ProBio

TECHNOLOGY TRANSFER

HANDBOOK

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TECHNOLOGY
TRANSFER

Outline

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INTRODUCTION TO TECHNOLOGY TRANSFER

As defined in ICH Q10, the aim of technology transfer is to achieve the commercial objectives of a product by transferring the product and process knowledge between R&D and production, either within one production site or between two production sites. This knowledge contributes to the foundation of bioprocess, control strategies, process validation methods and continuous improvement.

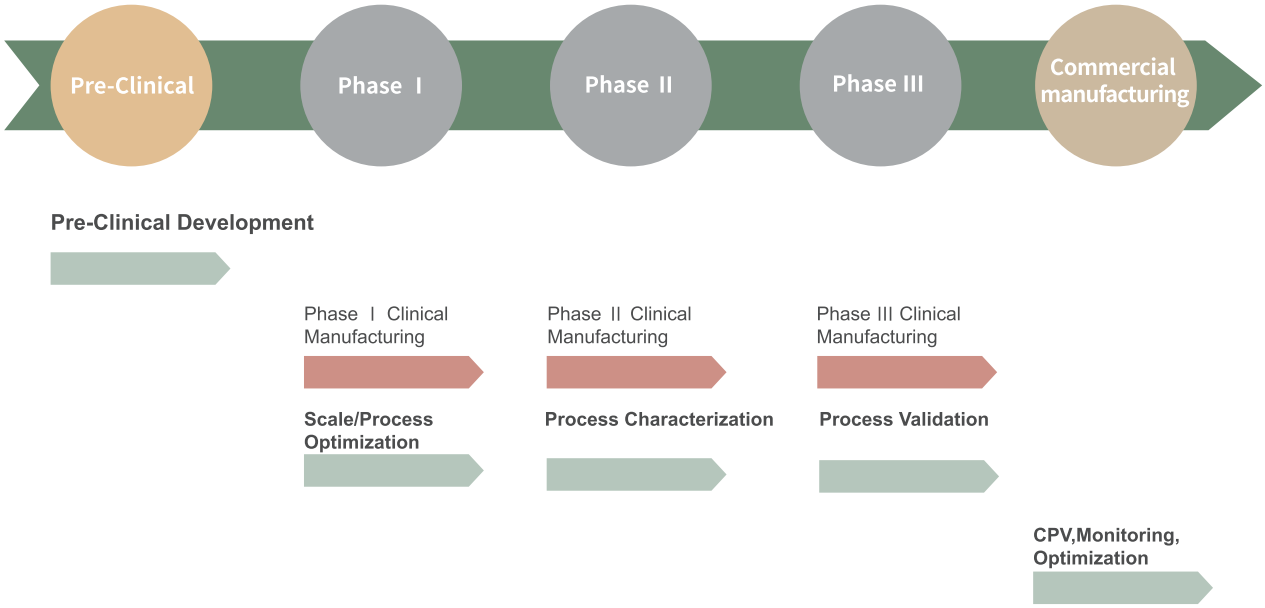

Figure 1. Technology transfer occurs throughout the life cycle of biotherapeutics

By definition, technology transfer occurs throughout the life cycle of biotherapeutics. From the early preclinical development stage to the phase I clinical trial, production site change and scale-up are often required. As clinical trials develop, scale-up is needed for phase II clinical manufacturing, where the technology transfer is also required. For phase III clinical manufacturing, it is recommended to use the same production site and scale as the future commercial manufacturing. Therefore, changes in the production sites and scale are often encountered. In the commercialization phase, when existing production scale doesn't meet the growing need of market sales, it is often required to establish new production lines, or lower the production cost by introducing new technologies. All of these require technology transfer.

Technology transfer may happen among different departments within the same company, and also between different companies. Within the same company, technology transfer is required to handle process scale-up, transfer of production site and management of process change activities from R&D to clinical and commercial production. The advantage of intra-company transfer is that the sending unit and receiving unit are under the same company system with similar procedures, philosophies and management systems, which benefits the management of technology transfer. Under this circumstance, the purpose of technology transfer is to transform the R&D process into a commercially feasible process with high durability and sustainable supply to the market.

For companies that work with CDMO, technology transfer is a routine and tedious operation, involving transfer of production process from one production site to another between two companies. The challenges here are even greater, as there are differences in equipment, facilities, quality systems and personnel, as well as difficulties in sending and receiving process information. In this case, one of the elements for a successful technology transfer is the willingness of the sending unit to share all technical details, not just the documentation.

