Breaking new ground on animal origin–free reagents

Background

In 2014, a long-standing client developing a nucleic acid therapy approached Thermo Fisher Scientific about enzymes manufactured under animal origin–free (AOF) conditions. AOF reagents offer tremendous benefits to therapeutics developers by increasing active pharmaceutical ingredient (API) safety as well as reducing regulatory and risk assessment burdens [1]. However, truly AOF reagents produced at relevant scales were not commonplace in the industry at the time. The client chose to bring their AOF reagent request to Thermo Fisher Scientific due to their previous experience with the OEM and Commercial Supply team's manufacturing R&D capabilities and well-proven problem-solving skills.

Challenges

For a reagent to be fully AOF, it can't have any possible contamination or interaction with materials from animals—meaning that the finished product cannot be made with any animal-derived materials, whether as starting materials or as common components in manufacturing processes from the primary level and beyond. Generating truly AOF reagents and products is much more easily said than done, since animal-origin materials—like bovine serum albumin (BSA)—are used in many biomanufacturing processes like fermentation, purification, formulation, and beyond.

Capabilities

Capabilities at Thermo Fisher Scientific that power project success:

- Decades of experience developing and manufacturing enzymes and nucleotides at scale for life science products, including through the use of *in vitro* molecular evolution, synthetic biology, and *in vitro* translation
- 2010 acquisition of Fermentas in Vilnius, Lithuania, led to expanded molecular biology enzyme production capabilities and expertise
- Anticipating the market need for AOF reagents, the OEM and Commercial Supply team at Thermo Fisher Scientific had already begun investing in R&D towards AOF enzyme production capabilities
- Rapidly forming and expanding a dedicated R&D team to accelerate AOF capabilities, resulting in pilot-scale samples of enzymes being quickly made available for client verification and use

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Partnership

Prior to this request, Thermo Fisher Scientific had worked with the client for approximately 8 years and had already built a foundation of success supplying a variety of raw materials, including cap analogs, nucleotides, and enzymes. This previous success and established trust in the R&D capabilities of Thermo Fisher Scientific convinced the client that the OEM and Commercial Supply team could execute their vision and deliver the critical enzymes free of animal-origin contaminants.

Results

- Shortly after the agreement was formed with the client, the dedicated R&D team sought to quickly generate pilot-scale samples of key enzymes for the client to verify in their AOF mRNA production processes. This included samples of restriction endonucleases, T7 RNA polymerase, inorganic pyrophosphatase, DNase I, poly(A) polymerase, capping enzyme, and 2′-O-methyltransferase.
- To accomplish AOF enzyme production, the R&D team based in Vilnius with expertise in enzyme manufacturing needed to generate bacterial media without Gibco™ Bacto™ peptone, ensure chromatography systems were fully synthetic, and create a synthetic alternative to BSA for formulation stability (Figure 1).
- The R&D team in Vilnius worked in unison with the client's own R&D team to verify, using analytical biochemistry, that the enzymes had the same performance and stability as animal-origin versions. Here, responsiveness and close collaboration were key to ensuring the verification process did not interfere with key development timelines and the client's path to market for their product. Thermo Fisher Scientific then worked with the client to issue a change notification (to regulatory bodies and customers) and develop a custom specification for this new AOF designation to support the approval process.
- With enzyme activity verified and manufacturing processes in place, Thermo Fisher Scientific opened up the Vilnius facility to a series of audits from the client and regulatory bodies alike, to help certify AOF enzyme production and secure regulatory risk reduction for the mRNA therapeutics made using these enzymes.

Summary

Thermo Fisher Scientific was able to quickly develop and execute manufacturing processes to deliver AOF enzymes at scale to the biopharmaceutical client. As a result, the client was able to adopt AOF enzymes into their mRNA bioproduction processes for manufacturing a variety of therapeutic candidates, thus reducing risk and regulatory burden in clinical trials.

In recent years, AOF enzymes have become more common in the development and production of therapeutics. That said, Thermo Fisher Scientific has continued to advance AOF reagent production processes to improve scale and reduce costs, while also expanding AOF enzyme and reagent portfolio offerings. This portfolio now includes a leading number of different restriction enzymes, polymerases, nucleases, and nucleic acid modifying enzymes for production of nucleic acid therapeutics. In addition to enabling this broad AOF enzyme portfolio, the AOF processes at Thermo Fisher Scientific also support the development and production of custom AOF enzymes for unique purposes and applications.

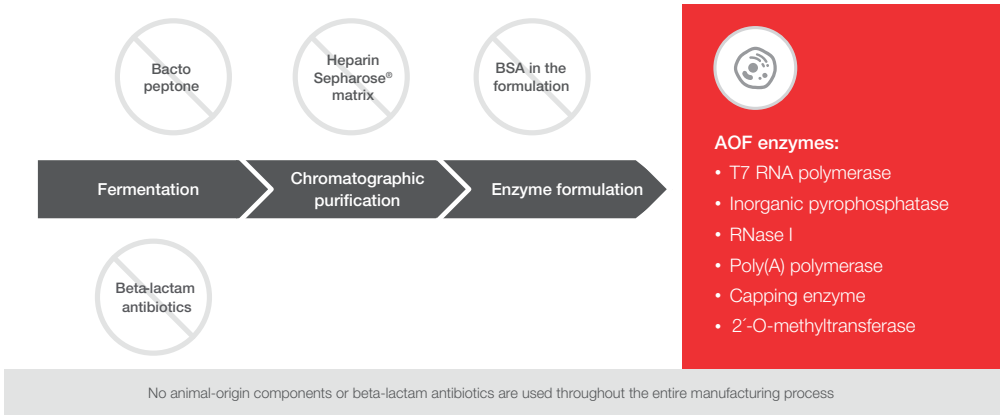

Figure 1. AOF components across the entire manufacturing process.

About OEM and Commercial Supply

When partnering with the OEM and Commercial Supply team at Thermo Fisher Scientific, you gain access to the tremendous resources and knowledge assembled through a track record of successful partnerships and as a world-leading scientific organization.

In addition to accessing our broad product portfolio, a partnership with Thermo Fisher Scientific also helps ensure success through our effective and well-demonstrated problem-solving. Our OEM and Commercial Supply team has seen firsthand that every project has its own specific challenges, but significant infrastructure and a technical approach to manufacturing go a long way towards circumventing and overcoming both common and one-of-a-kind problems. To this end, our expansive worldwide network of sites is populated with research-oriented manufacturing scientists who leverage their previous experience to quickly identify and resolve issues.

Our team is devoted to clear and open communication—an essential aspect of maximizing efficiency and seamlessly solving problems. The commercialization team will provide immediate points of contact to act as your advocates, devoted to putting the full weight and resources of our world-leading organization behind your project at every step of the commercialization journey.

Reference

1. Stramaglia M, Nampalli S, Donahue-Hjelli L et al. (2009) Strategies for sourcing animal-origin free cell culture media components. *BioPharm International* 2009(3).

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