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Quality Based Approach for Efficient Biologics Manufacturing

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***Abstract*—**To improve the manufacturing efficiency of biologics, such as antibody drugs, a quality engineering framework was designed. Within this framework, critical steps and parameters in the manufacturing process were studied. Identification of these critical steps and critical parameters allows a deeper understanding of manufacturing capabilities, and suggests to process development department process control standards based on actual manufacturing capabilities as part of a PDCA (plan-do-check-act) cycle. This cycle can be applied to each manufacturing process so that it can be standardized, reducing the time needed to establish each new process.

***Keywords*—**Antibody drugs, biologics, manufacturing efficiency, PDCA cycle, quality engineering.

I. Introduction

FIRST and second generation biopharmaceutical drugs currently available in the market are largely divided into two drug categories: protein formulations and antibody drugs [1]. Protein formulations mainly contain a biological component such as interferon or erythropoietin. They are clinically indicated for pathological conditions that results in an endogenous protein deficiency. Antibody drugs, on the other hand, are capable of binding to foreign matters in the body or particular antigens on cancer cells. Clinically, they are used to inhibit the activity of disease-specific proteins - often an antigen. Antibody drugs, especially, have shown processing efficacy, and are highly expected to help address unmet medical needs with various refractory diseases.

For pharmaceutical companies to improve the competitiveness of their drugs, problem-solving discussions based on a wider perspective beyond just research and development is required. However, in the development of manufacturing processes of biopharmaceuticals, the research cases involving such discussion have seldom been reported. Challenges include biologics are sensitive to changes in manufacturing conditions, manufacturing process is complicated, and final drug product is required to be of high quality [2]. In recent years, this problem has finally been discussed in the pharmaceutical industry, but an optimal manufacturing process, in which all manufacturing steps from drug substance to drug product are systemically optimized, has not been fully characterized [3]. Although product development and technologies for antibody drugs have been progressing rapidly, the manufacturing process remains non-standardized. Due to the strong concerns of the regulatory authorities about such non-standardized processes, GMP (Good Manufacturing Practice) compliance and safety have been given first priority. As a result, antibody drug research and manufacturing lag far behind after types of drugs in terms of cost efficiency.

This research was therefore aimed at optimizing control standards in the manufacturing process of antibody drugs. For this optimization, a procedure for improving the efficiency of the manufacturing process was examined by applying the framework of quality engineering. Here, the examination results are presented.

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II. Approach Based on the Framework of Quality Engineering

Drug manufacturing processes are developed according to stringent safety and efficacy criteria. In Japan, the development of a drug manufacturing process generally takes 9 to 17 years, under strict quality control until regulatory approval [4]. Most of this period is spent evaluating the safety and efficacy in accordance with regulatory criteria (Fig. 1).

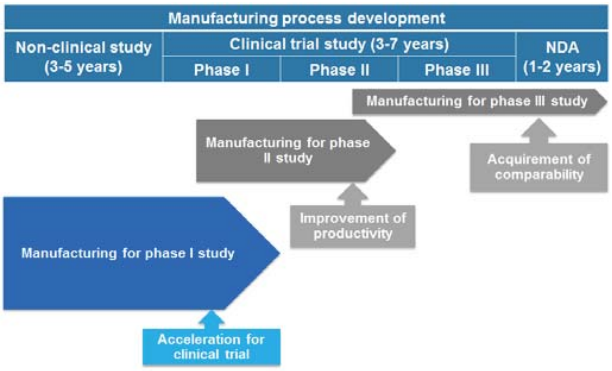

Fig. 1 Development phase of manufacturing process

The development of new biopharmaceuticals, including antibody drugs, is especially difficult because they are produced in living organisms, thus involving substantial uncertainties, and are then manufactured using highly advanced technologies. Many drug candidates are produced and subjected to multiple screening sessions to select the safest and most effective one, which will finally then be released into the market.

