Simplifying Progress

The Value of Spent Media Analytics for Optimizing Cell Culture Performance

September, 2023 | Tim Steffens, Katy McLaughlin

Keywords or Phrases:
Media analytics, spent media analytics, manufacturing, incoming inspection, trace elements, vitamins, cell culture media, process characterization

SARTORIUS

Introduction

Productive cell cultures require a controlled artificial environment, including a suitable growth matrix. As such, cell culture media are an essential part of biopharmaceutical applications and represent a valuable opportunity for optimization, process improvement, and troubleshooting.

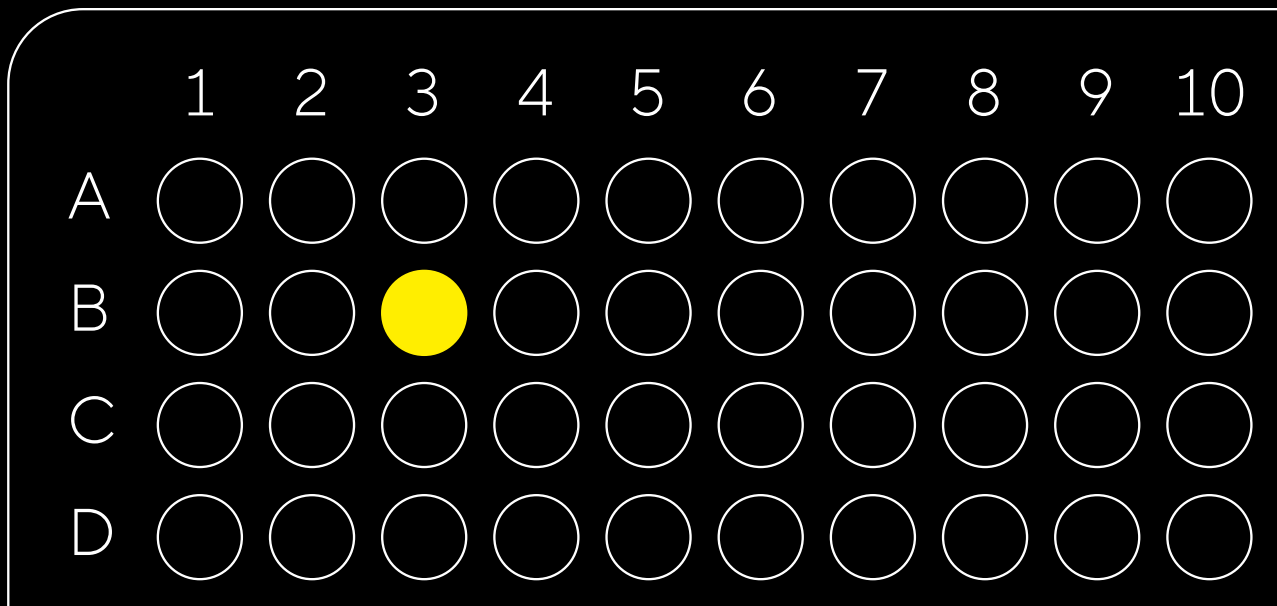
Multiple cell lines and processes are used for manufacturing biologics. Each has unique features and requirements that impact cell growth and viability, as well as the functional characteristics of the final drug product. To meet product yield and quality requirements, the medium should be capable of supporting the needs of the specific cell type and application. Limitations occur when the media composition does not meet the metabolic requirements of the cells during growth and | or production—leading to poor productivity. Process and media optimization can be complex and time-consuming due to the large number of components and process parameters influencing biomanufacturing productivity.

In this white paper, we discuss how the analysis of spent media can reveal valuable insights about the status of cells in culture and how this information can support the optimization of the medium formulation or culture parameters to support more productive processing.

Developing a Suitable Medium

Modern cell culture media consists of many diverse components, such as amino acids, carbohydrates, lipids, and trace elements. As such, although they are typically fully chemically defined, they are complex, challenging matrices. If the composition of the medium does not fully support the cells' requirements, manufacturing productivity and product quality can suffer.

An unbalanced medium could under or overfeed the cells. Underfeeding can lead to the premature depletion of nutrients and accumulation of growth-inhibitory metabolites, arresting cell growth. In contrast, overfeeding can lead to unwanted overflow metabolism and inefficient use of provided nutrients. Accumulating waste metabolites can also negatively impact culture performance.

