MEVAC KEMIN

UNDER THE PATRONAGE OF
UNITED ARAB EMIRATES
MINISTRY OF CLIMATE CHANGE
& ENVIRONMENT

MIDDLE EAST MEVMAS VETERINARY MEDICINE & ANIMAL SCIENCE CONFERENCE 2022

TECHNOLOGICAL PROCESSES USED FOR VACCINE MANUFACTURING IN MEVAC

Week of Innovation on VETERINARY SERVICES
7-10 FEBRUARY 2022

Leonid DUDNIKOV

CONTENTS

MEVAC CC Bio-API PRODUCTION

MEVAC's BIOTECH PHILOSOPHY

MEVAC: HISTORY

Evolution of development and manufacturing

2010 — Ideas, brainstorming team, knowledge power and adequate risk.
Two key products: FMDV + AIV

2013 — First private Egyptian GMP bio-API production facility. International collaboration.

2017 — New projects, new products
Scaling production facility.
International markets.
More international collaboration.

2020 — An increased interest in human vaccines scope. Issues such as organizational of the 3rd + 4th new facilities, corporate vision, and agility become the focus of development.

2023 — Total EU-GMP BSL-3 R&D and Pilot production unit.
Recombinant vaccine production and flexible bio-production facilities.

RESPECT FOR PEOPLE

Respect

Respect and understand country needs

Take responsibility

Build mutual trust

Knowledge kettle

Teamwork

Stimulate personal and professional growth

Create opportunities for development

Optimize team, working area and individual performance

CONTINUOUS IMPROVEMENT

Challenge

Create long-term vision to meet challenges

Foster creativity to realize the vision

Kaizen/Lean

Continuously improve development/ manufacturing/ business processes

Genchi Genbutsu

Make the right decisions by going to the source of the facts

Evolve and innovate

BUSINESS STRATEGY

Business Model 2022 (manufacturing link)

MISSION

Ensure safety, potency and efficacy of vaccines using international technology standards. To defend the community against the threats of emerging infectious diseases by customizing products for acute specific diseases

VISION

Providing High Quality Effective Solutions for Better Health with International Quality Standards. Education and training to ensure our employees are both satisfied and performing at the highest level

STRATEGIC OBJECTIVES

Our company strives to fully utilize all development + production capacities and strengthen our business activities in MEVAC's traditional markets and Europe

LONG-TERM OBJECTIVES

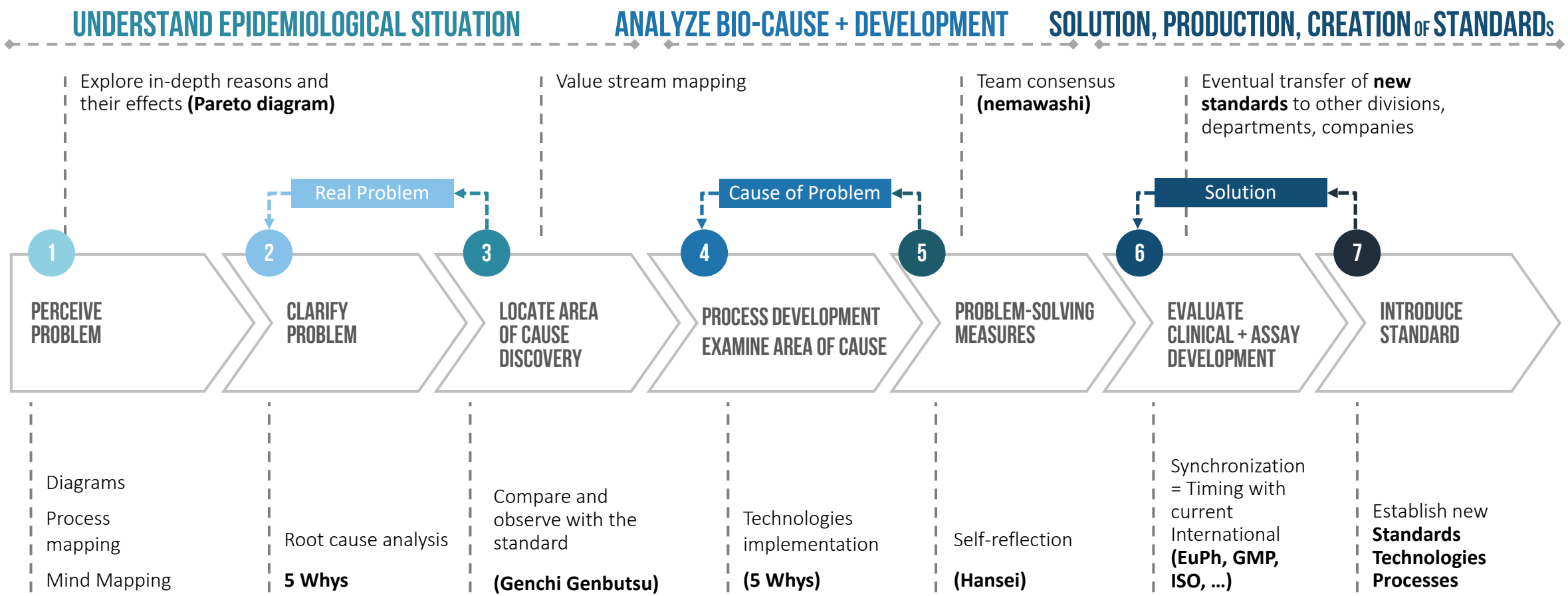
Our company expects to double revenue in the next three years

Start human vaccines development and production

ASSET BASE			
	Maintenance	4 maintenance facilities	
	B#1 BSL-3	R&D + QC + Cell Bank	COVID-19 Pilot
	500Lt Pilot → 5000Lt UVAC	50M doses FMDV 2023	Human vaccines > 3 types
	B#3 + B#4 Poultry rVaccines	Scaling production	Development
	Highly Qualified Product	International standard identity	
	Highly Qualified Staff	~100 new employees	International Reputation

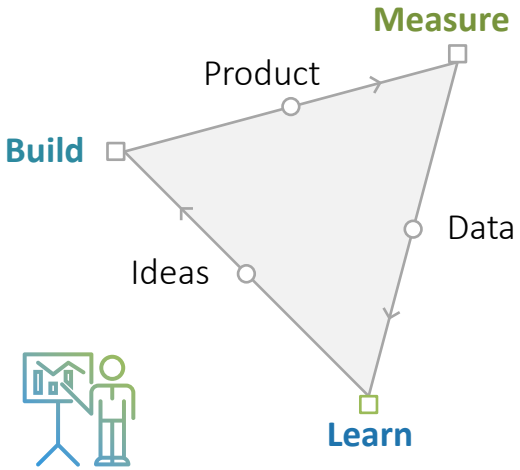
VACCINE DEVELOPMENT/PRODUCTION/QC IN MEVAC

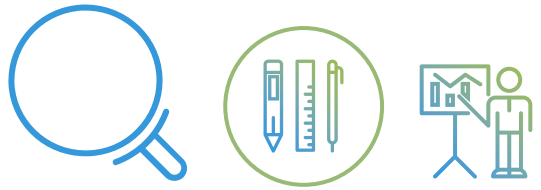
The Toyota Way: Practical Problem-Solving Process in Bio-Tech



MEVAC'S BIO-STARTUP METHODS

BUILD-MEASURE-LEARN-FEEDBACK LOOP





BUILD

Import substitution in biosafety area

From Lab to Facility (B#1, B#2, B#3 …B#n)

International reputation

From Minimum viable product (MVP) →

→ Exceptional viable product (EVP)

Small → Pilot → Industrial scale batches

MEASURE

Bio-API production

Interlaboratory comparison (ILC) tests

Cohort analysis

Innovation accounting

Continuous Development + Deployment

AARRR (Acquisition Activation Retention Referral Revenue)

LEARN

Collaboration

Analogs and antilogs

Customer archetype

Engines of growth

Five Whys

TRIZ in Bio

„Get out of the Building"

Pivot – Knowledge + People

Pull (hypothesis)

Validated learning

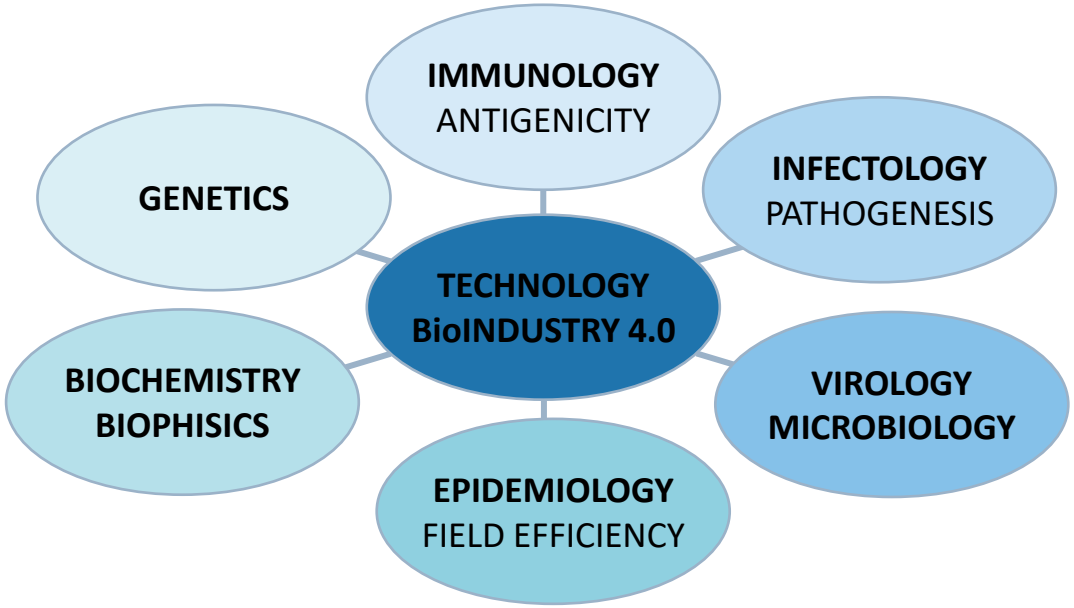
Waste / Value

Ideas → Build → Product → Measure → Data → Learn

MEVAC IMMUNOTECHNOLOGY

Brief overview of vaccines manufacturing

TYPES OF LICENSED VACCINES



- Inactivated toxins
- Inactivated whole fungal, bacteria or viruses
- Live attenuated fungal, bacteria or viruses

- Subunit vaccines
- Genetically engineered constructions:
  - Vector → Proteins
  - pDNA / mRNA
- Polysaccharide vaccines
- Conjugate vaccines
- VLPs-based vaccines (virus-like particle)

- There is no generic technology for making vaccines
- All vaccines are unique/different
- Even the same vaccine produced by a different manufacturer can be different

SCENARIO

Basics MEVAC’s trends

EGGS BASED MODEL

Scientific collaboration

Flexibility

Working experience and solutions

Maximum business value

Comprehensive evaluation and documentation

VS

CELL CULTURE BASED

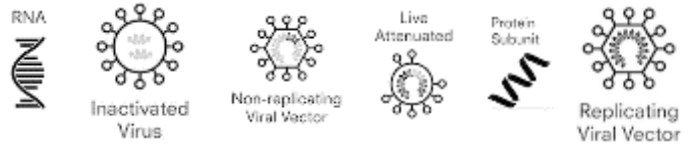
Contact negotiation

Working experience

Development

Rigid scaling and planning

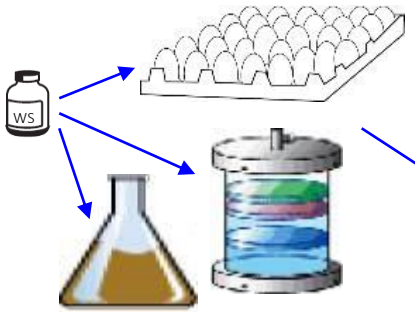
Comprehensive evaluation, documentation

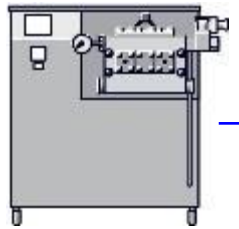


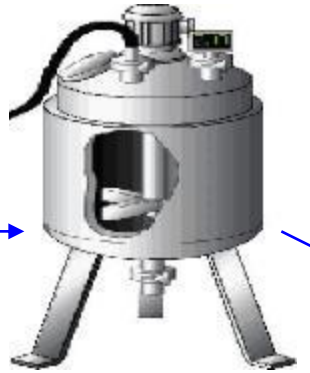
THE Bio-AGILE METHOD

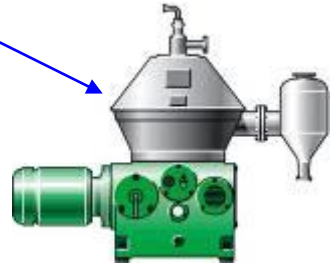
The agile approach to scientific project management encourages an environment characterized by development, delivery, collaboration, self-organization, and rapid results. It allows specialists from different academicals and science schools involvement in intellectual collaboration, project planning, and development from the very beginning

