Tofflon EPC and Technical Transfer- Vaccine

Joanna.Ding

EXPERTISE IN BIOPHARMACEUTICAL

Tofflon

Contents

1 EPC and Modular Construction Concept

What is EPC

In the field of biopharmaceuticals, EPC refers to the "Engineering Procurement Construction" mode.

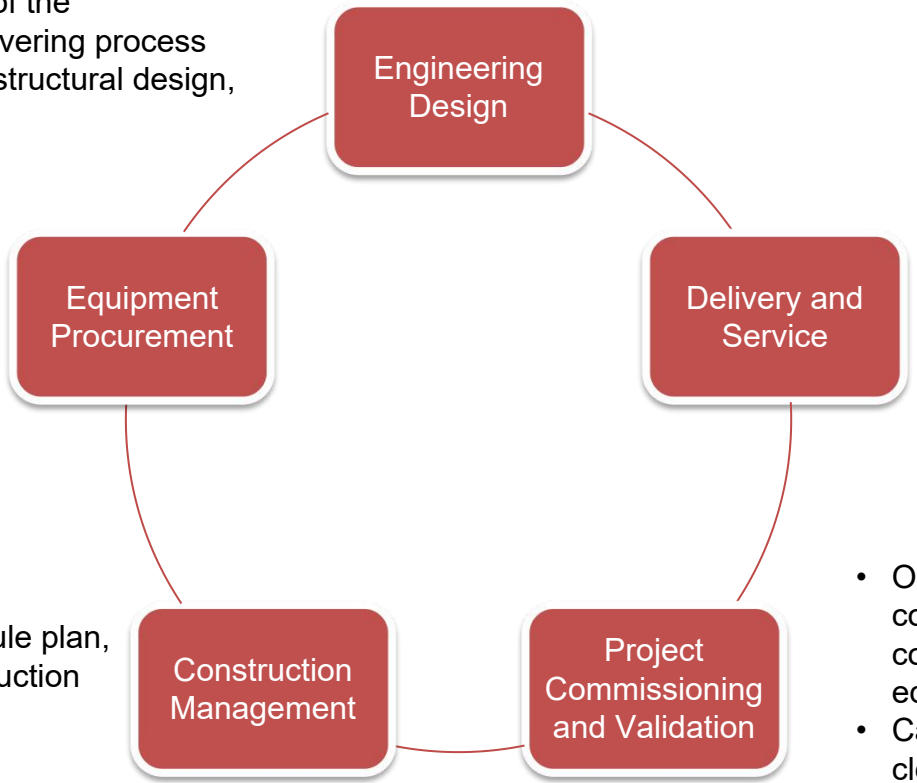
Definition: The EPC mode is a project management mode. In the biopharmaceutical field, the owner entrusts all a series of work such as the design, procurement, and construction of a biopharmaceutical factory construction project to a general contractor with rich experience and professional capabilities, namely the EPC contractor.

What is EPC

Complete the overall design of the biopharmaceutical factory, covering process design, architectural design, structural design, and utility engineering design

Prepare the equipment and material procurement list and select suitable suppliers for procurement

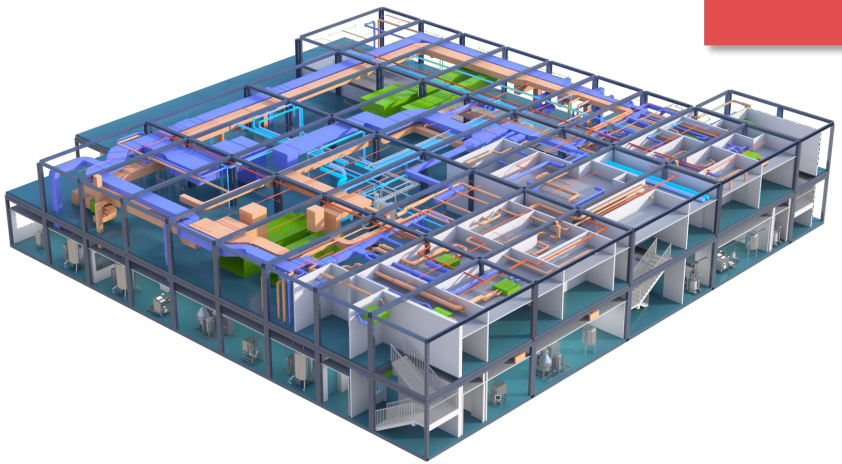
Develop a construction schedule plan, reasonably arrange the construction sequence and time nodes



- Provide relevant technical documents and operation manuals
- Provide personnel training
- Provide after-sales service

- Organize the single-machine commissioning and combined commissioning of the equipment
- Carry out process validation, cleaning validation etc.

What is Modular



*Take 4*2000L McAb as example.

