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CASE STUDY

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Using quality by design for process development and scale-up of a novel ALS drug product

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Amylyx Pharmaceuticals, an emerging biotech focused on developing new treatments for amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases, is joining the fight against ALS with its lead candidate, AMX-0035.[1] AMX-0035 is a fixed dose coformulation of the small molecules sodium phenylbutyrate and taurursodiol optimized to simultaneously target pathways originating in the endoplasmic reticulum and mitochondria. The goal is to preserve motor neurons typically lost and/or degraded during the clinical decline of an ALS patient.

Amylyx partnered with Thermo Fisher Scientific to advance AMX-0035 from development to a commercializable product. As it approached the pivotal milestone of Phase III studies, there were development and manufacturing factors, such as the inherent complexity of combining an acid and a base, that Amylyx and Thermo Fisher had to consider for process development and scale-up of registration batches. Thermo Fisher's stepwise approach to Quality by Design (QbD), an approach that drives consistent quality into manufacturing, became integral to the success of the AMX-0035 campaign.

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Meeting the manufacturing needs of AMX-0035

ALS is defined as a rare disease, but it affects an estimated 30,000 people in the United States alone.[2,3,4] The overall population-based lifetime risk of ALS is 1:400 for women and 1:350 for men.[5] It begins with muscle weakness or stiffness and quickly progresses to a debilitating illness that inevitably leads to paralysis and the loss of vital functions, such as speech, swallowing, and breathing and eventually death. Currently, there is no cure for ALS, and the total estimated cost of developing a drug to stop or slow the progression of the disease ranges anywhere between $2 and $3 billion. Despite substantial investment, only two molecules have been approved to treat the disease and even with these therapies the disease remains rapidly progressing and universally fatal.

Striving to develop a successful commercial product, Amylyx needed a CDMO with expertise to take AMX-0035 from the benchtop to commercial manufacturing. Otherwise, they would have to switch partners at critical points in their timelines, risking costly delays while the new partner learned the drug and its process. Specialized equipment and capacity were also on Amylyx's checklist, due to the volumes they needed to produce as well as the unique needs of their drug. For example, AMX-0035 contains two different APIs (sodium phenylbutyrate and taurursodiol) formulated with a complex mixture of excipients, flavorants, and tastemasking agents. Because the powders have different particle size distributions and flow properties, a granulation step involving roller compaction is necessary to improve flow and content uniformity, so doses are not under- or over-filled. In addition, manufacturing equipment often heats up while processing a high volume of materials. This would potentially melt the sugars used to mask the taste of AMX-0035, a key factor since it is taken orally. Additionally, sodium phenylbutyrate is extremely hygroscopic requiring careful monitoring during manufacture.

The ideal solution was to find an integrated partner with all the services and equipment Amylyx required under one roof, making Thermo Fisher Scientific best suited for their needs. Yet, what stood out most to Amylyx was Thermo Fisher's application of QbD methodologies to drug development and manufacturing. Although it is not required by regulators, QbD is highly recommended by the FDA, due to its emphasis on product and process understanding and process control. QbD can help decrease manufacturing deviations and failed/reworked batches as well as increase a company's success rate. Issues that affect product quality can lead to lost batches, which carry costs that are especially devastating for small companies with limited capital to recoup. Working with a CDMO with QbD expertise and experience offers confidence that a process design not only safeguards product and patient safety but also meets FDA submission guidelines and expectations.

A stepwise approach to controlling product quality and variability

There are several manufacturing variables that can impact the quality of a product from early phase development to large-scale commercial production. Phase III studies are when you typically begin to manufacture larger quantities of your product, so if there are any issues with your process or raw materials at this stage, any impacts to your product and process are magnified as well. For example, blending is a common unit operation in small molecule manufacturing, where diluents, fillers, binders, disintegrants, lubricants, and other materials, are blended during scale-up. When going from bench scale to large blenders, it is important to be aware of any changes in geometry that can lead to poor uniformity.

Generally, the critical quality attributes (CQAs) for a product are established using the FDA criteria for the dosage form of the product. In the case of AMX-0035, the dosage form is a powder-in-a-sachet formulation intended to be delivered as a suspension in a liquid. The client, or the CDMO, must also identify the quality target product profile (QTPP) for the product, which is a summary of the quality characteristics expected during development and a basis for process design. Understanding the interplay between the critical process parameters (CPPs) of any unit operation and the critical quality attributes (CQAs) of your product is crucial. It helps establish a design space for commercial production that includes ranges for the CPPs to ensure quality remains consistent throughout the overall process, so there are no surprises later. It also provides references to show regulators later, and the proof to justify them.

Figure 1: Overall QbD Process Flow Diagram for AMX-0035

There were multiple process variables that could influence the outcome of the CQAs for AMX-0035. For instance, it is made using a pre-blend process with excipients and active ingredients. After they are blended, the granules go through a roller compactor and are then re-mixed in a blender (Figure 1). Using a methodical QbD approach, Thermo Fisher established the optimal blending time as well as the roller compaction parameters (screen size, compaction force, and compaction gap). This study enabled the identification of the desired process space for pre-blending, compaction, and final blending in the manufacturing process.

Those results were tested against the CQAs in a statistical program to determine the relationship between any variations and their impact downstream on the finished product. A design of experiments (DoE) strategy was then used to map out the optimal design space and control strategy, so Thermo Fisher could consistently manufacture AMX-0035 in accordance with the defined limits and quality specifications. Thermo Fisher performs a formal risk assessment to identify and rank the parameters, process equipment, input materials, and impact on product quality using prior knowledge and any experimental data that has been generated.

Ensuring success in QbD execution

Successfully executing a QbD strategy is dependent not just on the expertise and experience of the CDMO. The key to a successful collaboration is having an open and transparent relationship where teams from both sides can openly communicate issues and work on solutions collaboratively. Open communication is critical to ensure the project is moving along at a steady pace. Site visits can help reinforce a strong relationship and provides opportunities for team building. When face-to-face interactions are not possible, such as with the COVID-19 pandemic, other alternatives include virtual visits.

Amylyx and Thermo Fisher addressed several technical challenges during their partnership. The strong foundation created through open, honest communication was a key factor in solving problems. For example, Amylyx was preparing a series of submissions for batches that were due to the FDA by a certain date. In order to meet the deadline, teams from both Amylyx and Thermo Fisher team pulled together, working weekends and doing whatever was necessary to make sure the deadline was met. Driven by the noble goal of delivering a drug to help improve the lives of ALS patients, the teams worked together to submit the documentation on time.

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In the CENTAUR trial completed in late 2019, AMX0035 demonstrated statistically significant treatment benefits for people with ALS, based on the ALS Functional Rating Scale (ALSFRS-R), with 92 percent of participants who completed CENTAUR electing to enroll in an extension study. Last year, it was announced that AMX-0035 demonstrated statistically significant treatment benefit for people with ALS in the CENTAUR trial.[6] CENTAUR also showed that AMX-0035 was generally safe and well tolerated.

The importance of collaboration was emphasized in a recent announcement about the drug's success. Dr. Sabrina Paganoni, M.D., Ph.D., principal investigator of the CENTAUR study, investigator at the Healey Center for ALS at Mass General, and Assistant Professor of PM&R at Harvard Medical School and Spaulding Rehabilitation Hospital stated, "Today marks a significant step forward in the fight to develop new treatments for ALS. The study results highlight AMX-0035 as a potentially beneficial new treatment for people with ALS, and the design and execution of the CENTAUR trial are a testament to true collaboration across the many stakeholders in this fight."[7]

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