The Statistical Evaluation of Cleaning Processes Using Process Capability and its Application to New Product Introduction

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The approach presented in this study uses process capability index results to establish sampling strategies for use with new product cleaning and to efficiently reduce the risk of insufficient cleaning.

Pharmaceutical development requires time and enormous cost, which can be an economic burden to pharmaceutical companies. Pharmaceutical companies, therefore, have been striving to make improvements, and since the 2000s, they have been focusing on activities such as operational excellence. Operational excellence is a concept proposed by M. Treacy and F. Wiersema in 1995, and it is one of the three competitive strategies for leading companies: operational excellence, product leadership, and customer intimacy (1). Many US and European firms, mainly major electronics manufacturers, employ operational excellence to reduce costs by optimizing processes. In firms where operational excellence is already implemented and the operation improvement process is well-established, a competitive edge can be assured. It is also considered that in such firms, the idea of constantly pursuing better operations is communicated to and understood by all personnel on site, and a mechanism that enables continuous improvement is already well established.

Operational excellence is just one of the concepts of task-improvement methods such as total quality management and Lean Six Sigma; the application to pharmaceutical products to minimize product risk has been limited and can be extremely difficult to implement. To strengthen the competitiveness of pharmaceuticals, it is necessary for the pharmaceutical industry to carry out discussions with a wide range of perspectives not only in research and development (R&D) but also in manufacturing. Despite the many challenges that must be addressed (e.g., pharmaceutical sensitivity to changes in the manufacturing process, complicated manufacturing methods, the need to meet high-quality requirements), few case studies discuss these manufacturing processes (2). In recent years, these issues have been discussed in the pharmaceutical industry, but in many cases, the manufacturing processes—including processes from API to finished pharmaceutical manufacturing from a holistic standpoint—have not been clearly identified. While biopharmaceuticals such as antibody drugs are greatly advanced in product development and technology, bioprocesses have variable factors that are distinctive to their processes. These factors attract the interest of regulatory authorities, and the highest priorities have been given to compliance with good manufacturing practice (GMP), safety, etc., which has caused a lag in research and manufacturing to provide pharmaceuticals more efficiently and economically without sacrificing the quality.

The demands for quality engineering methods are increasing globally, and the establishment of a system to carry out continuous process improvement is required to supply high-quality formu-

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lated products throughout the product lifecycle. The International Council for Harmonization (ICH) published three guidelines: Q8 *Pharmaceutical Development* (3), Q9 *Quality Risk Management* (4), and Q10 *Pharmaceutical Quality System* (5). The International Society for Pharmaceutical Engineering (ISPE) published a baseline guide called *Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)* in September of 2010, which provides a scientific, risk-based approach, based on ICH Q9 to manage the risk of cross-contamination in order to achieve and maintain an appropriate balance between product quality and operator safety (6). These guidelines, however, are mainly conceptual, and the realization of these concepts is left up to each pharmaceutical company.

Methodologies established in other industries (7) have been gradually spreading in the GMP environment to identify and understand pharmacological and toxicological risks and help ensure drug safety. In this research, a new method that could efficiently improve the manufacturing process by applying a quality engineering framework is examined and proposed as a more advanced methodology to improve the control strategies of manufacturing cleaning processes in biopharmaceuticals including antibody drugs, by utilizing risk management and scientific knowledge more widely.

Statistical analysis of cleaning process data

The manufacturing process of antibody drug substance is a combination of unit operations. Several reactors of different sizes are used in the culturing process, while chromatography systems and many tanks are used in the purification process. These processes often have multiple pieces of equipment with large areas to clean.

The most common cleaning process used to maintain the cleanliness of biopharmaceutical manufacturing equipment is cleaning with dilute sodium hydroxide as a cleaning agent, which is then followed by a sterilization step using high-pressure steam. Because it is necessary to maintain the cleanliness of manufacturing equipment after manufacturing activities for hygiene and quality control reasons, clean-in-place (CIP) and steam-in-place (SIP) are the major methods used. These methods clean the inside of the complex piping systems and tanks by running the cleaning agents through them followed by high-pressure steam without disassembly of the equipment. Parameters such as frequency and time of cleaning are optimized by measuring the actual residual amounts of product remaining on the equipment as found through swab, rinse, and other testing methods. For areas where cleaning may not be carried out effectively due to insufficient flow rate, a method to fill the system with a cleaning agent and holding it for a certain period time is applied.

After reviewing and organizing existing cleaning data obtained from the actual equipment used in the biopharmaceutical manufacturing, an evaluation of cleaning performance was conducted to confirm that the cleaning was effective in preventing cross-contamination, and to ensure consistent performance of the cleaning operation.