Many drug candidates are subjected to phase I clinical studies - the first clinical screening stage in which safety and efficacy can be evaluated, allowing a decision for or against further development (Go or No go). To accelerate the clinical

study stage, drug candidates should be manufactured as rapidly as possible.

At the manufacturing site, the process, involving living organisms, is actually adjusted in situ based on the knowledge and experience of skilled operators. To accelerate manufacturing operations, a new system should be designed in which quality-related data from the manufacturing process and accumulated manufacturing knowledge are combined so that process adjustment can be taken immediately. The study was implemented on the relationship between critical quality attributes and steps in the manufacturing process, which represent quality and knowledge, respectively.

A. Quality Engineering Framework

The guidelines for regulatory approval of drugs across the world require application of quality engineering procedures. The framework of quality engineering was therefore applied to the study of the relationship between critical quality characteristics and the manufacturing process. To improve the efficiency of the manufacturing process, identification of critical manufacturing steps and parameters, as well as examination and evaluation of manufacturing control standards, were carried out within this framework. The quality engineering framework was applied to efficiency improvement (Fig. 2).

Fig. 2 Quality engineering framework procedure

In Step 1, the critical quality characteristics of antibodies were studied and then, in Step 2, the manufacturing process was evaluated. In Step 3, critical quality steps were identified from the correlation between critical quality characteristics and the manufacturing process. Finally, in Step 4, critical manufacturing parameters in the critical quality step were studied and identified.

B. Step 1: Study of Critical Quality Characteristics

Among antibody drugs, quality test items required by regulatory authorities are almost the same, because antibody molecules, the target substances, have similar structures [5]. The critical quality characteristics are organized, based on regulatory review results (Fig. 3).

In this study, critical quality characteristics were determined by evaluating the safety and efficacy, which are described as evaluation indices in the regulatory guidelines. The critical quality characteristics are physical, chemical, biological and microbiological characteristics for which the actual values should be within appropriate limits, range, or distribution to ensure safety and efficacy. The study revealed that these test items would affect the safety and efficacy, and their designation as critical quality characteristics was thus justified.

Critical quality characteristics	Safety	Efficacy			
		Identity	Strength	Quality	Purity
Physical aspect				Yes	
pH				Yes	
Osmotic pressure				Yes	
Identity		Yes			
Purity	Yes				Yes
Titer		Yes	Yes		
Protein content				Yes	
Endotoxin limit	Yes				
Microbiological limit	Yes				
Mycoplasma free	Yes				
Virus free	Yes				

Fig. 3 Impacts of critical quality characteristics on safety and efficacy

C. Step 2: Evaluation of the Manufacturing Process

The manufacturing process of antibody drugs largely consists of two steps - culture and purification. In the culture step, animal cells, such as Chinese hamster ovary (CHO) cells, are cultured to produce an antibody. In the subsequent purification step, impurities and excess buffer are removed producing a more concentration antibody solution [6]. By following these steps, the antibody substance is manufactured. For antibody drugs, the culture engineering procedure by which the antibody gene is transferred into animal cells to express a desired protein has been commercially established. At present, the manufacturing process is mature, and the core technology for each step is in place (Fig. 4).

Criteria for the quality, economy, reliability and flexibility were established based on a multi-objective evaluation approach - an engineering-type evaluation tool. The core technologies for antibody drugs were comprehensively evaluated with respect to these criteria (Fig. 5).

D. Step 3: Study of Critical Manufacturing Steps

Using a matrix diagram (one of the quality engineering procedures), correlation between critical quality characteristics on the vertical y-axis and steps in the manufacturing process on the horizontal x-axis was studied to determine which manufacturing steps affect which critical quality attributes. All points of intersection between the vertical and horizontal axes were studied for their impact based on the biologics literature and critical steps for manufacturing of antibody drugs were identified (Fig. 6). For example, the literature showed that pH variation influenced glycosylation in turn affecting on antibody

characteristics [7]. Based on Fig. 6, the production culture step was judged to be a critical manufacturing step affecting critical quality characteristics.

