SHILPA BIOLOGICALS

MAY -2025

Vision & Strengths

R&D DSP Facility

Mfg. Seed Development Facility

100% subsidiary of Shilpa Medicare Ltd

Vision 2025

To be the 'Best' CDMO partner in Biologics from India

Services offered

- Microbial & mammalian clone dvpt, RCB, MCB, WCB & characterization, media optimization capabilities for achieving high titres
- Upstream, downstream & formulation process development, optimization, tech transfer, manufacturing capabilities
- Lot release, characterization & bioassay methods dvpt, validation, transfer, sameness & biosimilarity studies

Strengths

- State of the art R&D and world class mnf. facilities for dev. & mnf. of microbial & mammalian-based DS and DP products
- 50+ personnel in R&D with a blend of research and industry experience
- Strong manufacturing team with world class manufacturing infrastructure

Experience

- CHO platform - MABs, Fusion Proteins, ADCs, conjugated proteins - development and manufacture
- Microbial platform – E.coli/Pichia - FABs, conjugated proteins, peptides - development and manufacture
- Sub-unit vaccine development and manufacture

Cell lines /Clone to Manufacturing

Shilpa Biologicals

Biotherapeutic discovery

↓

Early-stage development
(process, analytical, formulation)

↓

Tox and early clinical supply

↓

Late-stage development
(process characterization)

↓

Manufacturing
(late phase and commercial)

People

- ***200+*** *member strong team from Process development to Manufacturing including support functions*
- ***50+*** *in R&D*
- ***50+*** *in Manufacturing (MFG)*
- ***50+*** *in Quality Control & Assurance*
- *Strong RA team*

Experience base

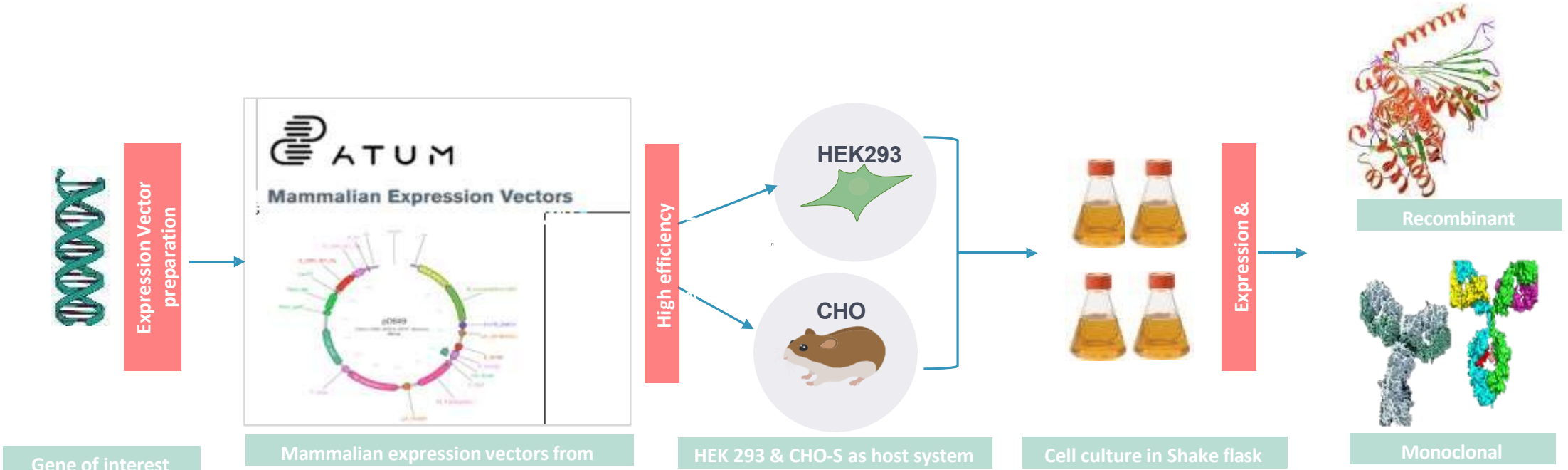
- ***E. coli, CHO, Pichia*** *platforms*
- *Experience in working with:*
  - ✓ *Recombinant proteins; Glycoproteins; PEGylated proteins; Multimeric protein complexes*
  - ✓ *Monoclonal antibodies; Antibody fragments; Blended mAb products*
  - ✓ *Live biotherapeutic products*

Modular or Integrated services

CHO-S, HEK 293, E Coli, Pichia

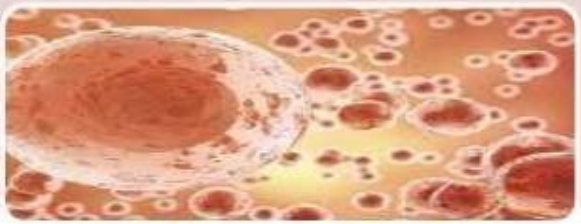
Transient Expression of Proteins

For supporting Discovery



- ✓ *HOST SYSTEMS: CHO, HEK 293*
- ✓ *VECTOR SYSTEMS: ATUM*
- ✓ *TRANSFECTION: LIPOFECTION*
- ✓ *DURATION: 10-14 DAYS*
- ✓ *EXPECTED PROTEIN TITER: **0.1 TO 0.3 GR/L***
- ✓ *PURIFICATION: **PROTEIN A***
- ✓ *TESTING: SIZE AND CHARGE VARIANT ANALYSIS*

Other Expression Systems



Mammalian (CHO and HEK293)

Platform Technologies
- Fed-batch process (3 – 5 g/L)
- Continuous manufacturing (PD) (≥ 4 - 8 g/L) available in PD

Antibodies & Proteins expressed
- IgG1, IgG2
- Bispecific Abs
- Complex glycoprotein

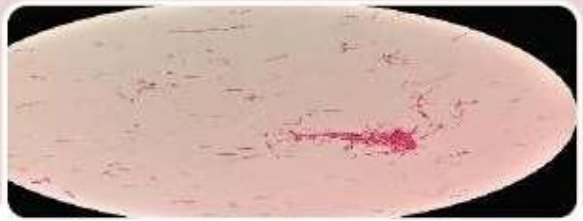
Viral Vector

Yeast

Pichia Pastoris

Platform Technologies
Fed-batch process (1.0 – 2 g/L)

Antibodies
Protein
Hormones
Glycoproteins



E.coli

Platform Technologies
HCD Fed-batch process (≥0.5 - 5 g/L)

Plasmid DNA manufacturing (C&GT, Vaccines)
Intensified fed-batch (≥ 0.5 g/L) in PD lab

mRNA manufacturing

Proteins & Peptides/fusion proteins

Plasmid DNA Purification

Cell & gene therapy, vaccine applications

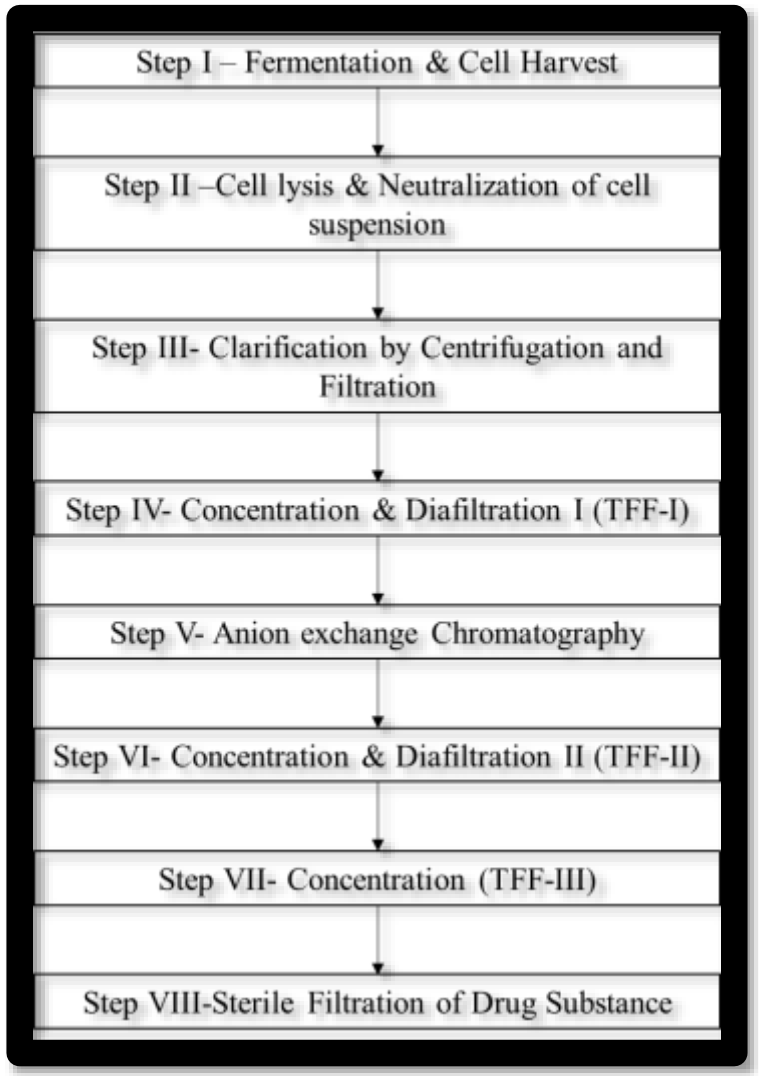
*EXPERIENCE WITH PLASMID **DS MANUFACTURING***