80%	12	5%
Off-site: 80%	Turn-key: 12 Month*	Cost predictability: 5%

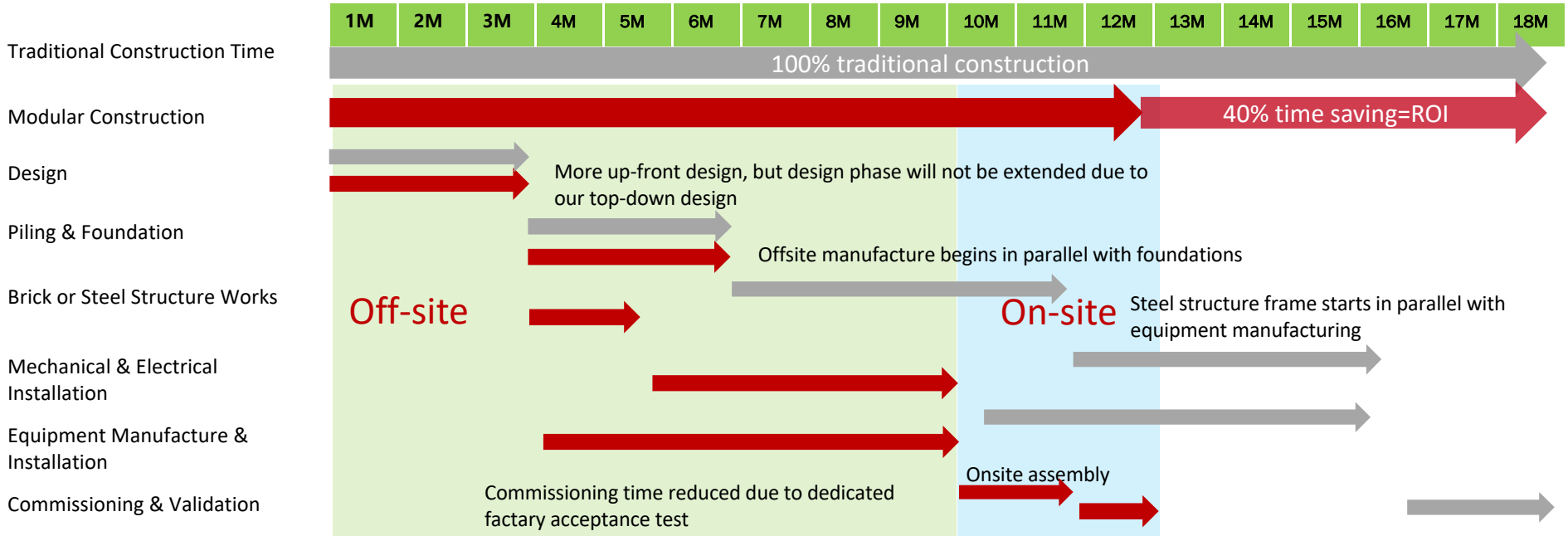
From Project to Product

Modular construction removes the 80% of the delivery of your project from the conditions on your final site. It includes all structural parts, building fixtures, clean room, HVAC, process equipment, utilities, power supply system, auto-control system etc. By Modular construction, we can deliver your project like an equipment.

Why modular

Modular for Speed - Time is money

Moving construction offsite and into a controlled factory environment reduces programme times by up to 50 percent. This is because ground works can be progressed on site at the same time as construction and fitout is underway in the factory.



Modular Facility Design Feature

Module size:

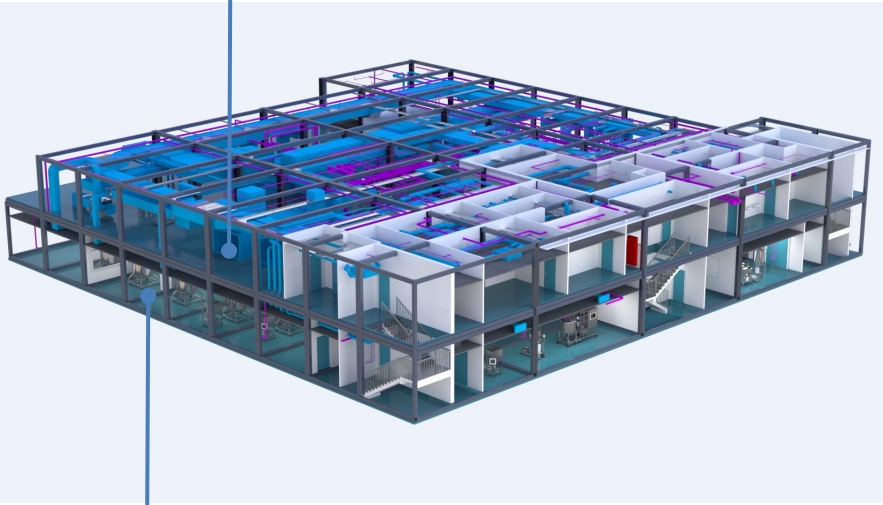
- Standard module size: 13.50m*4.50m*4.50m (L*W*H);
- Module size can be customized according to projects.

Modular including:

- Core equipment, including bioreactor, chromatography, UF, filling, etc.
- Building and structure: including beam, column, installation fixtures, etc.;
- Cleanroom: including clean board, floor, windows, doors, etc.;
- HVAC system: including AHU, exhaust fan, ducts, turret, valves, etc.;
- Fire protection: including hydrants, extinguisher, fire alarm, sprinkler, etc.;
- Piping system: including clean utility, black utility, piping, valves, etc.;
- Electrical: including power supply, lightning, socket, etc.;
- Telecommute: including entrance guard, interlock, network, CCTV, etc.;
- Control system : including BMS/EMS etc., SCADA system as option;
- Furniture: including wardrobe, bench, etc.;

Service scope:

- Engineering, procurement, fabrication, construction turn-key solution;
- Pre-engineering, pre-commissioning, pre-qualification, pre-validation;
- Commissioning, qualification, verification (DQ/IQ/OQ) and training;



Modular Considerations & Strategies

Modular Structure

- Structure calculations
- Connections & joints
- Transportation plan
- Foundation design
- Insulation & waterproofing

- ✓ Experienced design consultants
- ✓ Borrow experience from mature modular technique developed for other industries

Process Equipment

- Equipment integration
- Tailor made design for overweight, oversize equipment
- Equipment crossing modules
- Equipment fasten & transportation

- ✓ Customized control system
- ✓ Adaptive designed equipment
- ✓ SU system and intensified system

