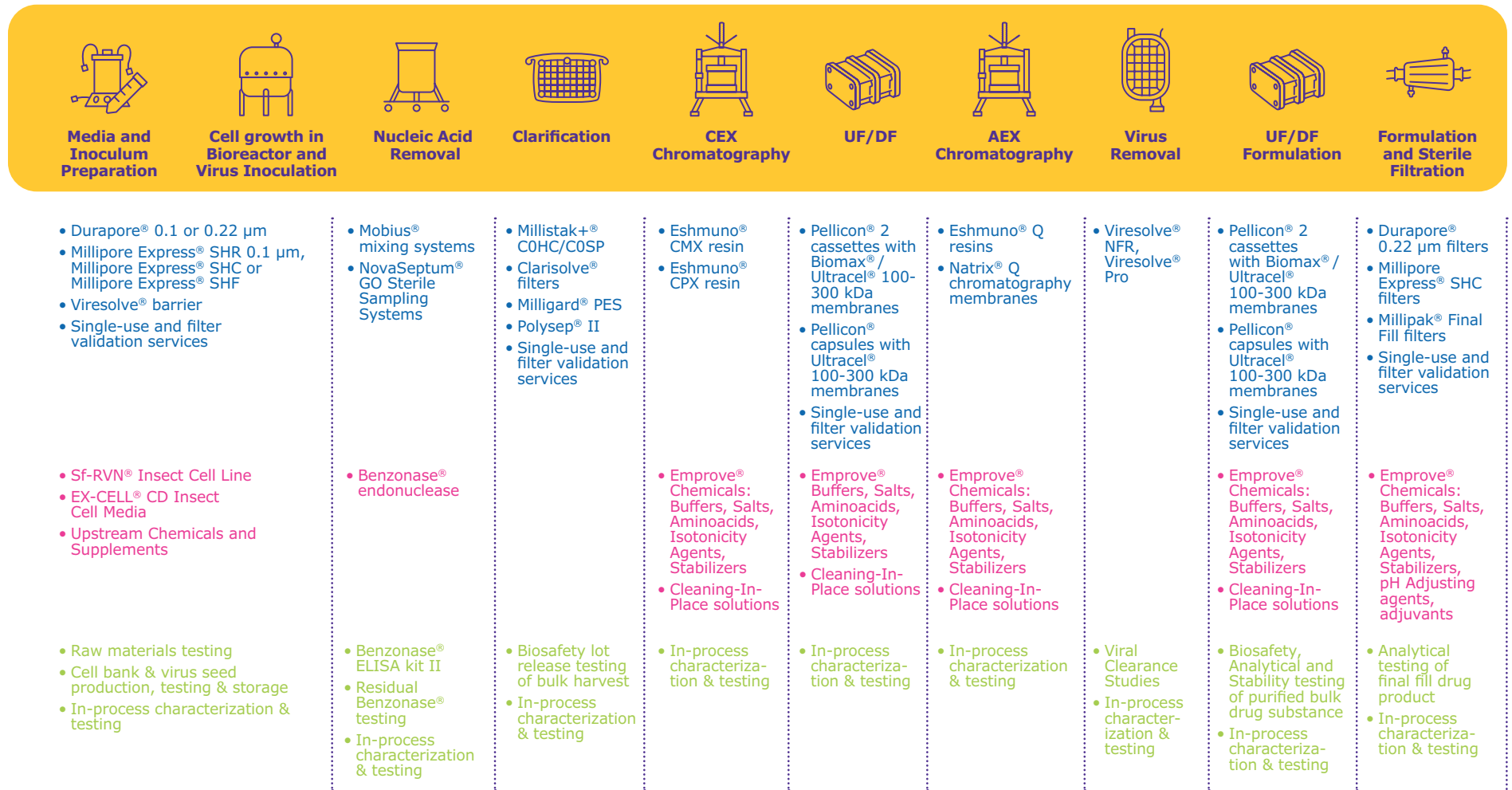
Following production of the antigen, purification includes clarification, IEX and/or HIC chromatography and TFF followed by sterile filtration.