*DEVELOPED PLATFORM PROCESS TECHNOLOGY INVOLVING **1000 L SCALE FERMENTATION***

***DS PROCESS VALIDATION** COMPLETED FOR DNA BASED VACCINE*

*ALL INFRASTRUCTURE REQUIRED FOR **ALKALINE LYSIS AND PURIFICATION** OF PLASMID IS AVAILABLE INHOUSE*

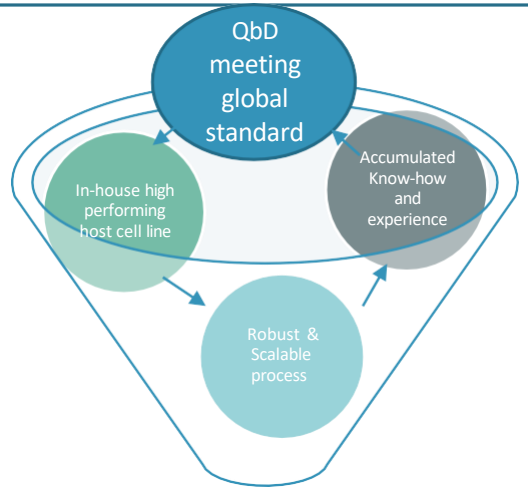
***IN-PROCESS AND RELEASE TESTING** IS DONE COMPLETELY INHOUSE*

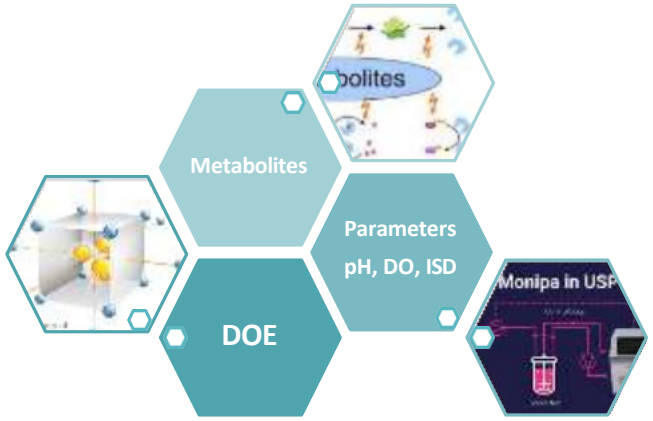


Clone & Upstream Process Dev.

Clone development	*Preparation of RCB*	*Characterization of clones*
Screening clones using Ambr	*Media optimization*	*Upstream Process from 2 to 50 litres*
Batch, Fed batch and perfusion – micro/mammalian	*Design space establishment*	*CPPs, CQAs*
Process Parameter Evaluation	*Process characterization studies*	

Upstream Process Dev. (Platform/Conventional)





Robust & Reliable Process

Platform Upstream for Timely project

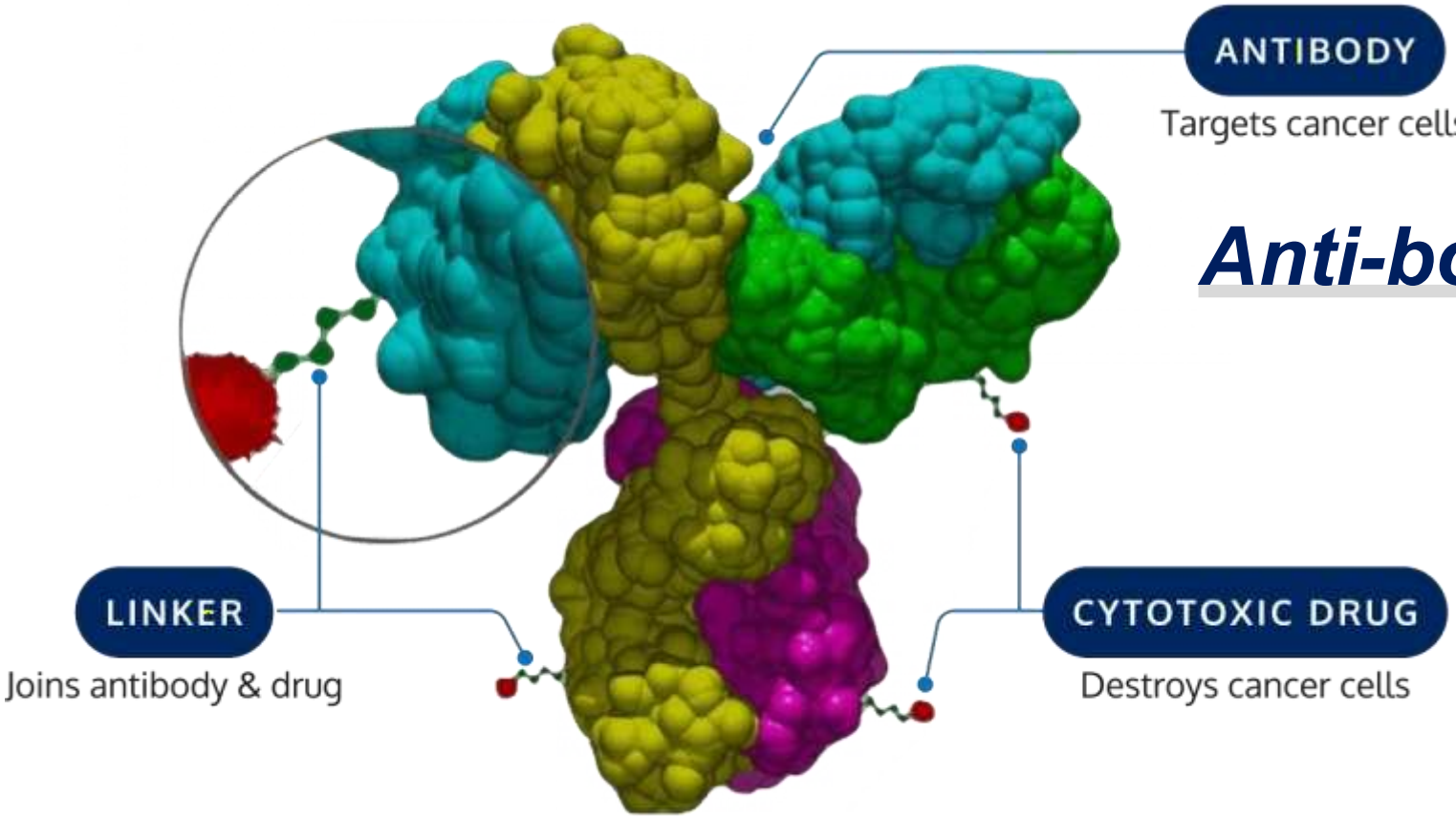
1	2	3	4	5	6
Cell Bank Transfer	**Basal / Feed media screening in shake flaks**	**Process optimization in Ambr/2L**	**Process verification runs in 2L/10L STR**	**Tox. Material production in 50L/200L STR**	**Clinical cGMP manufacturing in 200L to 2kL STR**
		Fortification studies in 2L			
○ Product information from client ○ In-house PEL CLD to USP	○ Commercially available basal/feed media screening	○ Fortification study ○ Parameters range establishment for manufacturability	○ Based on process conditions from process optimization / fortification study	○ Scale-up from 2L to 50L / 200L	○ Manufacturing of Bulk DS for clinical material

Downstream Process Dev.