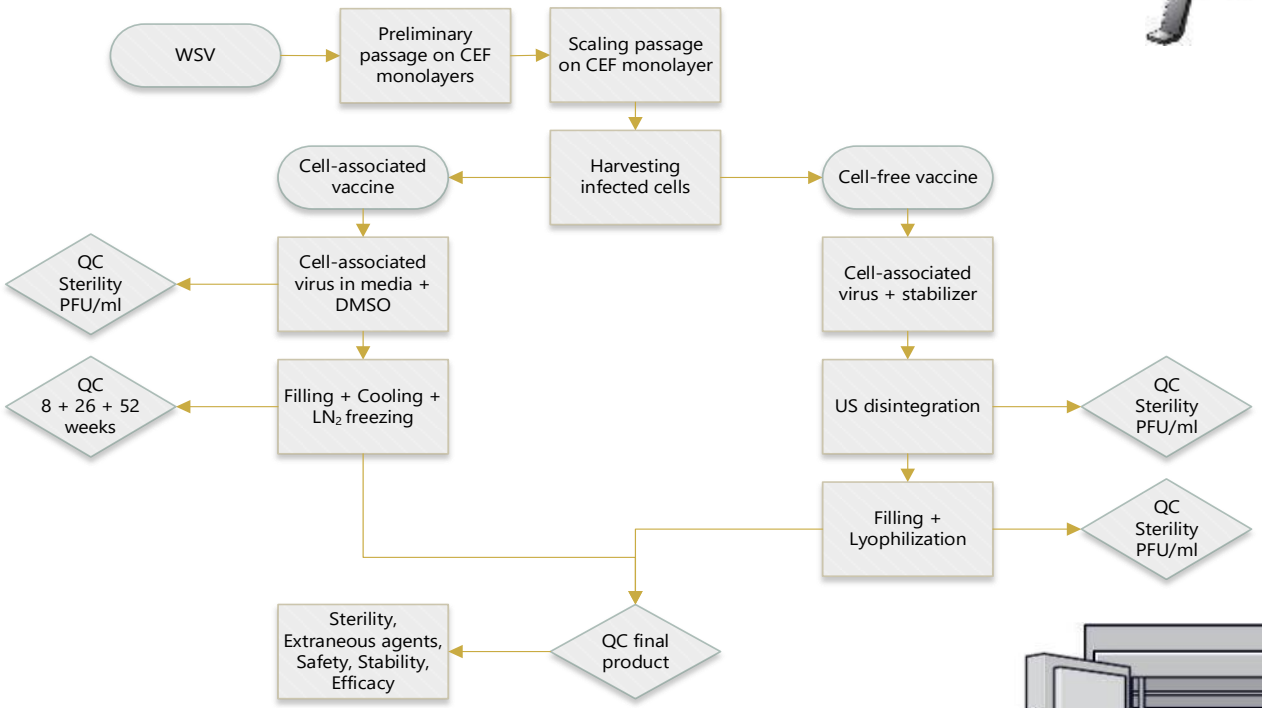
LIVE VACCINE PRODUCTION

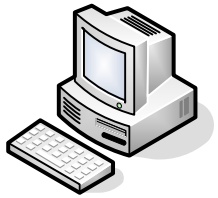


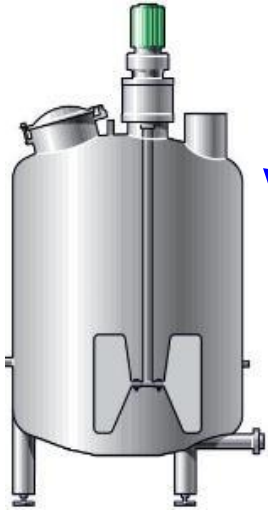


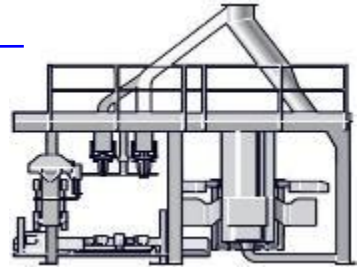


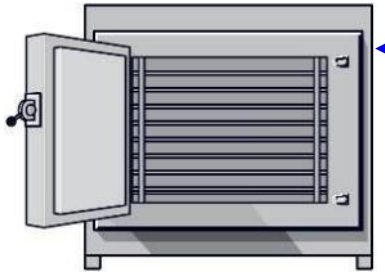












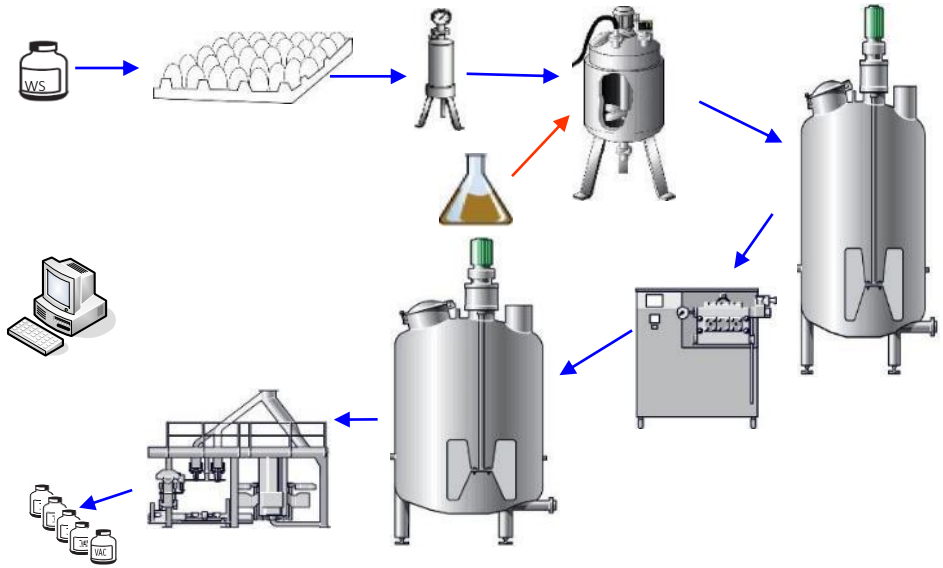
INACTIVATED EGG BASED VACCINE PRODUCTION (INFLUENZA)

Pre-streaming processes

Chickens Clean/SPF eggs ordering → Eggs desinfection → Eggs 10-11 days pre-incubation +37°C → Eggs transportation desinfection transferring

Upstream processes

Strains Bank → WSV vial thaw / re-constitution → WSV dilution $EID_{50/0,2mL/egg}$ calculation → 20 000 pre-incubated eggs inoculation → Infected eggs incubation +37°C → Infected eggs cooling +4…+8°C → Allantoic harvesting 200 Lt Process vessel



Downstream processes

Clarification Separation Microfiltration → AG 200 Lt +4°C holding tank → AG 200 Lt inactivation tank → TFF concentration → Ultraspeed flow gradient centrifugation 2X → +4°C holding tank

Ion Exchange Chromatography ← Buffer +4°C holding tank

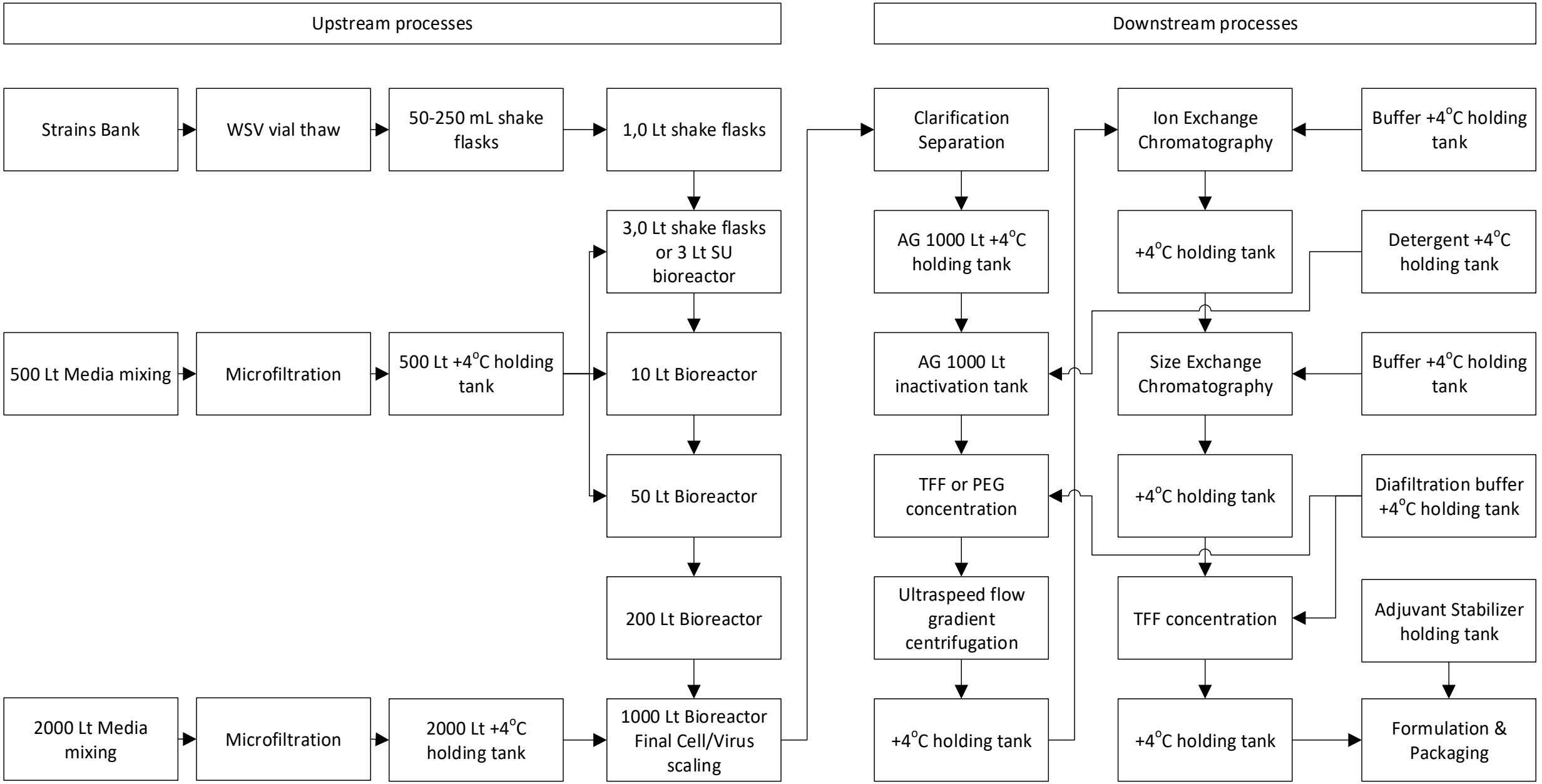
Ion Exchange Chromatography → +4°C holding tank → Size Exchange Chromatography ← Buffer +4°C holding tank

Size Exchange Chromatography → +4°C holding tank → TFF concentration Microfiltration ← Diafiltration buffer +4°C holding tank

TFF concentration Microfiltration ← Adjuvant Stabilizer holding tank

TFF concentration Microfiltration → +4°C holding tank → Monovaccines formulation & Packaging