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

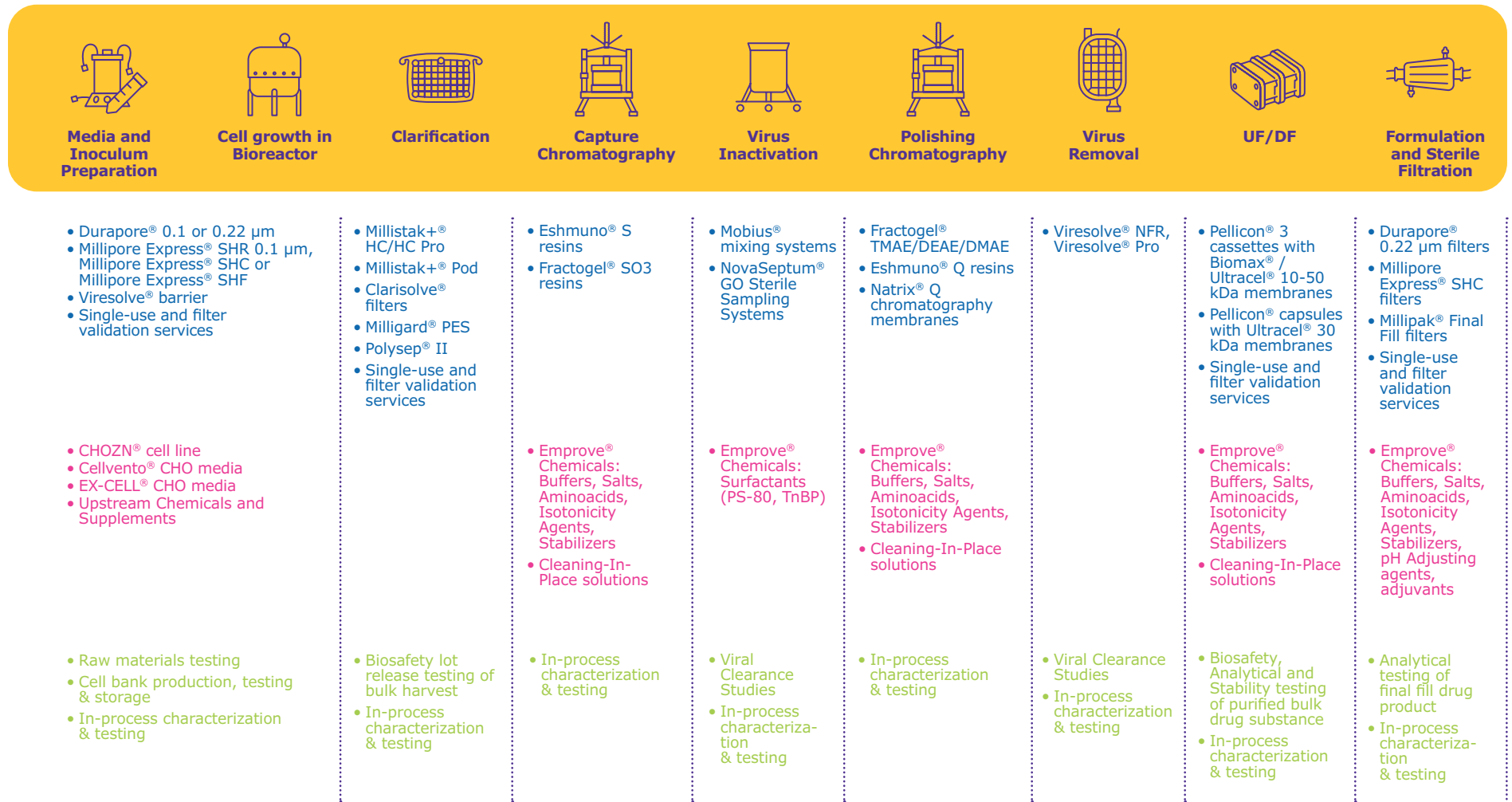
Insect Cell Expression System



Assurance & Regulatory Compliance

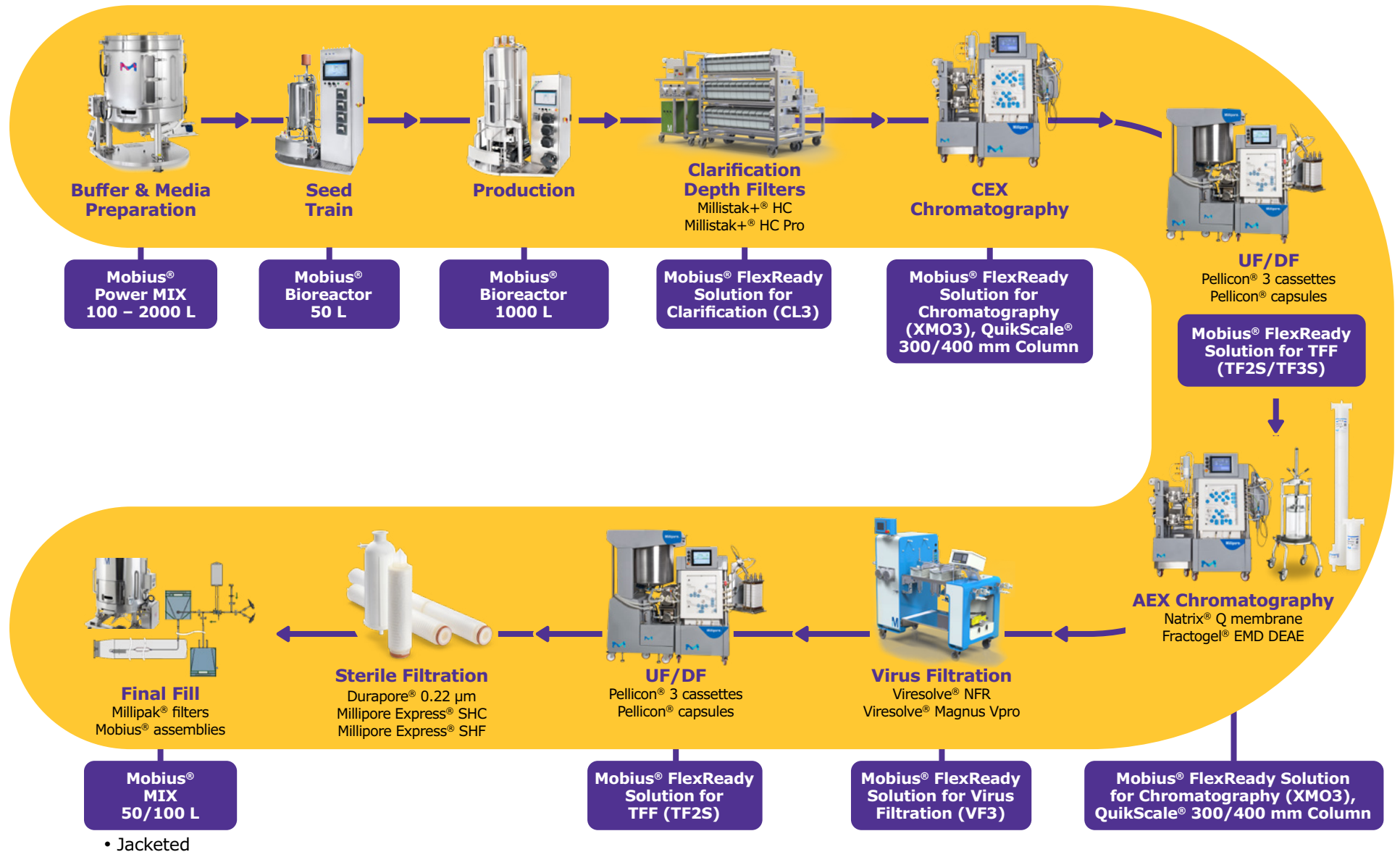
Production & Purification of Protein Subunit Vaccines

