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Implementation of QbD for the development of a vaccine candidate

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ABSTRACT

This case study provides an example of how Quality by Design (QbD) principles were applied to accelerate process development to manufacture a vaccine candidate at commercial scale. By leveraging an existing manufacturing platform process, a risk assessment was used to differentiate process parameters that could be defined using a combination of scientific and historical manufacturing knowledge from those that merited additional process characterization by experimentation. Select parameters, and their interactions, were evaluated by a Design of Experiment (DoE) series. This systematic approach required less time and fewer resources and resulted in the definition of a reliable and robust manufacturing process that meets regulatory requirements.

1. Introduction

Vaccines have historically and continue to make significant contributions to the prevention of infectious diseases and improvement of human health worldwide. Most licensed vaccines were developed on the basis of the original vaccination model dating back to the late 18th century. Traditionally, a disease-causing pathogen, or known antigenic component, is produced and injected to provide immunological protection [1]. Over time, process changes have been implemented to improve product safety and efficacy, but the overall strategy has remained the same. Vaccine production is particularly challenging because the final product is difficult to characterize and the mechanisms of production are typically not well understood. Due to the complex nature of biopharmaceutical products and the close interplay between biological processes and product quality, vaccines are accompanied by long development timelines and rigorous regulatory requirements that are based on facility, process definition, and product characterization.

With the advent of modern process development tools, such as metabolic engineering, systems biology, and high-throughput genomics and screening, the vaccine paradigm is changing and will lead to improved process understanding, quality and supply [2]. To emphasize the importance of process understanding and address regulatory expectations, the US Food and Drug Administration (FDA) adopted a Quality by Design (QbD) approach. These principles rely on pre-defined objectives and apply science- and risk-based approaches to define the final manufacturing design space [3]. This strategy is well defined for small molecule medicines and helps regulatory agencies and industry by improving review cycles and providing the foundation for the development of a robust and flexible process that is accompanied by fewer manufacturing deviations [4]. Application of QbD for biopharmaceutical production is challenging, less defined and often accompanied by industry concerns that these principles will increase time and resource requirements. However, analyses have revealed a strong business driver for QbD, highlighting the potential to streamline process development if used properly [5,6]. Aligned with these analyses, we present a case study demonstrating how the application of QbD principles streamlined microbial fermentation process development for a vaccine candidate. This approach ultimately saved time and resources and resulted in the definition of a robust and reliable final manufacturing process. This case study specifically highlights the fermentation process development strategy, but a similar approach was employed for concurrent purification process development.

2. Materials and methods

2.1. Platform process

A platform fermentation and purification manufacturing process was established for the routine manufacture of a licensed

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product family. This platform process is well-defined by center-point (CP) set-points with allowable operating ranges, classified as critical process parameters (CPPs) or non-critical parameters. The fermentation platform process includes 13 CPPs and 11 non-critical parameters. These parameters are the same for the entire product family with only minor modifications to accommodate strain-specific sensitivities. Adherence to CPPs ensures that each vaccine product achieves the pre-defined critical quality attributes (CQAs).

2.2. Risk assessment

The quantitative risk assessment was performed using a failure modes and effect analysis (FMEA). Each platform process parameter was given numerical rankings (1, low; 3, medium; 9, high) to account for the degree of risk associated with severity, detection, and occurrence. To categorize parameters, a risk priority number (RPN) was calculated for each parameter by multiplying the three rankings. To minimize bias, the entire FMEA process was performed by a cross-functional team, including representatives from process development, operations, and manufacturing technical support. This team established definitions and criteria specific to each parameter, risk, and numerical ranking.

2.3. Scale-down model

All experiments implemented a qualified, 100-fold scale-down model of the platform production process that was established during development of the original product family. The scale-down fermentation process is highly controlled and monitored. Process performance was evaluated by pre-defined product CQAs in addition to offline process characterization assays. Multiple biological replicates of the vaccine candidate at both development and manufacturing scale confirmed that all pre-defined CQAs were within expectations and additional process attributes, including final biomass and product concentration, were comparable between scales. The scale-down model was deemed representative of full manufacturing scale for the vaccine candidate and was used throughout process development.