Cleanroom & MEP

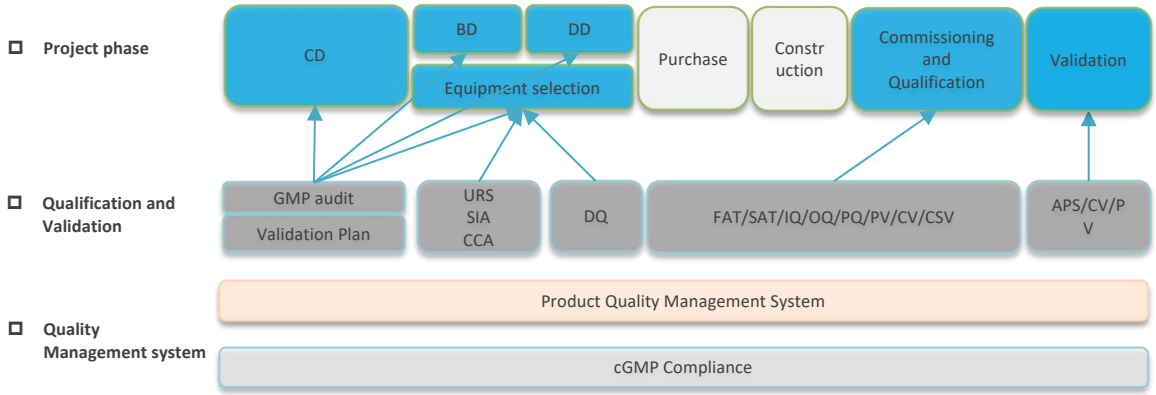
- GMP compliance
- Layout consideration
- EPC turn-key abilities
- Energy saving & cost saving

- ✓ Delicate design based on our understanding of the equipment
- ✓ 30 yrs cleanroom installation experience
- ✓ Innovative design of HVAC system
- ✓ Global partners Axiom

Modular Project Execution: Installation, Hook-Up and CQV

- After modules shipped assembled on the client's site, the indoor installation and hook-ups for equipment and systems on site.
- CQV activities will be carried out for the Site Acceptance Inspection and I/OQs.
- Tofflon provides full CQV service from the early design till the end of the project handover.

CQV Activities Performed Through All the Project Life Cycle!



Modular Project Execution: Fabrication & Disassembling

Offsite Manufacturing (1-6) and disassembling(7):

1、Steel frame transformed to Module Manufacturing Workshop for pre-assembly, floor & part of the wall installed simultaneously

2. Main duct, firewater piping installation.

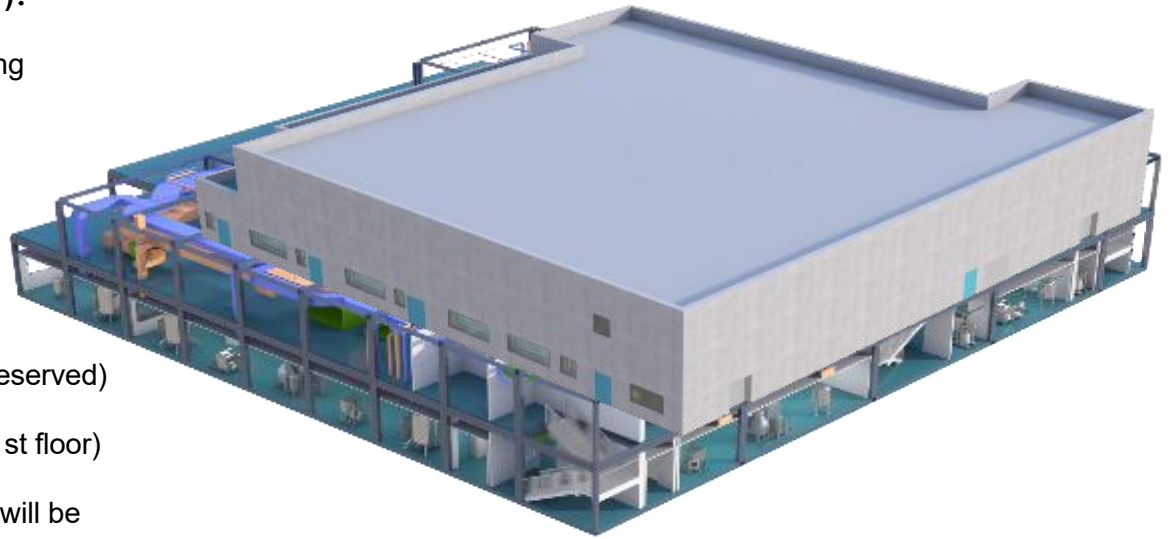
3. Piping, cable tray installation

4. Roof installation (onsite installation space to be reserved)

5. HVAC room (2nd floor) installation (in sync with 1st floor)

6. Before Factory Acceptance Test, key equipment will be pre-assembled, pre-engineered, pre-qualified in the modules.

7. Each modules will be shipped by trucks after disassembling



Tofflon's Modular Facility: Added Innovations and Values

Besides general modular facility advantages, Tofflon's Modular Facility Solution is developing the following added innovations and values to better solve many practical needs and challenges:

