WHITE PAPER

Enhancing CMC Regulatory Efficiency in Gene Therapy.

The Perspective of Viralgen's Regulatory Team

VIRALGEN

All-In AAV™

Abstract

This White Paper details the pivotal and expansive role that Regulatory Affairs plays at Viralgen, focusing on the specific benefits this department provides to its customers, offering feedback to regulatory agencies on CMC issues and delivering robust support. The proactive engagement offered facilitates key collaborations between CDMOs, customers, and regulators, resulting in faster speed to clinic and enhanced product quality and safety. Through this comprehensive analysis, we will demonstrate how this approach potentially accelerates development timelines, supports compliance, and ultimately strengthens the customer's business.

I. Introduction

The regulatory environment in which businesses operate today is increasingly complex and dynamic. In this landscape, the Regulatory Affairs (RA) team emerges as a linchpin, orchestrating strategies to ensure compliance with diverse regulations while facilitating product development and registration.

II. Current Regulatory Environment

Navigating the regulatory environment can be an overwhelming experience for therapeutic developers. Historically, regulatory compliance and documentation preparation for regulatory filings have been time-consuming and resource-intensive processes, often requiring extensive manual effort and coordination between stakeholders.

The regulatory environment and Health Authority expectations are developing faster than the associated guidelines and regulations. In addition, inconsistencies have been experienced across the reviewer program, and feedback requested from Health Authorities can lack clarity of action, with regional feedback not always in alignment with one another, impacting program strategy.

This has created uncertainty and additional burdens in seeking regulatory approval, rework, additional studies and challenges to prepare dossiers appropriately, leading to unnecessary extra work where expectations are not clear, causing delays to project development and a financial impact to companies.

This is of great relevance in the case of rare diseases. Historically, pursuing therapies for rare diseases has been challenging for sponsors, given the high costs and the very small patient populations.

Although in the last few years there has been a positive impact with changes in regulations that encourage developers to pursue therapies for rare diseases with orphan drug

development and expedited approval pathways, rare disease drug development continues to face the following obstacles: expedited programs typically requiring significant CMC investment; condensed timelines that cannot align with chemistry, manufacturing, and controls (CMC) elements such as validation work and stability programs; and a limited funding environment that many small biotechnology companies face.

II.2. Regulatory Challenges in Gene Therapy:

One of the biggest challenges the industry is currently facing is the lack of specific regulatory guidance for gene therapy, which requires developers to be ready for success from the very beginning in order to achieve a robust and consistent manufacturing of long-lasting single-dose therapeutics. The existing requirements are often general and not tailored to this innovative field **Error! Reference source not found.**,**Error! Reference source not found.**. Consequently, the pathway to regulatory approval can be uncertain and subject to evolve, with stringent requirements imposed by regulatory agencies. However, this does allow for flexibility, and the regulators are open to discuss innovative strategies.

Thankfully, the landscape is changing, and more public and private entities are joining efforts to provide support for these types of therapies, trying their best to improve the quality of the products.

As an example of an actual challenge, when it comes to analytical development, previously, the industry used ITRqPCR as a titration method which is used to calculate the dose that will be used in patients. However, and since the coefficient of variation of this technique is greater than 15% the regulators encouraged the industry to reduce this coefficient of variation, to be able to come up with a more accurate dose. ddPCR technology, however, was shown to convert uninterpretable results generated from qPCR to highly quantitative and reproducible data.

Regulatory agencies are also emphasizing consistency between clinical and commercial design strategies. Additionally, they are requesting for a late-phase release testing strategy including more than one independent measure for certain quality attributes (following an orthogonal approach) to ensure consistent Drug Product quality. And they are strongly recommending considering this as part of product development.
Setting acceptance criteria for quality attributes when there is insufficient data available to make informed decisions is another big challenge. This doesn't necessarily mean that the knowledge of the product is limited, but the data generated around a certain product, may be limited due to the characteristics of these therapies.

Three years ago, regulatory agencies were accepting the approach of not setting acceptance criteria for certain quality attributes in early clinical phases. However, recently, there has been an increasing demand from regulatory agencies to set acceptance criteria ranges for residual impurities even in early phases, that should be narrowed during development.