CHO Cell Expression System

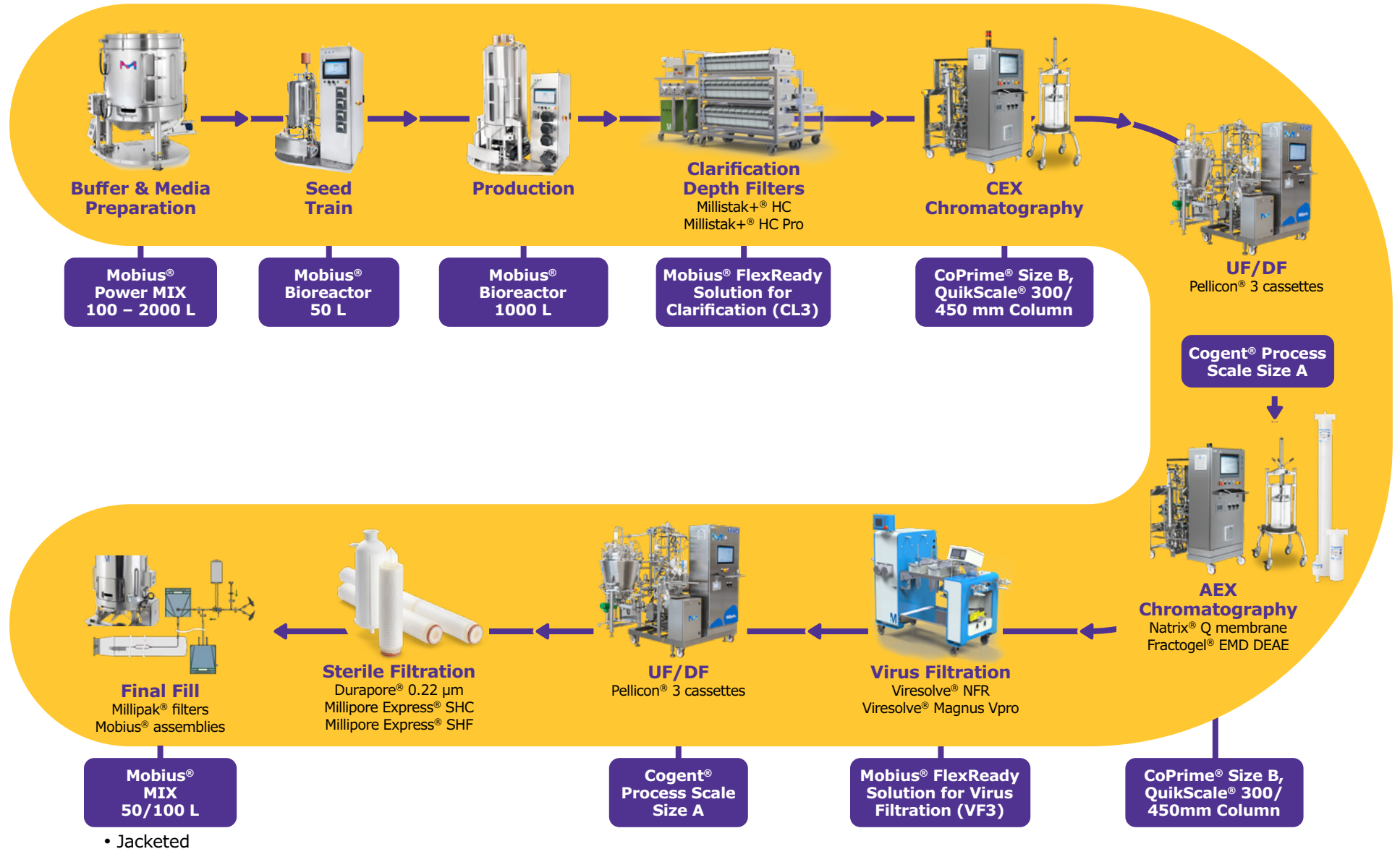


Assurance & Regulatory Compliance

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



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



*Mix of Single-Use & Multi-Use systems

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

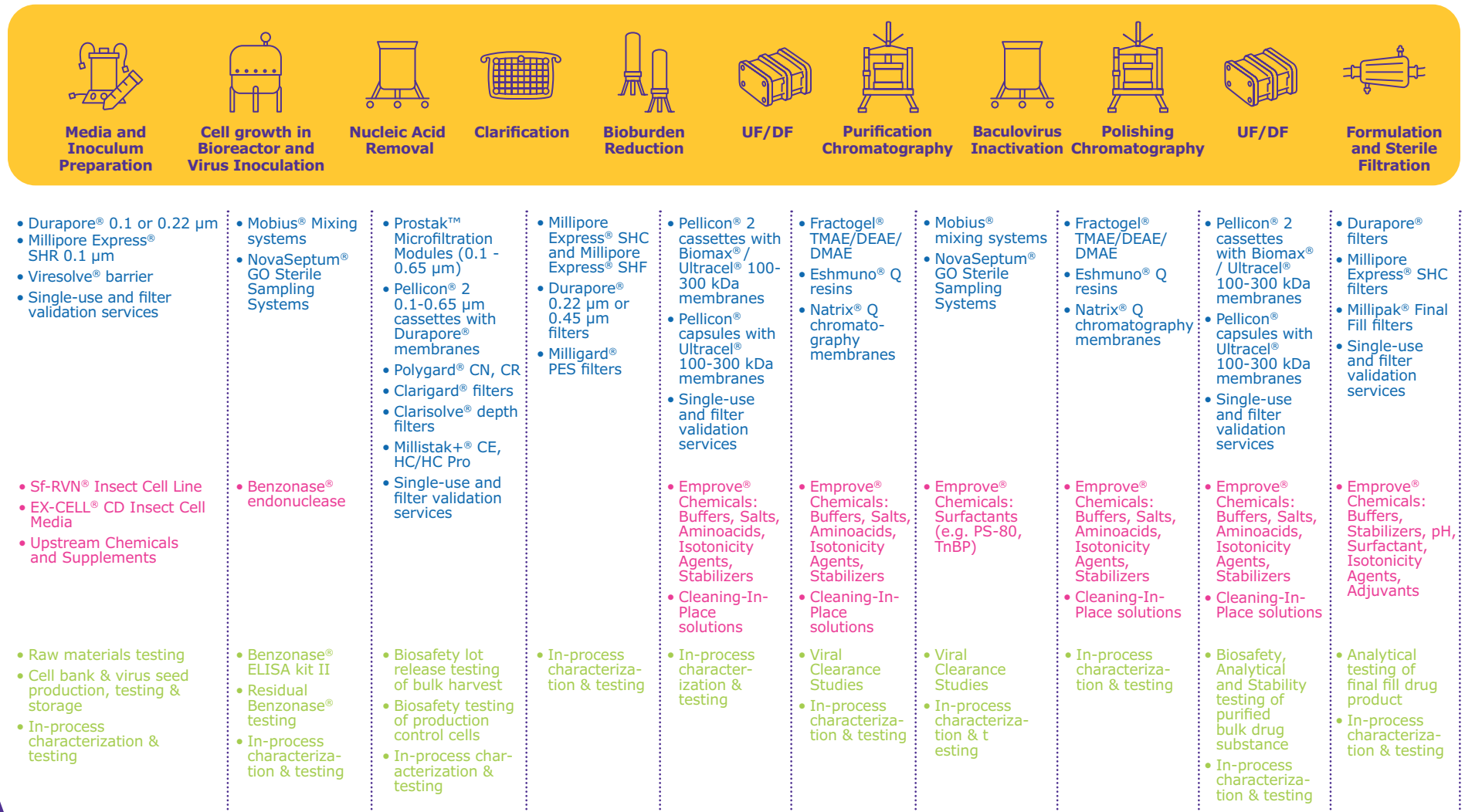
After VLP production, cells are harvested and separated into a pellet prior to being disrupted/lysed for the release of VLPs. The lysate is subsequently clarified. Further purification involves the use of UF/DF, chromatography, inactivation/removal VLP, final formulation and final sterilizing filtration.

3

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

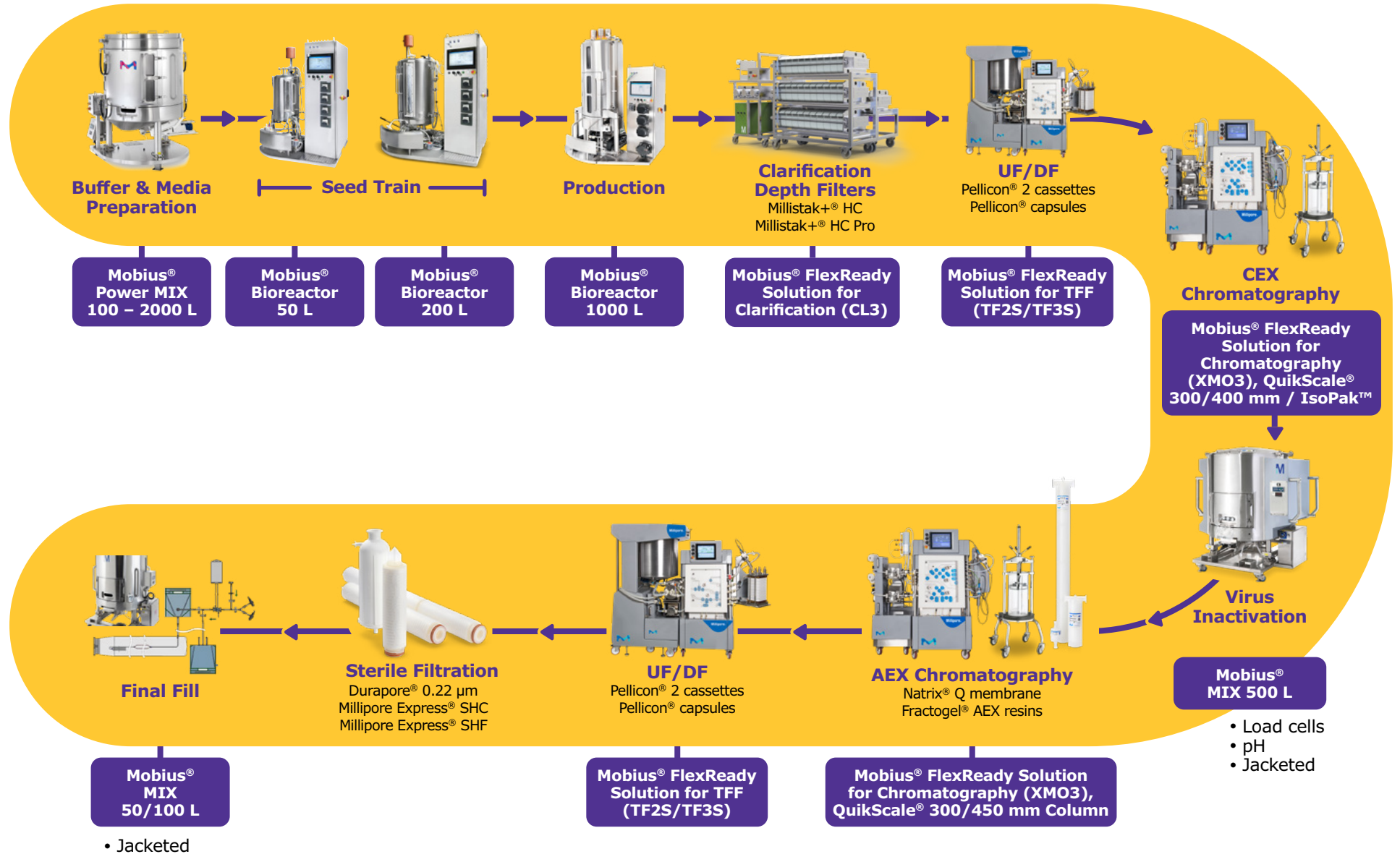
Production & Purification of VLP-Based Vaccines