For a process in control, the ability of the process to consistently achieve the desired level of quality (specifications) is called process capability (Cp). Cp is a simple, straightforward comparison of the spread of the process data (variability) to the spread of the specification limit for that process data. Basically, it is a measure of how well the data fit within the specifications. The calculation of Cp is shown in **Equation 1**:

$$Cp = \frac{\text{Upper Specification - Lower Specification}}{6\sigma}$$

[Eq. 1]

Sometimes data are not centered within the specification range and are significantly closer to one specification limit than the other. In these cases, a modification of the Cp calculation is used that only looks at the distance of the mean to whichever specification is closest to the mean. This is called the process capability index (Cpk). Also, for data that have no lower specification limits (such as cleaning data), a variation of the Cpk can be used instead that calculates a Cp based on only one specification. This is the Cpu (upper) and is also a simple comparison of the spread of the data (its variability) to the distance from the data mean to the upper specification limit. In a cleaning process, the Cpu is determined using only an upper specification limit because cleaning processes are carried out so as to reduce the residual amount of pharmaceuticals, cleaning agents, etc., to the level below an acceptance limit. The calculation for the Cpu can be seen in **Equation 2**.

$$Cpu_{(\text{upper limit})} = \frac{\text{Upper Specification Limit - Mean}}{3\sigma}$$

[Eq. 2]

When evaluating the cleaning process capability, therefore, the mean values and the standard deviations used in the formula should be those derived from the cleaning data, and the process capability index (Cpu) of the cleaning process will be defined by **Equation 3**.

$$Cpu_{(\text{upper limit})} = \frac{\text{Cleaning Limit – Cleaning Data Mean}}{3\sigma \text{ (of cleaning data)}}$$

[Eq. 3]

In this study, the capabilities of the cleaning processes were statistically evaluated using the Cpu. The manufacturing equipment for antibody drug substance were classified into equipment groups based upon their manufacturing cleaning processes. First, the cleaning data of the products were converted into a percentage of their cleaning limits because these actual values are confidential and could not be used in this article. After that, the mean values, the standard deviations, and the Cpus were derived (see **Table I**).

The bioreactor group, harvest group, and ultrafiltration/diafiltration (UF/DF) group had high Cpu values indicating that the capability of cleaning process was good. On the other hand, the Cpu values of the chromatography system

group and the purification tank group were lower compared to the other groups, although their data still fell below their cleaning limits.

The many horizontal and U-shaped piping pieces with smaller than 25.4 mm of diameter used in the chromatography system make these systems difficult to clean; this is considered to be the reason the Cpu value of the chromatography system group was not as high as the other groups. It is also presumed that the reason for relatively low Cpu value of the purification tank group was due to the relatively large variability in data, which was probably caused by various process tanks with capacity of over 2000 L and wide surface area that comprise this group.

A proposed Cpu-derived limit based on "overall cleaning performance"

Statistical evaluation of the capability of the cleaning process can be viewed from two directions. The first direction is whether the cleaning process is capable of removing the substance subject by cleaning to a level below a limit based on the acceptable daily exposure (ADE); which is synonymous with the permitted daily exposure (PDE), as used in the European Union. This viewpoint is suitable for evaluating if the target substances being cleaned can be removed to a level that ensures the safety of patient based on the cleaning limit of the substances subject to cleaning. This evaluation is particularly essential for commercial plants in which several items are manufactured.

Another viewpoint can be considered useful for evaluating the facility's overall cleaning performance, regardless of the cleaning limits of the substances that are subject to cleaning; this approach is new to the pharmaceutical industry. The effectiveness of process evaluation based on "overall cleaning performance" will be examined in this section.

If **Equation 3**, which is used to derive the Cpu, is rearranged, a minimum desired Cpu could be substituted into the equation along with the known cleaning data parameters and a limit based on process capability calculated for use in all subsequent cleanings (**Equation 4**).

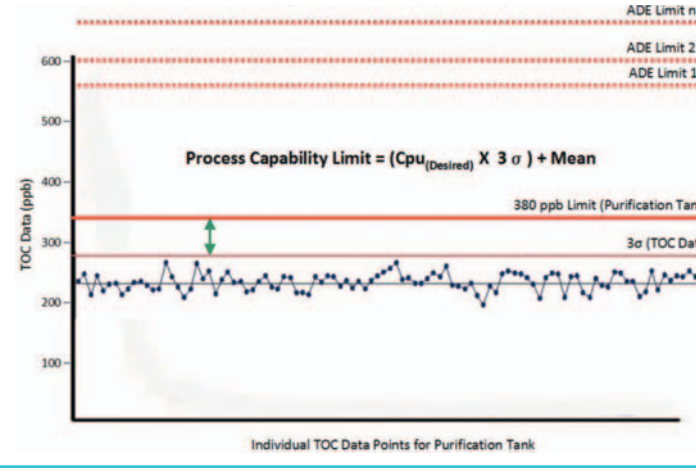
Table I: Process capability (upper limit) (Cpu) from product cleaning data based on equipment groupings.