- *Patent evaluation & selection of non-infringing process*
- *Downstream Process development from **1l to 50l** ensuring*
  - ✓ *Viral clearance*
  - ✓ *BET removal*
  - ✓ *Pigment removal*
  - ✓ *Control of HCP/HCD/PA leachates*
  - ✓ *Quality*
  - ✓ *Yield*
- *Scaleup and scale down models*
- *Resin usage establishment*

Analytical Capabilities

- ***Method development, qualification/ validation, method transfer of***
  - ✓ *Lot release methods*
  - ✓ *Characterization methods*
  - ✓ *Bioassays*
- ***Analytical qTPP***
- ***Comparability/biosimilarty studies***
- ***Impurity purification and characterization***



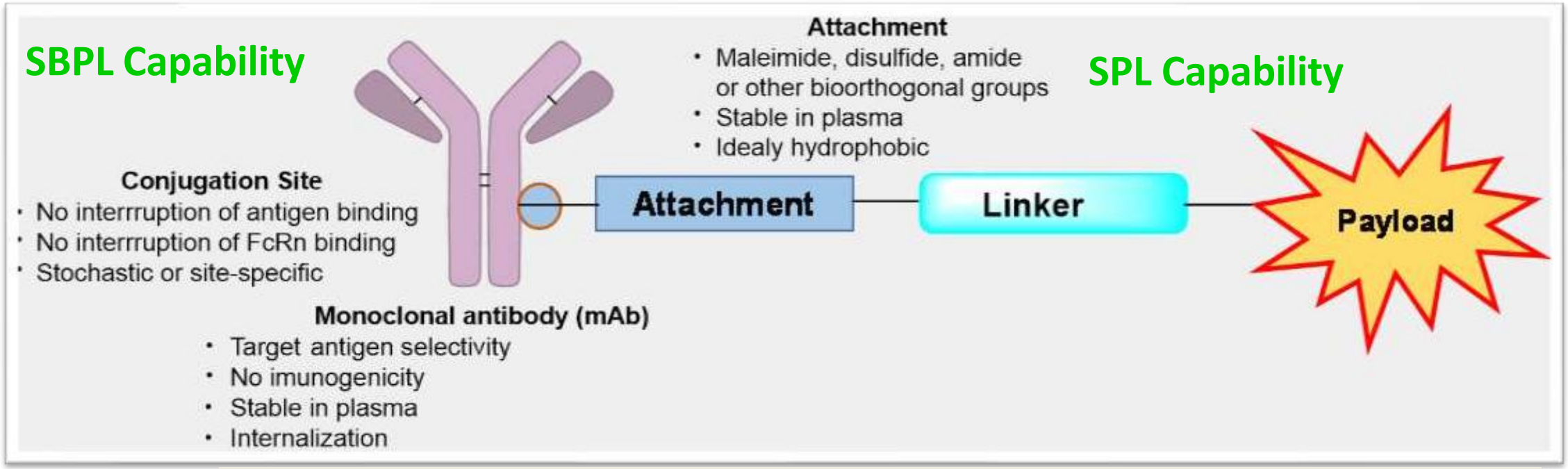
Anti-body Drug Conjugation

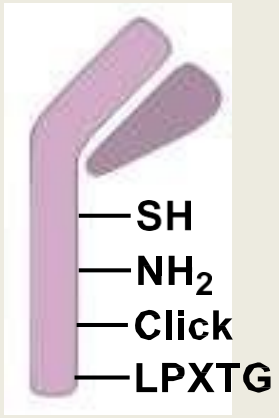
(ADC)

ADCs present significant challenges in development and manufacturing. We provide a comprehensive solution that streamlines the value chain and fast-tracks the journey to the clinic or market

ADC –Capability & Process

Shilpa Biologicals





Linker

Payload

Conjugation

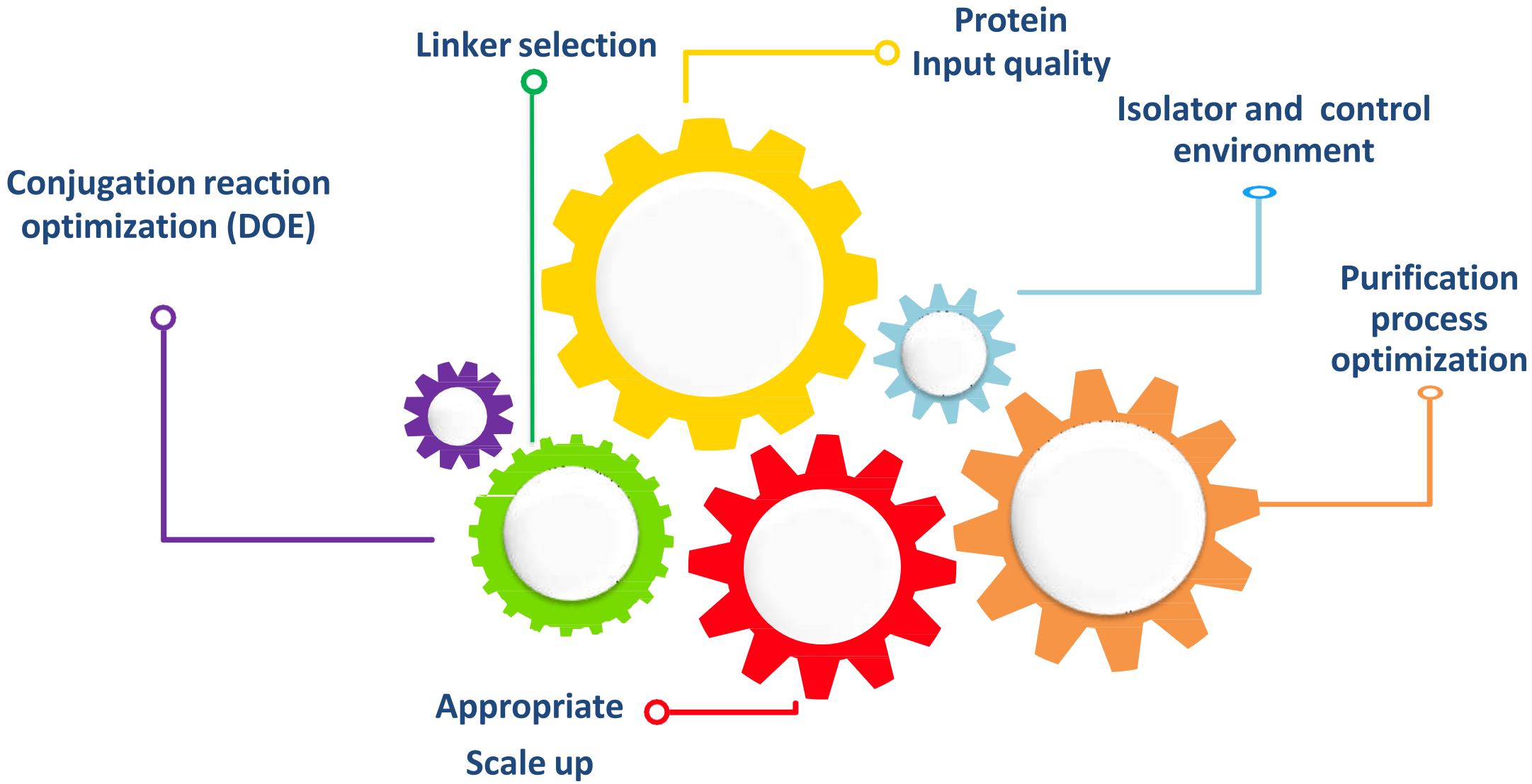
- Chemically
- Enzymatically

Linker

- Clevable or non-clevable
- Stable in plasma
- Degradation of releasing payload after internalization
- Idealy hydrophilic

