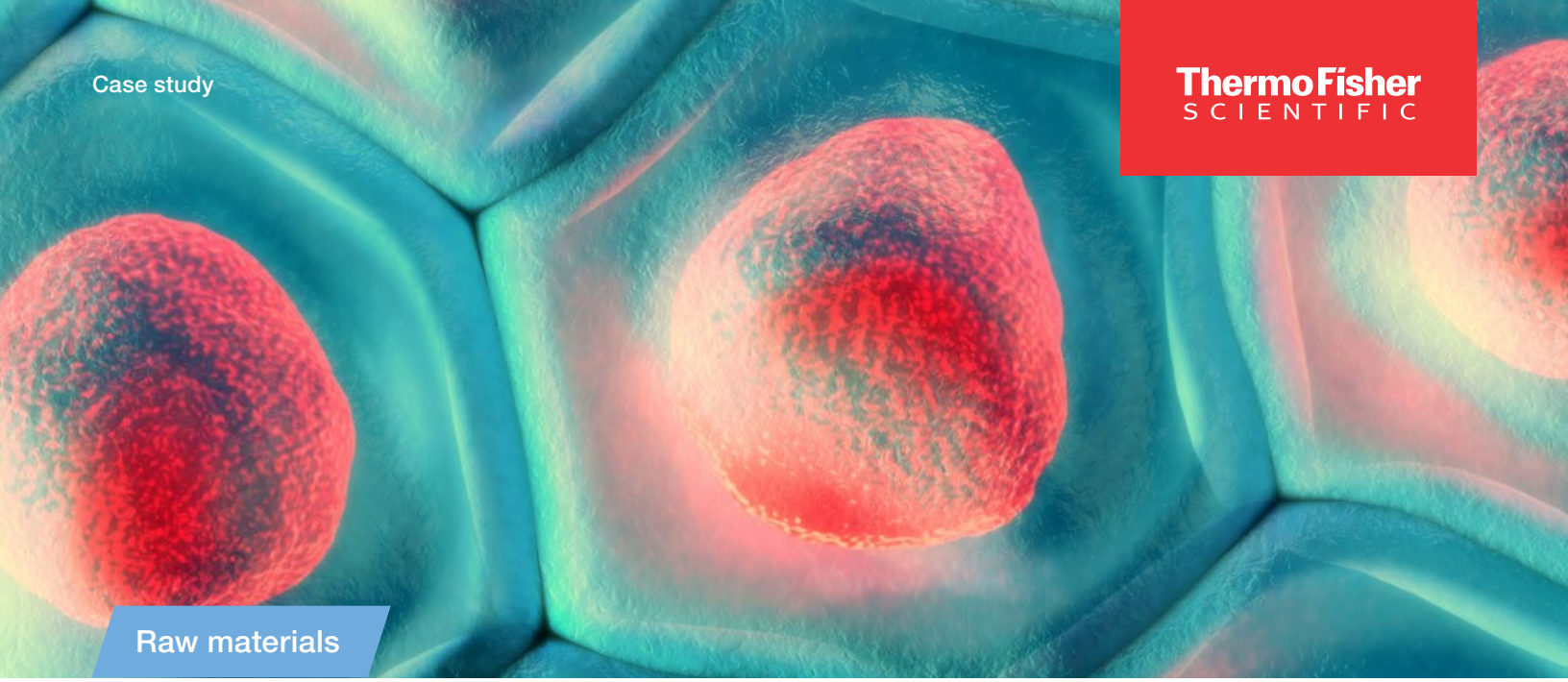

Case study

Raw materials

A collaborative study for understanding trace element variability in custom cell culture media

In this project, Thermo Fisher Scientific worked with a multinational biopharmaceutical company to investigate trace element variability in its custom cell culture media. Within a year, using a risk-based, collaborative approach, both teams were able to thoroughly characterize incoming specific raw materials and implement proactive measures for reducing the risk of impurities, ultimately providing the company with a long-term risk mitigation strategy.

Introduction

Trace elements are included in cell culture media formulations as they are known to be important for cell culture performance. At desired concentrations, they can positively impact cellular growth and biotherapeutic efficacy, as well as protein quality attributes like glycosylation [1]. However, if trace elements are introduced as impurities through incoming raw materials, concentrations can drift outside of acceptable ranges, which may indicate a need for tighter control to improve media consistency.

In this case, the company had conducted internal studies, including multivariate analysis, to assess how its product performance was affected by cell culture media variability. The results indicated that variability in the concentrations of some trace elements—in particular, manganese (Mn)—was influencing the performance of some custom media formulations.

The raw material characterization program is an offering of Thermo Fisher media manufacturing services. The program offers customers a comprehensive range of custom media quality control tests, including in-depth raw material characterization. For this project, the team collaborated with the company to analyze the raw materials used in the custom media formulation and determine whether trace elements were being introduced as impurities. This allowed both teams to identify, understand, and proactively monitor trace elements of interest, thereby enabling optimization of the company's formulation and the development of a long-term manufacturing risk mitigation strategy.

Approach

The first stage of the project was to develop a risk-based approach to raw material characterization in the company's custom media. To do this, the team conducted a risk assessment whereby raw materials were scored on their likelihood of introducing impurities (Figure 1), based on historical data collected by Thermo Fisher. The highest-risk materials were then selected for analysis via inductively coupled plasma-mass spectrometry (ICP-MS) to characterize the trace elemental variability. At this stage, it was important for future testing to standardize the characterization procedure between the company and the raw material team, due to the high sensitivity of the ICP-MS methodology. This involved the subject matter experts from both teams working together to ensure the protocols and instrument parameters were properly aligned.