MANAGEMENT OF TECHNOLOGY TRANSFER

Technology transfer management is a challenge for any company, especially the organizing and communication segments. Technology transfer typically adopts a three-tier organizational structure. The first level is high level committee of the sending unit, which is responsible for decision-making, budget, timeline and approval of major changes of the technology transfer project. The second level contains the project manager and the heads of each function, who are mainly responsible for project management and problem solving. The third level is the front-line personnel of each functional group, including R&D, manufacturing, analytics, quality control, regulatory affairs, construction, finance, supply chain, legal and EHS department, mainly to solve the technical problems of each module.

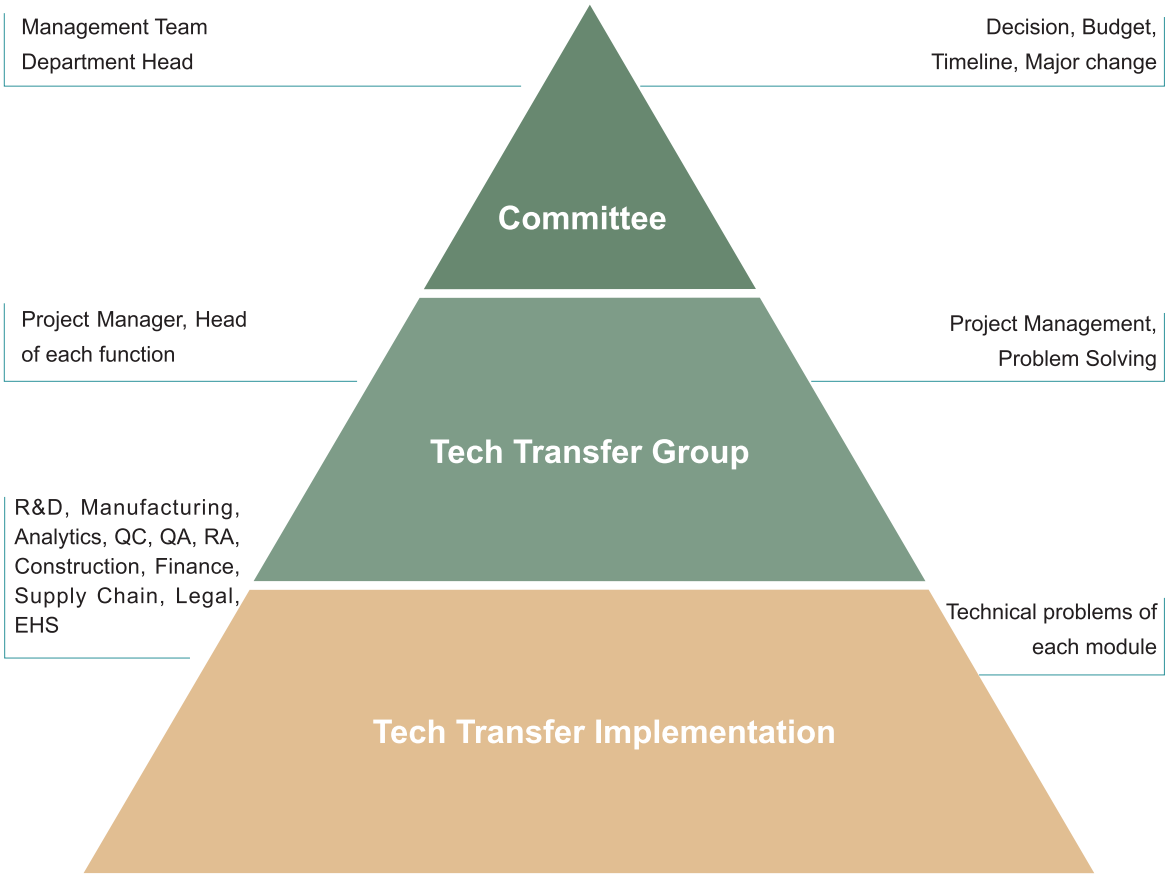

Figure 2. Organizational structure of technology transfer management

PROCESS OF TECHNOLOGY TRANSFER

1. Feasibility study

Quality agreement, technology transfer team, acceptable transfer standard

2. Information exchange and formulating technology transfer plan

Gap analysis, risk assessment, actions to lower the risk, finalize technology transfer plan

3. Technology transfer implementation

Small-scale validation, documentation establishment and validation equipment validation materials release, analytical methods validation, engineering batch and validation batch PPQ

4. Technology transfer report

Similarity of process and comparability of product quality, stability report, technology transfersummary