- High Potent
- Drug
- Stable in target cell

ADC Process Dev.- Challenges & Mitigations



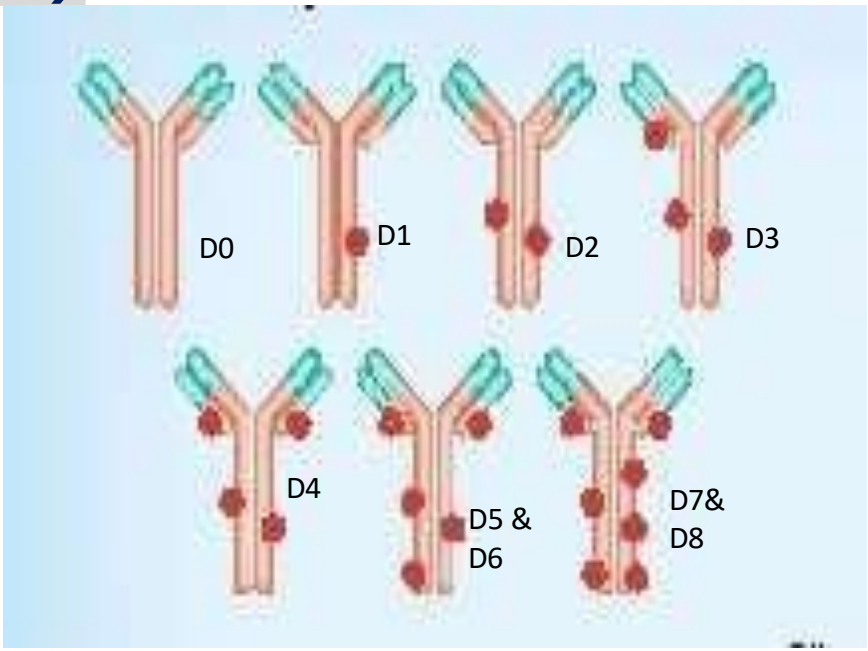
ADC- Complexity (Lysine Conjugation)

Shilpa Biologicals

1

Non-uniform Drug Attachment

Lysine residues are abundant on antibodies > leading to random drug attachment at multiple sites > result in a heterogeneous population of ADCs with varying DAR



2

Consistent multiplicity required

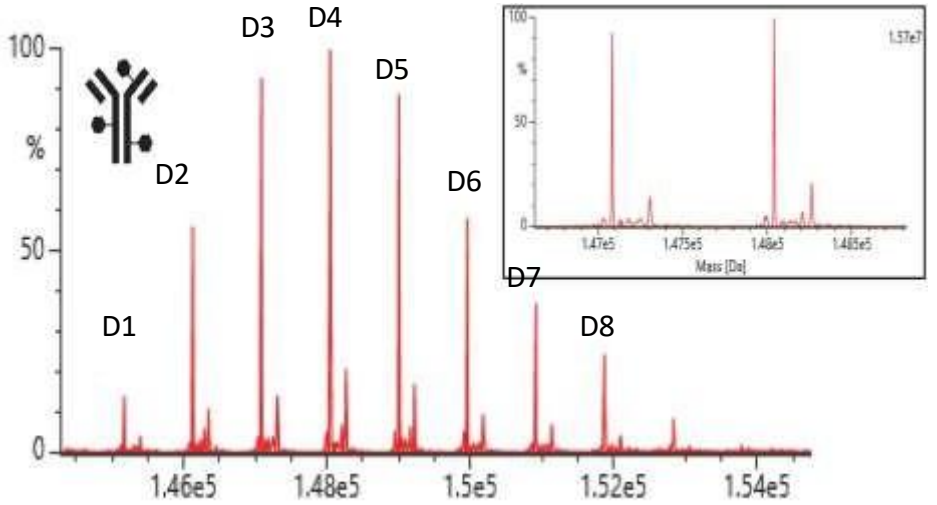
Higher chances of higher multiplicity species >9

Higher DAR may increase cytotoxicity but also might affect PK, while a lower DAR may reduce efficacy

3

New impurities removal

Removing unreacted drug and byproducts from the conjugation reaction is challenging



4

Scaling up, Stability of molecule, Handling cytotoxic material in lab

Scaling up the lysine conjugation process while maintaining uniformity in the drug conjugation and quality of the final product is difficult

ADC- Complexity (Cystine Conjugation)

Interchain Disulfide Reduction & Re-oxidation: partially reducing the interchain disulfide bonds in the antibody to expose cysteine thiol groups

1 Heterogenicity in drug

Variable conjugation sites & Drug-to-antibody ratio (DAR) variability

2 Stability Issues

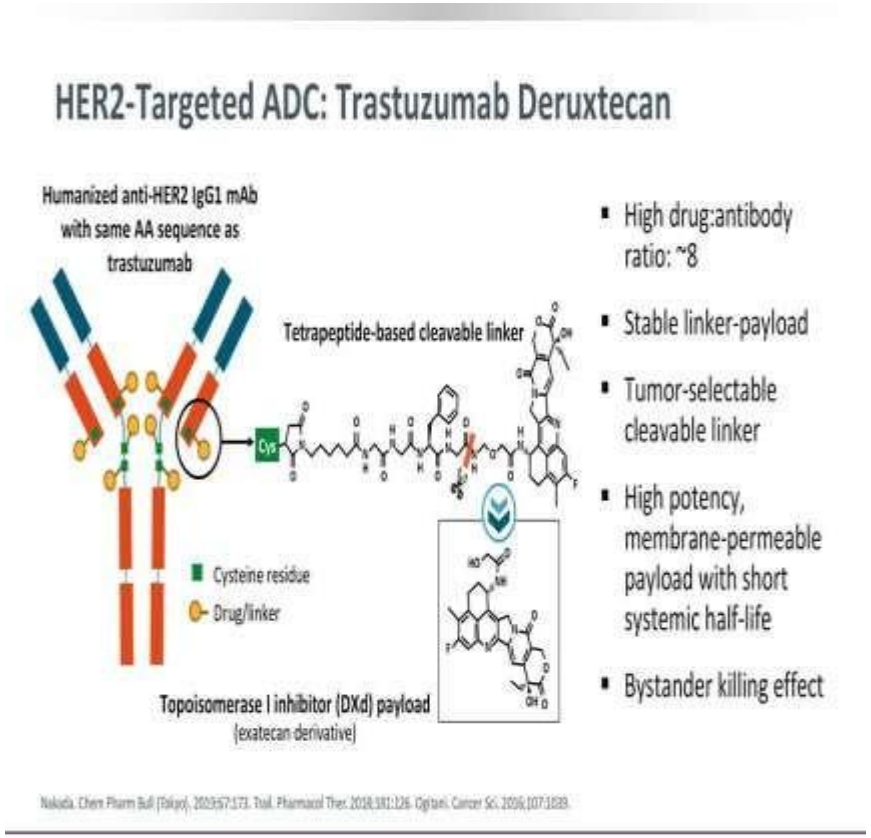
Disulfide bond disruption and Conjugate instability

3 Aggregation & Solubility

Some drug-linker molecules increase hydrophobicity, causing aggregation.

4 Manufacturing Complexity and Handling Cytotoxic material in lab

Purification challenges: Removing unconjugated drug and ensuring homogeneity adds complexity



