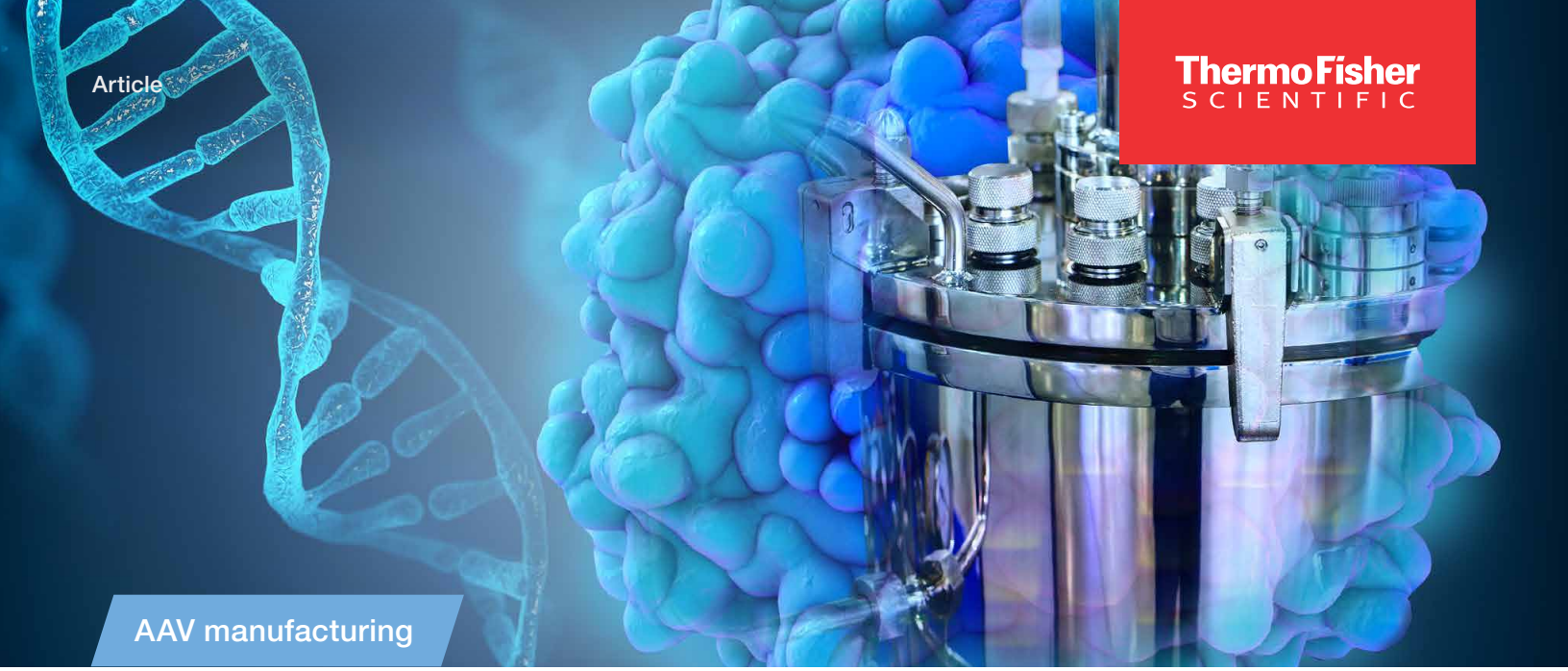

Format follows function: media considerations for future-proofing AAV manufacturing processes

Although the potential of gene therapy has been established for decades, it is only in recent years that the industry has seen a major turning point with the first therapies receiving approval in the late 2010s [1]. As the potential of these therapies is realized, the question of the hour is: how do we manufacture AAV gene therapies sustainably in the long term?

Convenience and cost

The choice when it comes to cell culture medium format is a small one, but it is often not simple: liquid vs. dry. While liquid media are well established at the R&D scale, managing thousands of liters of liquid media can become cumbersome as an AAV process is scaled up.

As the vast majority of gene therapy processes are still operating at relatively small scales, liquid is currently the format of choice for most manufacturers. However, as process scales increase, the cost and logistical challenges of storing and shipping large volumes of liquid media must be considered. The specialized warehousing requirements for cell culture media may make it necessary to use large areas of manufacturing facilities to store raw materials rather than use those areas for production. This could even lead to additional costs if third-party warehousing is needed to accommodate raw materials.