CELL CULTURE BASED VACCINE PRODUCTION

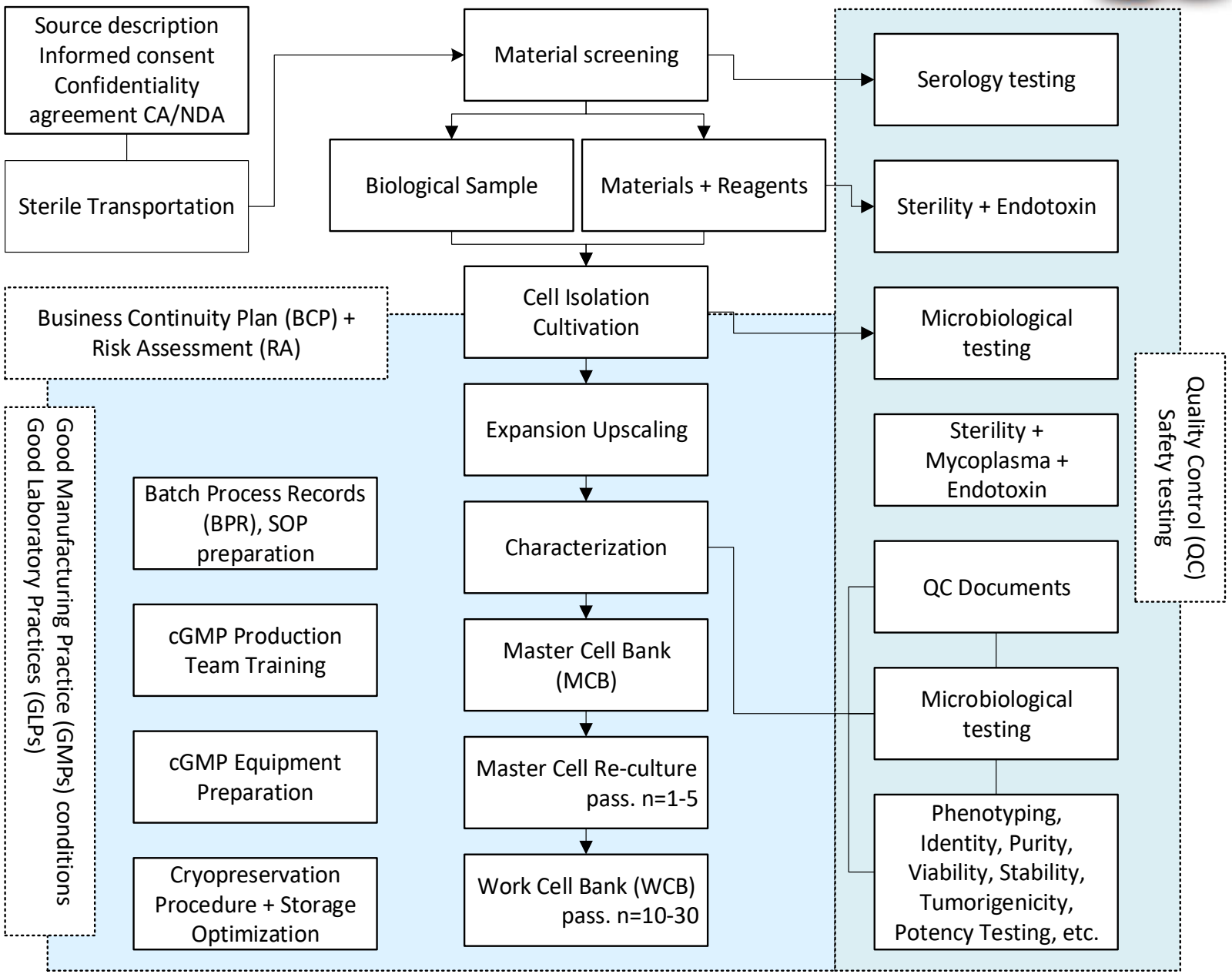


CELLS BANKING under cGMP

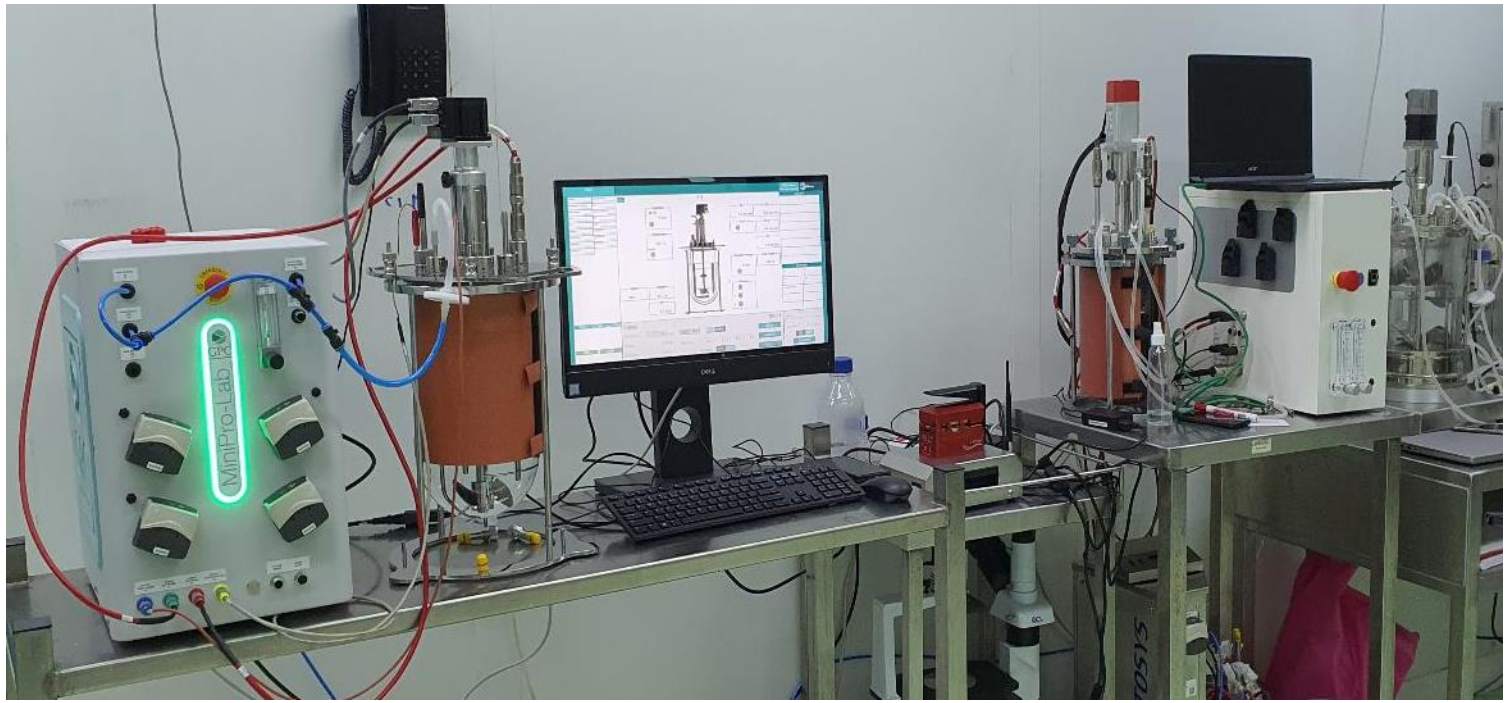
Schematic of the cell expansion process

Cell-specific productivity (q_P) = CQAs:

- Process parameters during cell expansion:
  - cell densities, viabilities, metabolites, pH, pCO_2, pO_2, T^o, etc.
- Index proliferation:
  - cell age (defined as the number of doublings before flask/roller/bioreactor inoculation) reflecting growth duration
- Growth rate (the average specific growth rate of cells derived from the cell-expansion process) reflecting the state of the cells
- Cell-specific perfusion rate (CSPR) + productivity *(example)*:
  - virus titer ($CCID_{50/mL}$)
  - $146S^{FMDV}$ component yield (ug/mL)



Scale-X hydro bioreactor
UNIVERCELL, Belgium



BIO-Compact Bioreactor
Solida Biotech
Germany-Italy
(not recommend)

GLOBAL PROCESS
CONCEPT (GPC)
France

TFF concentration

- MM Cogent-M1 (Germany) 0.1 sq.m. from 2018
  300-1000 kDa
- Cobbette (Italy-China) 1.0 sq.m. from 2020
  300 kDa


BAILUN BIO

ADJUVANT=IMMUNIZERS DEVELOPMENT IN VACCINES MILESTONES

Oil Alum Triterpenoid glycosides

As a substance that when added to the antigen would improve the immune response

LPS, DNA, LPP
Aluminum salts:
- Potassium Sulfate
- Phosphate
- Hydroxide

$Ca_3(PO_4)_2$
Freund's CFA/IFA
- w/o

Natural derivatives
Oils, Surfactants
Saponin/Gypsophilin
- Quil-A
- Allohrasid

Single Adjuvants

Need to induce proper immune response against difficult low immunogenic pathogens

Synthetic derivatives/oils (silicon)
ISCOM's
Liposomes
QS-21 MF59 MPL
Al_2O_3 / V_2O_5 / ZnO_2 / TiO_2 / SiO_2
Multiple/Double Emulsions
Virosome
IFA
- w/o o/w w/o/w o/w/o

Ge Ce Au Ag
CF and IL-15

Adjuvant Systems

Insufficient response produced by challenging vaccines; to stimulate the production of a long lasting response

Amorphous hydroxylphosphate sulfate
Chitosan + Cyclodextrins + β-glucan
ISCOMATRIX
Flagellin
R837/848
Surface Arrayed Therapeutics SATx™
TLR9 ligand (oligonucleotide)
- Toll-like receptor 9 agonists
- CpG ODN

M-CSF = MGI-IM = CSF-1
EGVac system
Glycoside Cholesterol Complex (GCC)
rIF

Molecular Adjuvants for mRNA / DNA Vaccines

Safe immune Ag target stimulants prolong lifetime immunogenicity.
Class's org. personalized immunotherapy

Nano / Microparticles/ Emulsion / Colloids
- Novavax Matrix™
- Poly(DL-lactide-co-glycolide)
- Polystyrene (latex)
- Chitosan nanoparticles (IBV-CS)

Lipid / Aqueous Two-Phase Systems, Smart Polymers
- Cationic peptide complexed/liposome
- VCL-HB01 (Vaxfectin)

Immuno-active patches
- Dendrimers
- Quantum dots (QDs)
- Magnetite (Fe_3O_4)
- Nanostructures Graphene
  - nano-tubes
  - nano-cells/spheres/balls
  - nano-foam/net/grid

NanoBot = NanoRobots

Detoxified mutants dmLT
TLR5 ligand protein (Flagellin) linked to Ag
- VAX2012Q, VAX125

TLR4 ligand protein +MPL + Al(OH)
- RS529 GLA-SE

Squalene + Pluronic®L121
Co-Adjuvants: polyU/C
CAF01, SSI
dsRNA polymer analogue + TLR3 ligand
- Poly I:C = PIC,PICLC,PIC12U,PICKCa®
- (Rintatolimod=Ampligen®)

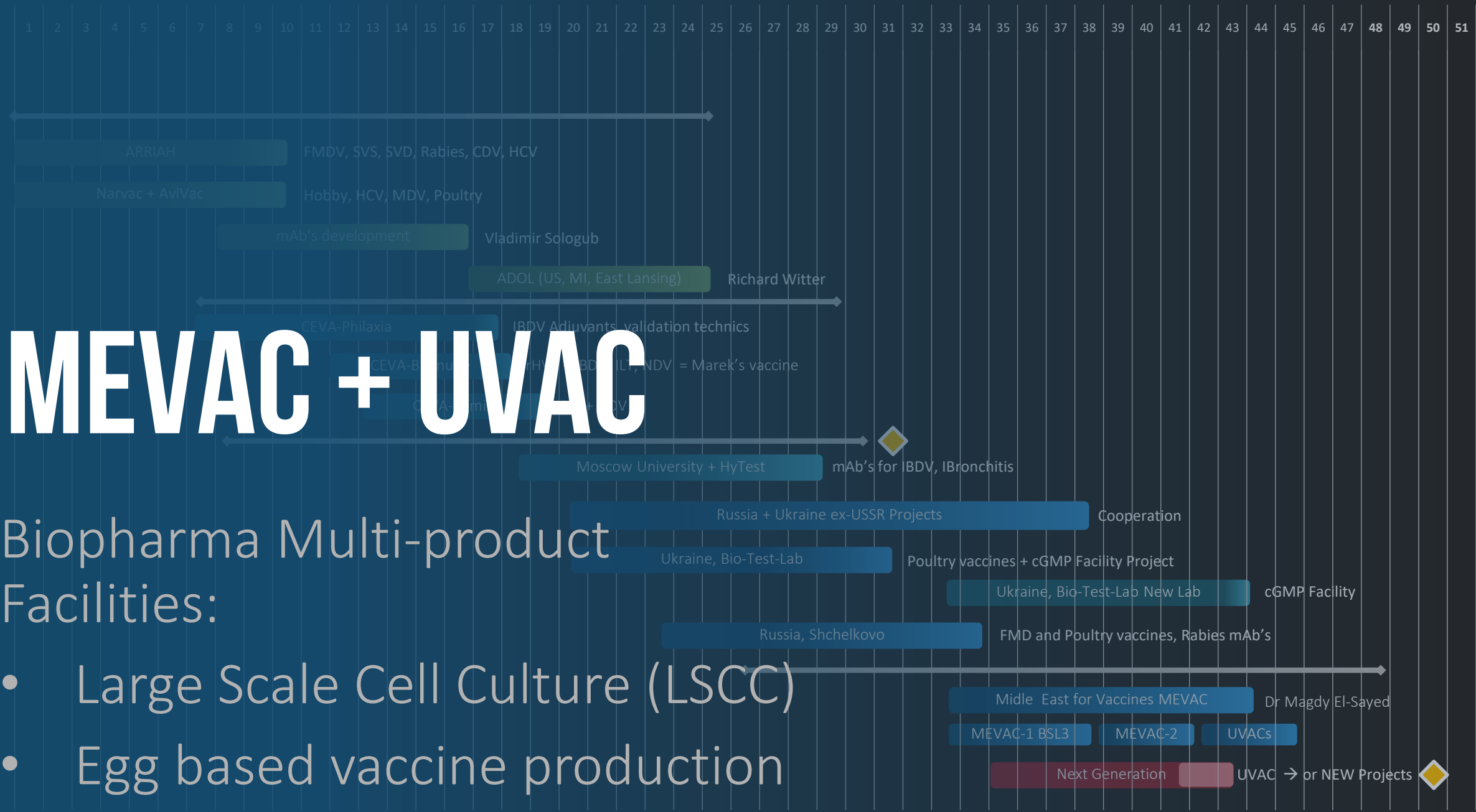
Inulin=Advax™ (β-d-[2 → 1] poly(fructo-furanosyl) α-d-glucose)

pre-Classical Industrial Biotechnology — 1930's
Classical Industrial Biotechnology — 1980's
Recombinant DNA Biotechnology — 1990's
Post Genomic Biotechnology — 2000's