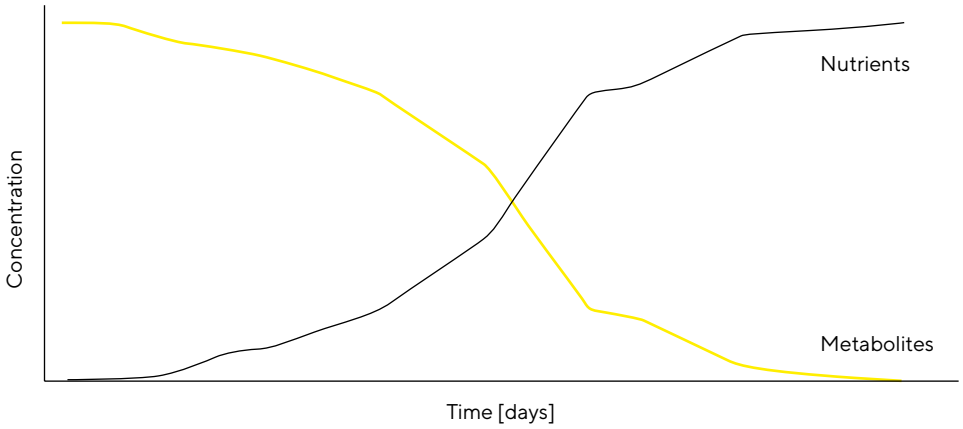


Spent Media Analytics

Spent media is the media that remains at the end of the cultivation. It can harbor rich information about the status of cells in the culture, including the nutrients they are consuming and the waste products (metabolites) they release (Figure 1).

Spent media analytics reveals key features of the medium, including the depletion of important components and the accumulation of potentially harmful metabolites, delivering actionable insights to improve the growth, viability, and performance of the cells.

Figure 1: *Schematic Overview—How the Levels of Nutrients and Metabolites in the Medium Change Over Time*



Regular monitoring of changes in sugars, metabolites, vitamins, and amino acids in spent media can help select the cell culture medium, feed strategy, and harvest times that promote high cell viability, maximize titer, and ensure high product quality. Spent media analysis can also be carried out in response to production issues, as it can help flag potential problems in the cell culture.

Applications of Spent Media Analytics

Spent Media Analytics Services Have Various Applications

- Accelerate media development by gaining valuable insights into cell requirements
- Monitor nutrient consumption to quickly identify any adverse outcomes
- Optimize feeding strategies to maximize cell viability and productivity
- Troubleshoot production processes and find opportunities for improvement
- Diagnose poor culture performance and providing data to inform quick formulation changes

Customer Case Study

In the following case study, we showcase the value of spent media analysis in diagnosing poor culture performance and quickly making required changes to the formulation.

Our client was a small biotechnology company producing monoclonal antibodies. The performance of their established process suddenly declined, and cell growth was inhibited (Figure 2). They sought to investigate the cause and quickly rectify the issue.

During their research, they discovered that their contract manufacturing organization (CMO) changed their production site and raw materials. They expected that these changes were impacting the performance of the culture—likely due to an imbalance of vitamins or trace elements.

They employed Sartorius' Spent Media Analytics Platform to assess the root cause and impact of the changes. Spent media was compared between a batch from the new production site and a functioning reference batch.

Figure 2: *Viable Cell Density and Viability of Two Cell Cultures in the Same Media*