ADC -Process Flow

Input Protin

Conjugation

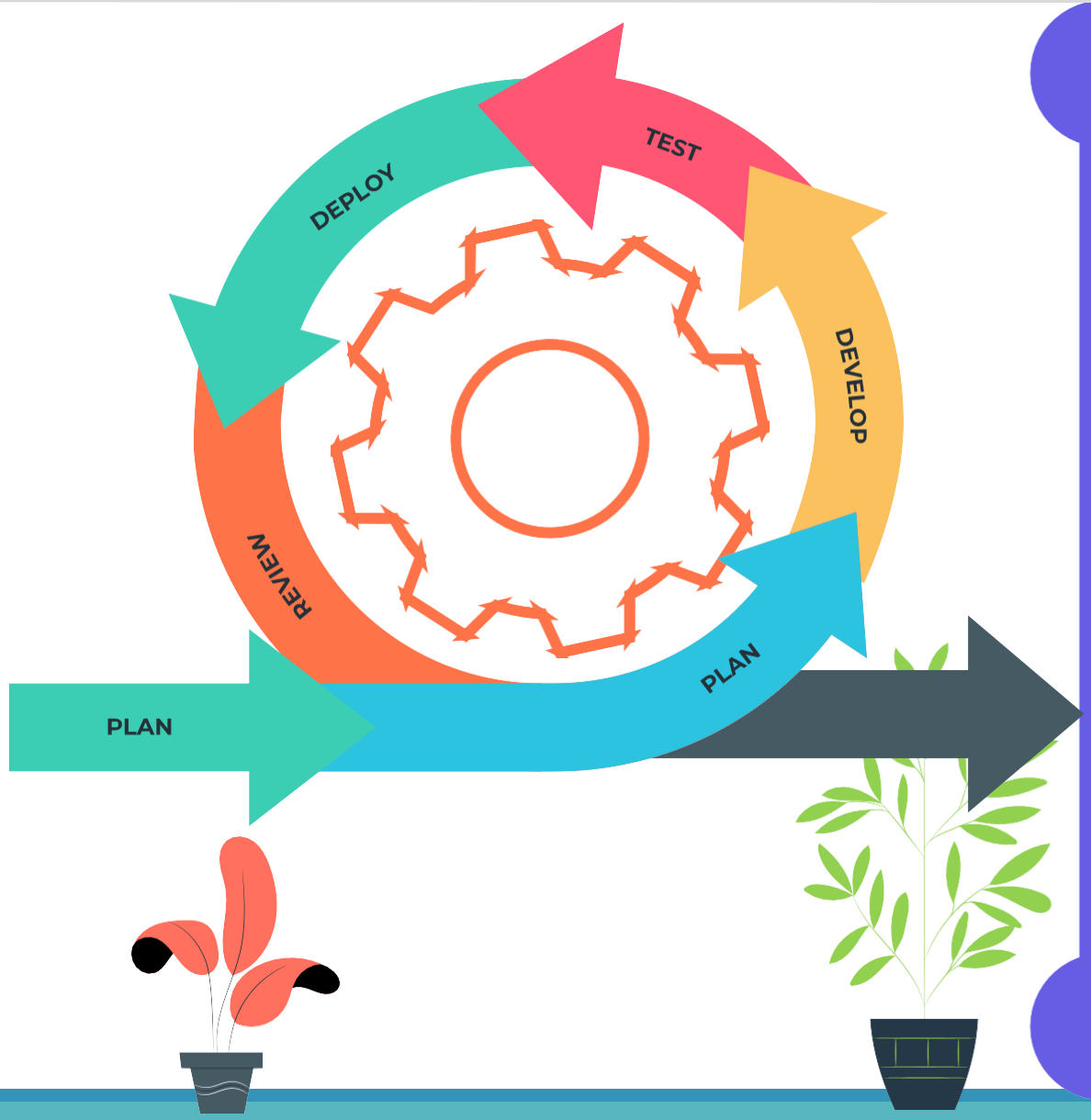
TFF

Chromatography

TFF& DS Preparation

Lyophilization & Drug product

Shilpa biological's Capabilities for Payloads, linkers & Intermediated



a

- **ADC Linker and Payload Development and Supply**
  ADC linkers conjugated with payloads such as MMAE, MMAF, Maytansine, DM1, Dolastatin, Tubulysine, Amanitin, Tesirine, and PBD.

b

- **Peptide and PEG-Linker Synthesis**
  Proficient in synthesizing peptide-based and PEG-based linkers tailored for ADC applications.

c

- **Amino Acid and Protection Chemistry**
  Expertise with various amino acids protection chemistry (orthogonal protection strategy)

d

- **Hands on experiences on ester, carbamate and carbonate formation chemistry**

e

- **Payload Sourcing and Complex Multi-step Synthesis.**

ADC : Process development (Early stage)

Conjugation

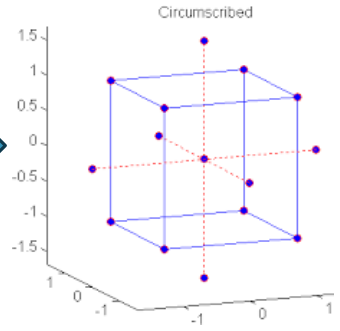
- Lysine Conjugation
- Cystine conjugation
- Enzymatic conjugation
- Site specific conjugation of engineered antibody

Chromatography

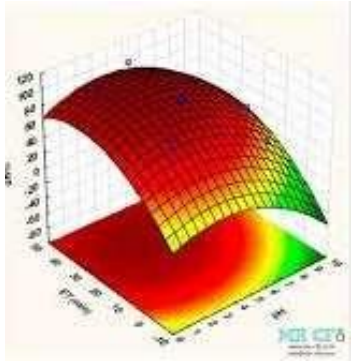
- Removal of aggregate
- removing impurities
- Removing/reducing extra DAR species
- Modulating drug to antibody ratio

Approach for Process development (QbD)

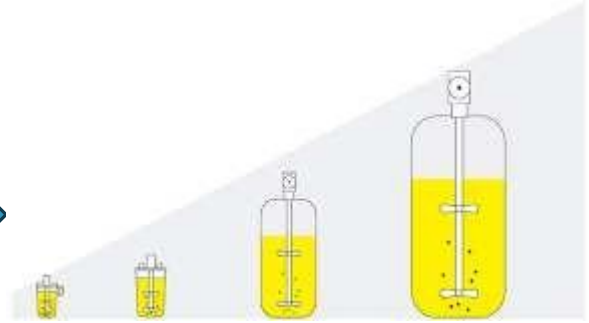
One factor at time



DOE full factorial

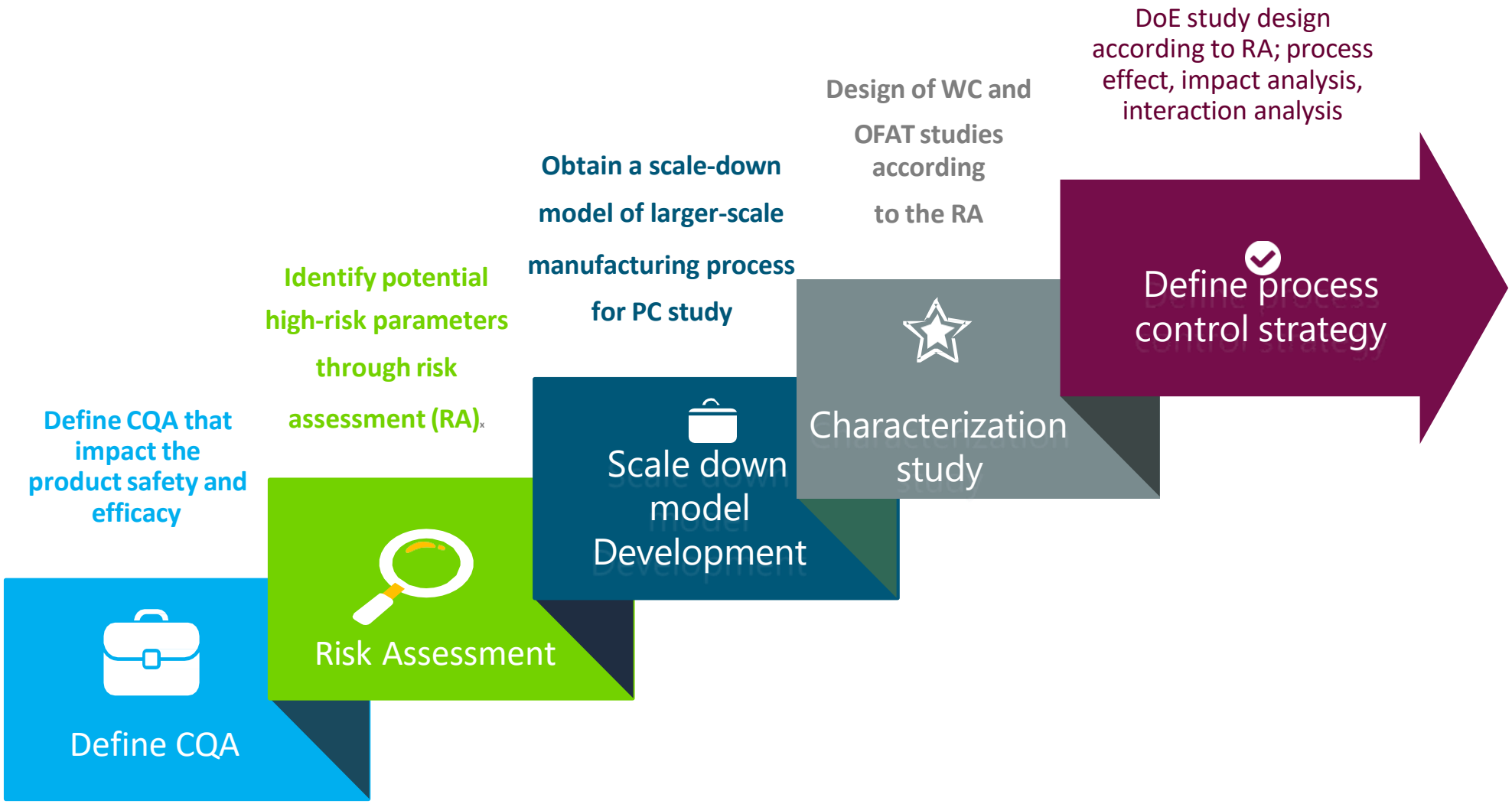


DOE response surface



Scale down and Scale up

ADC : Process development (Late stage)