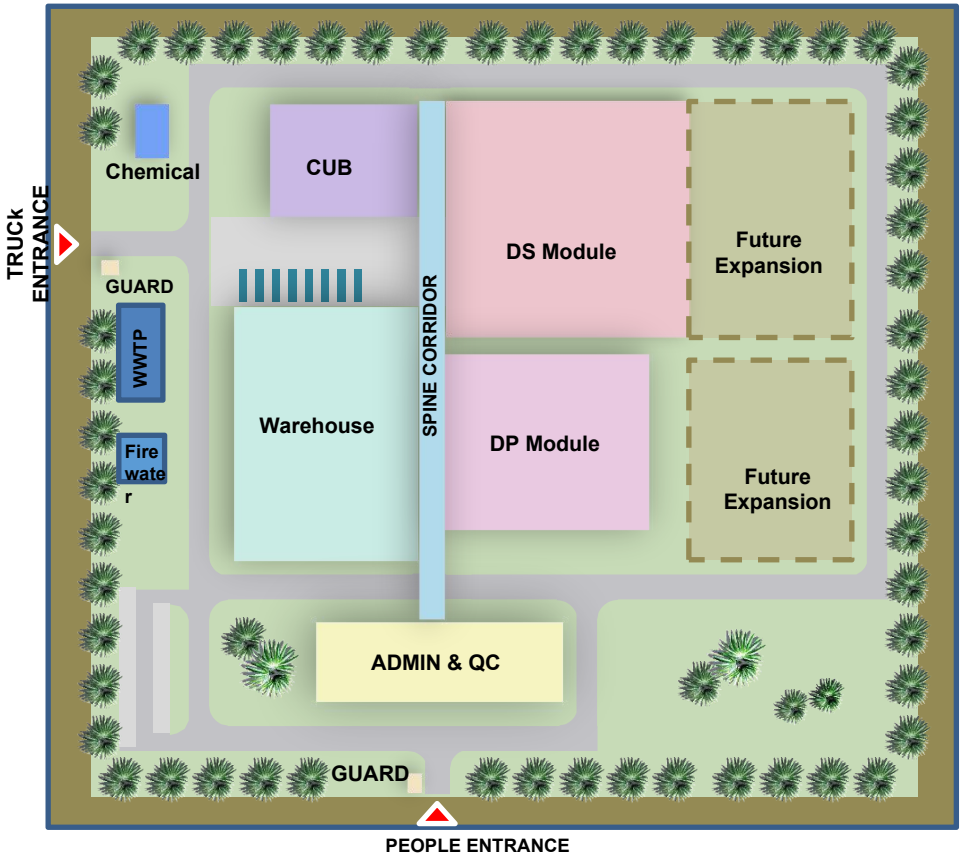
✓ **One-Stop Service: minimize complex interfaces** of many suppliers and sub-contractors
- *Tofflon can **One-Source Supply** Modular Facility and Engineering, DS Equipment (Single Use System and/or Stainless Steel System), DP and DPP Equipment (Fill-Finish) and Clean Facility (Cleanroom, HVAC, Water System and Distribution System, etc) from A to Z.*

✓ **Key equipment pre-assembled, pre-engineered and pre-tested** will be integrated into modular unit to **further secure on-site quality, timeline and cost**
- *Customized developed DS stainless steel equipment (for example media and buffer skid and pipeworks) for cross modular units*
- *Customized developed DP equipment (for example isolated filling line and freeze dryers) for cross modular units*

✓ **Strengthened Technical Support** for Start-Up Biotech Customers
- *Process Support (oncology, mAbs, vaccine, biosimilars and CGT)*
- *Pre-qualification documentation support in compliance with international GMP regulation*
- *Technical training and PQ support to develop local biotech talents*
- *Bio Consumable Strategic Supply Agreement (bags, media, resin, filter membranes)*

2 Vaccine Manufacturing Facility

Tofflon concept: Proposed Site Master Plan



The site will possibly include the following buildings and premises:

- ✓ CELLDULE DS Module Building – Pilot scale mammalian cell culture facility for bulk vaccine drug substance;
- ✓ CELLDUE DP Module Building – Pilot scale filling suite for vaccine drug product fill & finish;
- ✓ Admin and QC Building: Offices, analytical and QC laboratories; central CNC gowning; meeting rooms
- ✓ Central Utilities Building (CUB) – substation, chilled water generation, cooling water, boiler, etc.;
- ✓ Warehouse Building: including high and low bay warehouse; dock levelers, raw material sampling and QC lab; cold room and freezers storage rooms, etc.;
- ✓ Spine Corridor – CNC corridor linking all building;
- ✓ Other Ancillary Buildings such as WWTP plant, chemical store, firewater pump station, guardhouse;

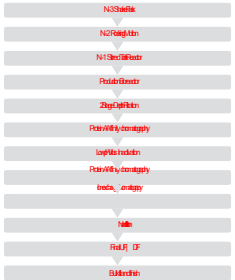
Process Design Considerations

Process Design

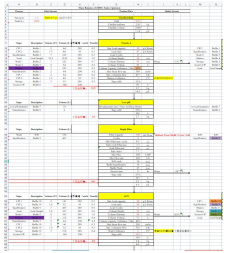
1 Product & capacity analysis

Dose(mg)	Biosimilar product	Nominal capacity (vial)	Nominal capacity (kg)	Estimated batches per year (2000L@3 g/L)	Estimated batches per year (500L@3g /L)
40	Adalimumab 40MG/0.8ML VIAL	18,942	0.75	1	1
100	Bevacizumab 100MG/4ML VIAL	19,803	1.98	1	2
400	Bevacizumab 400MG/16ML VIAL	9,041	3.61	1	4
100	RITUXIMAB 100MG/10ML VIAL	12,915	1.29	1	2
500	RITUXIMAB 500MG/50ML VIAL	8,610	4.30	2	5
150	TRASTUZUMAB 150MG VIAL	6,458	0.96	1	1
440	TRASTUZUMAB 440MG VIAL	10,332	4.54	2	5
	Total	86,101	17.46	9	20

