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ANTICIPATING CHANGE: ENSURING AAV GENE THERAPY DEVELOPMENT'S PATH TO SUCCESS

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The path to success within AAV gene therapy can be complex with many challenges. This article will focus on how anticipating change can reduce uncertainty whilst still supporting innovation and resilience.

Progression of AAV Gene Therapy, Analytical Methods and Comparability During the Development Process

The advanced therapies industry is rapidly evolving with budding innovation propelling the creation of life-changing research, knowledge and potential treatments for unmet medical needs. The desire for a smooth process from early development to the final product is an ideal scenario for any innovative product. Upkeep with the quick progress can be tedious as the cell and gene therapy industry continues to advance. The ideal situation, especially during the later stages and clinical development, is to have a reality where there are no product, process, or manufacturing changes from early development to the final product.

The concept of creating a treatment solution from theoretical science to a practical product is no easy ride. When starting, it is not always obvious what the challenges may be from a product point of view. There are general challenges, like material constraints or limited process knowledge in early stage, but each product also varies in its own way. Challenges may warrant changes to the method and eventually, the product – a constant domino effect; every time something changes, more changes follow, and change is inevitable.

The development of analytical methods and manufacturing processes continues to progress within AAV gene therapy. For instance, an anticipated change could be a facility change from an academic manufacturing facility in the early development stage

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to a commercial manufacturing site in the late stage.
To minimize the potential risks that may apply to future approvals, a comparability strategy needs to be incorporated as a vitally integral part of the early development processes.

On the other hand, developing such a strategy is not without its challenges. Limited process knowledge, a small number of available batches, and material constraints make the assessment of a comparability strategy both essential and daunting. When changes are made, it is obligatory to demonstrate comparability by showing that there are no adverse impacts on the quality, efficacy and/or safety of a product. This is necessary for the regulatory authorities to be able to evaluate and understand the clinical safety and efficacy of the final product.

The comparability assessment should consider all quality attributes which might be impacted and where the structure-function relationship of the product does not change.
To achieve this, potential manufacturing changes need to be anticipated.

Determining the Initial Methods that Should Be Integrated to Mitigate Potential Problems

The problem lies in determining suitable acceptance criteria and defining the comparability strategy based on the requirements for non-clinical and clinical studies. This often requires an extensive panel of methods to be integrated into the analytical testing from the beginning. Depending on the stage of the development process, the methods for analytical data collection can be quick and easy which is suitable during the research and development stage. However, in later stages, a more comprehensive and precise collection of data may be needed. The shift from early development to later pre-clinical and clinical phases follows a fundamental change in the demand for data quality. Considering this, it is indispensable to incorporate more evolved methods early on. Comparability studies are highly likely to occur while the product enters further development stages. Overlooking suitable data collection can create issues leading to major challenges when the demonstration of comparability of the early-stage product and the late-stage product will be required e.g. a manufacturing change.

Careful evaluation of currently available analytical methods and the analytical development status is necessary especially when considering important attributes such as:

- Qualification/ validation status
- Variability of methods
- Detection of possible small changes in the quality attributes
- Changes in method during development

The continuous influx of methods and instruments suitable for the analytical development of viral-based gene therapy products represents a major challenge for the evaluation process. All methods have their advantages and disadvantages. While some may require specifically trained personnel and come with an expensive investment for instruments, others can be more straightforward and less expensive regarding cost per sample. Determining the internal acceptance criteria at an early stage will make it much easier to make informed decisions on the panel of suitable methods.

Furthermore, comprehensive comparability assessment requires comparative results from all relevant stages and manufacturing processes, including side-by-side testing of pre- and post-change samples. However, material constraints are a significant challenge, where especially viral-based gene therapies are often

produced on a small scale with comparatively low yields and there may simply not be enough supply for extensive testing. Nevertheless, these challenges can be overcome much easier when considered from the beginning of the process.

Oftentimes, a limited understanding of relevant critical quality attributes (CQA), such as genome titer and virus capsid titer, aggregation affecting potency, purity, and safety, creates further complexities to be considered.

Addressing the Need for Commercially Available Reference Materials in AAV Gene Therapy Production

To address these challenges, a comprehensive characterization of the product at all stages of the process is crucial. Though the regular authorities have not prescribed specific methods to be used for product characterization, they strongly recommend the use of orthogonal methods to achieve more accurate data on the product. Many companies decide to go with a selection of established analytical methods, e.g. ddPCR and ELISA (both recommended by the FDA), representing gold standard methods within the field of AAV gene therapy, supplemented with newer techniques, which might be less renowned. The Food and Drug Administration (FDA) further recommends the comprehensive demonstration of the validity of the analytical methods used for characterization using suitable reference material or standards, allowing comparability of the assays performed at different stages. When evaluating CQAs, the ability to streamline analytical development processes could reduce development time whilst ensuring consistency.

However, since commercially available international reference standard material for AAV is only available for AAV2 and AAV8, there is a lack of standards for other AAV serotypes and capsid variants. The in-house development and manufacturing of standards, as well as the necessary in-house qualification of the reference material, may not be feasible for every AAV gene therapy manufacturer, especially at the beginning of the development process.

In this regard, it is evident that there is a dire need for commercially available reference material which is comprehensively characterized and qualified to ensure comparability and safety of AAV gene therapy product development. Besides, having readily available standardized reference material not only accommodates internal comparability assessments but also aligns comparability across the AAV gene therapy industry. Globally available AAV reference material allows standardization, qualification and comparability whilst facilitating the interpretation of data collected during pre-clinical and clinical stages, most likely accelerating release processes.

There are a few companies, e.g. PROGEN that have started to address this problem. By providing AAV standard material for a variety of serotypes and analytical methods used in the AAV gene therapy community, PROGEN supports AAV gene therapists worldwide.

Conclusion – Anticipating Change Can Support Accelerated Clinical Development to Aid Delivery of Safe and Effective Gene Therapies

Anticipating change is a crucial challenge to be prepared for when developing gene therapies. As the field continues to develop and mature, it is imperative to establish comprehensive strategies and standards to maintain comparability throughout the entire development process – from early stage to late stage and beyond.

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This requires key collaborations amongs industry stakeholders, standards organizations and regulatory authorities to ensure the availability of commercially viable reference materials. The AAV field is still young in theoretical science and development and with this, the knowledge and criteria surrounding regulatory authority continually adapt. By anticipating change, risks can be minimized where possible supporting accelerated clinical development and eventually delivering safe and effective gene therapies to patients in need.