Culture step	Seed culture	Batch culture		Perfusion culture	
	Expansion culture	Batch culture		Perfusion culture	
	Production culture	Fed-batch culture		Perfusion culture	
	Cell separation	Centrifuge / Depth filter		Filter aid	Tangential flow filter
Purification step	Capture	Affinity chromatography		Ion-exchange chromatography	
	Inactivation	Low pH		Heat	
	Polishing	2 chromato (Ion-exchange)	2 chromato (Hydrophobic, Ion-exchange)	2 chromato (Mixed-mode, Ion-exchange)	2 chromato (Ion-exchange, Membrane)
	Virus removal	20nm filter		50nm filter	
	Concentration	Ultrafilter / Diafilter			
	Final filtration	Antiseptic filer			
	Filling	Bottle	Bag	Cryotank	

Fig. 4 Core technology of antibody manufacturing

Criteria of evaluation		
Quality	F1	Criticality on patient safety
	F2	Criticality on efficacy
Economy	F3	Initial cost
	F4	Running cost
Reliability	F5	Equipment reliability (performance)
	F6	Process reliability (reliability)
	F7	Operational simplicity (automation)
Flexibility	F8	Process flexibility
	F9	Equipment flexibility

Fig. 5 Criteria for manufacturing core technologies

E. Step 4: Study of Critical Manufacturing Parameters

In critical manufacturing steps, the controlling system was organized by function to investigate controlling parameters. A system chart was used to identify control parameters substantially affecting the critical quality characteristics. The system chart is a conventional procedure based on the quality engineering concept and one of the Taguchi methods used for parameter design [8].

As an actual example, the system chart of the production culture - the main operation in the culture step - is shown (Fig. 7).

In the system chart, the System represents the temperature control - a control factor which involves Input, Output and Noise.

Critical quality characteristic	Manufacturing process							
	Seed culture		Expansion culture		Production culture		Cell separation	
	Impact	Rationale	Impact	Rationale	Impact	Rationale	Impact	Rationale
pH	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH.	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH.	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH
Osmotic pressure	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH.	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH.	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH	No	pH is adjusted in UF/DF process. Upper processes have no impact on product pH
Identity	No	No impact on molecular structure	No	No impact on molecular structure	Yes	pH control during the cultivation can affect glycosylation	No	No impact on molecular structure
Purity	No	No impact on molecular	No	No impact on molecular structure	Yes	Low viable cell ratio can lead to increas	Yes	HCP and DNA should be removed

: Critical manufacturing steps

Fig. 6 Study of critical quality characteristics and their impact on the manufacturing process / excerpt

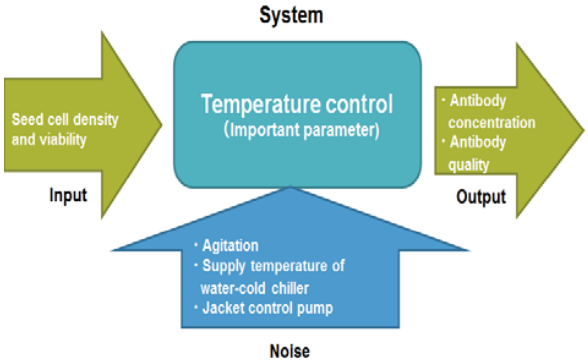

Fig. 7 System chart of production culture

Critical quality characteristic	Major equipment	Process function	Process aspect	Manufacturing parameters
Identity	Production Bioreactor	Tank pressure	Control system	Pressure
		Temp. control	Control system	Temperature
		DO control	Control system	DO
		pH control	Control system	pH
		DCO_2 control	Control system	DCO_2
		Sampling	Sampling system	Pressure
		Discharge	Transfer system	Pressure

: Critical manufacturing parameters

Fig. 8 Critical manufacturing parameters in the production culture

The Input consists of factors affecting the Output through the System, such as viable cell density and viability rate of the seed culture, while the Output consists of factors affected by the System, such as antibody concentration and antibody quality. The Noise consists of potential factors adversely affecting the Output through the System, such as chiller feeding temperature and jacket pump operation.