2.4. Experiment execution

Fermentation experiments were designed using DoE. The DoE specified set-points for targeted parameters, but all other fermentation parameters were operated at the platform process CP targets. Bulk fermentation material was processed by the CP scale-down purification platform process. Each experiment was evaluated on the basis of fermentation and purification CQAs, in addition to select process characterization assays.

3. Results

3.1. Process development strategy

The vaccine candidate is similar to an existing product family. Both products share the same expression platform to produce cell-associated antigens characterized by the same CQAs. The existing product family is manufactured using a world-wide licensed platform process. The vaccine candidate was produced at proposed manufacturing scale using the fermentation and purification platform process operated at CP conditions. This resulted in a product with acceptable CQAs, confirming that the established platform process had a high probability of success for the production of our vaccine candidate.

In accordance with regulatory guidelines, operation within the platform process design space must be demonstrated to consistently produce the vaccine candidate with acceptable CQAs. With 13 CPPs in the legacy platform process, if each parameter were evaluated at two levels experimentally, a one factor at a time design would require a minimum of 26 experiments, and a DoE would require even more. This development approach is not efficient and has a significant resource burden. Aligned with regulatory risk management guidance, existing process and manufacturing knowledge was leveraged to prioritize experiments using a systematic, risk-based approach (Fig. 1) [7]. This methodology identified low risk non-critical parameters and distinguished CPPs that required additional characterization from those that could be justified using existing process and manufacturing knowledge, reducing development timelines and enabling effective resource allocation. Each parameter was also independently evaluated to identify strain-specific parameters. This may not always be a consideration for a risk-based analysis, but the existing product family process development revealed select strain-specific sensitivities, making it an important consideration for the development of the vaccine candidate. Using the risk analysis as a guide, a select number of experiments were executed to evaluate high-risk and strain-specific parameters. The compilation of new experimental data and historical manufacturing experience was sufficient to justify the design space, resulting in a robust final manufacturing process that reliably meets pre-defined CQAs.

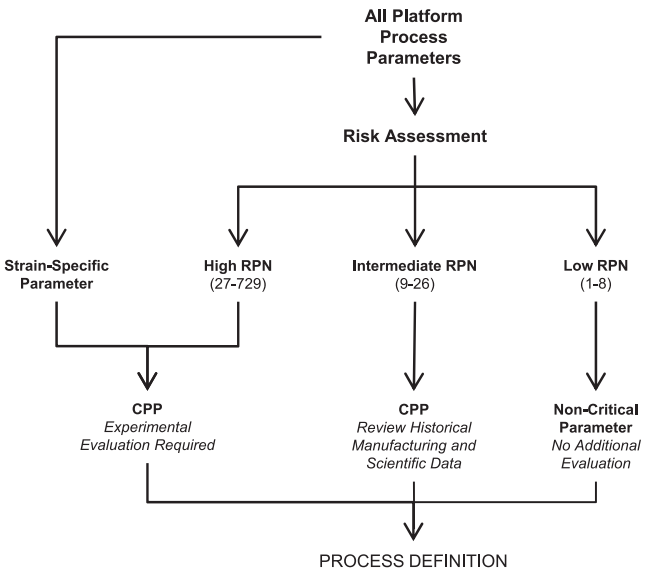

Fig. 1. Process development strategy.

3.2. pH and temperature identified as parameters that warrant experimental characterization

3.2.1. Strain-specific parameters

Evaluation of the fermentation platform process identified pH and temperature as parameters that may have strain-specific sensitivities based on previous experience with this expression platform. Both parameters required additional characterization by experimentation to confirm platform process acceptable operating ranges.

3.2.2. Risk analysis

As shown in Fig. 2, two legacy platform process CPPs, pH and temperature, had high RPN scores revealing a need for additional characterization, in addition to the previously identified strain sensitivity. Eleven CPPs had an intermediate RPN score, and as such were not evaluated through experiments, but by using