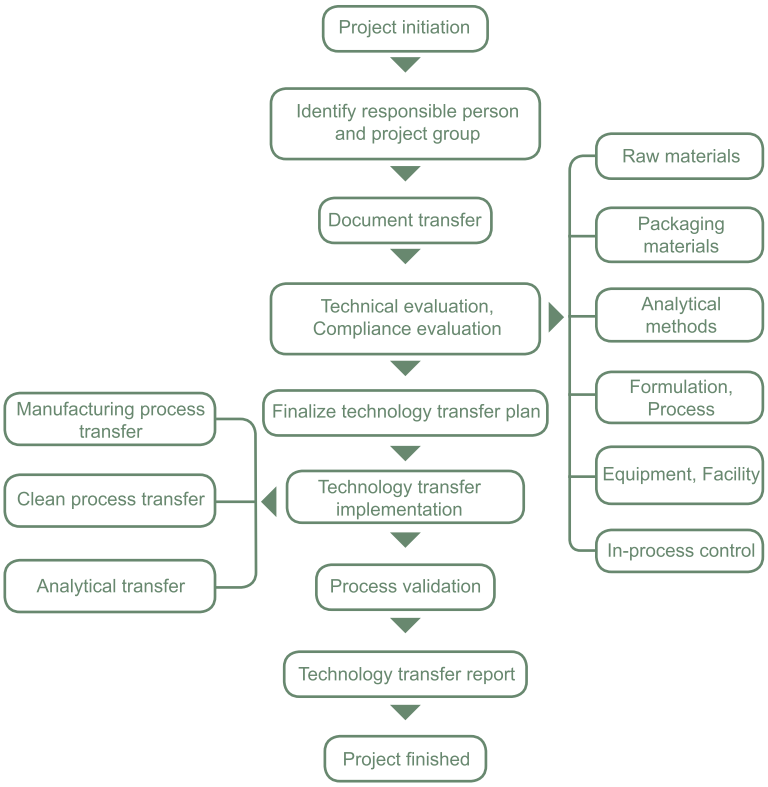

Figure 3. Process of technology transfer

There are detailed descriptions about the content and process of technology transfer in PDA (parenteral drug association) TR65. Usually, technology transfer process can be divided into four steps.

The first step is **feasibility study**, which is conducted by the management team. The feasibility study includes project feasibility, quality agreement, building a technology transfer team and acceptable transfer standard establishment. The feasibility study should be finished before the beginning of project transfer.

The second step is **information exchange and technology transfer plan development**, which is the basis of a successful technology transfer. Sending unit and receiving unit should analyze the gap of equipment, consumables, process, and personnel according the collected information. Then they conduct risk assessment about the gaps and propose risk mitigation plan. The technology transfer plan is ready when all these aspects are accomplished.

The third step is **technology transfer implementation**, which includes analytical method transfer, process transfer, clean process transfer and successfully performed corresponding engineering batch and validation batch.

The fourth step is the completion of **technology transfer report** according to the assessment of similarity of process and comparability of product quality.

KEY POINTS IN TECHNOLOGY TRANSFER

During the technology transfer process, adequate information exchange at the second step is very important. Next, key points in the information exchange and technology transfer will be introduced in details.