Prepared liquids are convenient, because fewer quality checks and less preparation time are required. The use of liquid media, however, does require careful forecasting. Their shorter shelf life means liquid media and any additional components, such as buffers, must be ordered and received in line with production requirements so they can be used prior to expiry. The validation of a liquid medium is also coupled with the validation of its packaging, so the future availability of the primary packaging must also be considered. Packaging availability became an even more prevalent concern in the wake of SARS-CoV-2, because supply chains were significantly challenged [2].

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Prepare for the future with powder

A number of these logistical challenges can be alleviated with dry media formats. Dry powdered media (DPM) are well established in other sectors of the biologics industry, particularly in monoclonal antibody manufacturing where DPM is the default format for commercial production [3]. However, the benefits of adopting a dry format are less well known within the gene therapy industry. As scales increase, it becomes much more economical to ship and store powdered media and reconstitute them in-house. DPM also have longer shelf lives that enable stockpiling of supplies, which allows manufacturers to take advantage of economy of scale when buying in bulk.

Longer shelf lives also increase process flexibility. The ability to reconstitute media on demand reduces the need for large storage areas and reliance on supply chains. Choosing to reconstitute in-house also gives manufacturers more control over their processes since all sterilization and QC checks take place in-house, and manufacturers have more options when it comes to validating different components like filters. Powders also offer more flexibility in terms of packaging, allowing manufacturers to validate multiple single-use assemblies and mitigate supply concerns.

Even if a decision is made to primarily use a liquid format, it may be wise to validate a dry format option. Conversion to a fully dry-format facility may be unachievable or require additional investment in high-quality water for injection (WFI) systems, which are required to reconstitute media in commercial volumes. However, most facilities will be able to accommodate occasional reconstitution of media in emergencies. This allows manufacturers to pivot to DPM without halting production if there are any challenges with their primary supply of liquid media. Even when outsourcing manufacturing, validating both formats could prevent the loss of a manufacturing slot due to unavailability of raw materials.

Advancing with an alternative format

One of the primary barriers to the adoption of DPM is the labor required for reconstitution. The Gibco™ Advanced Granulation Technology (AGT™) format offers a solution that minimizes preparation time and maximizes efficiency, and it provides better solubility and consistency than regular DPM [4].

AGT media are most often one-part powders, meaning they are homogeneous and do not require additional pH or osmolality adjustments. This simplifies supply chains and bills of materials and improves safety for process technicians, who are no longer required to handle strong acids and bases. The granular nature of the format also reduces the dust generated when using DPM, making its handling easier on the operators and the HVAC system.

The inherent scalability of the AGT format means it can be adopted even for small-scale manufacturing, such as during early-phase clinical trials. This supports the rapid progression of gene therapies through regulatory evaluation, allowing customers to have a commercially viable workflow in place very quickly after approval [5].

Evaluating and optimizing the formulation

Although the process considerations listed in the previous section could help drive the decision towards a particular format, the primary consideration is the formulation itself. Despite the fact that most catalog formulations designed for bioprocessing are available as dry powders, not all cell culture media formulations can be readily converted to dry format and maintain performance. This means the formulation should be evaluated for its suitability when considering conversion to a dry format. Gibco™ PD-Express™ Services can be utilized to support this assessment. We can help you quickly manufacture non-GMP media prototypes to assess formulation changes like changing your format, and we have other analytical offerings to assist you with formulation optimization.

Optimizing a gene therapy manufacturing process as early as possible is key to meeting challenging regulatory timelines and the growing demand for gene therapies. Cell culture media format is one element of the process that should not be overlooked. Taking into consideration the specific process and facility capabilities to choose the ideal format could have a dramatic impact on the efficiency and profitability of processes in the long term. Although making these process changes can be intimidating, leveraging the expertise and support of an experienced and trusted supplier is key to achieving success in commercial AAV manufacturing.

Even when outsourcing manufacturing, validating both formats could prevent the loss of a manufacturing slot due to unavailability of raw materials.

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