Insect Cell Expression System

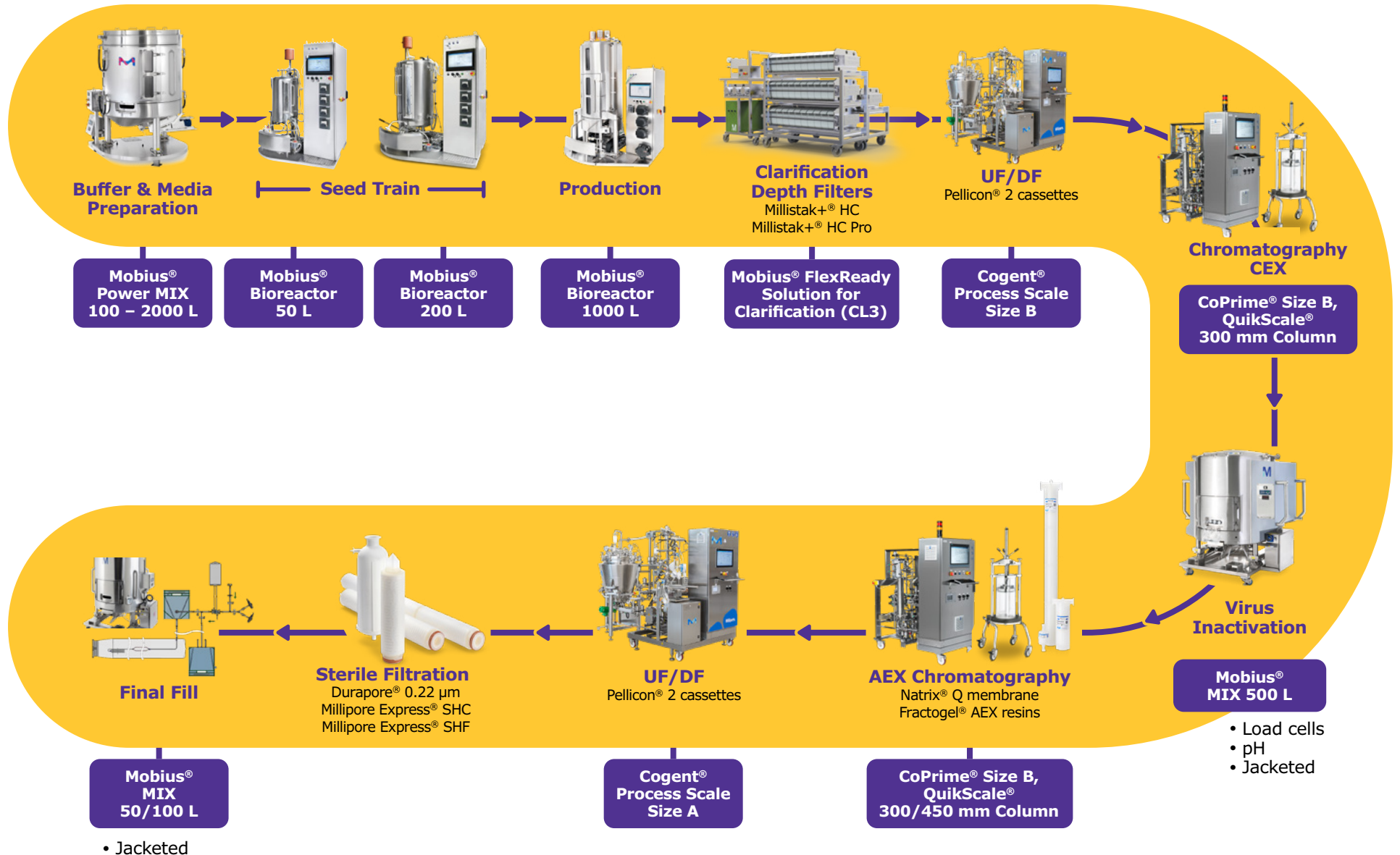


Assurance & Regulatory Compliance

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



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



*Mix of Single-Use & Multi-Use systems

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

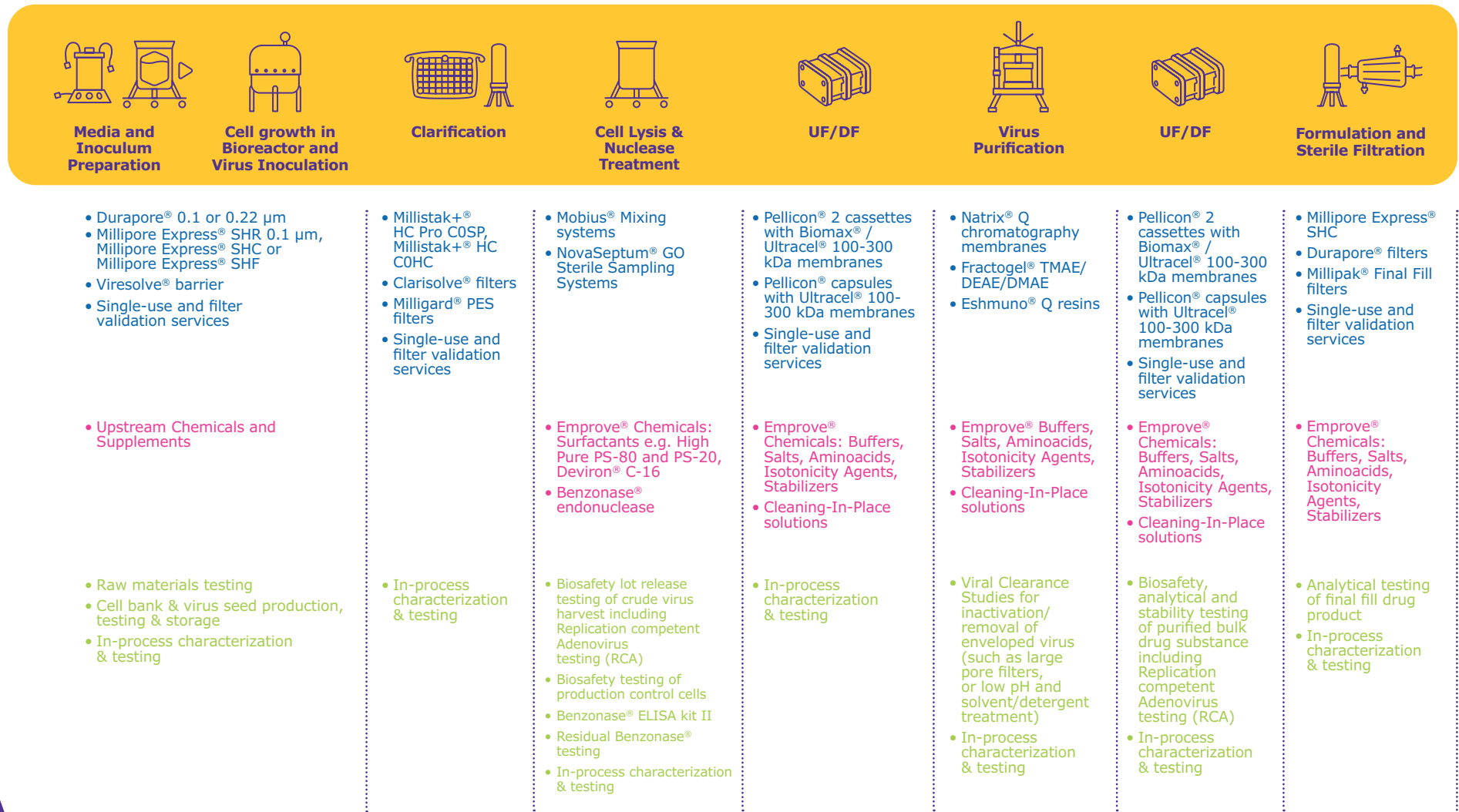
Typical viral vectors purification process included cell harvest followed by cell lysis and nucleic acid treatment. Subsequent steps including UF/DF, chromatography, final sterilizing filtration may or may not be used, depending if the size of vector is too large for filtration. In this case, closed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

3

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

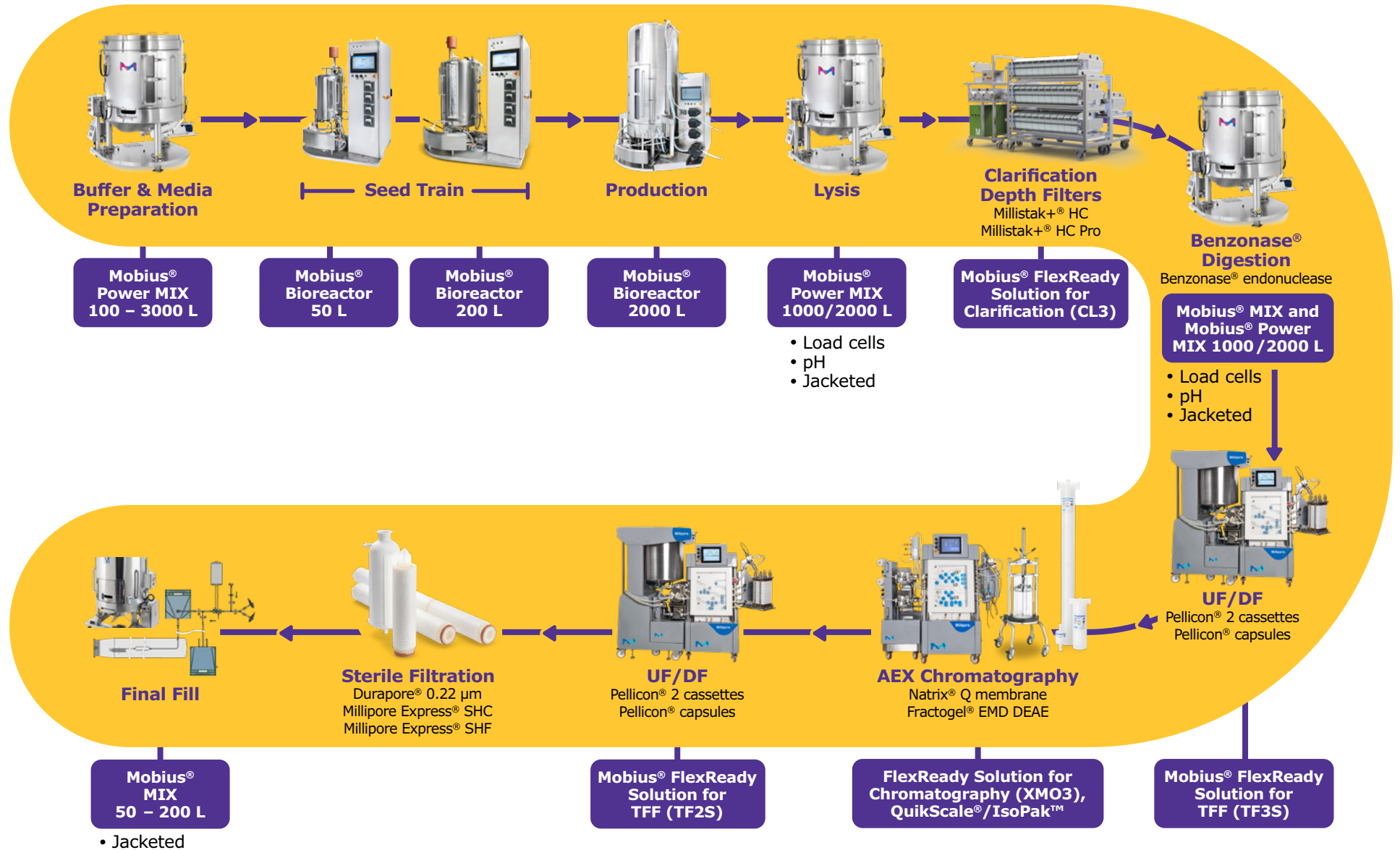
Production & Purification of Viral Vector Vaccines