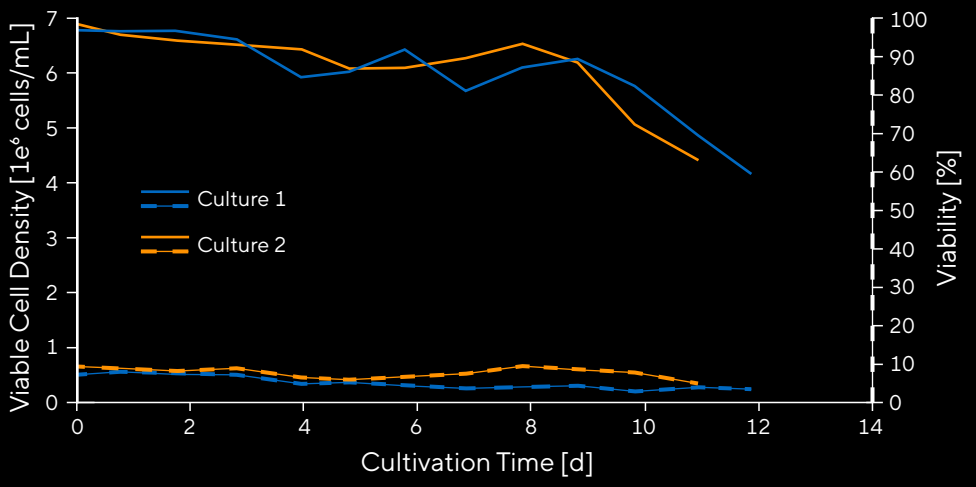
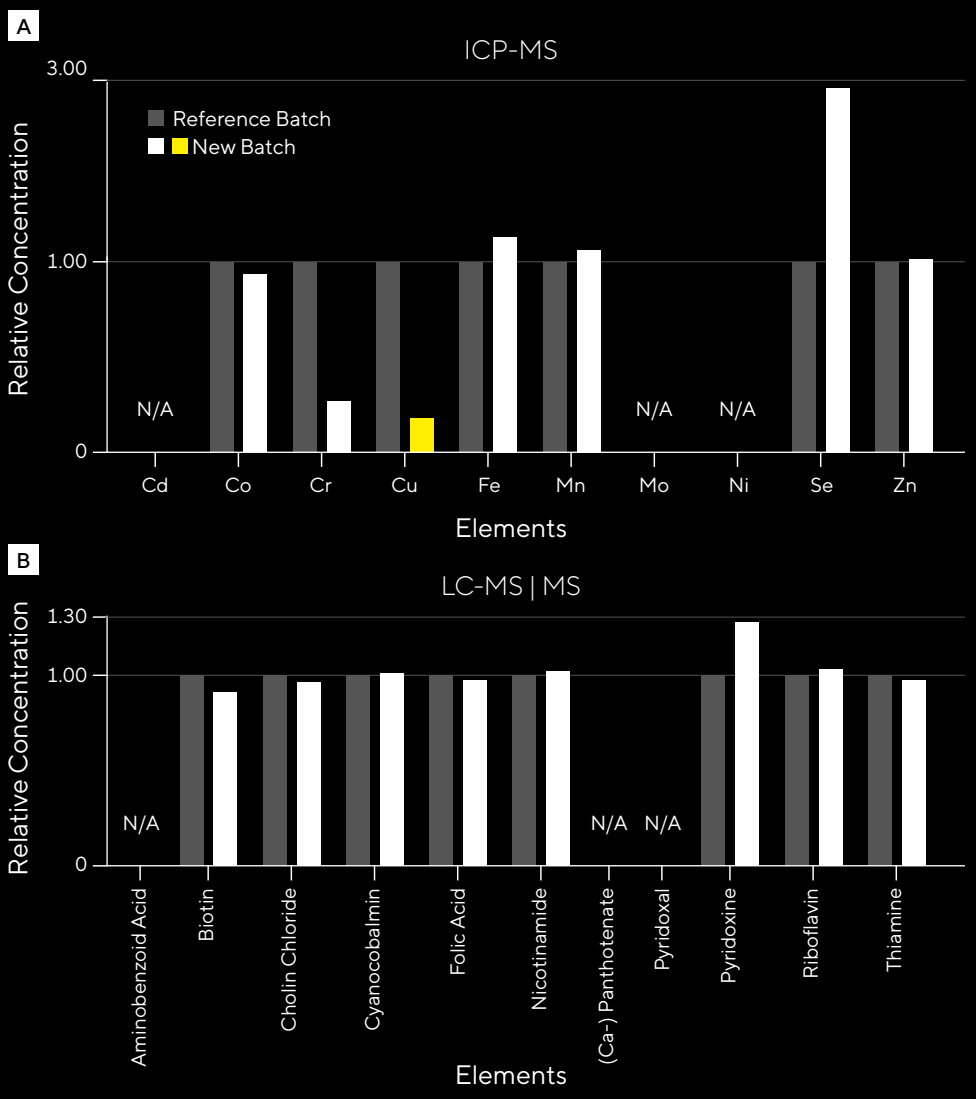


Figure 3: *Generated Results*



Note. A functioning reference batch was tested against a new batch, produced at the new site.
N/A = Analyte is part of the analysis but was not detected

Investigation and Solution

Our role was to analyze vitamins and trace elements in the old and new spent media samples. The vitamins were largely similar across the two samples (Figure 3A). However, three different trace elements showed vast differences between the two samples: chromium, copper, and selenium (Figure 3B).