Document Transfer

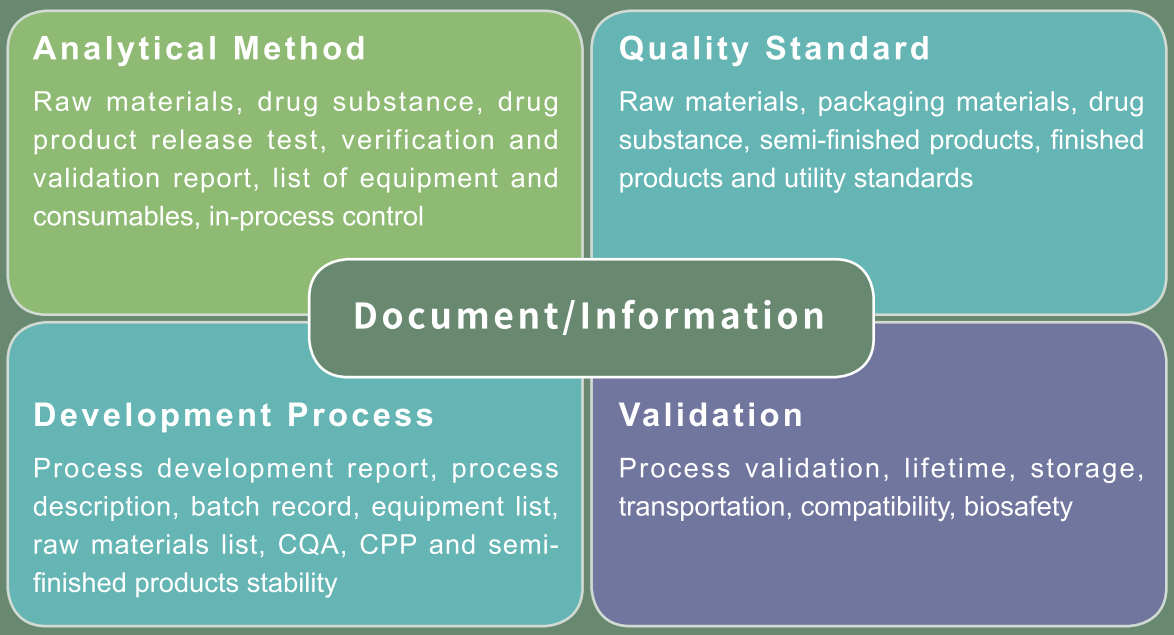

Figure 4. Key points of technology transfer-document transfer

For document and information transfer, it is suggested to consider the following four aspects:

1. Analytical method: Including raw materials, in-process control, drug substance and drug product release test method and validation report, list of all analytical equipment, essential reagents and consumables

2. Quality standard: Including raw materials, packaging materials, in-process control, drug substance, semi-finished products, finished products and utility standards.

3. Development Process: including process development report, process description, batch record, equipment list, essential materials list, CQA (critical quality attributes) assessment, CPP (critical process parameters) and semi-finished products stability.

4. Validation: This part is usually needed in clinical phase II&III, including process validation, column lifetime study, transportation validation report, storage validation report, compatibility report of packaging materials and biosafety-related validation report.

It is recommended that the sending unit and receiving unit prepare technology transfer document list in advance and make confirmation according to the list. Taking analytical method transfer as an example, the documents list during technology transfer includes the following items:

- Reference quality standard and CoA
- DS/DP release test SOP
- DS/DP release test validation report
- DS/DP release test development report
- IPC test method SOP and report
- Raw materials test method validation and SOP
- List of all analytical equipment, essential reagents and consumables