In Fig. 7, the antibody quality is critically determined by the temperature control, by which the temperature appropriate for

antibody production is maintained. Temperature control is thus judged to affect identification in terms of the molecular structure and quality characteristics - critical manufacturing parameters (Fig. 8). This system chart is highly useful in characterizing the Input, Output and Noise, and in identifying critical factors. Therefore, this system chart should be applied to all the critical manufacturing steps to analyze all control systems and identify the critical manufacturing parameters (Fig. 9).

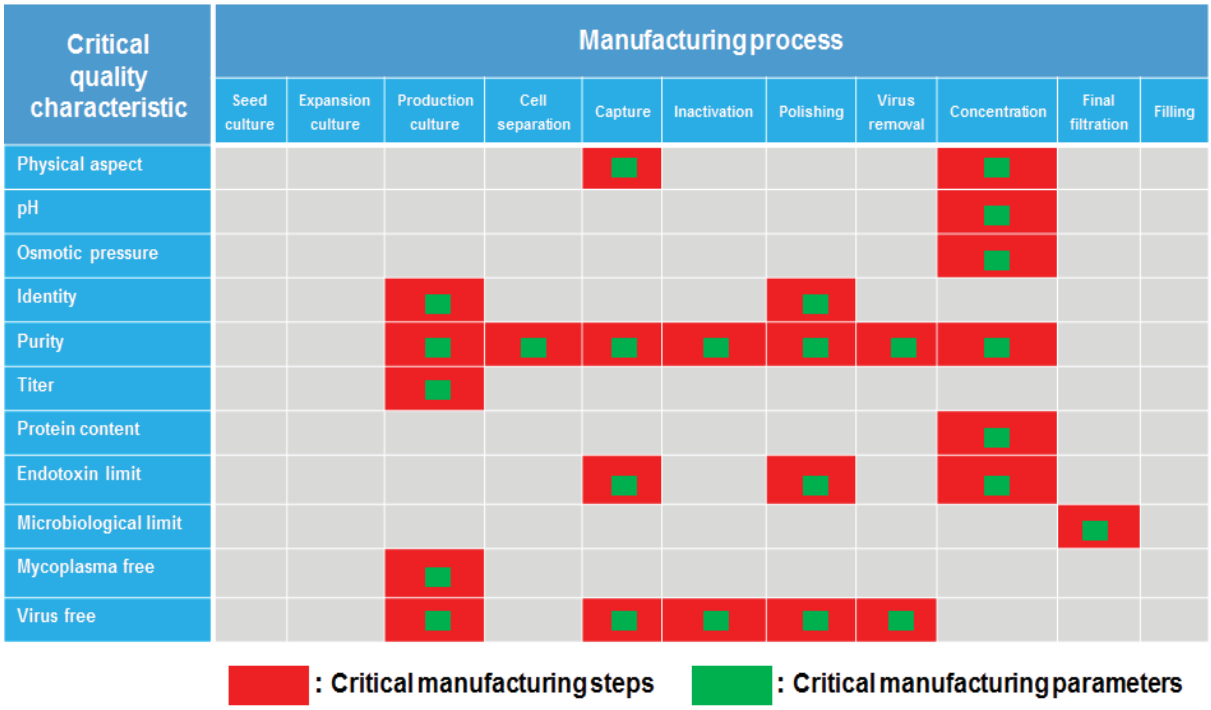

Fig. 9 Impacts of critical manufacturing parameters on antibody manufacturing process