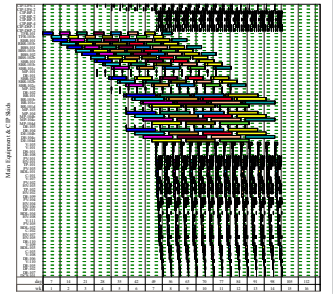
2 Block flow diagram



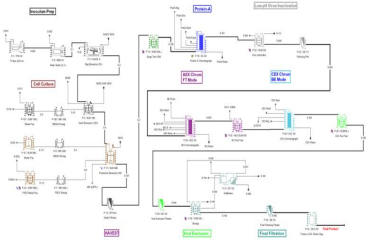
3 Preliminary mass balance



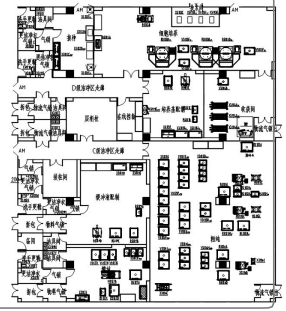
4 Process scheduling & debottle-necking



5 PFD P&ID

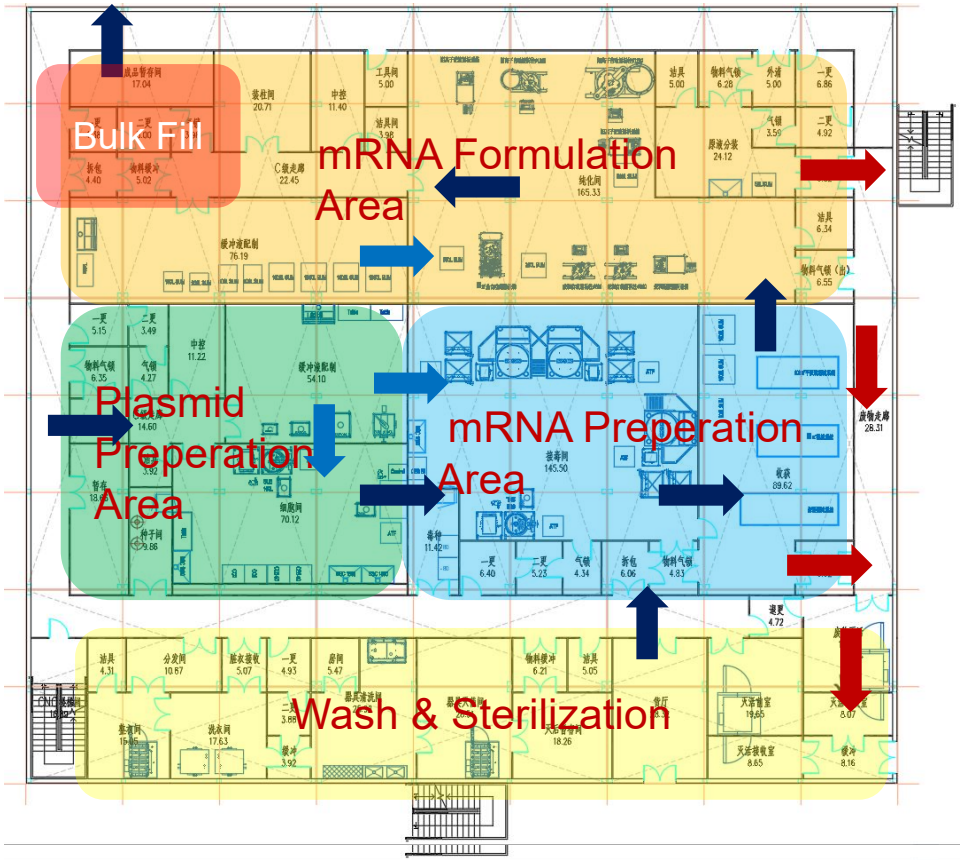


6 General Process Layout



mRNA Drug Substance Modular Solution

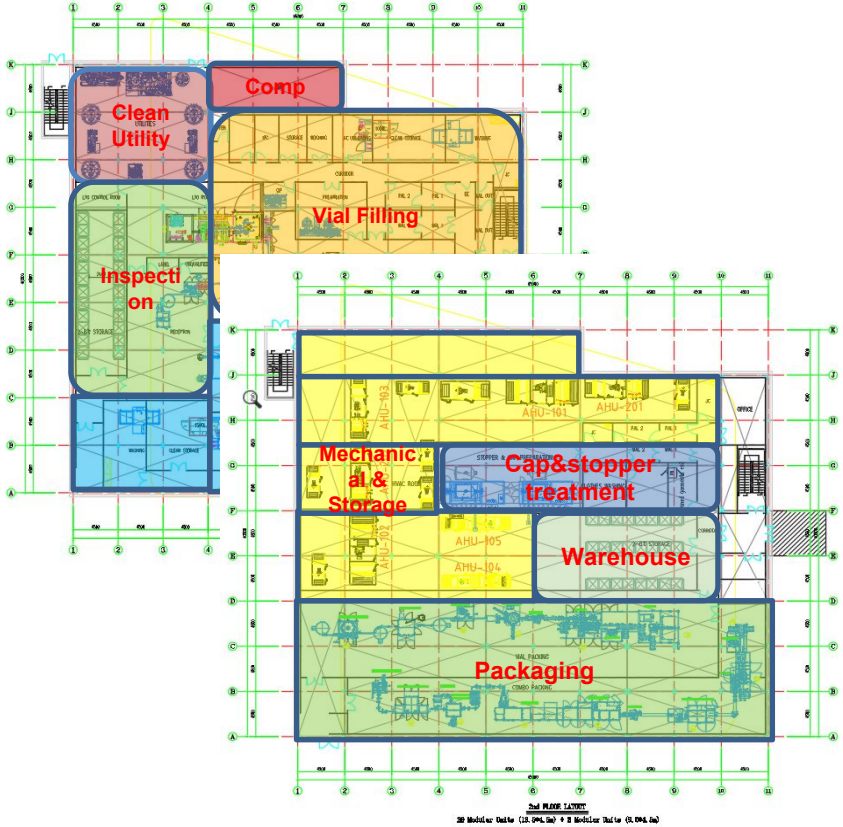
- **Main Equipment:**
  - 1x 100L Wave Bioreactor, 1 x 1000L SUB
  - 4x Choro. System
  - UF/DF/VF
- **Layout Philosophy:**
  - 3rd-4th floor: Production core(IVT,Purification,filling)
  - 1st-2nd floor: Formulation, lyophilization, pilot trials
- **Facility Information:**
  - Total area: about 3300 m^2;
  - 50~60 module units;
- **Area classification:**
  - Plasmid fermentation,IVT, purification, bulk fill, prevent cross contamination.