Document Transfer

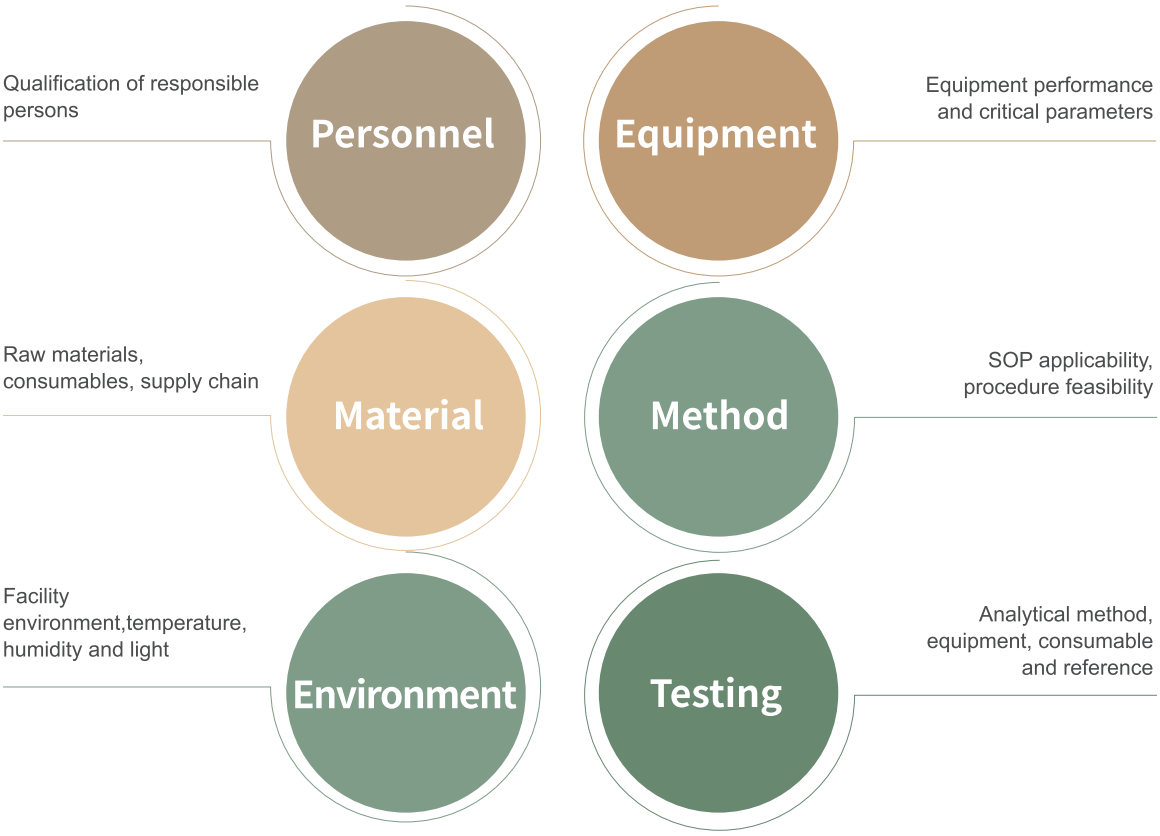

Figure 5. Key points of technology transfer-gap analysis

After collecting the needed information, we can make gap analysis from the following six aspects.

1. **Qualification of responsible persons:** Biologics clinical manufacturing process requires the responsible persons with technical background. Therefore, it is essential to make sure that all responsible staff members have received adequate training.
2. **Equipment:** Besides the key manufacturing and process equipment parameters, gap analysis is also needed for the in-process analysis equipment.
3. **Material:** Consistency of raw materials and consumables is should be considered as well as supply chain to support the manufacturing use.
4. **Method:** Possibility of repeating at the receiving unit.
5. **Environment:** Mainly focus on the facility, clean grade, temperature, humidity, and light difference analysis during the manufacturing site transfer.
6. **Testing:** Mainly focus on the difference of analytical methods, equipment, consumables and reference standard.