FDA standard recommendation for products made in continuously dividing cells that are tumorigenic or tumor-derived is to limit the amount of residual host-cell DNA to less than 10 nanograms per dose and the DNA size to below 200 base pairs. However, and as stated by the FDA in OTP townhalls**Error! Reference source not found.**, the agency understands

that it can be challenging to meet these limits for products such as AAV, since AAV capsid can package host-cell DNA in a nonspecific manner, which is then resistant to nuclease treatment. 4,5,6

III. Addressing Challenges

Regulatory interactions in gene therapy are complex and can be difficult. As industry understanding of AAV grows, so too do the challenges of submission and approval of these therapeutics. To respond to this challenge affecting therapeutic developers, Viralgen's RA team offers a robust planning and preparation that is essential to succeed in addressing challenges mentioned above, and ultimately in CMC development. Viralgen is well-versed in regulatory requirements and can help ensure that pharmaceutical products meet the necessary quality and compliance standards for safety, purity, and efficacy. To date, 100% of all of Viralgen's CMC submissions for our customers have been accepted by health authorities globally.

Successful compression of a development timeline demands early contact with regulators. CMC regulatory support provided by Viralgen can be beneficial to companies/sponsors that have the expertise in the condition to be treated but may be limited in their regulatory capabilities. Combining the manufacturing expertise from Viralgen altogether will lead to successful outcomes with the Health Agencies.

Viralgen's Pro10™ platform with experience of >1500 batches is a significant strength, allowing the development of an approach that leverages the years of historical data with all batches produced. By using this platform manufacturing process and analyzing the collected historical data statistically, the data can be clustered and consequently increase the dataset.

III.1. CMC Support

Viralgen is committed to the sponsor's success in those interactions with regulatory agencies. As a part of our inclusive pricing, we provide with whatever level of support is required for the Chemistry, Manufacturing and Control (CMC) areas of each submission – from providing template articles to authoring them, in addition to, and participation in information exchanges with regulators either in writing or in person (see Figure 1.).

Viralgen has developed a streamlined production platform process, ensuring uniformity across all vectors produced. The main benefit of using a platform instead of individual processes is the ability to leverage data across different processes within the platform as much as possible.

Viralgen can establish and justify limits based upon assessment of several manufactured lots from the same serotype, sharing the same manufacturing platform. A statistical

analysis of the data distribution is assessed in order to apply the most suitable methodology for specification limits definition.

Such assessments and data analysis tremendously increases the knowledge of each process, reduces development timelines of new processes, supports troubleshooting, and reduces risks of failure.

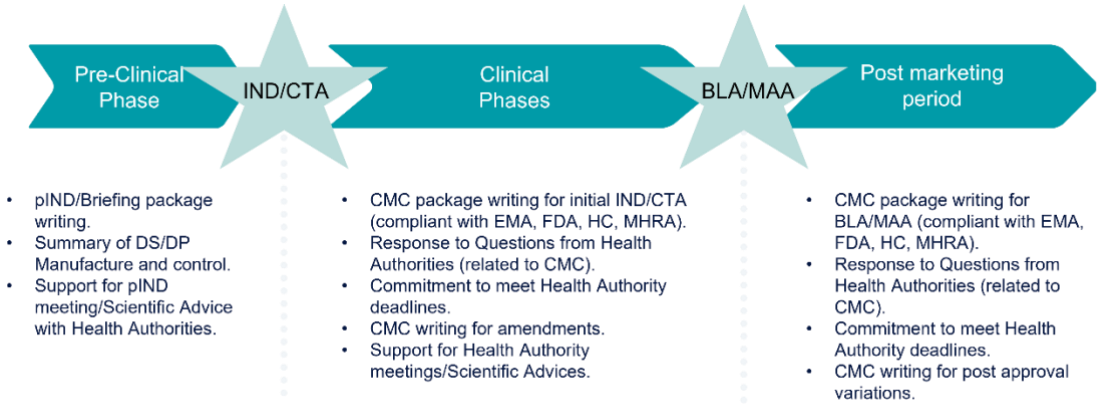

Figure 1: Regulatory CMC support and deliverables. Pre-Investigational New Drug application (pIND); Drug Substance (DS); Drug Product (DP); Chemistry, Manufacturing and Control (CMC); Investigational New Drug application (IND); Clinical Trial Application (CTA); European Medicines Agency (EMA); U.S. Food and Drug Administration (FDA); Health Canada (HC); Medicines and Healthcare products Regulatory Agency (MHRA); Biologics License Applications (BLA); Marketing Authorisation Applications (MAA).