Production line Buffer line Waste line

mRNA Drug Product Modular Solution

- **Main Equipment:**
  - Vial filling: 400vpm,automatic cap/stopper process machine.
  - Combo filling: 5000 doses/hr, RTU PFS, vial (0.5ml).
  - Isolation: Isolator to reduce building footprint.
  - Packaging: Automatic packaging equipment
- **Layout Philosophy:**
  - 1st floor: vial filling line, combo filling line, inspection and temperary storage, clean utilities
  - 2nd floor: HVAC, cap/stopper processing, secondary packaging
- **Facility Information:**
  - Building footprint: 5500 m^2;
  - Total area: 3000 m^2;
  - 52 module units;
- **Layout Considerations:**
  - Reducing connections between modules;
  - Proper design to segrate filling line;
  - Sectional design of tunnel to reduce size;
  - Customized Isolator & BIBO design to reduce height;
  - Customized centralized control system & cabinet;
  - Adjustment of modules to allow process layout more reasonable;

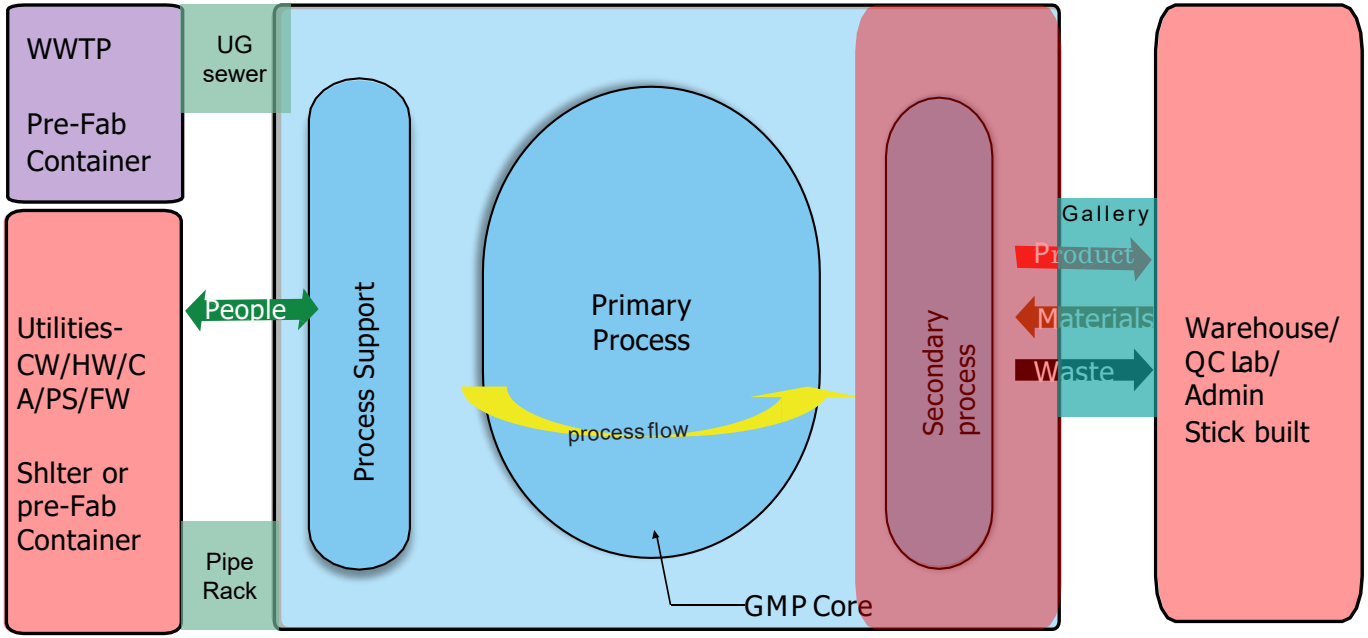


Tofflon's Scope of Supply

General Scope Matrix			
Scope by building blocks	Tofflon	Client or Appointed GC	Remarks
Tofflon Bio DS Module Building	Yes		
Tofflon Bio DP Module Building	Yes		
Admin & QC Area	Yes		
Central Utility area	Yes		
Warehouse		Yes	
Auxiliary facilities such as WWTP, firewater pump station, hazardous material storage		Yes	
Outdoor area works (planting, paths, roads, parking lots, etc.)		Yes	
Public development and infrastructure (sewage, streets, electric, etc.)		Yes	
Temporary water and electricity		Yes	