Risk Assessment

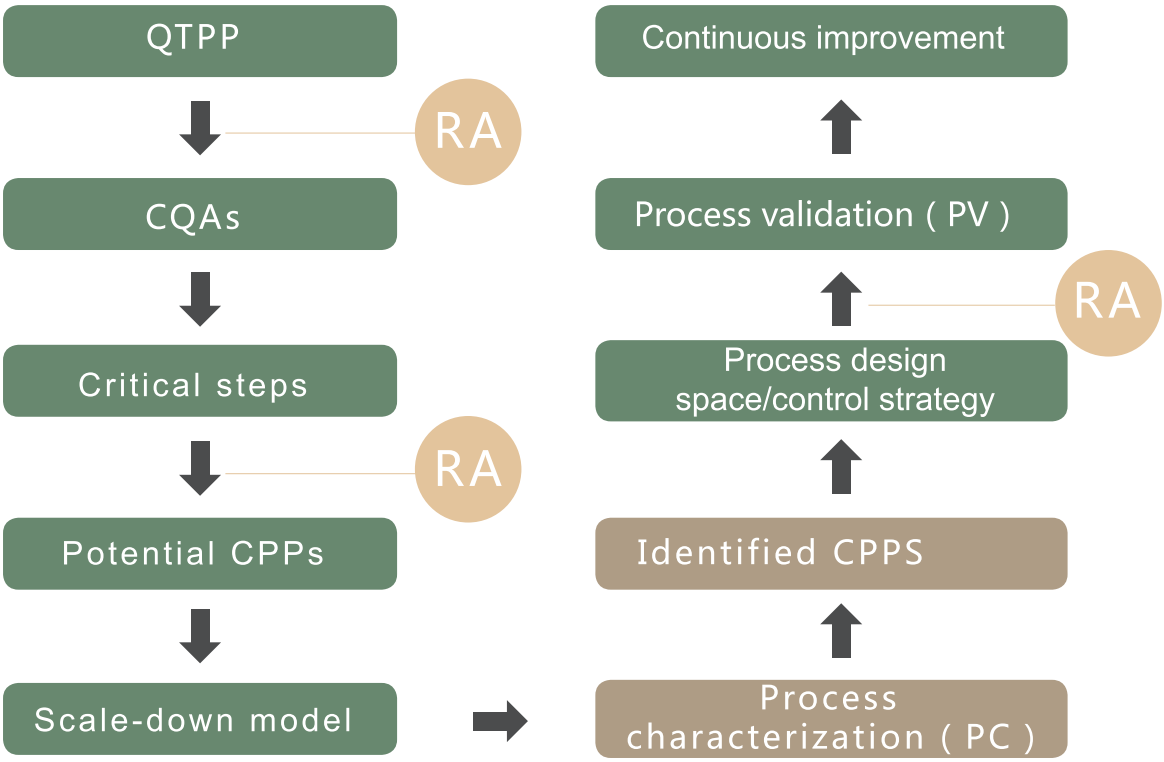

Figure 6. Key points of technology transfer-risk assessment

Risk assessment is made on the basis of gap assessment. Risk assessment is implemented throughout the life cycle of drug development. In early stage, initial risk assessment should be carried out to figure out CQA and CPP. This risk assessment on CQA and CPP should continue according to further understanding from process characterization and process validation. Risk management tools are recommended by ICH Q9, such as FMEA (failure model and effects analysis), FMECA (failure model effects and criticality analysis), FCTA (failure cause tree analysis), HACCP (hazard analysis and critical control point), HAZOP (hazard and operability analysis), etc.

Risk Assessment

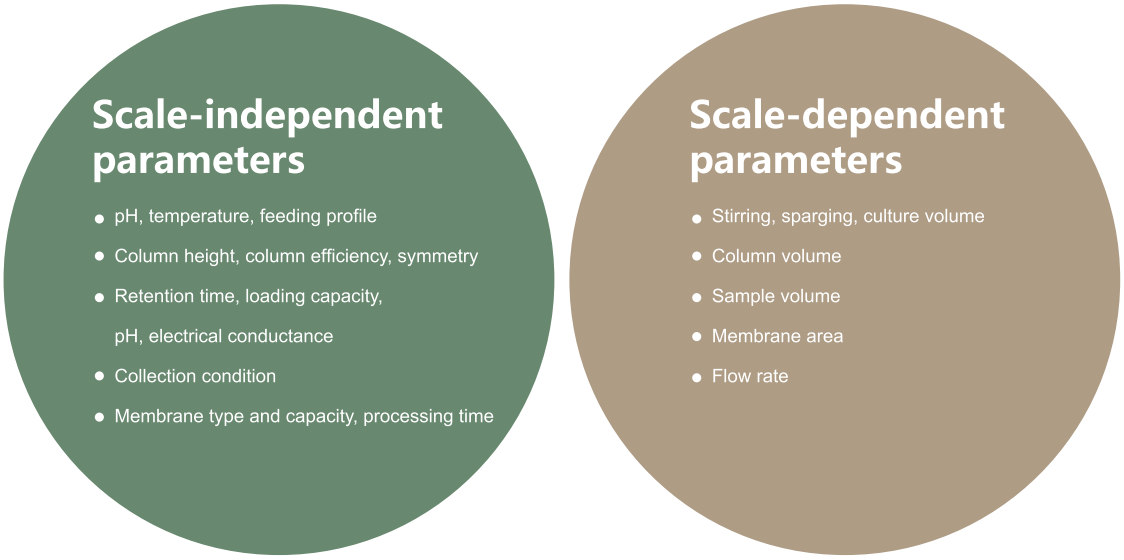

Figure 7. Key points of technology transfer-parameter conversion in scale change

In the course of technology transfer, impact on technical parameters caused by scale change should be considered. Scale-dependent parameters should be converted through calculation. In cell culture process, parameters like pH, temperature and feeding profile, are irrelevant to scale, while stirring speed and sparging should be calculated according to culture volume. In purification process, column height and column efficiency are usually kept in the same range. Retention time, loading capacity, and elution condition remain constant. However, the column and sample volume varies depending on the scale. In filtration process, membrane type and capacity are the same, while membrane area and flow rate varies depending on scale.

CASE STUDY

In this chapter, gap analysis in technology transfer will be demonstrated with specific cases. For technology transfer of cell culture process between different bioreactors, temperature, stirring speed, and sparging are CPPs requiring parameter transformation through calculation. For chromatography, the UV absorbance sensitivity among different equipment varies and testing should be carried out to match the difference if any. For ultrafiltration process, membrane area and pump speed should be considered if the equipment principle is the same. Pump speed should be evaluated to meet the process requirement. As to raw materials, e.g. NaOH, COA should be compared between different suppliers.