Adenovirus Production Platform

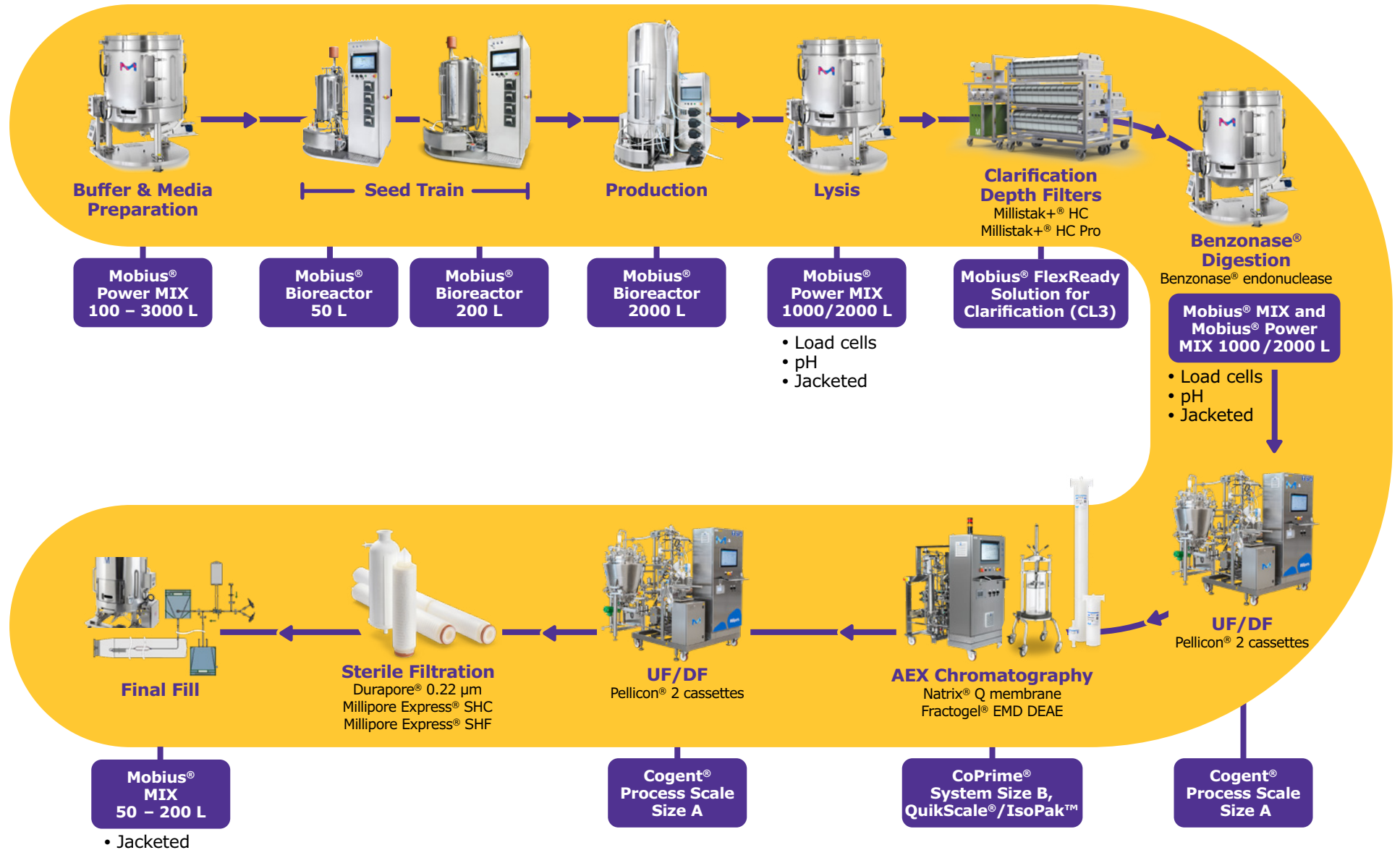


Assurance & Regulatory Compliance

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



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



*Mix of Single-Use & Multi-Use systems

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

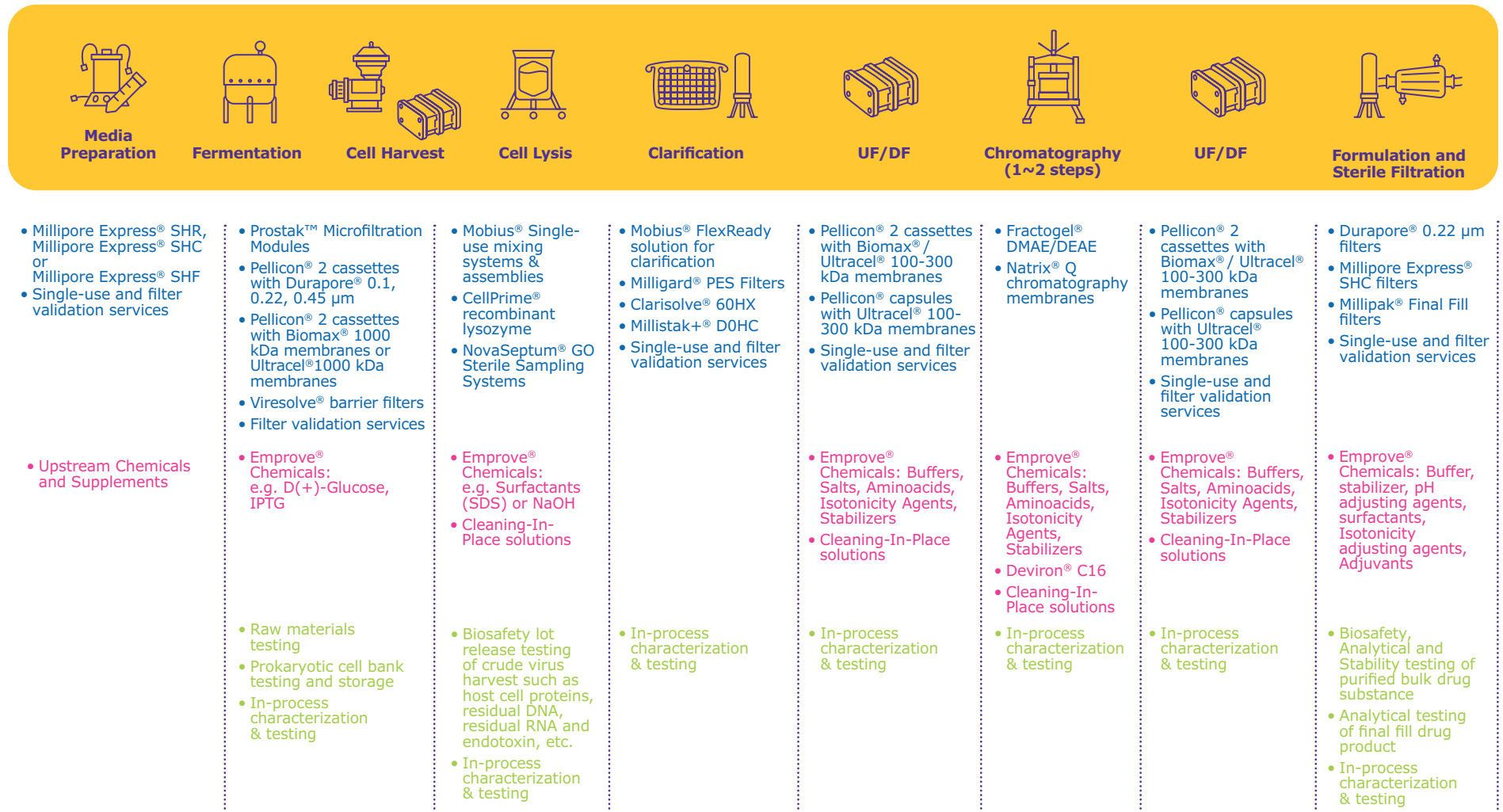
After harvest, cells are lysed and clarified. Downstream purification includes TFF, chromatography, and final sterile filtration.