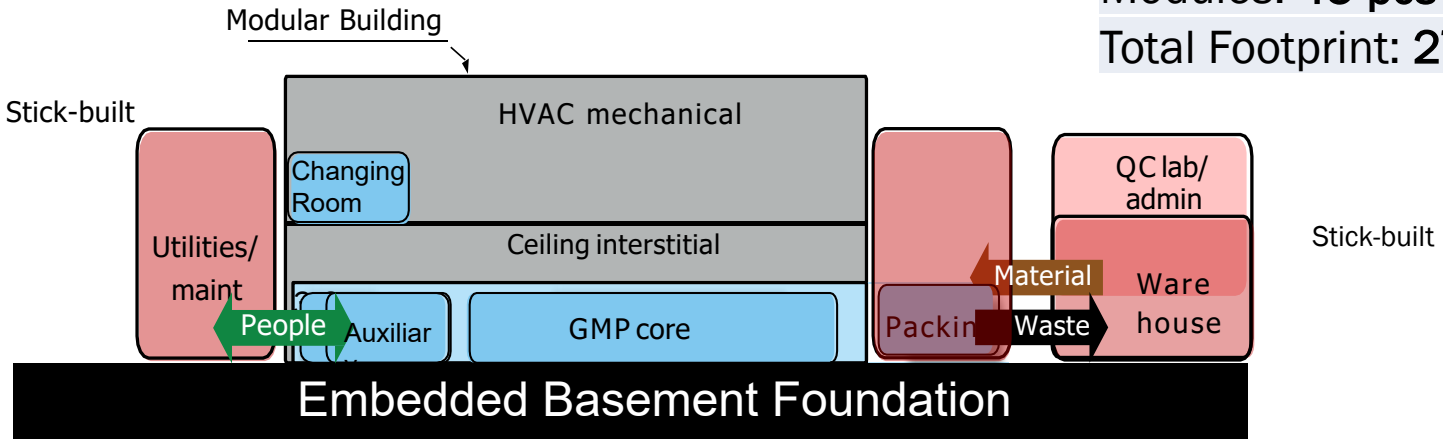
Tofflon Bio Modular Facility			
Scope by structure and systems	Tofflon	Client or Appointed GC	Remark
Clean rooms including wall, ceiling, floor, windows, doors etc.	Yes		
Fixed furniture such as laboratory working benches, dust hoods	Yes		
HVAC system, including air conditioner, exhaust fan, ducts	Yes		
Fire hydrant, fire extinguisher, sprinkler and terminal fire alarm system	Yes		
Power distribution system, lighting and receptacle system	Yes		Not including transformers, diesel generator
Security system, interlocking door system, telecommunication system	Yes		Tie-in at 1m outside production building
Process Equipment	Yes		
Clean utility equipment including PW & WFI & PS generation and distribution	Yes		
Black utility piping, not including generation equipment	Yes		Tie-in at 1m outside production building
BMS & EMS	Yes		
Hook-up of all site utilities / infrastructure	Yes		
Engineering, procurement, manufacturing, installation, project management	Yes		
Laboratory analytical equipment		Yes	
Crane, scaffolding, lifting devices/operators for erection/construction		Yes	

Project Preliminary Site Layout (Top View) Overseas



Project Preliminary Site Layout (Side View) Overseas

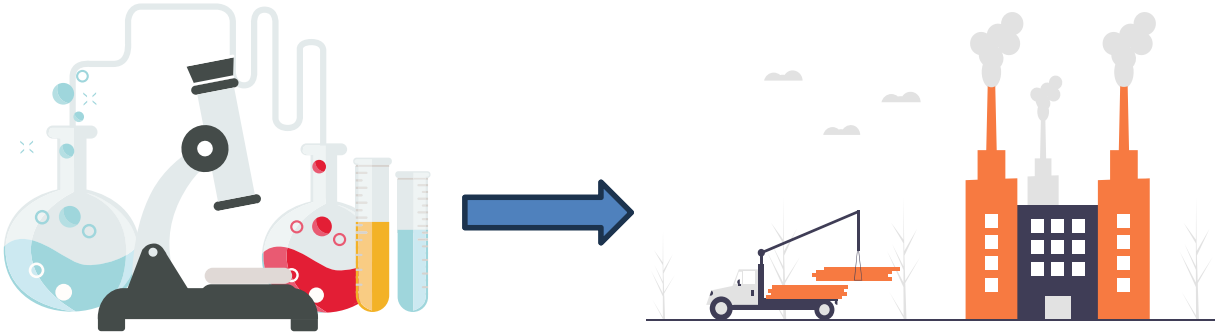
1st Floor + 2nd Floor:
Modules: **45 pcs**
Total Footprint: **2700m²**