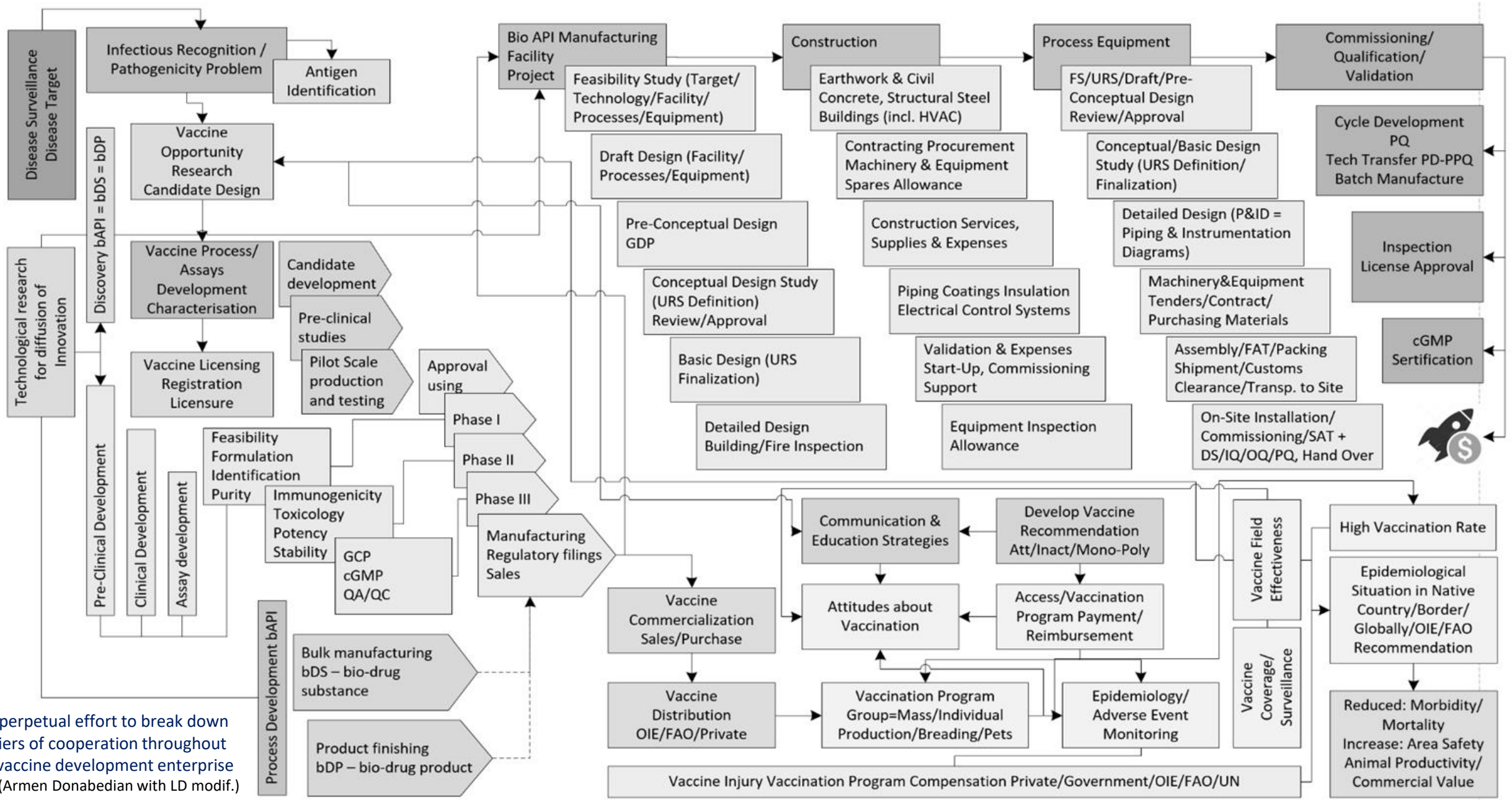
MEVAC + UVAC

Biopharma Multi-product Facilities:

- Large Scale Cell Culture (LSCC)
- Egg based vaccine production



VACCINE R&D + PRODUCTION + DISTRIBUTION MODEL

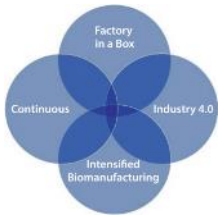


The perpetual effort to break down barriers of cooperation throughout the vaccine development enterprise

(Armen Donabedian with LD modif.)

INDICATORS FOR SIMULATION MODEL

UVAC-2 Innovation Case Study
Next-gen + Factory of the Future + Smart Bioprocessing



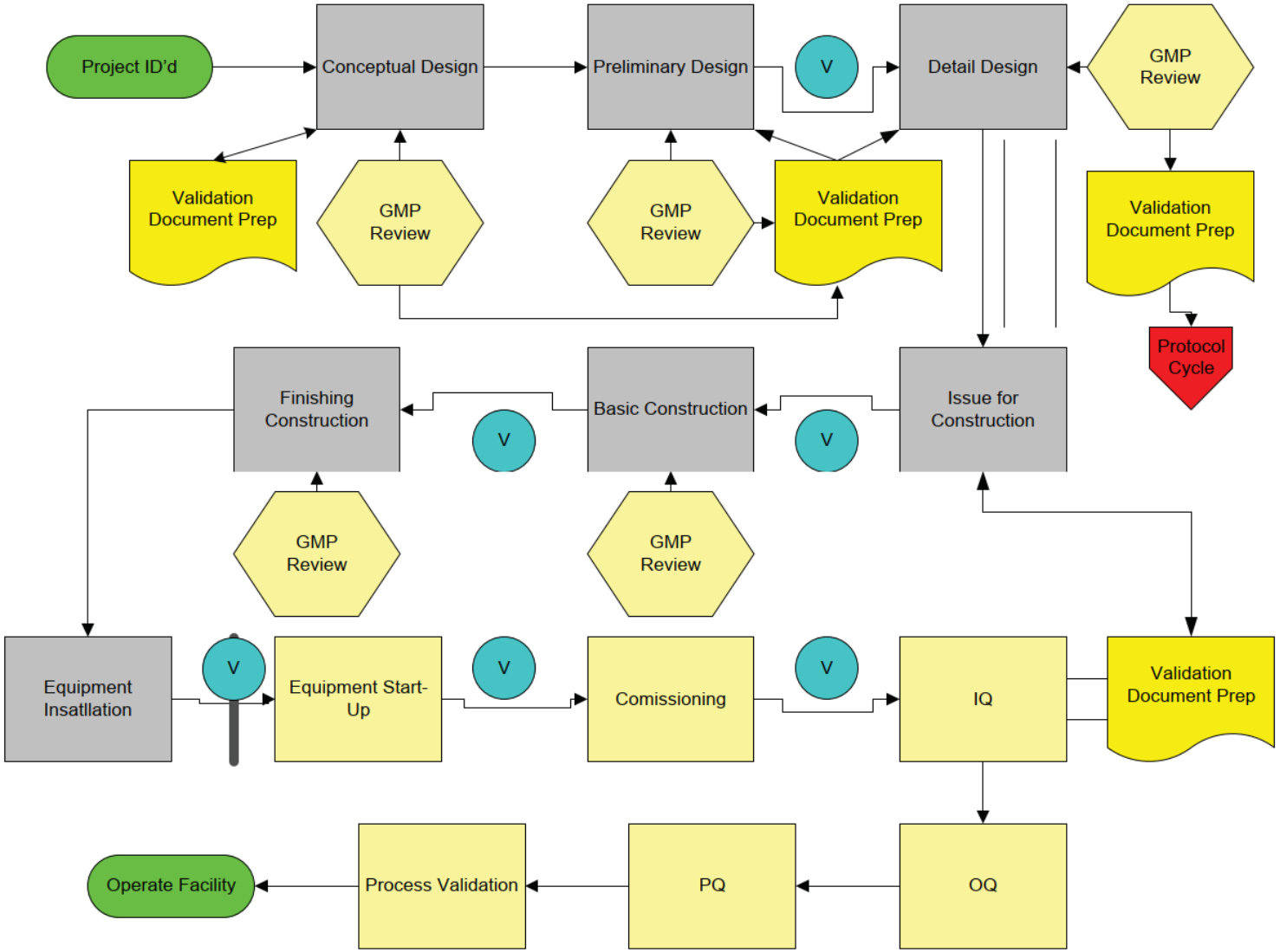
Product information	System elements	Material flow information's
from the production program Orders / products - type - amount - time period **from parts lists** - assemblies - parts - stock **Loading strategy** - sequence - order of arrivals	**from the workshop layout** - workplaces - storage systems - buffers - conveyor system - funding aid e.g. with the following information: - type - number - topology - capacity	**from the work schedule** - technological order - economic batch size - setup time - time / unit - assembly time - used machines - multi-machine operation

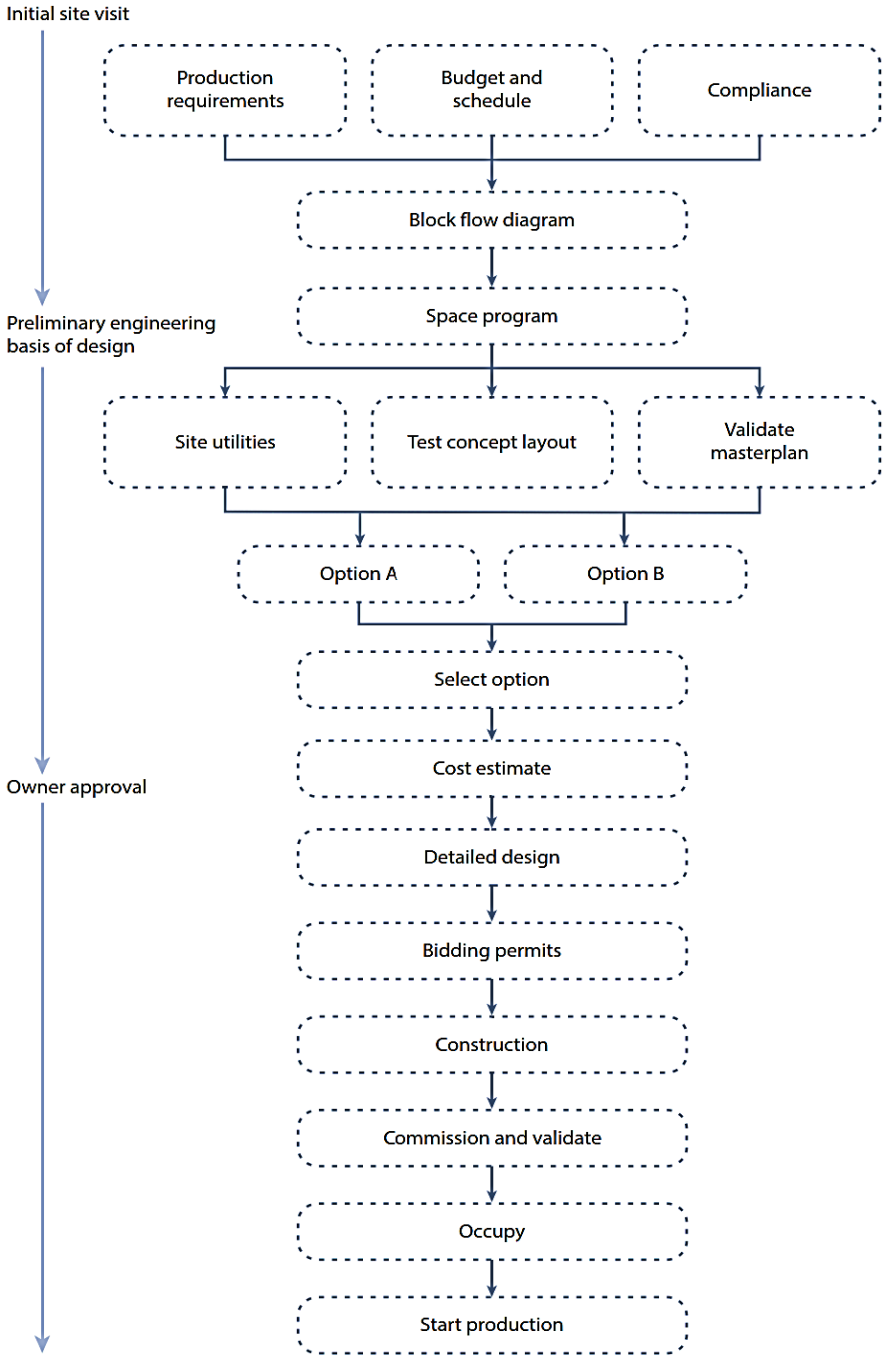
✓ Factory in a Box	✓ Continuous Manufacturing	✓ BioPharm 4.0	✓ Intensified Production
Future proofing	Connected and closed	PAT, MAM	Train simplification
Modular / Podular (Isolators)	Contiguous, not closed	APM, OPM	Footprint productivity
Single-use system (SU)	In-line fluids conditioning	Adaptive plant	Temporal productivity
Hybrid-SU systems	Straight-through processing	Cloud, AI, IoT	Economic productivity
Standardized vs Free	Perfusion-based continuous	Improved monitoring	Volumetric productivity
Integrated, enterprise	Pseudo- and quasi-continuous	ERP→MES+EBR→LIMS	Cell/WSV-specific productivity
Shared services plant	Intensified perfusion continuous	Model predictive control	Improved clonal expression
Platform agnostic suites	Integrated continuous processes	Real-time product release	Improved process and/or medium
Entity and mode flexible	Repeated fed (or intensified) batch	Automation, autonomation	Many bioprocess simplifications
Shortened process train	Continuous but unjoined operations	Integrated, real-time analytics	Perfusion intensified seed (n^{-1})
Prefabricated cGMP facilities	Enterprise continuous production	Continued process verification	Implementation of columns to left