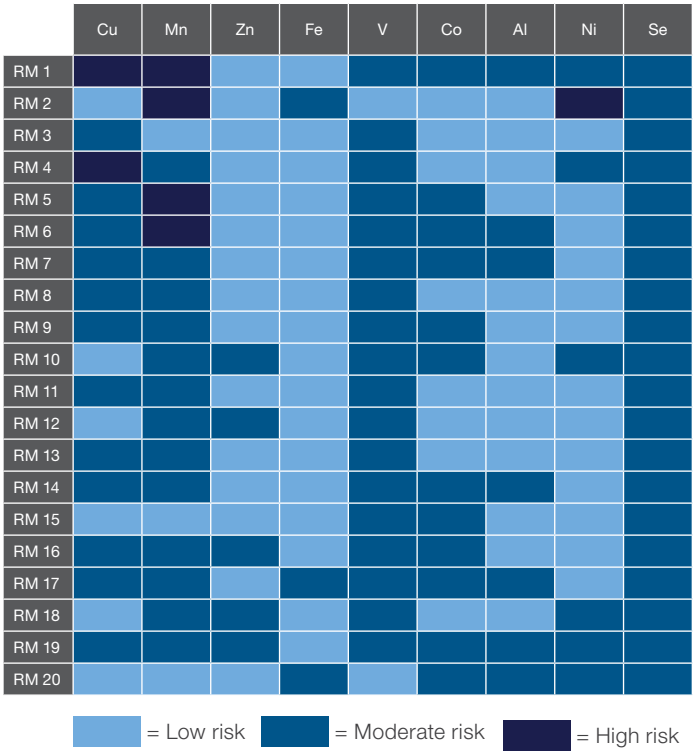

Figure 1. A risk heatmap of the raw materials used in one of the company's custom formulations. Based on a risk assessment conducted as per BioPhorum raw material (RM) variability workstream guidelines [2], using historical variability data collected by Thermo Fisher.

Using this information, Thermo Fisher was able to monitor the high-risk raw materials on a proactive basis and set up alerts for when any trace elements fell out of an acceptable range, as well as develop risk mitigation strategies to minimize elemental variability and the impact on final media performance. Trace element variability data were shared with the company electronically, and this transparency was crucial for the efficient and effective running of the project.

After characterizing the high-risk media components, Thermo Fisher helped determine which raw material was causing the unwanted manganese variability. This formed the second stage of the project: optimizing the cell culture medium to ensure that the required amount of manganese originated from the intended source. The two teams also worked closely to identify the most appropriate solutions to mitigate any manufacturing concerns going forward.

The Thermo Fisher media manufacturing service offers customers a comprehensive range of custom media quality control tests, including in-depth raw material characterization.

Outcomes and benefits of collaboration

As a result of this collaboration, the biopharmaceutical company was able to achieve consistent trace element concentrations (Figure 2). To ensure its custom media formulation performed reliably in the future, Thermo Fisher was able to use its media manufacturing expertise to develop well-defined media specifications and thorough risk mitigation strategies.

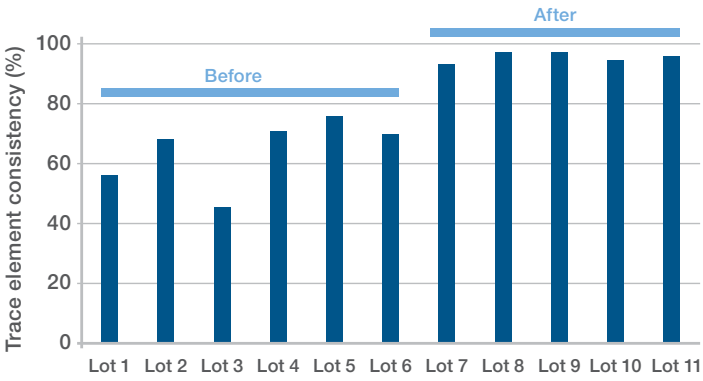

Figure 2. Cell culture media trace element variability.
Trace element consistency of manganese before and after optimization.

Despite the challenges posed by SARS-CoV-2, the project was successfully completed within a year. This was largely due to the two teams working closely at every stage to ensure continued sharing of insights and data. Though all in-person meetings were conducted virtually, there was regular communication including multiple initial calls to scope out the requirements of the project and regular online meetings to discuss progress. Aligning the mass spectrometry protocols and electronically sharing the trace element data were hugely beneficial, as they allowed the project to progress efficiently without needing to meet face-to-face. Ultimately, the success of this project is a testament to the importance of communication, collaboration, and close partnerships between the biologic manufacturer and media supplier.

Find out more about our raw material characterization program here: Custom Media QC Tests

Ultimately, the success of this project is a testament to the importance of communication, collaboration, and close partnerships between the biologic manufacturer and media supplier.

References

1. Loebrich S, Clark E, Ladd K et al. (2019) Comprehensive manipulation of glycosylation profiles across development scales. *mAbs* 11(2) 335–349. https://doi.org/10.1080/19420862.2018.1527665.
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