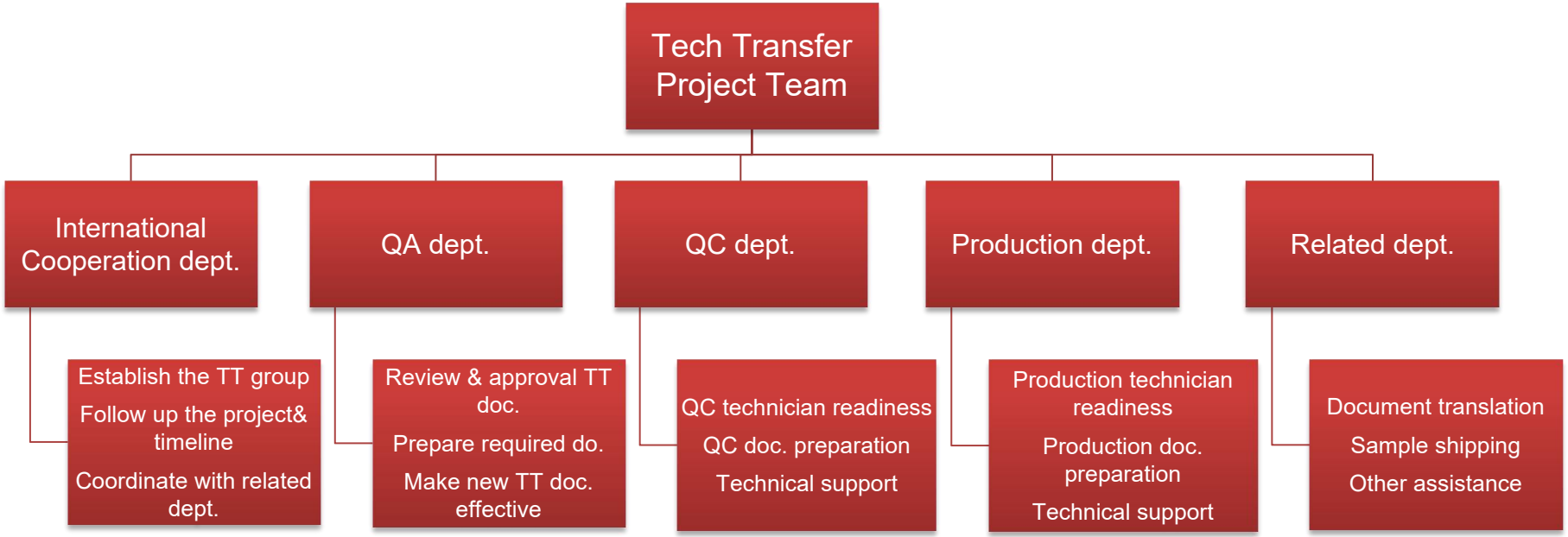
3 Technical Transfer

Pharma Technology Transfer

- The technology transfer of biopharmaceutical products (Pharma Technology Transfer) is a systematic process of transferring drug research and development, production processes, analytical methods, and related knowledge from one team or site (the transferring party) to another team or site (the receiving party), ensuring that the receiving party can stably and compliantly reproduce the original product or process.
- In the field of biopharmaceuticals (such as monoclonal antibodies, vaccines, gene therapy products, *etc.*), the complexity and risks of technology transfer are relatively high, and strict compliance with regulatory requirements (such as GMP, ICH guidelines) is necessary.



Technical Transfer Project Team



Pre-Transfer and Implementation

Pre-Transfer Planning

- Gap Analysis: Assessment
- Technology Selection: Choose the appropriate vaccine technology
- Stakeholder Engagement
- Regulatory Compliance

Implementation and Scale-Up

- Quality Control and Assurance: stablish robust quality control and assurance systems
- Regulatory Compliance: ensure that all production activities comply with the relevant regulatory requirements

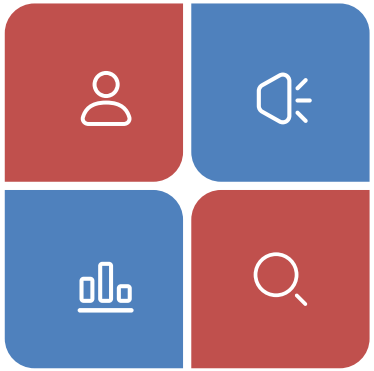
Infrastructure and Equipment

Production Facilities

Transfer of knowledge and expertise related to the design, construction, and operation of vaccine production facilities.

Maintenance and Calibration

Providing training and support for the maintenance and calibration of equipment



Equipment and Supplies

Ensuring that the recipient has access to the necessary equipment, raw materials, and supplies to produce the vaccines.

Transfer of Knowledge and Skills

Training Programs

- Develop training programs for the recipient's personnel
- Covering all aspects of vaccine production
- Include both theoretical and practical training sessions

Documentation and SOPs

- Provide detailed documentation
- Including standard operating procedures (SOPs), batch records, and quality control guidelines.

Technical Support

- Offer ongoing technical support during the initial stages of production.
- Sending experts from the originator company to the recipient site to provide hands- on guidance

Intellectual Property and Licensing

Intellectual Property Rights

- Addressing intellectual property issues.
- This includes obtaining necessary licenses and ensuring that the recipient has the right to use the technology for vaccine production.

Licensing Agreements

- Developing and negotiating licensing agreements.
- This includes defining the scope of the license, royalty payments, and any restrictions on the use of the technology.

Innovation and Collaboration

- Encouraging innovation and collaboration between the originator and recipient.
- This can lead to the development of new vaccines and improved production processes.

General phase and responsibilities

Phase	Receiving Party	Transferring Party	Third Party
Preparatory Phase	• Define technical requirements • Establish transfer team	• Evaluate the recipient's technical absorption capacity • Prepare technical documentation (patents, process files, standards, etc.)	• Provide technical evaluation services • Assist both parties in drafting a technology transfer roadmap
Technology Delivery & Training	• Training and record questions/difficulties • Prepare production/testing facilities and supporting equipment	• Deliver complete technical documentation • Arrange on-site technical guidance, operation training, and Q&A sessions	• Provide equipment installation and debugging services • Assist in building technical validation platforms
Implementation	• Conduct trial production/tests based on technical documents and record data/issues	• Resolve technical issues remotely or on-site during implementation	• Perform performance testing and calibration for supporting equipment

Conclusion

01

Impact on Global Health

Enhance global health security by increasing vaccine supply, improving access to vaccines in developing countries

02

Challenges and Opportunities

- Several challenges associated with vaccine technology transfer
- Technical difficulties, regulatory hurdles, and intellectual property issues

03

Importance of Collaboration

Requires close collaboration between originator and recipient entities, as well as support from governments, regulatory authorities, and international organizations.

Tofflon

Tofflon Vision:

Smart Pharma Factory Builder