Process	Name	Brand	Critical Parameter	Name	Brand	Critical Parameter	Gap
	Sending Unit			Sending Unit			
Cell culture	20L EZ-Control bioreactor	Applikon	micropore size 15ummacropore size 1mmpH, DO, temperature, stirring speed	Hyperforma 200L single-use bioreactor	Thermo	Temperature, stirring speed, sparging, DO	Parameter difference between different bioreactors Need scale-up analysis
AC/AEX/CEX chromatography	AKTA Avant/ AKTA Pure25/ AKTA Pure150	Cytiva	UV optical path 2mm max flow rate 25ml/ min/150ml/min	AKTA Ready	Cytiva	1. UV optical path 2mm2. flow rate: 3-175L/H（Low flow kit）3. flow rate：7.5-500L/H（High flow kit）	Confirm the absorbance difference with supplier Comparison test with the same sample
Ultrafiltration	SMTTFF20008	Millipore	Single-use system, pump flow rate 200 LMH	MC0SP01FS1	Millipore	Stainless, Max pump flow rate 5L/min	Same principle Evaluate whether the pump flow rate can fulfill the production requirement according to the membrane area
Raw materials	NaOH	Merck	USP	NaOH	Jiangsu Qinfen	CHP	Used in system clean No direct contact with product COA comparison

Figure 8. Gap analysis case studies

	Bioreactor A			Bioreactor B			
Parameters	3L	15L	B-50	B-200	B-500	B-1000	B-2000
Standard Parameters							
Max Working Volume(L)	2.1	12	50	200	500	1000	2000
Min Working Volume(L)	0.6	3	22	40	100	200	400
H/D	1.5	1.45	2.3	1.5	1.5	1.5	1.5
Di/Dt	0.34	0.34	0.72	0.39	0.35	0.34	0.34
Impeller diameter (in) applikon (mm)	45	74	8.7	8.7	10.4	12.7	16.5
Impeller type (M40E)	marine	marine	blade	blade	blade	blade	blade
mpeller Np							
Max Agitator (RPM)							
Headsweep (sLPM)							
Air sparge (sLPM)-1 mm							
Max Oxygen sparge (sLPM)-20 um							
P/V (W/m^3) * Must < 100 W/m^3							
Modified P/V (W/m^3)*							
Tip speed (m/s) * Must < 2.5 m/s							

Figure 9. Parameter conversion between different bioreactors

Besides the gaps of production equipment, analysis equipment should be also considered. For example, testing for cell density and viability, different equipment may lead to variance of testing results. Thus, risk assessment should be carried out to match the difference.

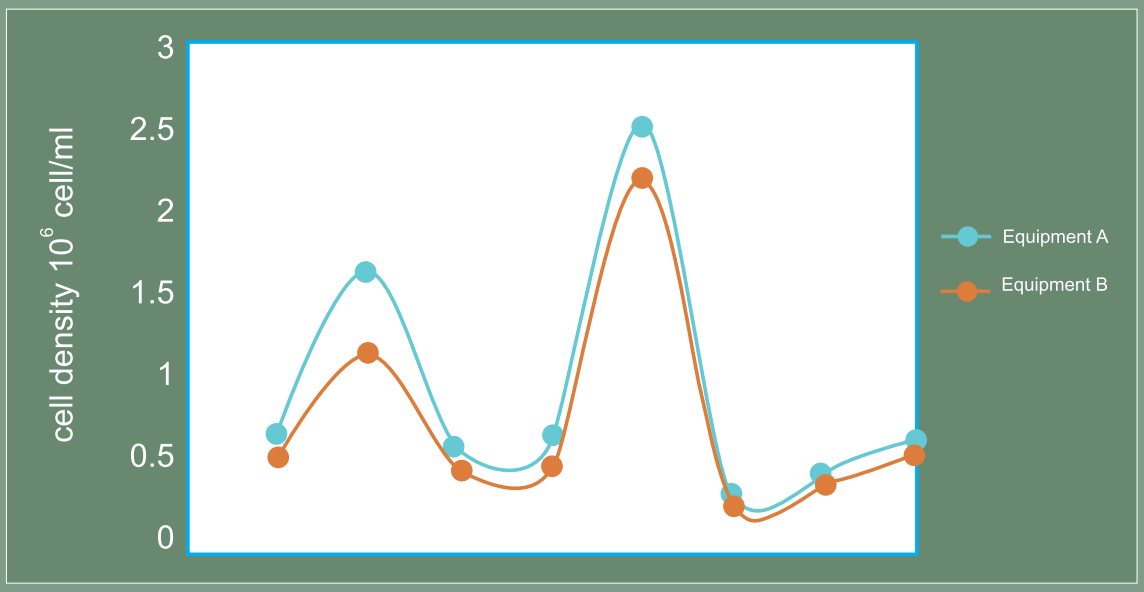

Figure 10. Parameter conversion between different analytical instruments

	Bioreactor C				Bioreactor D	
	C-50	C-50	C-250	C-500	D-200	D-500
	2:1	5:1	5:1	5:1	4:1	4:1
	50	50	250	500	200	500
	25	10	50	100	50	125
	1.5	1.5	1.5	1.5	1.8	1.8
	0.318	0.318	0.335	0.332	0.38	0.38
	111.1	111.1	200	251	225	310
		marine	marine	marine	blade	blade

Brands and scales of bioreactors may be different during the technology transfer. Collecting parameters of different bioreactor and calculating P/V value to match scale change are needed. Scale-down and scale-up experiments should be set up as well. Another way for technology transfer is starting from small scale transfer and scaling up according to experience of receiving site. GenScript ProBio has built conversion parameters model for most bioreactors. There are some data shown in Figure 9.