ADC Process Equipment Capabilities

AKTA Pure

AKTA PCC

Isolator

TFF System

Freeze Thaw system

Spectrophotometer

AKTA Pilot

Lyophilizer

Analytical Services-ADC (Development & Characterization)

Quality	Particle	Potency	Safety	Raw material	General attribute	Purity	Impurity	Characterization
• Concentration • Titer	• Visible • Subvisible particle matter	• ELISA • Cell based • Affinity (ADCC, ADCP. CDC)	• Endotoxin • Sterility • Bioburden	• Compendial • Method	• Appearance, color, clarity • pH, osmolality • (Liquid) Extractable volume • Lyo) reconstitution time, water content	• SEC • IEX/ iCIEF • DAR • NR & RCE	• Residual HCP • Residual DNA • Residual Protein A • Residual free drug , Free Mab determination	• Peptide mapping by enzyme hydrolysis • LC-UV/MS/MS, • Disulfide Linkage , • DAR determination, • Drug load distribution , • Site of conjugation and their occupancy, • Oxidation • Glycan Analysis • DSC • UV –CD

Mass Spectrometry

Capillary electrophoresis

UPLC

Analytical Services-ADC (Development & Characterization)

Osmometer

CD spectrophotometer

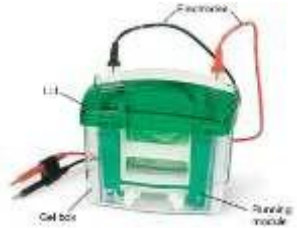
Zeta sizer

Nano DSC

Spectrophotometer

Spectro fluorometer

Gel doc

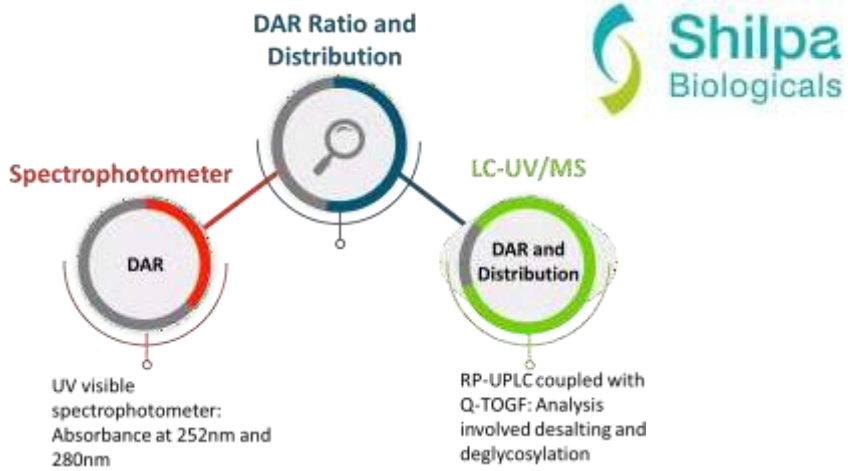


Gel unit

Gel powerpack

HPC

Analysis: Drug to antibody ratio (DAR) and Bioassays



Characterization of ADC using Bio-Layer interferometry (BLI)

FC region Characterization by ADCC and CDC

Cell Based assay for potency determination

Process impurities analysis
Safety Characterization

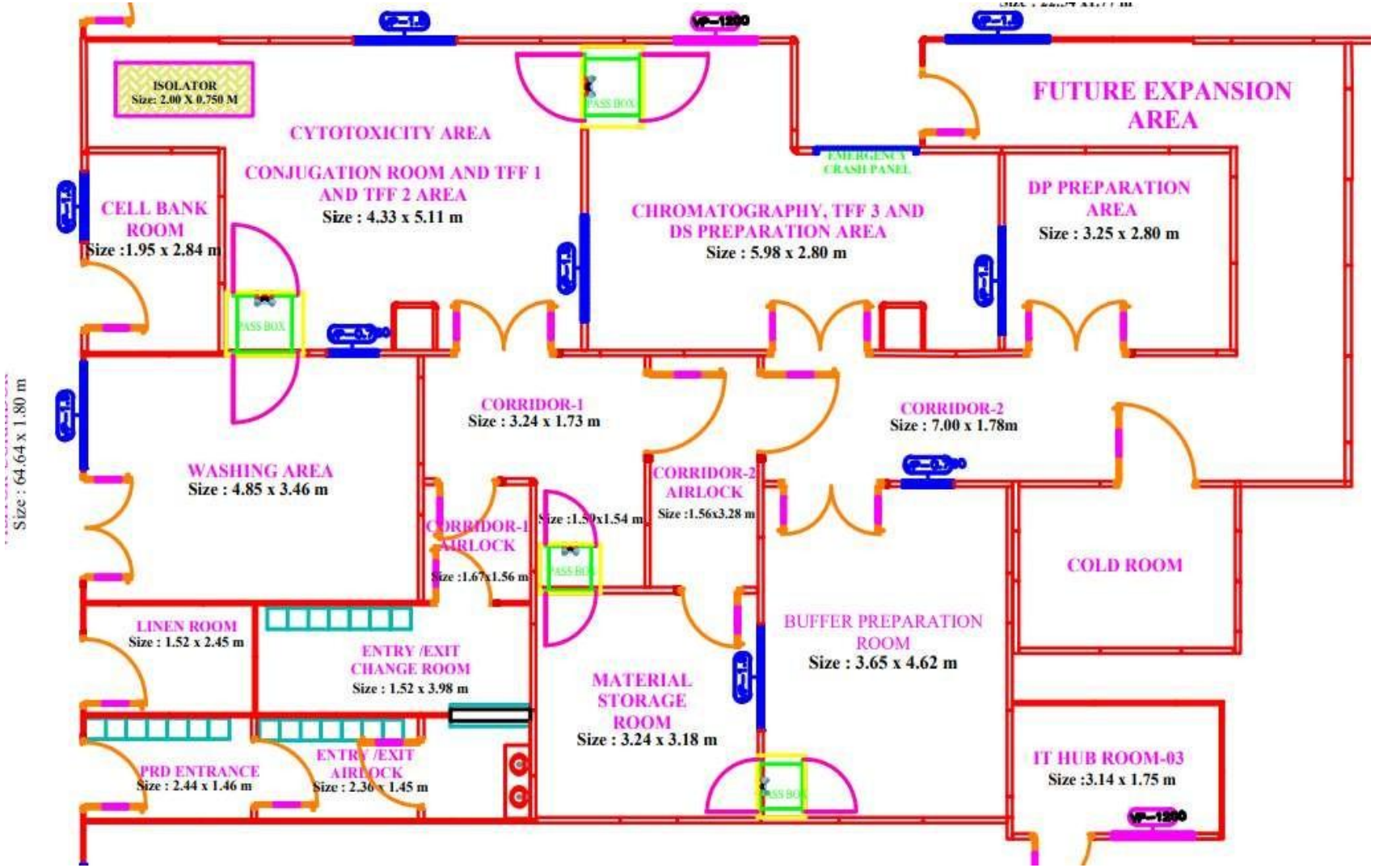
Octet

Multi Mode Reader

Biosafety Cabinet

Florescence Microscopy

ADC- Infrastructure and Capacity



- ***Scale of Conjugation reaction volume***
  200 L conjugation reaction volume

- ***Lyophilization Capacity***
  Lyo capacity ~65 kg .