Equipment group	% of cleaning limit (residue/limit * 100)	Standard deviation	Cpu
Bioreactor	29.07	12.82	1.84
Cell separation	15.93	9.22	3.04
Chromatography system	32.25	17.41	1.30
Purification tank	29.29	17.21	1.37
Ultrafiltration/diafiltration	17.86	6.79	4.03

Table II: Process capability limits for total organic carbon (ppb) for equipment groups based on desired process capability index (Cpu).

Equipment group	Desired Cpu		
	Cpu=1	Cpu=1.33	Cpu=1.67
Bioreactor	270 ppb	340 ppb	400 ppb
Cell separation	160 ppb	200 ppb	240 ppb
Chromatography system	360 ppb	440 ppb	510 ppb
Purification tank	310 ppb	380 ppb	450 ppb
Ultrafiltration/diafiltration	160 ppb	190 ppb	220 ppb

Figure 1. Process capability limit and acceptable daily exposure (ADE)-based limits. TOC is total organic carbon.



$$\text{Process Capability Limit} = (Cpu_{(Desired)} \times 3\sigma) + \text{Mean} \quad \text{[Eq. 4]}$$

In other words, the desired Cpu becomes the starting point for calculating a limit for all residues on all product contact surfaces. For example, if the desired Cpu is 1.33, in **Equation 4**, it can then be used to define the analytical limits for swab sampling for all products. This approach would be particularly useful and easy to apply in a manufacturing facility where the analytical method is common (e.g., total organic carbon [TOC]), where all the manufactured products are similar (e.g., Immunoglobulin Gs that have a common molecular structure), and where the difference in cleanability between products is expected to similar.

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FIGURE COURTESY OF THE AUTHORS.

Symbiosis

The relationship between emerging bio/pharma companies and the CDMO industry is truly symbiotic: one could not exist without the other. Thanks to the economics cited previously, the emerging bio/pharma sector depends on CDMOs for at least 80% of its development and manufacturing requirements and is similarly dependent on CROs for their preclinical and clinical testing needs. CDMOs have enabled the formation of virtual companies with just a few staff overseeing a network of service providers.

On the other hand, the availability of funding for emerging bio/pharma drives the fortunes of the CDMO industry. Following the sharp decline in funding for emerging bio/pharma in the wake of the global financial crisis, many CDMOs hung on by their fingertips and some went out of business altogether. By contrast, in today's environment, most are growing at double-digit rates and are sought after by private equity firms wanting to acquire then at valuations as high as 15 times earnings.

Emerging bio/pharma companies are much more important to CDMOs than they are to clinical CROs. The ability of CROs to reduce clinical research costs by absorbing large numbers of clinical staff from company payrolls and implementing advanced information technology made them valuable partners for global bio/pharma. By contrast, global bio/pharma have been much less willing to outsource their manufacturing operations.

Risks and opportunity

The two biggest risks to the emerging biopharma and CDMO industries would seem to be a downturn in macroeconomic conditions that would make investors more skittish about investing and a major change in the willingness and ability of the US healthcare industry to pay for expensive new drugs. Both of these risks are real. Many economists see the likelihood of a recession in the United States in 2019 or 2020; the Trump administration campaigned on the promise to bring down drug prices; and US corporations look to be getting more aggressive in managing healthcare costs, including the cost of drugs.

Nevertheless, CDMOs look well-positioned to ride the wave of emerging bio/pharma success into the foreseeable future. The year 2018 has started off well for new financings, and public companies have often been able to raise sufficient funding to last them for a number of years into the future. Further, while global bio/pharma companies have dominated new product approvals in recent years, thanks largely to their acquisitions and in-licensing, pipeline data suggest that more emerging bio/pharma companies are willing and able to remain independent entities. **PT**

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Such a process capability limit can be easily and quickly calculated for all equipment groups for any possible desired Cpu (**Table II**). A process capability limit provides a single limit for target equipment group and avoids the difficulties of using multiple limits based on the ADE, which will vary from product to product (**Figure 1**). The suitability of these process capability limits can be reinforced by incorporating ongoing cleaning data into the calculations from different antibody drug substances employing the same cleaning processes. Such continuous improvement of processes based on the accumulation of process understanding is completely consistent with the basic concept of FDA's 2011 process validation guidance.

Summary

At first, the capability of cleaning process was evaluated for an antibody drug manufacturing facility using the Cpu, which is one of the common methods to evaluate the process capability in quality engineering. Consequently, the authors succeeded in evaluating the capability of the cleaning processes for all equipment used in the actual production by classifying the equipment into groups. The study demonstrated that the cleaning process for bioreactor group, cell separation group, and UF/DF group had high process capabilities. It also indicated that the chromatography system group—which is a purification process with a combination of unit operations and having a structure that is difficult to clean—and the purification tank group had relatively low Cpu values compared to other groups, yet they still fell within their cleaning limits.

It is also generally known that in the purification processes of antibody drug substances the purified antibody proteins are likely to adhere onto the process equipment due to the process characteristics mentioned in this study and product properties, making them difficult to clean.

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