ThermoFisher SCIENTIFIC

CASE STUDY

Midsize pharma company stabilizes API

Accelerates time to clinic from three months to three weeks

Introduction

A midsize South Korea-based biopharmaceutical company that focuses on process and portfolio innovation was developing an mRNA therapy for disease control in patients with immune-mediated inflammatory diseases. The company wanted to progress its therapy from early development to late-phase clinical trial stage, but it needed a CDMO partner to provide support in formulation analysis so that it could stabilize its product and successfully reach its clinical studies milestones.

Situation

Formulation analysis encompasses multiple steps requiring instruments, process expertise, and regulatory experience that will help a company successfully move its formulation through early development. Budgets, timelines, and a highly competitive marketplace require that all processes are efficient and that they minimize errors and delays. Without formulation analysis support, this company would not achieve product stabilization and would not progress to clinic so that patients could benefit from the use of its mRNA therapy.

Because the company did not have the resources or expertise in-house to rapidly test multiple samples, it outsourced this effort to Thermo Fisher Scientific. Having worked with Thermo Fisher on previous projects, the company knew it could rely on the Thermo Fisher scientists, technicians, and project managers for their expertise, flexibility, and ability to optimize and adhere to challenging timelines.

Solution

The customer recognized the capabilities within Thermo Fisher's site in Ferentino, Italy, which specializes in integrated sterile liquid and lyophilized product development and commercial manufacturing, including high-potency products and large-volume parenterals (LVPs). The site's location and team of scientists and technicians, with a track record of excellence in getting biopharmaceutical companies to clinic quickly, make it a center of expertise. The customer needed this partnership to provide a comprehensive scientific rationale for formulation analysis while adhering to cost and timeline factors.

Thermo Fisher's scientists and technicians optimized formulation parameters, aiming to stabilize the final drug product using a multivariate statistical Design of Experiments (DoE) and applying biorthogonal analytical methods. This approach enabled the customer to build a strong regulatory position when liaising with local authorities regarding product development.

A project team comprising customer stakeholders and Thermo Fisher experts was also established. This team manufactured and analyzed samples according to the high-throughput (HT) formulation workflow in place at Thermo Fisher's development laboratories (see Figure 1). Essentially, the process began with experiment design, including establishment of a dedicated statistical model and definition of the parameters and levels to be challenged: pH, ionic strength, and different classes of stabilizing excipients. Through automated liquid system handling, various formulations were generated and different critical quality attributes were verified. In the final step, data was statistically evaluated to inform the selection of the lead formulation.

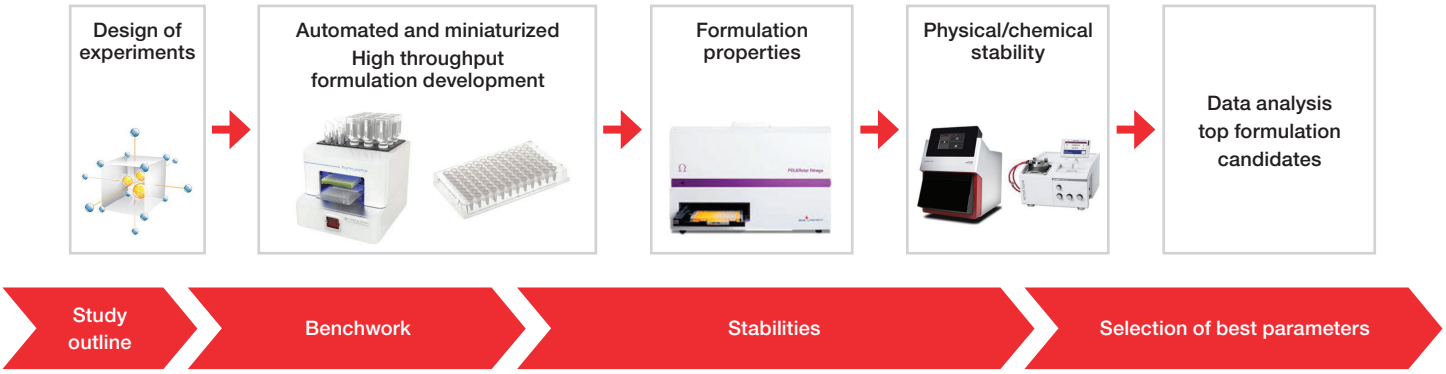

Figure 1. A solution for formulation analysis and product stabilization

In this case, the robust expertise and high level of competencies present in Thermo Fisher's development laboratories enabled its team to generate an appropriate matrix in a short time frame. Investigated ranges were then established in accordance with a scientifically based approach using historical data acquired over the previous 20 years of activity. A statistical full-response surface model challenged all three factors—pH, ionic strength, and excipients—to elucidate the best formulation for the molecule under study. The core of the design was prepared to evaluate how the final product composition could affect different critical quality attributes, such as protein concentration, thermal unfolding, particle sizing, aggregation, and thermal stability.