For downstream purification equipment, sensitivity and optical path of UV absorbance is a key parameter and calculation should be carried out in case of any difference. Typically, standard samples are tested to match the difference and convert parameters.

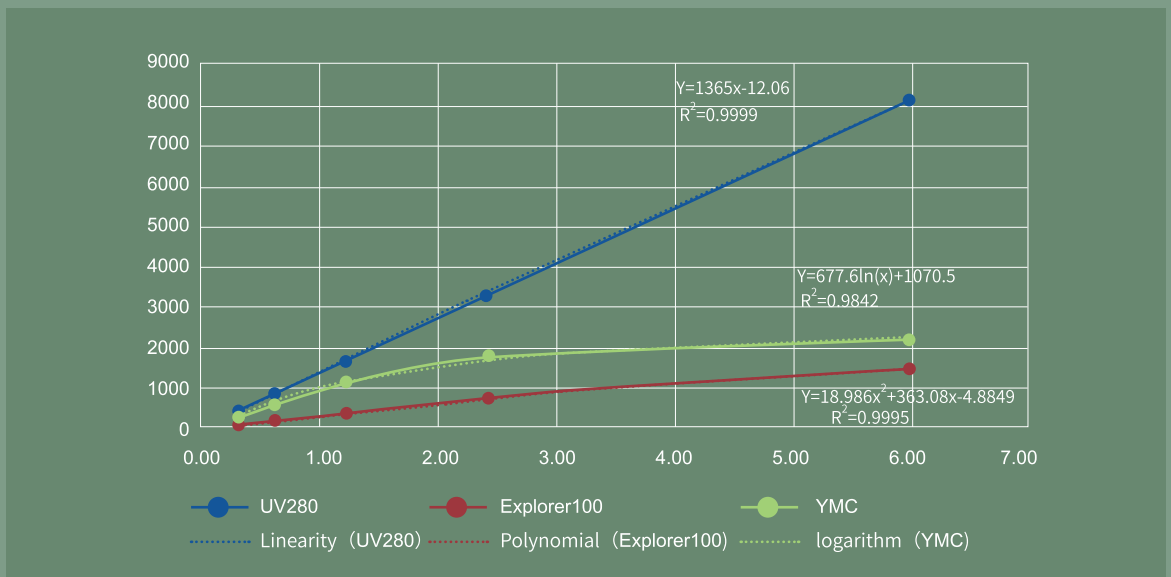

Figure 11. Parameter conversion between different UV absorbance in chromatography

SUMMARY OF TECHNOLOGY TRANSFER

Technology transfer runs through the whole life cycle of biologics. Besides the following process and guidance, there are other factors affecting the success of technology transfer. Good work relationships and fair, trusted and respected principles will benefit the communications between sending unit and receiving unit. Sending unit shall be willing to share their knowledge, including but not limited to documents. Both sides should communicate the details of process at the early stage and build suitable control strategies to boost the success of technology transfer. At the same time, technology transfer should be based on the cooperation of teams, shooting the transfer success as the same target to solve the problems quickly.

This handbook is a brief introduction about the process and key elements in technology transfer. For more detailed information, please refer to PDA TR65 Technology Transfer and WHO (World Health Organization) Guidelines on Transfer of Technology in Pharmaceutical Manufacturing.

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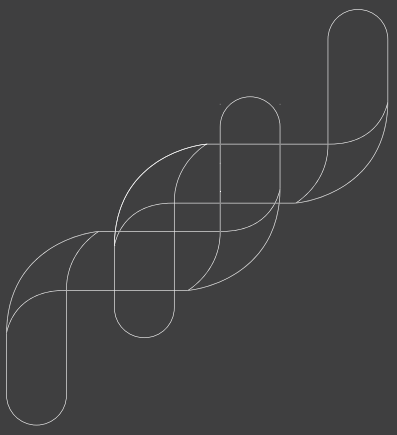

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