- **Manufacturing facility**
  Appropriate control, equipment and process to handle the cytotoxic drug in facility

- ***Purification system***
  Akta Pilot, Akta Process, TFF system, higher scale columns

ADC – Offerings Across Platform

Scale up (Late stage)
Process characterization and process validation

Fill n finish & Lyophilization
Lyo cycle Optimization

Manufacturing service for ADC
Clinical & Commercial

Process development of ADC (Early stage)
Conjugation (Lysine, Cystine, etc.) and different purification techniques

Analytical Development & Characterization
For payloads, linkers, and intermediates

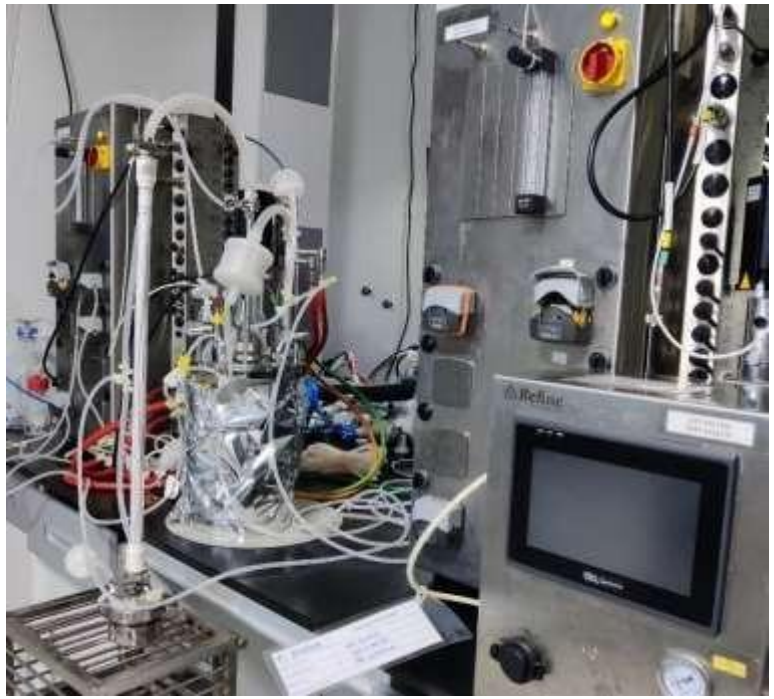
Payloads, linkers & Intermediated
Preparation and Supply

Mammalian DS Mfg. Facility

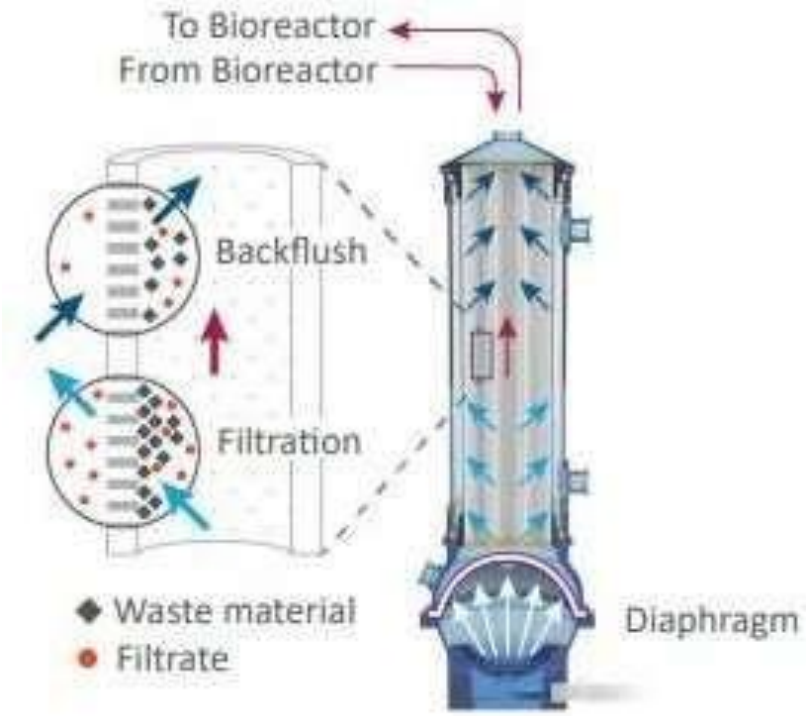
- *All **Single use consumables** including Bioreactor bag, liners, mixers and filters*
- ***1000 L×3** bioreactors with individual seed train, subsequent DSP*
- ***2000 L x 2** bioreactors with individual seed train, subsequent DSP*
- ***200L×6** Bioreactor*
- ***50Lx3** Wave Bioreactors*

40+ GMP Batches Executed for Clinical/ Commercial Manufacturing

Perfusion Systems



Perfusion System ATF 2 (10 L)



Perfusion System ATF 6 (50 L)

DSP Facilities

- ***Akta Pilot*** *Chromatography System*
  - ✓ *GE Akta Pilot 600 & 600R - Bench top chromatography system with maximum flow of 7200 L/hr*
- *Bioprocess* ***IC Hybrid*** *system*
  - ✓ *GE – Inline conditioning chromatography system – Capacity – 600 L/hr*
- *Bioprocess* ***Modular*** *system*
  - ✓ *GE – Small scale chromatography system – Capacity – 60 L/hr*
- ***BPG columns*** *of different sizes*
- *Different* ***TFF Holders***
- *Nanofiltration Skid*
- *Walk-in* ***Cold Rooms***

Fill Finish Capacities

Our facilities are designed as per 'USFDA' & 'EMA' standards

- ***3 independent*** *FF suites- automated filling lines where* ***"Ready to fill / Ready to sterilize"*** *primary packing materials*
- *Facility is available for* ***secondary packaging*** *and* ***visual inspection*** *before releasing prefilled syringes / vials for clinical or commercial distribution*

oRABS RTU combi line (AST Line)

- ***AST O - RABs*** *based RTU format*
- *Facility for* ***vials, cartridge*** *and* ***PFS***
- *Machine designed to handle following formats:*
  - ***0.5 mL to 1.0 mL PFS*** *in nested tubs*
  - ***2R vials*** *liquid fill in nested tubs*
  - ***3mL to 10 mL*** *cartridges in nested tub*
- *Rated Filling* ***speed****: 20 PFS / min, 20 vials / min, 20 cartridge/min*

oRABS RTS vial line (NKP Line)

Vial Filling & Stoppering Line: Make – NKP

- *Vial size **2R to 50R** and 100H*
- *Line speed **16,000 vials / hour***
- *Range of volumes: from **2mL to 100 mL***

Vial Washing & Sterilization

Automatic rotary vial washing machine (NKRVW - 400H)

- *Designed to wash internal and external surface of vials ranging from **2 ml to 100 ml** with different sets of change parts; the process removes particulate matter inside and outside the vials*

Capacity: 300 vials / min

Sterilizing & Depyrogenating tunnel (NKSP - 950)

- *Designed to depyrogenate vials by hot air at 300°c to 350°c which ensures reduction of endotoxin count by greater than 3 log*