3

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

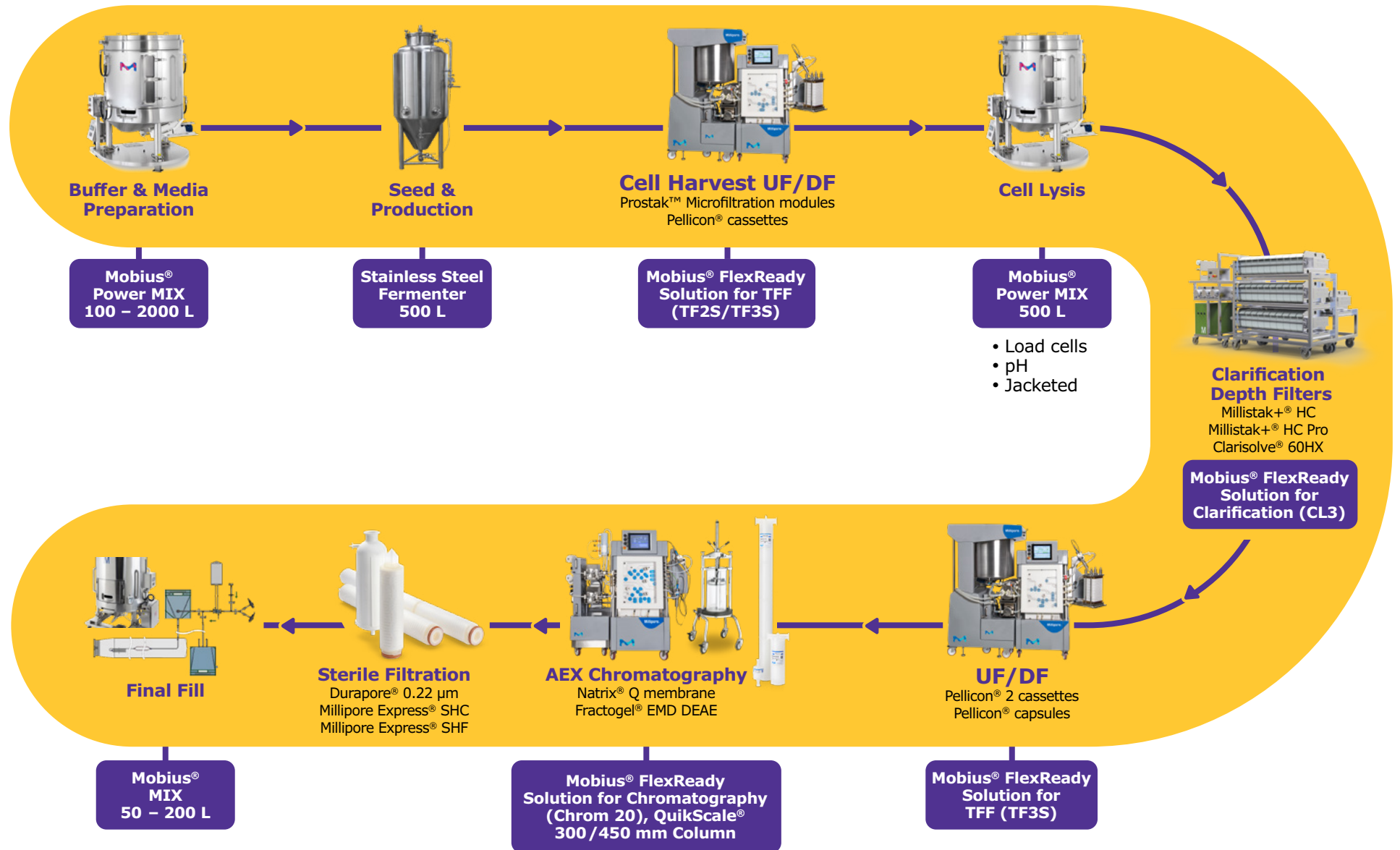
Production & Purification of pDNA Vaccines

pDNA Production Platform

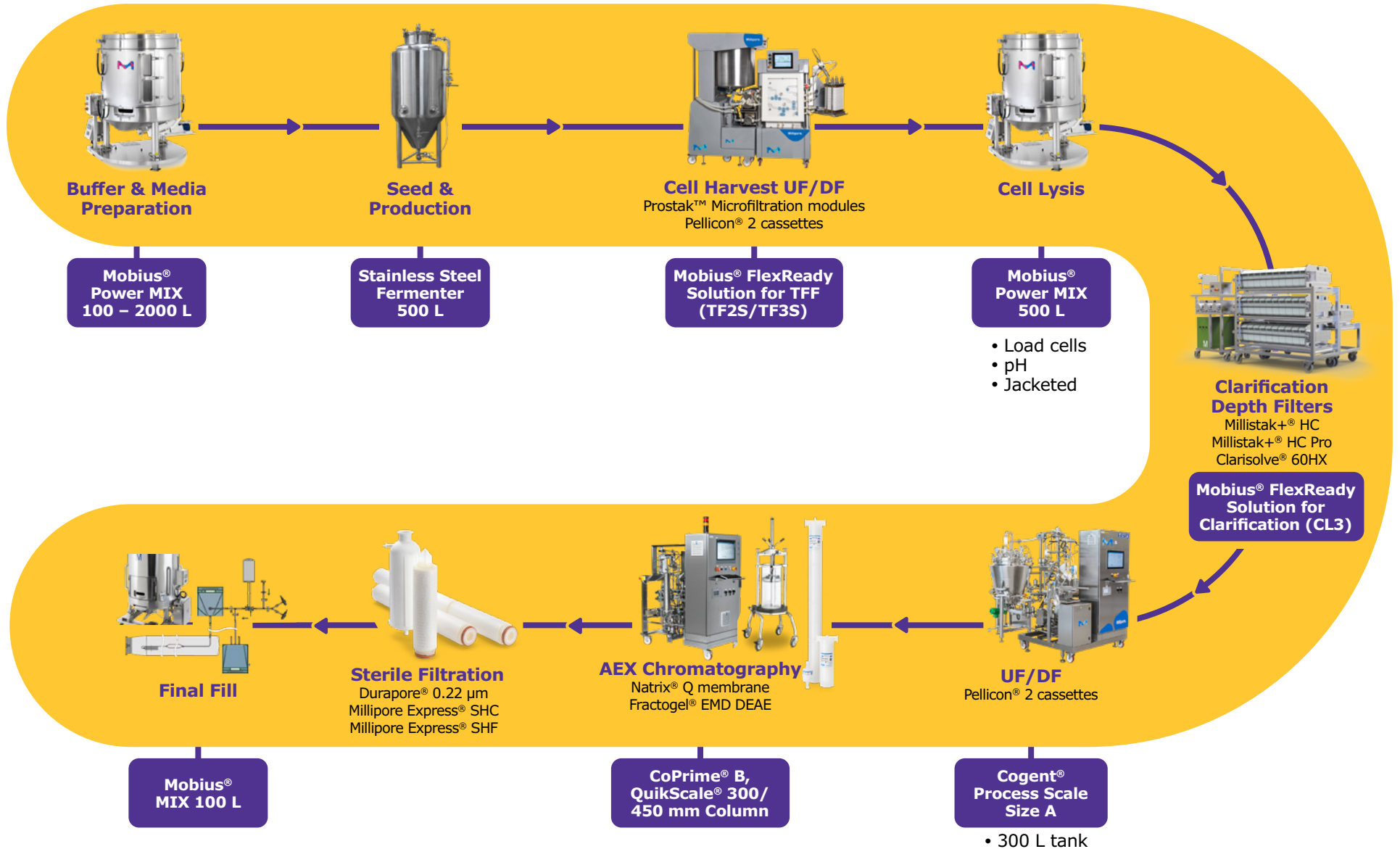


Assurance & Regulatory Compliance

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



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



*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).