Whitford and Nelson, BioProcess International 17(6) June 2019

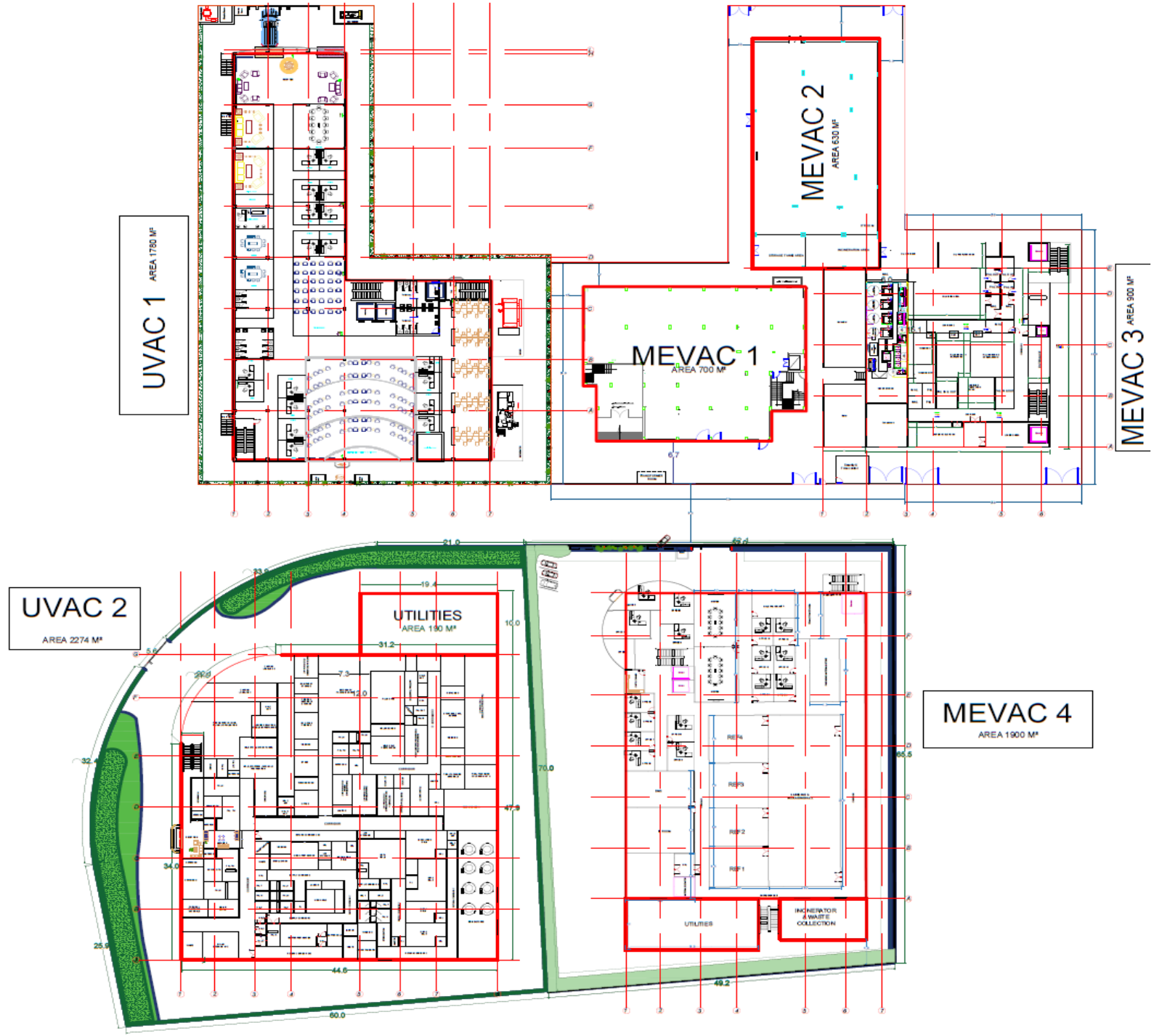
TYPICAL PROJECT SEQUENCE

Principles and following of Facility Design



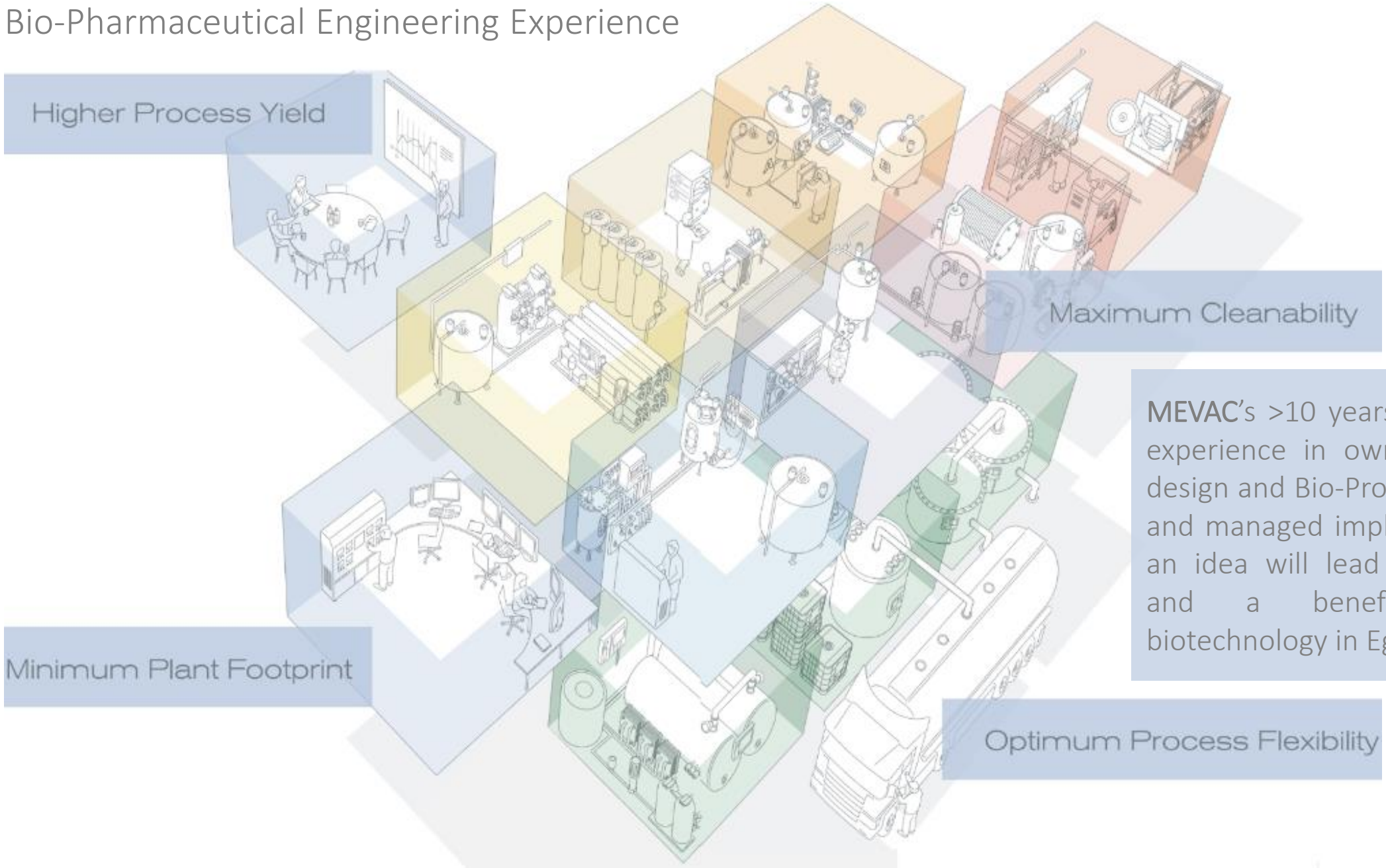



B.2
U-VAC
BSL-3
B.1
B.3
Me-Vac
U-VAC
MEVAC
U-VAC
WS
MEVAC
WS
W.1


UVAC 1
AREA 1760 M²
MEVAC 2
AREA 630 M²
MEVAC 1
AREA 700 M²
MEVAC 3
AREA 900 M²
UVAC 2
AREA 2274 M²
UTILITIES
AREA 190 M²
MEVAC 4
AREA 1900 M²
REF4
REF3
REF2
REF1
UTILITIES
INCINERATOR & WASTE COLLECTION

VACCINE PRODUCTION PROCESSING

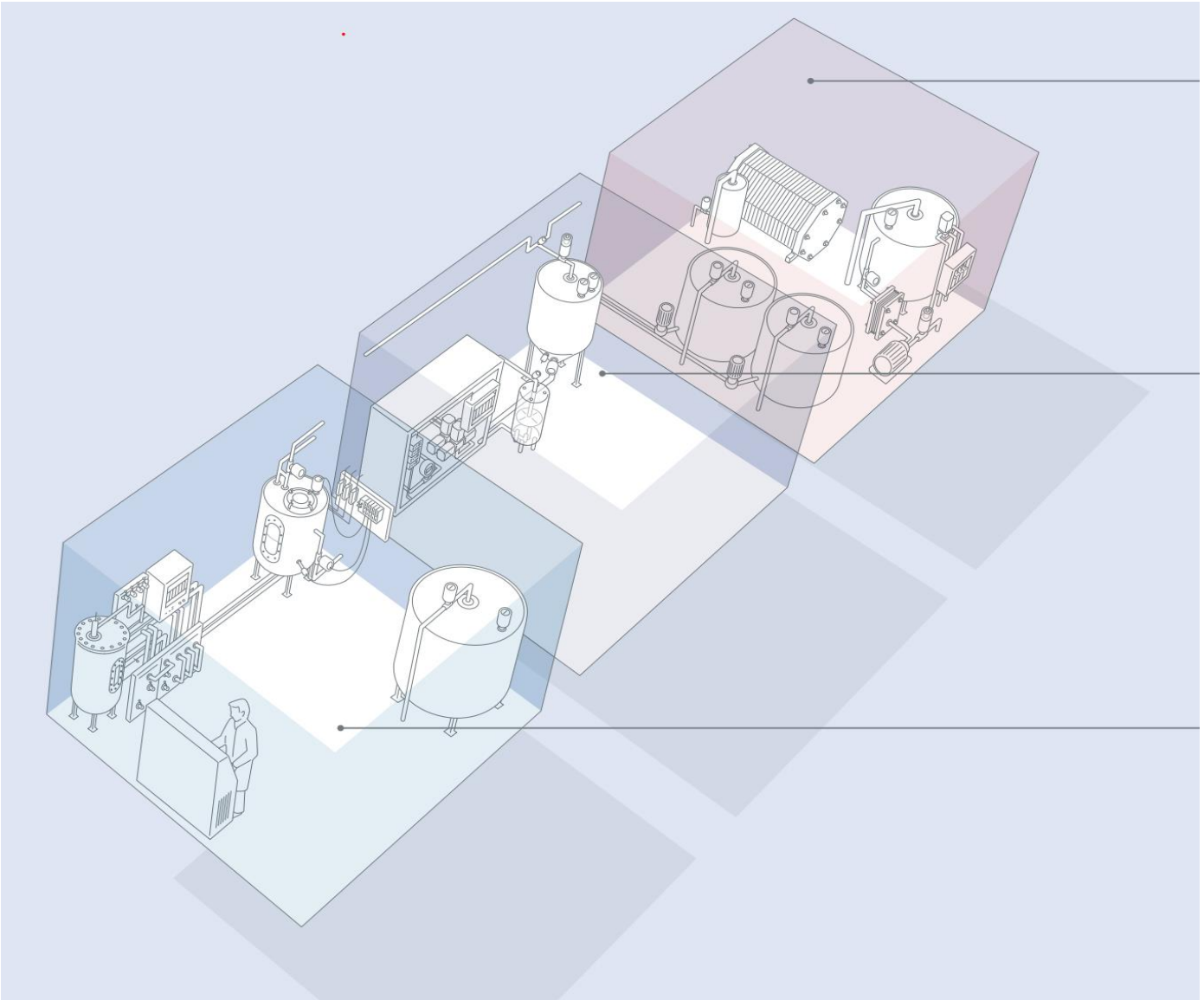
Bio-Pharmaceutical Engineering Experience



MEVAC's >10 years of successful experience in own Bio-Facilities design and Bio-Project realization and managed implementation of an idea will lead to innovation and a benefit of the biotechnology in Egypt

IN-PROCESS PROFESSIONAL SUPPORT

Up/Down Streams Processing



Separation, Filtration, TFF Concentration, Inactivation

Downstream processes of identifiable and specific Bio-API require our unlimited know-how and modularity to save you valuable plant space and offer you peace of mind from aimless spending and cross-contamination.

Purification/Chromatography

Obtain as much immunogenic antigen yield as possible in the right place with the least amount of waste. This is the area where the combined vaccinology competence and process/application understanding is fully utilized to deliver fast flow shifts, minimum dead space, and reduced footprint.