Viralgen's platform has enabled the creation of CMC templates compliant with regulatory standards in the EU, US, UK, and Canada, expediting the documentation process and reducing turnaround times. By incorporating feedback from regulatory agencies, Viralgen continually enhances and updates its CMC templates to meet evolving requirements, ensuring regulatory data and documents are developed in Viralgen format. Using these CMC templates, Viralgen develops the client specific CMC package for their regulatory procedures. Additionally, Viralgen assists in drafting briefing documents, responding to questions , and participating in meetings with health authorities.

III.2. Digital Support

In order to manage the regulatory documentation effectively, insight into global regulations and standards, detailed product specifications, testing, performance and a full record of all regulatory registrations and processes are needed.

Regulatory Information Management (RIM) systems serve as a "single source of truth" for RA teams. They store and manage regulatory documents, integrate with systems across the company, and create a traceable record of all regulatory activities. All this information is linked to individual products and countries or regions, making it much easier to find. RIM systems can have a tremendous impact on RA teams. By centralizing information,

they improve team productivity by ensuring that up-to-date information is always easily available and consistently applied.

Submission authoring solutions (authoring templates) facilitates efficient creation of submission-ready regulatory documents compliant with International Conference on Harmonization (ICH) and regional structure and formatting requirements.
With the implementation of the above-mentioned digital solutions, Viralgen ensures:

- ✓ Enhanced Documentation Management
- ✓ Efficient Handling of Health Authority Feedback (HAF)
- ✓ Streamlined Dossier Preparation
- ✓ Improved Regulatory Compliance

III.3. HAF Database

Viralgen has developed a comprehensive solution (database) by gathering feedback from every regulatory interaction. This allows Viralgen to streamline the preparation of responses to Health Authority Questions (HAQs) by leveraging the body of data, in a very efficient manner, with reduced timelines in accordance with Agencies' requests.

This Regulatory asset allows Viralgen to advise its clients on their clinical and commercial strategies.

III.4. Lifecycle Management

Managing and keeping up with changes is one of the greatest challenges for organizations in the context of risk management and compliance.

Change control management is a systematic process that involves evaluating, documenting, and approving alterations to pharmaceutical processes, equipment, facilities, change control systems, and even personnel. Change control aims to minimize risks and ensure that any modifications made within the pharmaceutical manufacturing process do not negatively impact product quality, safety, or efficacy.

A thorough assessment of the potential impact of the change on product quality, safety, efficacy, and compliance is critical to informed decision-making.

The first stage in regulatory change management is finding the regulatory changes that might impact the documentation submitted. Viralgen's Quality Management System (QMS) software allows regulatory compliance where modifications are assessed, documented and implemented in a structured way. Support is also provided for managing any changes to the product or process ensuring that the product continues to meet regulatory requirements throughout its lifecycle.

As of September 2024, 28 clinical trials with material produced at Viralgen have been approved by FDA, MHRA, HC and different European and rest of world (ROW) Agencies (Figure 2).