Capacity: 16,000 vials in Tunnel

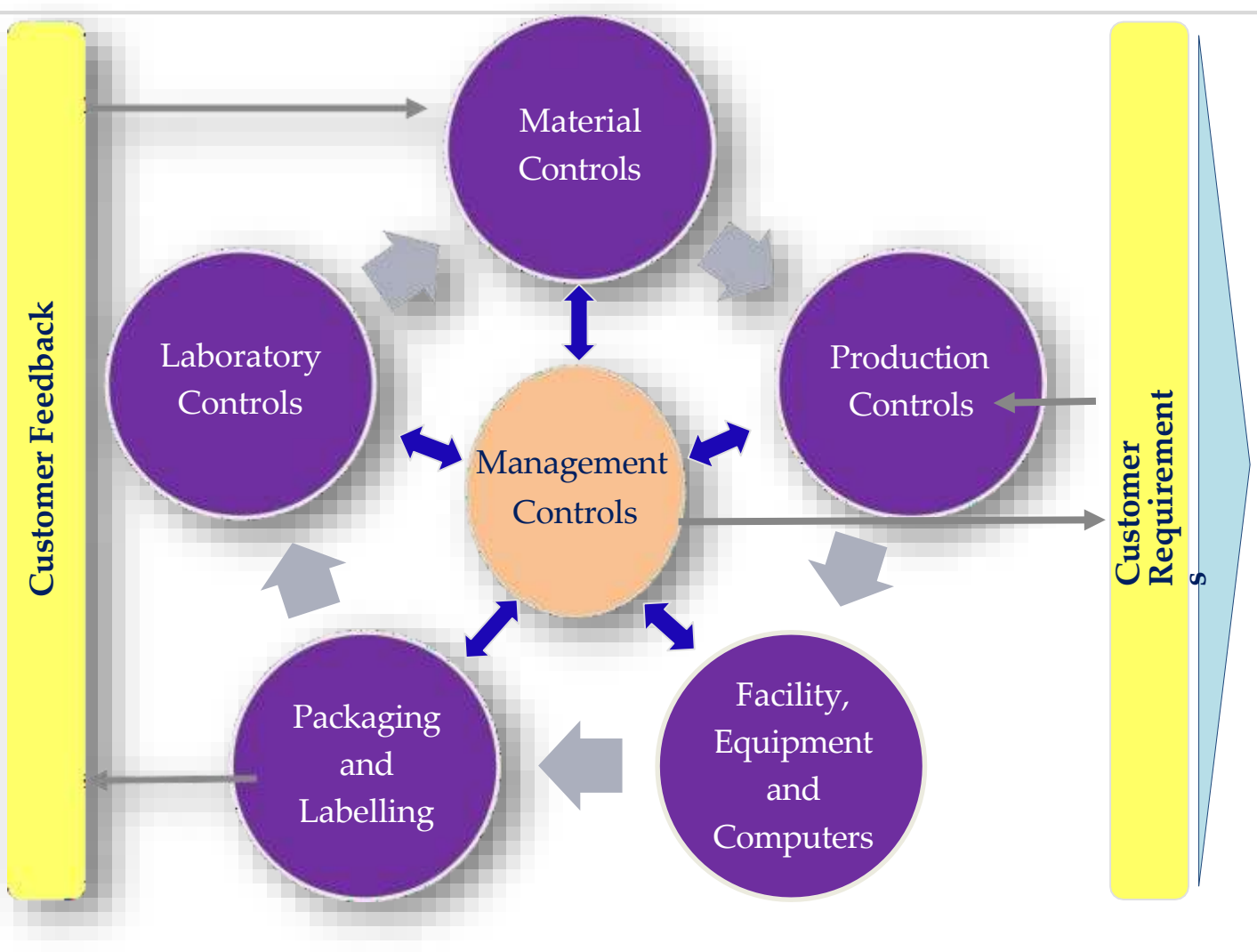
Isolator RTU Combi Line (Snowbell) with Lyophilizer

- ***Isolator based (RTU)*** *format facility for vials and PFS integrated with Lyophilizer*
- *Machine designed to handle :*
  - ✓ ***0.5 mL to 1.0 mL PFS*** *- nested tubs*
  - ✓ ***2R to 50R vials*** *(full stoppering & half stoppering) for liquid & lyophilized products in tray formats*
- *Usable shelf area of the Lyophilizer Rated Filling speed:* ***40 vials / min of 2R & 4R vials is 3.32m***

Quality Management System

Quality System

- ✓ *An Integrated Quality system meeting regulatory and customer requirements to ensure Quality, Safety, and Efficacy of the products*
- ✓ *Customer Feedback is considered for continual improvement of the Quality System*



Quality Assurance

- ***Documentation:*** *Three tier approach followed for documentation:*
  - ✓ *Electronic system **DocuZen** and **EduZen** implemented*
  - ✓ *Dedicated **Compactor Cell** for safe storage*
  - ✓ *Verticals IPQA, QMS, Validation, Vendor Management, Trainings, Documentation Cell, AQA*
- ***Quality system*** *is driven through written procedures are as below:*
  - ✓ *Incident / Deviation and CAPA Management*
  - ✓ *Change Management*
  - ✓ *Laboratory OOS / OOT / OOL*
  - ✓ *Quality Risk Management*
  - ✓ *Self inspection / Internal Audit through planner*
  - ✓ *Training management*
  - ✓ *Vendor and Material Management*
  - ✓ *Qualification / validation and periodic validation through VMP*

Quality Control

- ***Quality Control Laboratory***
  - ✓ *Analytical (Chemical, RM/PM testing, Mol. Biology and Bioassay) and Microbiology*
- ***Trained, Dedicated, Experienced*** *and* ***Qualified*** *analysts are involved for testing and releases*
- *Only* ***Authorized*** *personals are allowed with defined PPE's*
- *Equipped with* ***classified areas*** *for performing cell-based bioassays, mycoplasma, microbiological analysis*
- *Labs is equipped with all infra-structure, sophisticated 21 CFR / CSV compliant instruments / equipment*

Testing and Release

- *Equipped with required resources for testing:*
  - *material*
  - *in-process*
  - *release*
  - *stability*
- *Approved Specifications, procedures are followed for testing*
- *Raw data is written on worksheets-*
  - *reviewed by reviewer*
  - *final approval by Lab QA*
- *Analytical methods are fully validated as per ICH guideline*
- *Equipped with classified areas for performing mycoplasma analysis & cell-based bioassays, -Apoptosis, neutralization, proliferation, cytotoxicity, and receptor binding assays*
- *Dedicated Microbiology testing facility*

Stability Studies

- *Qualified and dedicated stability walk in chambers for performing stability studies for different ICH Zone*
- *Access controls and alarm/excursions are communicated through SMS and email for immediate actions*
- *Temperature data is recorded electronically and evaluated within 24 hrs. for any excursions and major excursions are investigated*
- *Stability studies are done through approved protocol and SOP and data is reviewed by Lab QA, further evaluated for trend, and investigated*

Analytical Capabilities – Microbiological Testing

- ✓ **Separate entry** – for general Quality Control areas through air-locks followed by change rooms for entering classified area from unclassified
- ✓ **Dedicated area-** for Sterility Testing equipped with Isolator. This area has separate entry and exit change rooms
- ✓ Other **classified areas** includes Microbial Limit Test area and isolated Live Culture Handling Area with separate entry
- ✓ Other **support areas** like Incubation room, media storage, Instrumentation room, sample receipt room and washing room
- ✓ Dedicated Sterilization and Decontamination Autoclaves
- ✓ Microbial Identification by Vitek 2 compact System

Eng. & Utility System

HVAC:

Entire facility is equipped with Air Handling Ventilation units.

WATER System:

- ✓ *Pre-treatment water plant of capacity 8m³ per hour with circulating Ozone Loop and Med-Pressure UV*
- ✓ *PW generation system of capacity 1200 LPH*
- ✓ *WFI generation system of capacity 2200 LPH through Vapor Compression System*
- ✓ *Pure Steam Generation 500 & 1000 kg per hour*
- ✓ *Compressed Air generator (Moisture & oil Free) of capacity 310 CFM (2Nos.)*
- ✓ *Boiler: 4TPH (1 No.) & 2 TPH (1 No.)*
- ✓ *Air Cooled Chiller: 240 TR (3 Nos.)*
- ✓ *Water cooled chiller: 300 TR (1 No.)*
- ✓ *Nitrogen Generator: 20 NM³ (1 No.)*
- ✓ *Diesel Generator: 750 kVA (3 Nos.)*
- ✓ *Elec. Transformer 2500 kVA (1 No.) running with dedicated UPS for individual building with 2000 kVA transformer as standby.*
- ✓ *Liquid Oxygen Storage tank 20 KL (1 No.)*
- ✓ *Gas bank System & Liquid Nitrogen Receiver Tank*
- ✓ *Cooling towers 100 TR, 300 TR, 400 TR (each 1 Nos.)*

Env. Health & Safety

The site is ZERO DISCHARGE unit, equipped with,

- *40KLD Effluent treatment Plant (ETP) with Primary, Secondary and Tertiary Treatment*
- *35KLD Sewage treatment plant (STP) with Primary, Secondary and Tertiary Treatment*
- *40KLD Multiple Effect Evaporator (MEE)*

Bio-Waste Management

- *Liquid waste is being decontaminated chemically and collected in an underground tank, then transferred through drain lines to central ETP for heat treatment*
- *Waste Management: Solid waste is segregated and handled through approved agencies – M/s. Mother Earth, for treatment*
- *Waste management: Biomedical waste is segregated and is handled by an approved agency M/s. Rio-green, for treatment*
- *Pest control is in place to minimize rodents, insects, and flies within the premises by an approved agency M/s. Terramica, On a periodic basis*

- Commercial Manufacturing License (Form 28D)
- WHO-GMP Certificate
- Good Manufacturing Practice (GMP) Certificate
- Good Laboratory Practice (GLP) Certificate
- Licenses (Form 29) to manufacture the new drug for clinical trial purpose
- Licenses (Form 29) to manufacture the new drug for manufacturing of batches of experiment, test and analysis purpose
- Production Capacity Certificate

EMA inspection conducted in Feb 2025 with No critical or major observations

In Plan- PICS Country Audit in April 2025


Thank you!