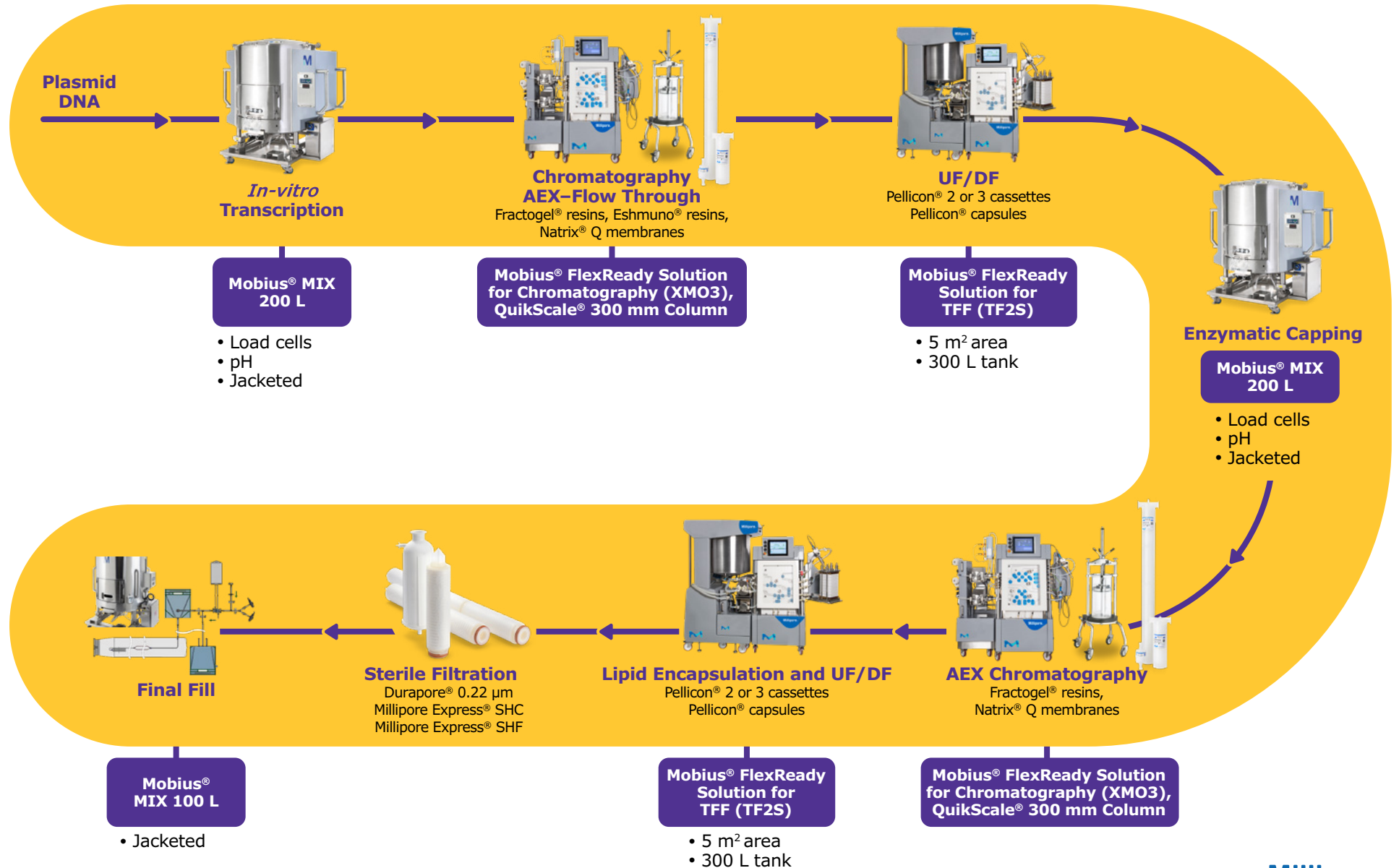
Production & Purification of mRNA Vaccines

mRNA production platform

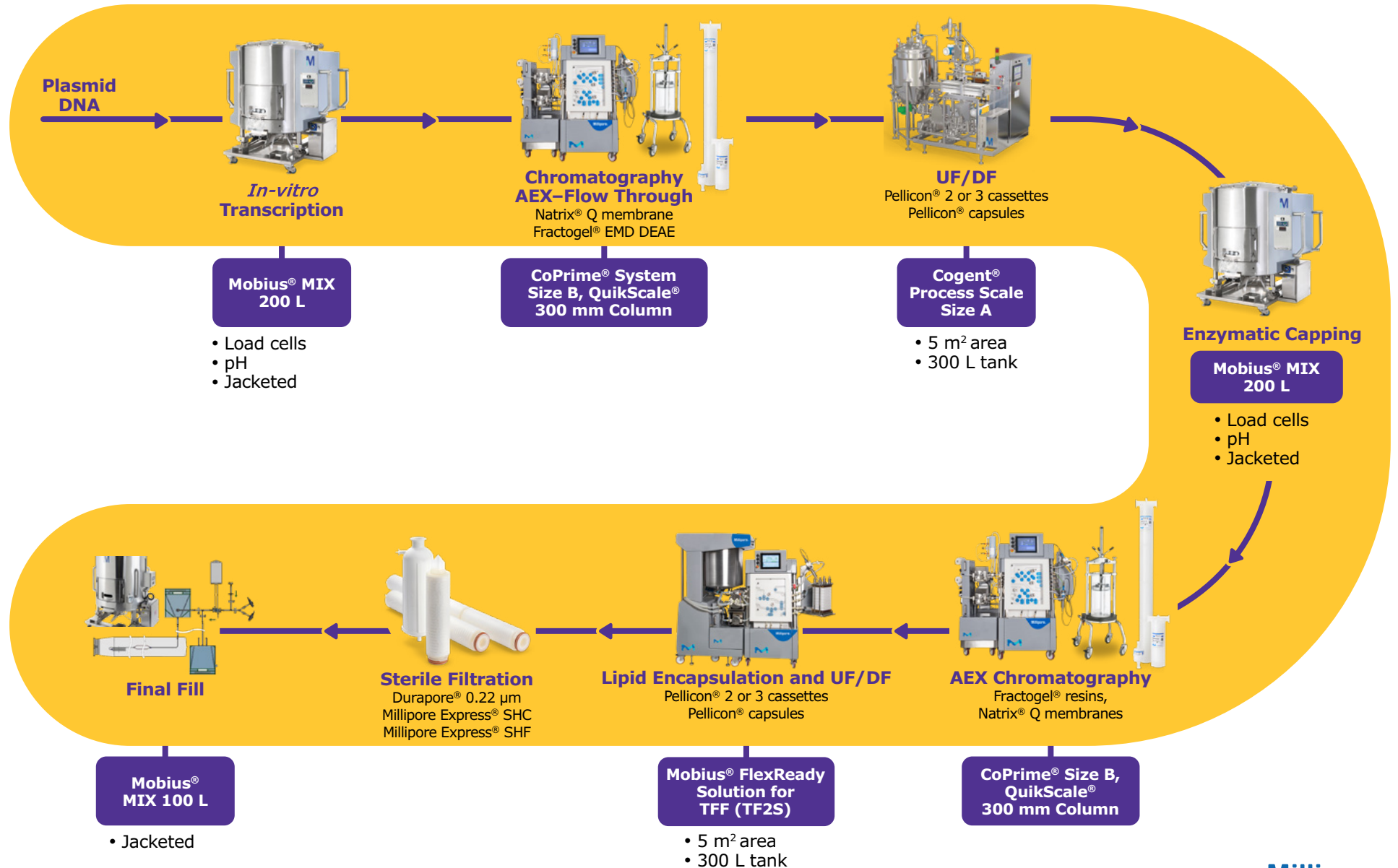
Plasmid linearization	Chromatography and/or UF/DF	In-vitro transcription	Chromatography and/or UF/DF	Enzymatic capping	Chromatography	UF/DF	Encapsulation & Formulation	Formulation and Sterile Filtration
<ul style="list-style-type: none"> Mobius® single-use mixing systems & assemblies Single-use and filter validation services 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Mobius® single-use mixing systems & assemblies NovaSeptum® GO Sterile Sampling Systems 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Mobius® single-use mixing systems & assemblies NovaSeptum® GO Sterile Sampling Systems 	<ul style="list-style-type: none"> Natrix® Q chromatography membrane or AEX Fractogel® resins DEAE and DMAE Single-use and filter validation services 	<ul style="list-style-type: none"> Pellicon® cassettes with Biomax® / Ultracel® 30-300 kDa membranes Pellicon® capsules with Ultracel® 30-300 kDa membranes Single-use and filter validation services 	<ul style="list-style-type: none"> Mobius® single-use mixing systems & assemblies Mobius® encapsulation assemblies NovaSeptum® GO Sterile Sampling Systems Single-use and filter validation services 	<ul style="list-style-type: none"> Durapore® 0.22 µm filters Millipore Express® SHC filters Millipak® Final Fill filters Single-use and filter validation services
<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers 	<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers Cleaning-In-Place solutions 	<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers, Reagents (e.g. HEPES) 	<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers Cleaning-In-Place solutions 	<ul style="list-style-type: none"> Emprove® chemicals: e.g. Tris 	<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers Cleaning-In-Place solutions 	<ul style="list-style-type: none"> Emprove® Chemicals: Mineral Salts and Buffers Cleaning-In-Place solutions 	<ul style="list-style-type: none"> Emprove® Chemicals: solvents, salts, stabilizers Custom and standard Lipids: cationic Lipid, PEG Lipids, Synthetic Cholesterol, helper lipids 	
<ul style="list-style-type: none"> Biosafety testing In-process characterization & testing 	<ul style="list-style-type: none"> In-process characterization & testing 	<ul style="list-style-type: none"> Analytical testing In-process characterization & testing 	<ul style="list-style-type: none"> In-process characterization & testing 	<ul style="list-style-type: none"> Analytical testing In-process characterization & testing 	<ul style="list-style-type: none"> Biosafety testing In-process characterization & testing 	<ul style="list-style-type: none"> In-process characterization & testing 	<ul style="list-style-type: none"> Biosafety testing In-process characterization & testing 	<ul style="list-style-type: none"> Biosafety testing In-process characterization & testing
<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> mRNA CDMO 	<ul style="list-style-type: none"> Lipids CDMO LNP CDMO 	<ul style="list-style-type: none"> Final Fill CDMO