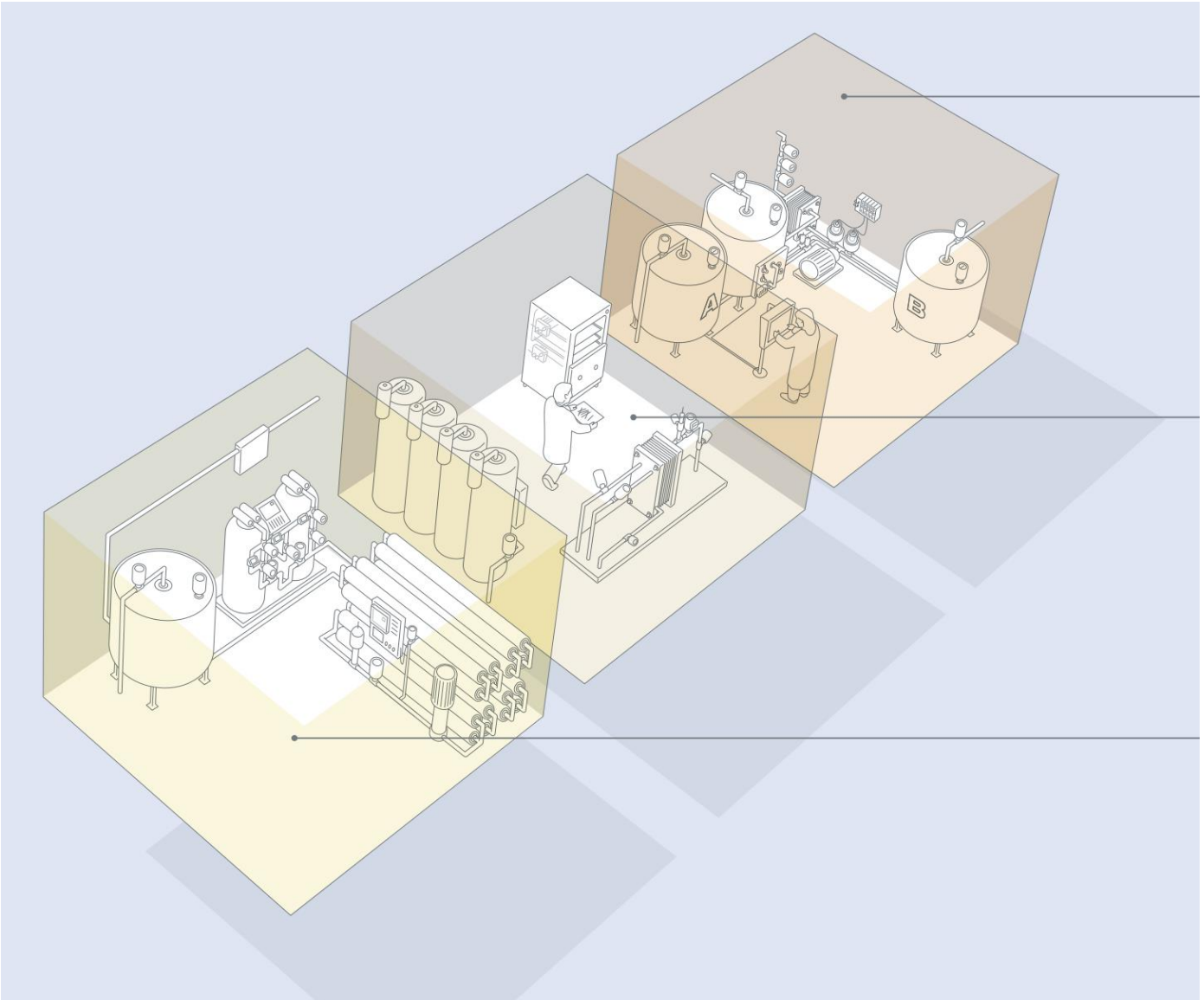
MEVAC's know-how solution, extending the principle that the highest possible return on investment is generated from this area of the Bioplant.

Cells/Virus Cultivation/Propagation

Significant time and money are already invested in preparing the ingredients for the cell/virus cultivation process. On reactors, cell-factories, growth quality materials, and engineering. The result is a completely reliable environment control for the antigens creation; we combine that with exceptional components for parameter control, and solutions, which are used to join up separate reactors within coordinated processing lines.

IN-PROCESSES OF THE BACKGROUND

Bio-Pharmaceutical manufacturing relies on Utilities, Liquids, Gasses, Waste treatment



CIP/SIP = Clean-in-Place / Sterilize-in-Place

Customers trust your product and safety is related to MEVAC's brand. Each stage of your CIP/SIP regime can be controlled and safely documented according to EU-cGMP requirements and we know how to do it. All of the CIP/SIP parameters are safe in MEVAC's hands allowing us to make our vaccines with confidence.

Utility and Clean Steam / BSL-3 waste treatment

MEVAC cares about biohazardous agents and post-processing treatment. We using cutting edge solutions for that.

Water Quality, WFI preparation and Availability

In the biopharma sector water as the most important ingredient. Water quality is therefore often essential to the success of the product. It affects the quality, sterility of an injectable saline solution, buffers, cell/virus growth media preparation traceability and certification of water quality is standard procedure. We are involved, we have concept technology, reliable equipment manufacturers in the complete water supply chain from groundwater treatment and incoming water supply, processing to your most stringent requirements, inline verification and final decontamination, treatment and/or neutralization.

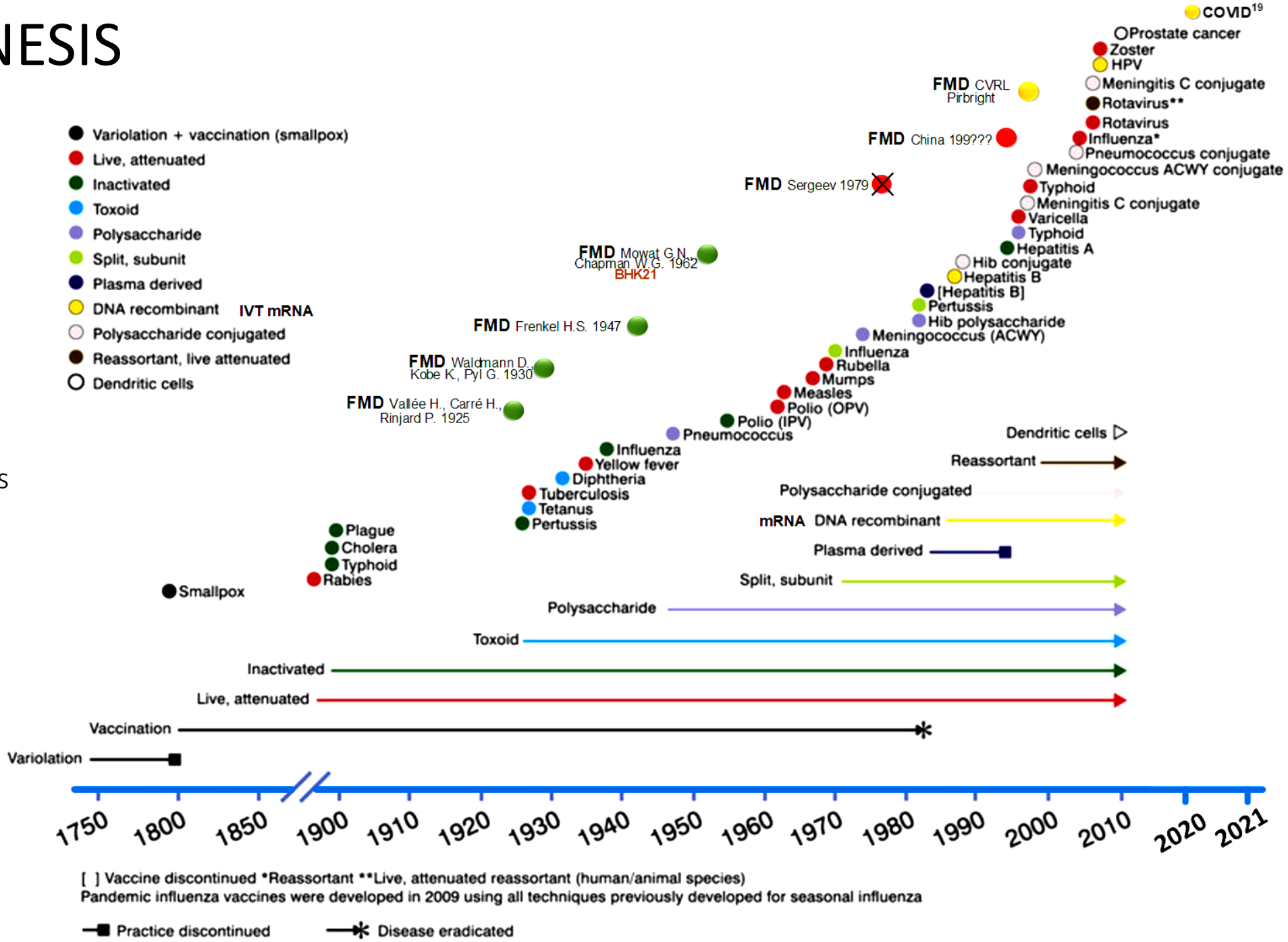
FMDV PRODUCTION TECHNOLOGY CASE

Idea → R&D → Pilot → Manufacturing

VACCINE GENESIS

Development & Production

Permanent improvements in vaccines acting to increase antigen/protein translation, modulate innate and adaptive immunogenicity and improve delivery



WORKFLOW for FMDV BANKING

Research Design Questions

RQ1. What are stakeholder expectations in the context at the FMDV?
RQ2. How can internal stakeholders perceive the FMDV Isolation, Adaptation, Vaccine Development protocols as a valuable element in the performance of their work?
RQ3. How can external stakeholders perceive the FMDV Isolation, Adaptation, Vaccine Development protocols as a valuable element in the relationship with the consulting/outsourcing/collaboration company?

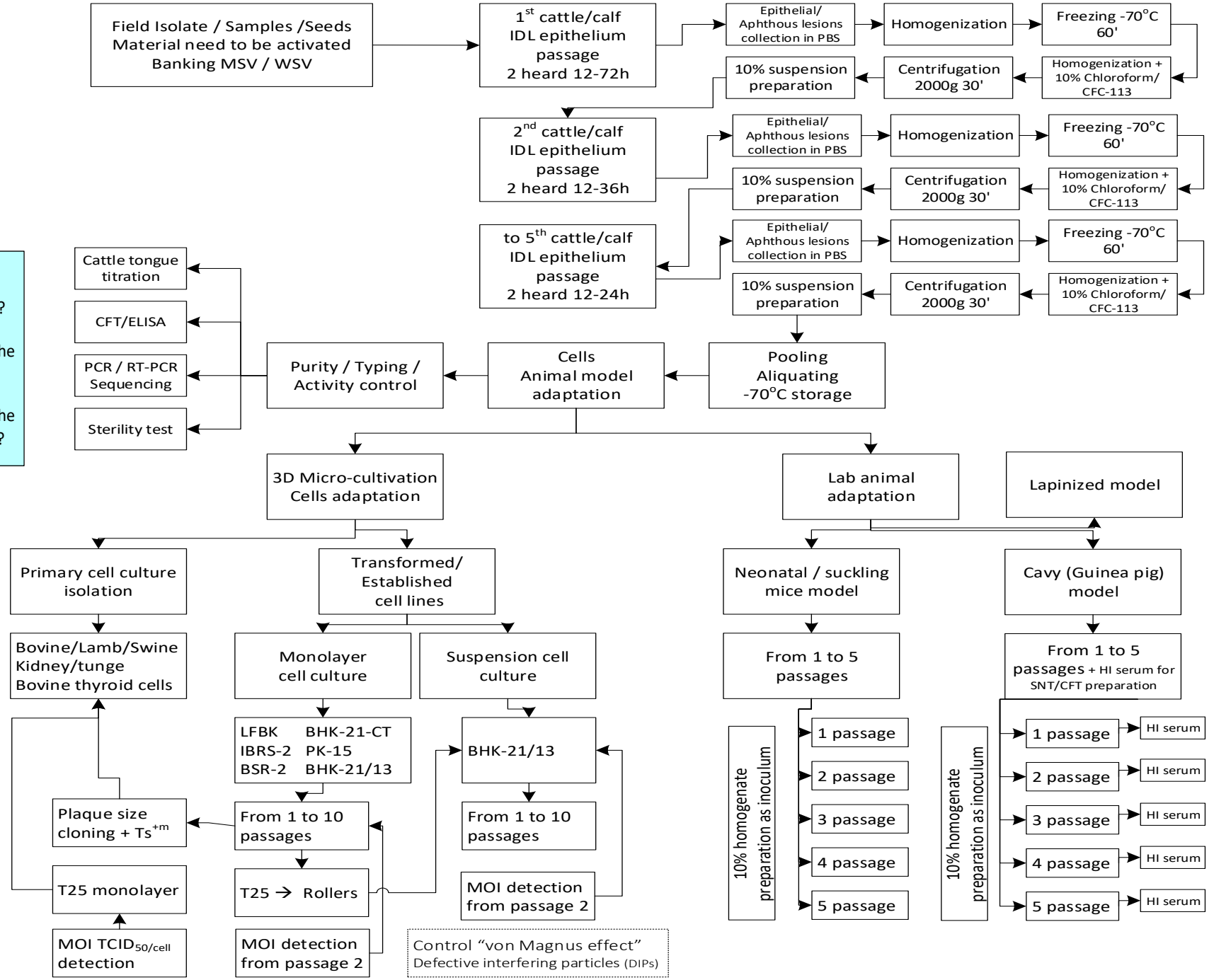
Electronic Search

Articles/Patents identification
Title & abstract analysis
Exclusion & filter applied
Selected articles/patents

Literature Review

Involving the chosen Keywords
("FMDV isolation" or "FMDV vaccine development") and (FMDV "production" or !manufacturing protocol")