Results

The Thermo Fisher experts evaluated the data obtained and selected the lead formulations. This enabled the customer to obtain a robust formulation, even in the early development phase, with minimal impact on the project timeline and with extremely limited consumption of active pharmaceutical ingredient (API). The process also generated a broader understanding of the formulation space overall.

Through this approach, the team was able to manufacture 18 drug products to challenge the established parameters. Thermal stress, mechanical stress, and freeze and thaw trials yielded results that identified the best conditions for the API (see Table 1).

After statistical evaluation of data applying the desirability optimization methodology shown in Figure 2, the expert team selected five formulations for differential scanning calorimetry (DSC) analysis. Results obtained by DSC analysis confirmed the trend observed and the best conditions for stabilization.

The HT formulation workflow resulted in a reduction of hands-on time and run time from three months to three weeks, enabling the customer to gain more than two months in the project execution phase and save 90% of API compared with the traditional

Sample	Conc NaCl	pH	Excipients*	ON (Scattering)	IP 2 (Ratio 350 nm / 330 nm)	ON (Ratio 350 nm / 330 nm)	ON (Turbidity)	ON (Cumulant Radius)	Thermal stress: 3 days at 40°C	Shear stress	Freeze/thaw stress
1	50	7	1								
2	50	7	3								
3	10	7	1								
4	10	7	2								
5	50	7	2								
6	10	7	3								
13	50	6	1								
14	50	6	3								
15	10	6	1								
16	10	6	2								
17	50	6	2								
18	10	6	3								
7	10	5	1								
8	50	5	1								
9	10	5	2								
10	10	5	3								
11	50	5	3								
12	50	5	2								

Color code legend: green = good result; yellow = acceptable result; red = poor result
*Excipient 1 = Trehalose 10% w:v; Excipient 2 = Arginine 2% w:v; Excipient 3 = Mannitol: Sucrose 2%:2.5%

Table 1. Summary of analytical results from multiple trials across multiple samples

approach. In addition, the DoE approach maximized product knowledge and excipient interactions. Furthermore, the ability to immediately challenge critical parameters generated a robust data package for dossier submission and ultimately accelerated the timeline. Ultimately, matching the quality target profile of the drug product established for the early clinical phase enabled the team to formulate a robust and stable product to be used for upcoming clinical phases.

Additionally, the customer established an excellent working rapport with Thermo Fisher, stating, “All of the members in each responsibility are active [and] cooperative!... [the team at the Ferentino site] provided a service that [exceeded] our expectations!” The customer indicated its intention to continue partnering on future projects.

Summary

New and emerging midsize pharmaceutical companies benefit from collaborating with partners that complement their existing strengths with expertise and resources in areas where they are lacking. In this case, the customer needed help stabilizing its product to progress it to clinic. Implementing a DoE exercise leveraging lessons learned across 20 years of experience at Thermo Fisher helped the customer streamline the selection of parameters, which reduced this aspect of the timeline from three months to three weeks and enabled the customer to seamlessly bring its product to clinic.

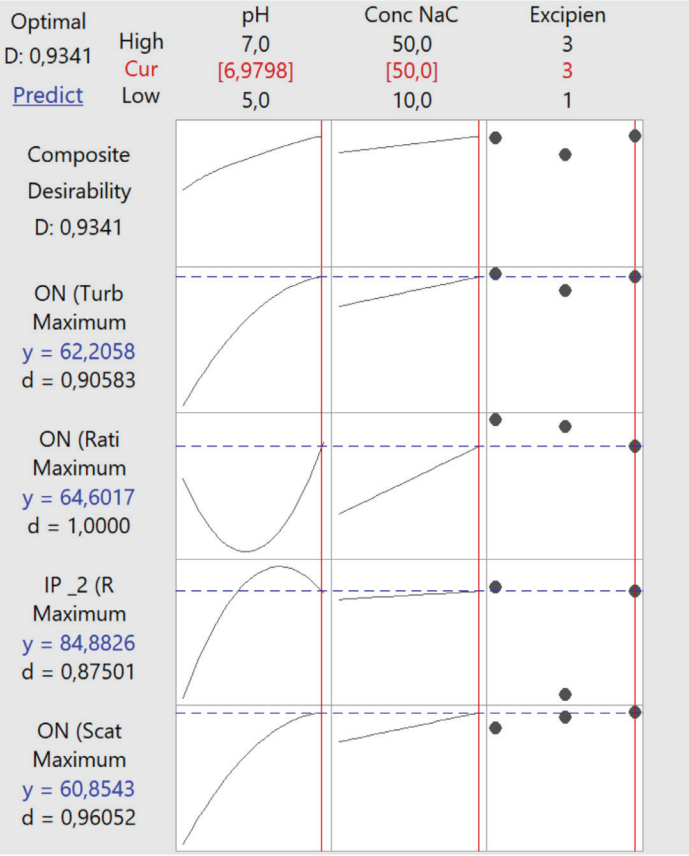

Figure 2. Statistical evaluation on the overall results (surface model graphics)

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