Assurance & Regulatory Compliance

mRNA Based Vaccines – 200 L Single-Use



mRNA Based Vaccines – 200 L Hybrid*



*Mix of Single-Use & Multi-Use systems

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.

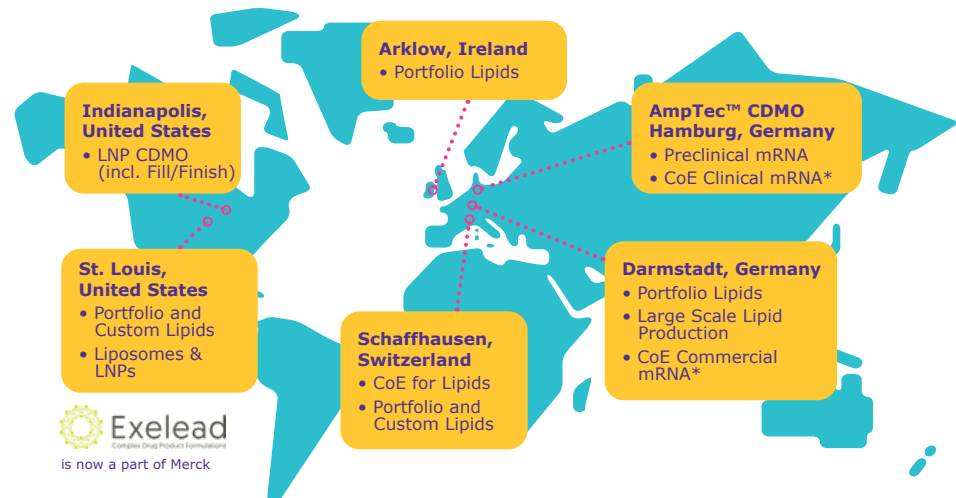
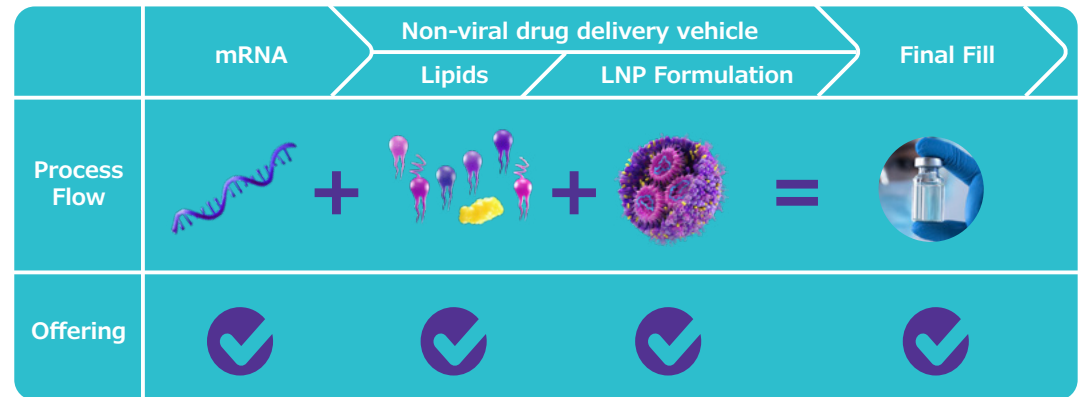
BioReliance® upstream services include:

- 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

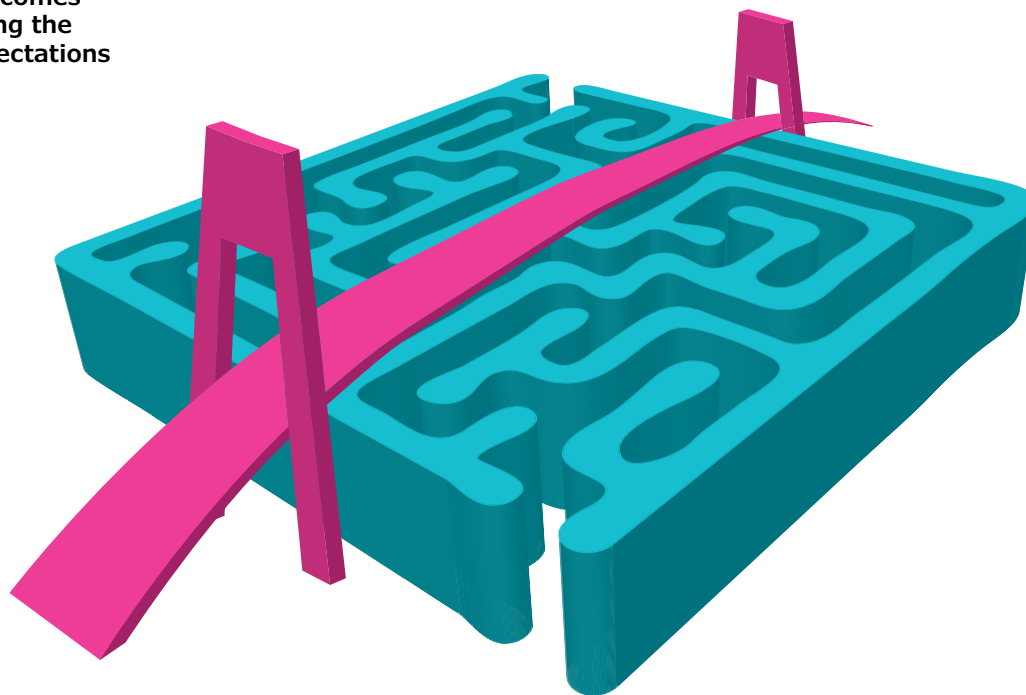
Specifically developed for high-risk applications, our buffers, salts and stabilizers are low in bioburden and endotoxins. Supported by our Emprove[®] program, our excipients have extensive documentation, helping minimize regulatory and quality-associated risks in your manufacturing. All this simplifies 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



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.

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.



vaccines, empowered



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Italy: 848 845 645

Spain: 901 516 645 Option 1

Switzerland: 0848 645 645

United Kingdom: 0870 900 4645

For other countries across Europe,
please call: +44 (0) 115 943 0840

Or visit:

[MerckMillipore.com/offices](https://www.MerckMillipore.com/offices)

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[MerckMillipore.com/techservice](https://www.MerckMillipore.com/techservice)

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