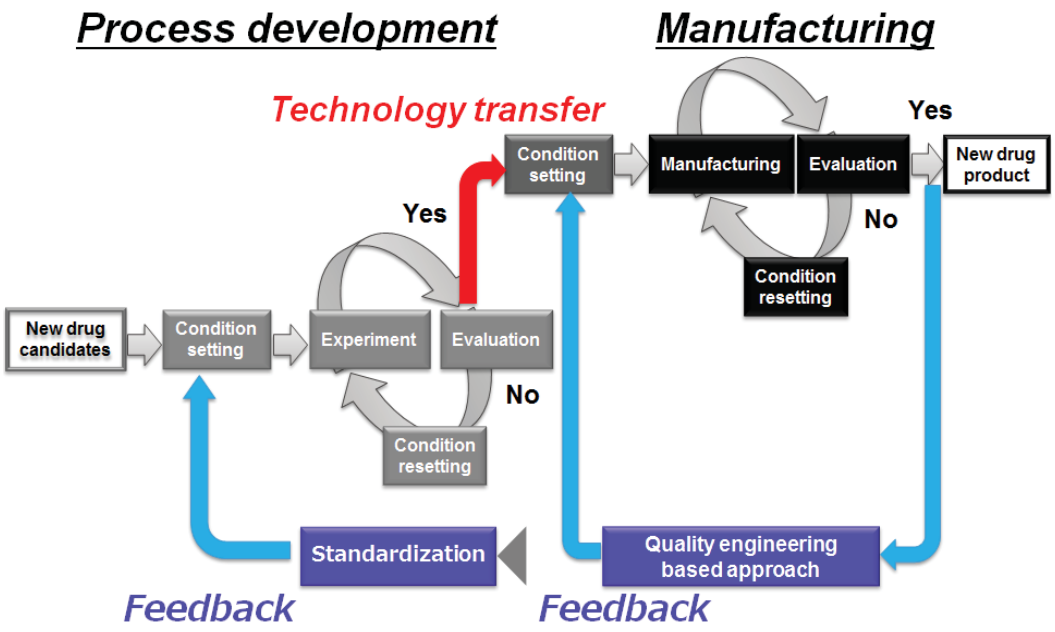

Fig. 10 Product flow from a new drug candidate to a new drug product

III. Discussion

According to process architecture theory, drug manufacturing is classified as an integral-type process industry, because the product design and process design are integrated and cannot be separated, and thus division of labor between work sessions, as found in the automobile industry, is not applicable [9]. With drugs, causal relationships between function and structure are complicated; for example, the presence or absence of the adverse drug reactions and efficacy, and their mechanism are not clear. Accumulation and integration of knowledge are, therefore, considered to be critical in the pharmaceutical industry.

In the product flow from a new drug candidate to a new drug product, technology transfer between small cycles in process development and manufacturing departments helps the project proceed from one stage to another (Fig. 10).

Such transfer plays an important role in bridging knowledge gaps. In this study, a procedure for identifying critical parameters in manufacturing was established by use of a quality engineering approach, allowed control standards for manufacturing equipment to be characterized.

Theses progress in characterization and standardization of critical parameters enable feedback to both process development and manufacturing departments. Application of this large PDCA (plan-do-check-act) cycle will lead to establishment of a robust, front-end loading model, by which the manufacturing capability can be determined even at the initial process development stage.

IV. Conclusion

In the development of manufacturing processes of biopharmaceuticals, research cases involving discussions based on a wider perspective beyond just research and development have not been reported. This research proposed optimizing control standards in the manufacturing process of antibody drugs. A procedure for improving the efficiency of the manufacturing process was clarified by applying the framework of quality engineering.

As a result, we established a robust manufacturing system technology transfer and feedback between process development and manufacturing departments such as PDCA cycle. Process development and manufacturing are linked to each other like two wheels connected through technology transfer and feedback. We will strive to improve the manufacturing efficiency of biologics and contribute to better health for people worldwide. Here, the final achievements of this research are as follows:

- Clarification of critical parameters in antibody manufacturing based on a quality engineering framework
- Establishment of study and evaluation procedures within a quality engineering framework for antibody manufacturing

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