Global literature and trends mapped against a timeline and key themes



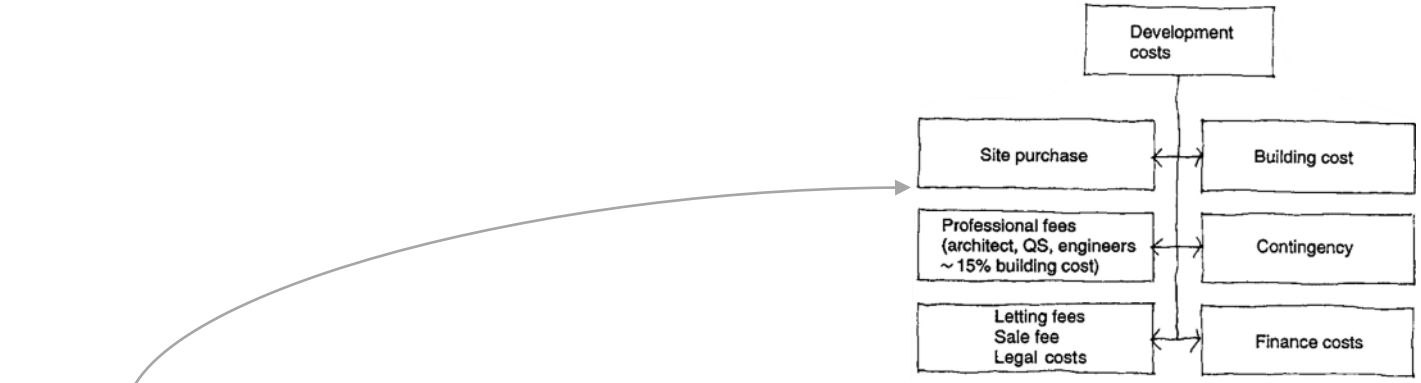
UVAC-2 CASE STUDY

General Figures

Total land area around **4000** sqm

Production areas **55%**

- Production (adherent/suspension):
  - Inactivated (FMDV, RVF)
    - BSL-3 → UPS/DSP
    - DSP → Blending + filling
  - Live cell culture vaccines = Attenuated (freeze-dried)
    - UPS/DSP
    - DSP → Blending + filling + lyophilization
- QA + QC + R&D laboratories
- Technical + Engineering
- Utilities + Waste treatment (BSL-3)
- Administration and auxiliary



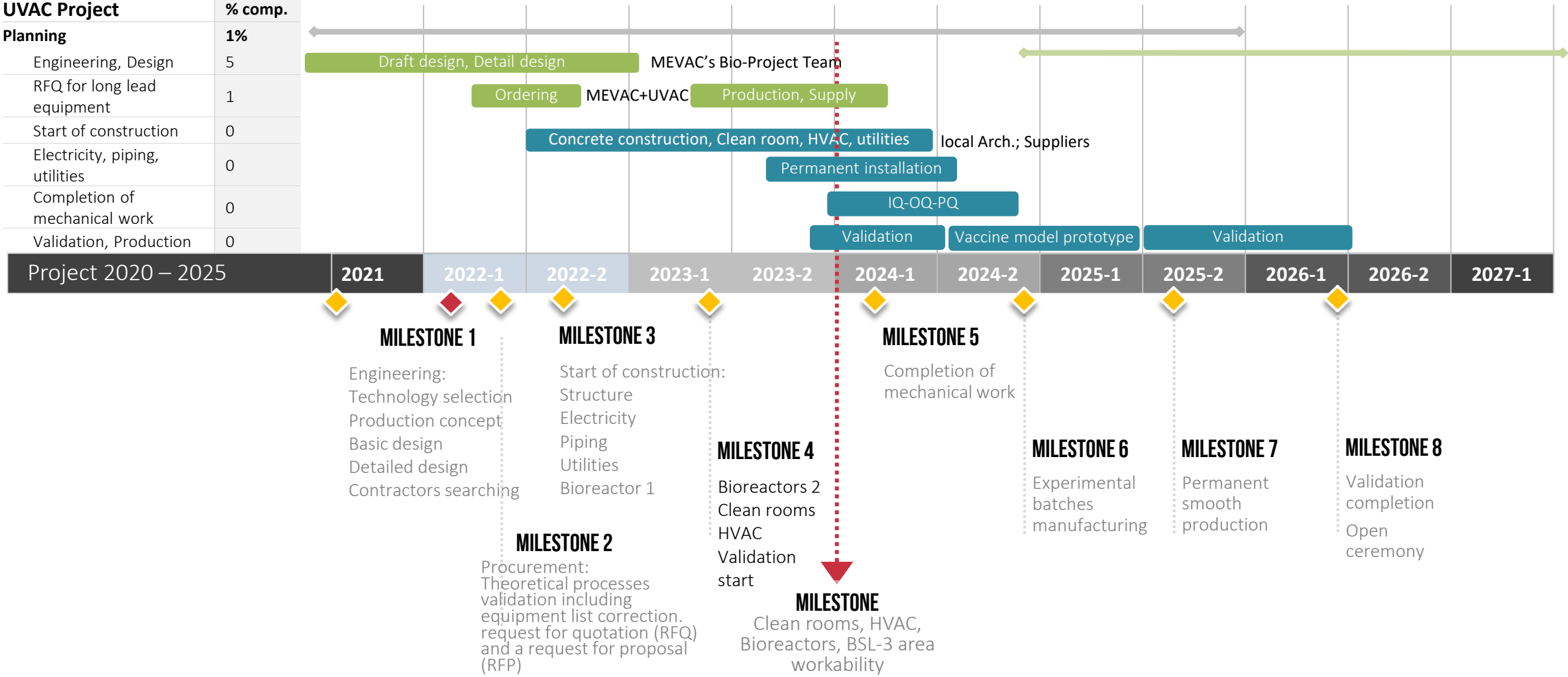
Project Plan Activities Term (months):

Land Purchasing	done
Brief/Draft Project Design	done
Project Design/Documentation	6
Authorities: Permissions, etc.	3
Utilities, Networks	6
Tenders, Buildings, Constructions	24
Equipment: URS→DQ/IQ/OQ→PQ	12
Installation + Validation	6
Launch of production (3 batches)	6
GMP-certification	6

PROJECT PLAN GANTT & TIMELINE

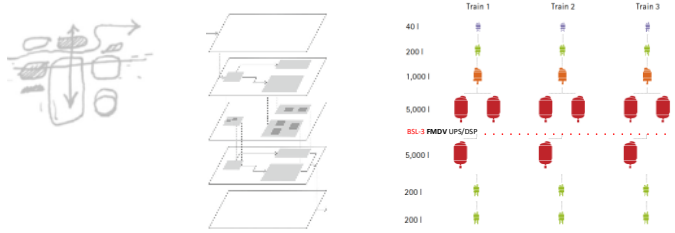
2022 – 2026 half-years timeline with a facility and product profile

UVAC Project	% comp.
Planning	**1%**
Engineering, Design	5
RFQ for long lead equipment	1
Start of construction	0
Electricity, piping, utilities	0
Completion of mechanical work	0
Validation, Production	0



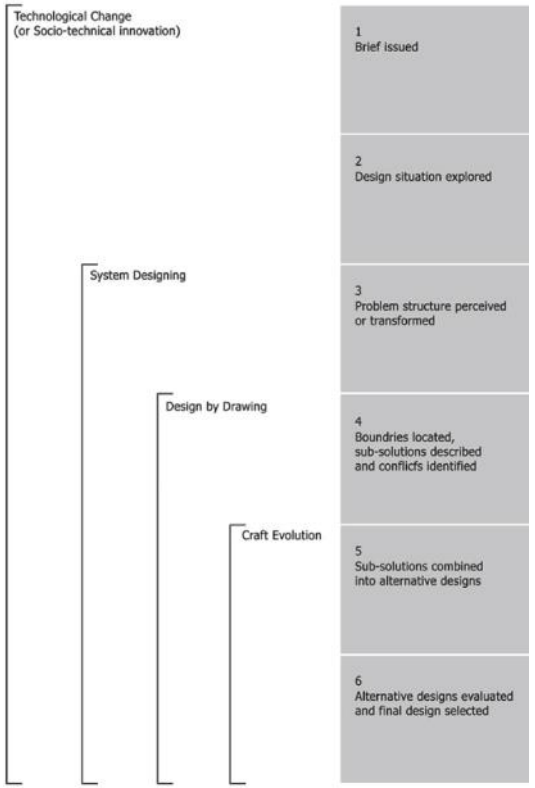
TIME LINE & EXECUTION PLANNING

Bioreactors from Tendering to Validation

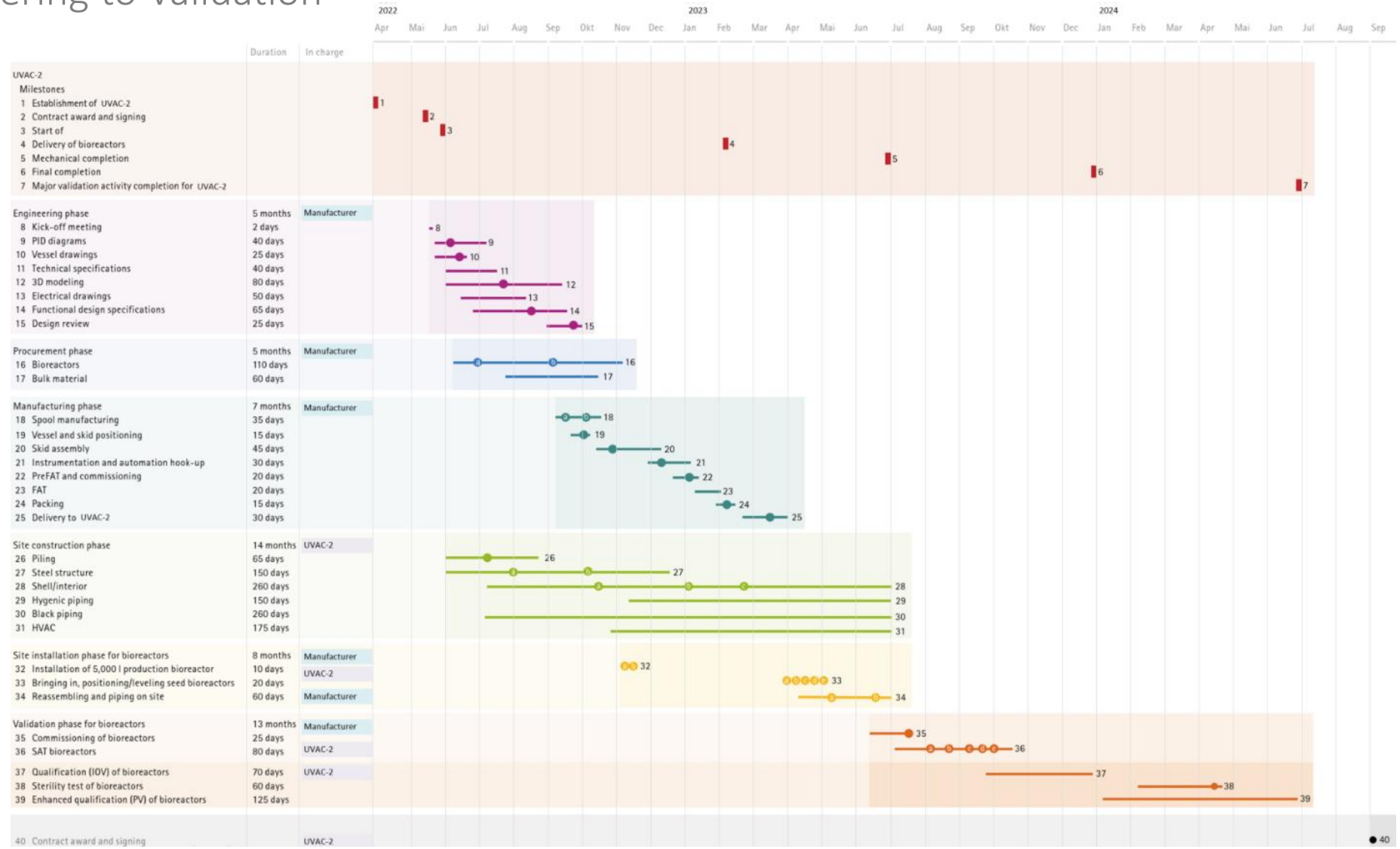


Execution planning
- project management
- applying for permits
- tendering
- relocation planning