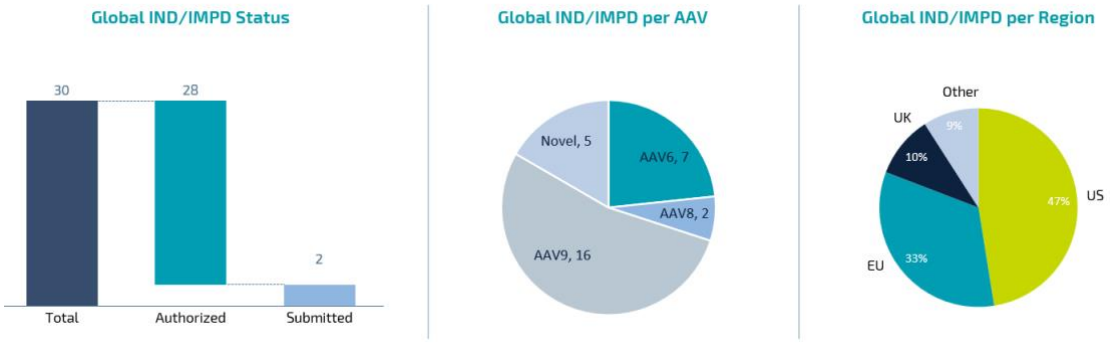

Figure 2: Overview into Viralgen's experience with Regulatory Submissions. Gene therapy products produced at Viralgen have been approved in 28 regulatory procedures as of September 2024. Programs include multiple different serotypes with submissions spanning worldwide.

IV. Future Outlook

As we look ahead to the future of gene therapy, several key trends and principles will shape the landscape of regulatory efficiency:

- Faster Development Pathways
  - The industry is pushing for accelerated pathways that reduce the time from discovery to patient access.
- Priority Review
  - Regulatory bodies will increasingly prioritize gene therapy products to expedite their approval and market availability.
- Prepare for Success from the Beginning
  - Early planning and robust data collection will become essential to navigating the regulatory process smoothly.
- Alignment with Global Agencies
  - Harmonizing regulations across different regions will facilitate global market access for gene therapy products.
- Science is Moving Fast, Regulation is Moving Slow
  - There's a growing disconnect between the rapid pace of scientific advancements and the slower rate of regulatory adaptation. Bridging this gap will be crucial.
- Simplified and Leaner Regulatory Procedures
  - Streamlining regulations will not only speed up approvals but also reduce costs.
- Bring Costs Down
  - Efficiency improvements in manufacturing and regulatory processes will contribute to cost reduction.
- More Affordable Products
  - As costs decrease, gene therapy products will become more accessible to a broader patient population.
- Improve Efficiencies in Manufacturing
  - Adopting advanced manufacturing techniques will lead to faster and more consistent production.
- Faster and Cheaper Developments

- Overall, the goal is to make the development of gene therapies faster and more cost-effective.
- One Size Fits All is Not Going to Work
  - Tailored regulatory approaches for different types of therapies will become the norm rather than the exception.
- Align on Standards
  - Establishing common standards will simplify the regulatory landscape and foster innovation.
- Movement Towards Standardization
  - Adopting standardized development platforms and selective process characterization will expedite approvals for certain therapies.
- Need a Platform Approach
  - A unified platform approach will enable collaboration and shared resources among stakeholders.
- Break the Mental Block
  - Shifting from a mindset focused on individual gains to one that emphasizes shared knowledge and resources will be crucial.
- Data Generated Can Be Leveraged
  - Utilizing data effectively can provide valuable insights and streamline the regulatory process.
- This Industry Needs Different Approaches
  - Traditional regulatory models designed for small molecules may not be suitable for gene therapies.

V. Conclusion

The Regulatory Affairs team at Viralgen plays a pivotal role in supporting clients from the preparation of clinical trial applications to regulatory submissions and interactions with health authorities. Through efficient processes and template-driven documentation, Viralgen facilitates regulatory compliance, expedites market entry, and enhances client visibility.

Looking ahead to the future of gene therapy, several key trends and principles will shape the landscape of regulatory efficiency. The industry is pushing for faster development pathways and priority review by regulatory bodies to expedite approval and market availability. Early planning and robust data collection will become essential for navigating the regulatory process smoothly. Additionally, aligning regulations globally will facilitate market access for gene therapy products.

Despite the growing disconnect between rapid scientific advancements and the slower pace of regulatory adaptation, bridging this gap will be crucial. Simplified and leaner regulatory procedures will not only speed up approvals but also reduce costs, making gene therapy products more accessible. Adopting advanced manufacturing techniques will lead to faster and more consistent production.

A one-size-fits-all approach will not work for all therapies, highlighting the need for flexible and adaptable regulatory strategies. Collaboration among stakeholders and effective use of generated data will streamline the development and approval of innovative gene therapies.

In conclusion, the future of regulatory efficiency in gene therapy lies in embracing innovation, collaboration, and adaptability. By aligning with global standards, streamlining processes, and fostering a culture of shared knowledge, we can accelerate the development and approval of life-changing gene therapies.

VI. References

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