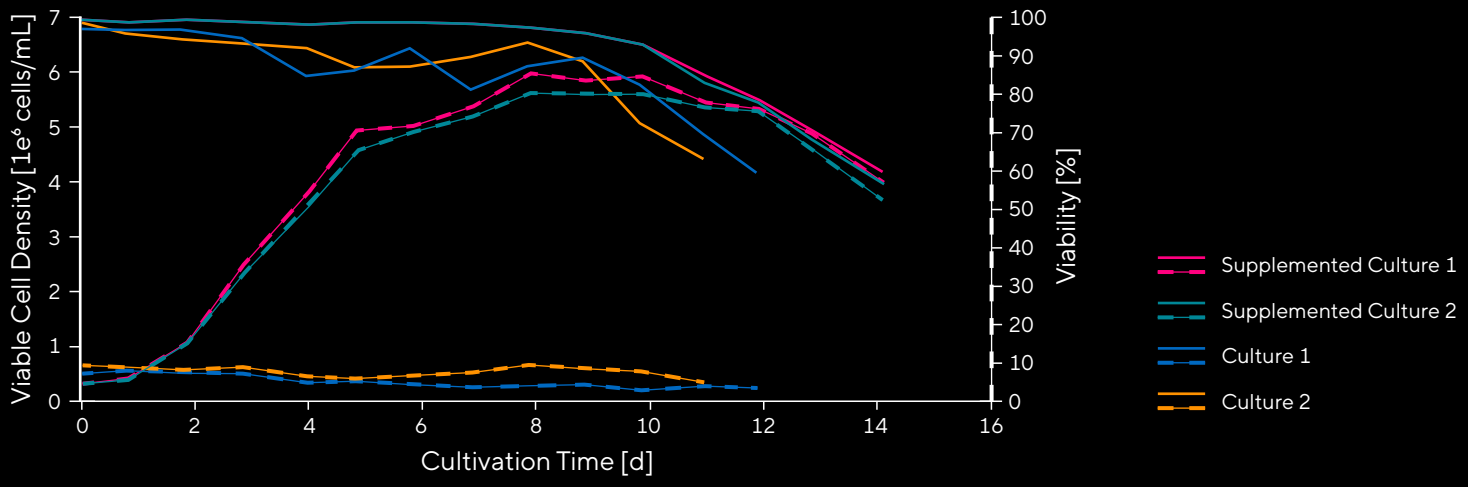
Selenium was almost 3x more abundant in the new batch compared to the reference culture.

However, we theorized that the growth inhibition was more likely caused by a component missing from the culture, rather than an element at too high a concentration. Therefore, we focused on the trace elements that were lower in the new batch compared to the reference batch: chromium and copper. Copper is known to influence cellular activities[1] and was more strongly affected. Therefore, it was our most probable candidate.

Different cell cultures were used to test the impact of copper on growth and viability. We compared the existing media supplemented with copper to the existing media without any additional supplementation. The media were used in cell culture processes run in duplicate and in parallel (Figure 3).

The different approaches yielded very different results. While the medium without supplementation showed no cellular growth, the supplemented culture restored the expected cellular behavior (Figure 4).

Figure 4: *Cell Cultivation With New Medium Supplemented With Copper Compared to the Existing Medium*



Outcome

Trace elements can be actively introduced into the cell culture medium. However, they can also originate from raw material impurities or be introduced during the production process. In this case, copper was not part of the defined medium formulation and was inadvertently introduced by, for example, raw materials in the original site.

While the new site used the same quality grade of raw materials, less copper was incorporated during the preparation of the medium. However, this copper impurity was important for cellular performance. As such, the medium formulation was changed, and copper concentration was actively controlled to ensure its levels were not inhibiting growth.

This case study shows that even in a modern production process, some elements are not controlled and can have huge impacts on the resulting product. Spent media analytics quickly identified the cause and prompted the necessary changes, restoring cell culture performance.

Conclusion

Dedicated spent media analysis can improve process understanding, representing a valuable tool for continuous process monitoring and improvement as well as illuminating root causes of deviations. As such, spent media analytics can support the creation of a more robust, high-yielding cell culture process.

Sartorius' comprehensive and flexible analytics toolkit provides fast, reliable analytics to enable you to make informed decisions during media optimization and process development.

Explore our media analysis portfolio:
https://shop.sartorius.com/at/p/spent-media-analysis/Spent_Media_Analysis

Author Bio

Tim Steffens
Ph.D.,
Manager Analytics
Sartorius Xell GmbH

Tim is the Manager of Analytics within Cell Culture Media and Testing at Sartorius, a position he has held since 2021. He has a Master of Science in Genome Based Systems Biology and earned his PhD in Industrial Biotechnology from Bielefeld University.

In 2017, he joined Xell AG, first as a Project Manager of Analytics and later as a Director of Analytics. Xell AG became part of Sartorius in 2021.

Katy McLaughlin
PhD,
Scientific Content Writer,
Sartorius

Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

References

1. Yuk, I. H., Russell, S., Tang, Y., Hsu, W. T., Mauger, J. B., Aulakh, R. P. S., ... Joly, J. C. (2015). Effects of copper on CHO cells: Cellular requirements and product quality considerations. Biotechnology Progress, 31(1), 226–238. https://doi.org/10.1002/btpr.2004

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

UK
Sartorius Stedim UK Ltd.
Longmead Business CentreBlenheim Road,
Epsom, Surrey KT19 9QQ
Phone +44 1372 737100

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For more information, visit
www.sartorius.com

Status: 10 | 2023