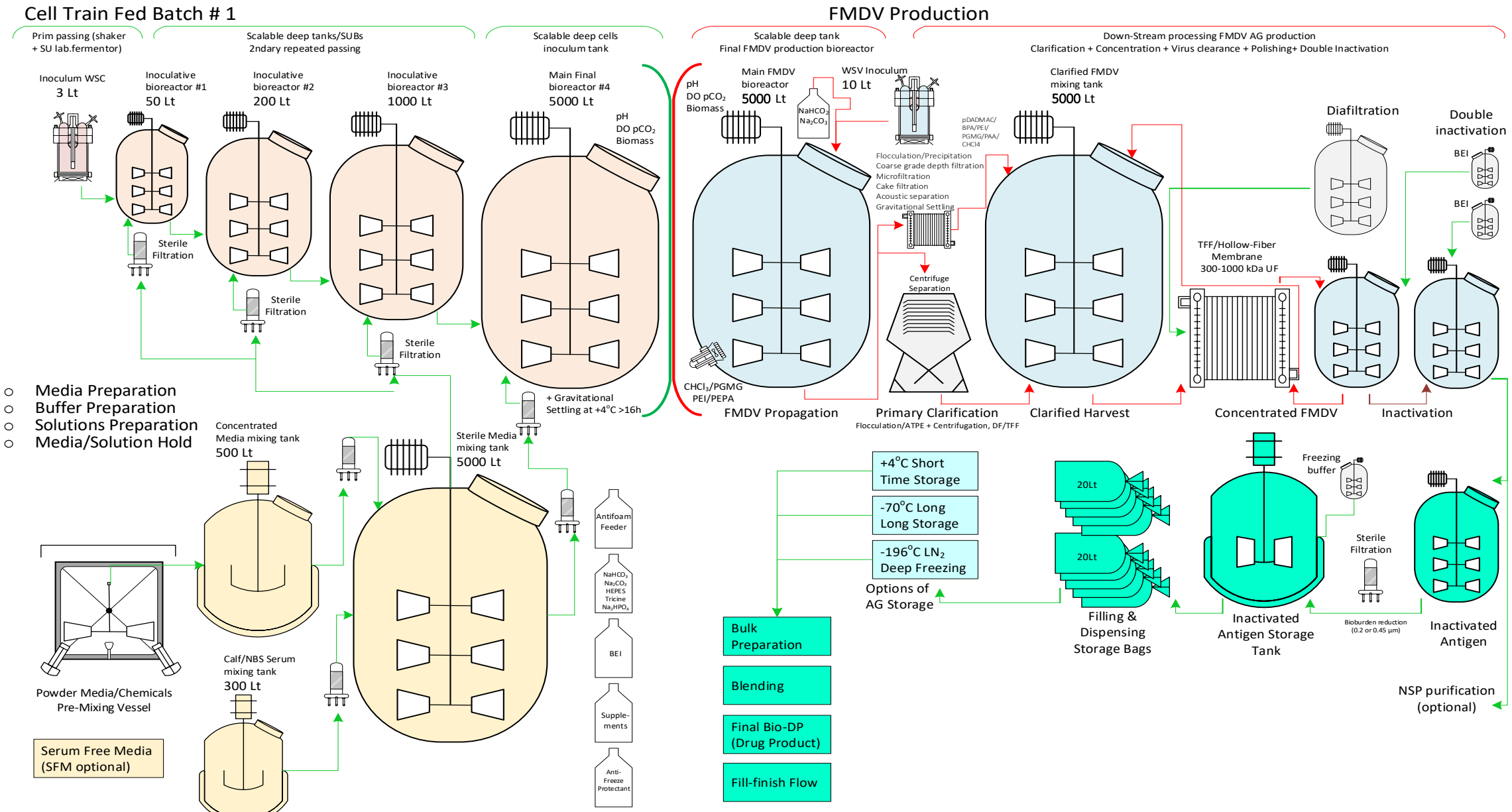
Execution
- supervision
- staff training
- acceptance test
- commissioning and billing



Creativity & Design processes + Execution



5000 LT BIOREACTORS INDUSTRIAL PRODUCTION LINE



BUDGETING/FIXED CAPITAL COSTS (FACILITY MATRIX)

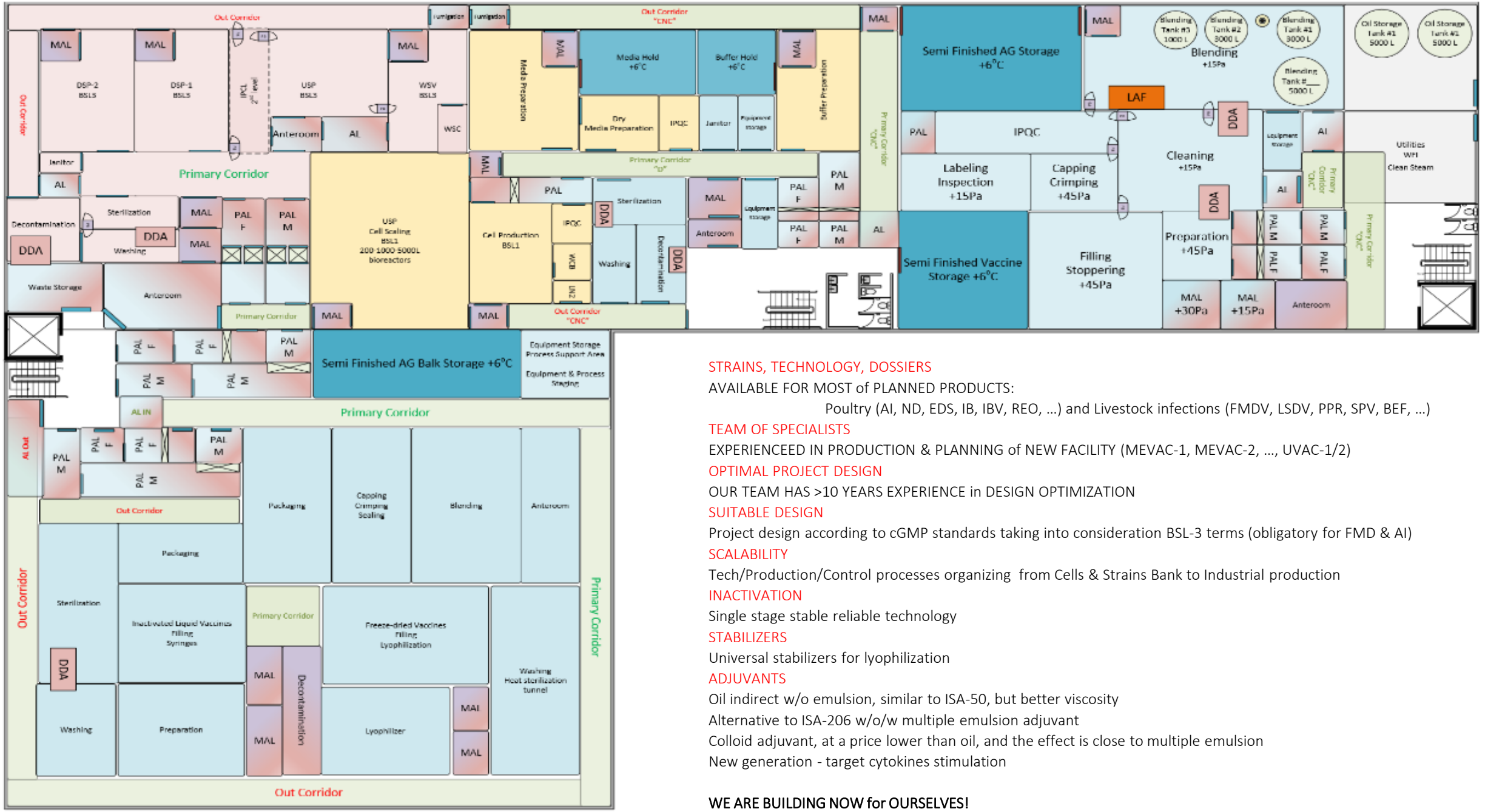
Need data from:
Economic Evaluation (EER)
Cash Flow Analysis (CFR)
Itemized Cost (ICR)
Production SAP/Excel reports
ERP → TOTALY

Cost calculations related to the capital expenses (CAPEX)

Total Plant Direct Cost (TPDC) (physical cost)	%	%
1. Equipment Purchase Cost		7.80
2. Installation		4.21
3. Process Piping		2.73
4. Instrumentation		3.12
5. Insulation		0.23
6. Electrical		0.78
7. Buildings + Celan rooms + HVAC		31.19
8. Yard Improvement		1.17
9. Auxiliary Facilities + Utilities		3.12
TPDC	54.35	
Total Plant Indirect Cost (TPIC)		
10. Engineering		13.59
11. Construction		19.02
TPIC	32.61	
Total Plant Cost (TPC = TPDC+TPIC)		
TPC	86.96	
Contractor's Fee & Contingency (CFC)		
12. Contractor's Fee		4.35
13. Contingency		8.69
CFC	13.04	
Direct Fixed Capital Cost (DFC = TPC+CFC)		
DFC	100	%

Labor, consumables, etc. not included

##	WORK PACKAGE			PLANNED TOTAL COSTS (M $$$)		
				LOW	MID	HIGH
1	Building					5.88
2	Clean rooms: Production	*4000 sqm*				10.00
3	Clean rooms: QC + R&D	*500 sqm*				1.90
4	Production Utilities/ Side Functions					3.12
5	Equipment:					**33.68**
6	Production DSP/USP + R&D/Diagnostic					3.56
7	Process Machinery + Spares					2.30
8	Storage					0.63
9	Engineering		10%			5.73
10	Qualification		10%			5.73
11	Unforeseen		20%			3.39
	TOTAL					**80.28**



STRAINS, TECHNOLOGY, DOSSIERS

AVAILABLE FOR MOST of PLANNED PRODUCTS:

Poultry (AI, ND, EDS, IB, IBV, REO, …) and Livestock infections (FMDV, LSDV, PPR, SPV, BEF, …)

TEAM OF SPECIALISTS

EXPERIENCEED IN PRODUCTION & PLANNING of NEW FACILITY (MEVAC-1, MEVAC-2, …, UVAC-1/2)

OPTIMAL PROJECT DESIGN

OUR TEAM HAS >10 YEARS EXPERIENCE in DESIGN OPTIMIZATION

SUITABLE DESIGN

Project design according to cGMP standards taking into consideration BSL-3 terms (obligatory for FMD & AI)

SCALABILITY

Tech/Production/Control processes organizing from Cells & Strains Bank to Industrial production

INACTIVATION

Single stage stable reliable technology

STABILIZERS

Universal stabilizers for lyophilization

ADJUVANTS

Oil indirect w/o emulsion, similar to ISA-50, but better viscosity

Alternative to ISA-206 w/o/w multiple emulsion adjuvant

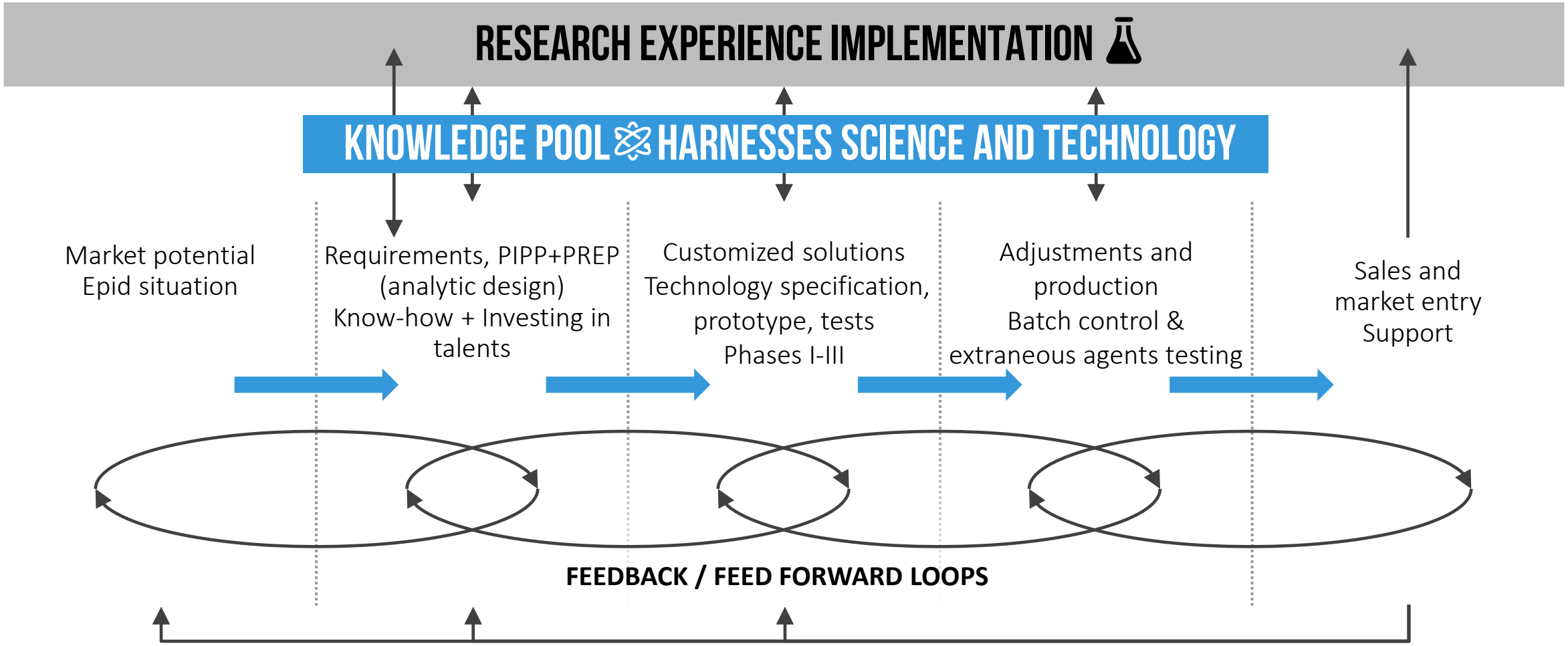
Colloid adjuvant, at a price lower than oil, and the effect is close to multiple emulsion

New generation - target cytokines stimulation

WE ARE BUILDING NOW for OURSELVES!

MEVAC + UVAC + KEMIN INNOVATION

Chain-linked model with independent research, knowledge pool and feedback forward loops



VISION 2022-2026