Bespoke Gene Therapy Consortium (BGTC) Regulatory Playbook Version 1.0

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Revision History

Date	Version	Description	Author
February 6, 2024	1.0	Published preliminary version 1.0	BGTC

Prologue

The Accelerating Medicines Partnerships® (AMP®) Bespoke Gene Therapy Consortium (BGTC) recognized the need for a comprehensive playbook that would serve as a guiding framework for the development and regulatory submission of adeno-associated virus (AAV) gene therapies for rare diseases. Building out this playbook to support the key processes up to a sponsor's first-in-human (FIH) trial required a collaborative and modular approach. Version 1.0 of the playbook is designed to serve as a one-stop-shop guide and roadmap to investigational new drug (IND) submission for these innovative gene therapies.

To ensure the playbook's credibility and integrity, the BGTC embarked on an ambitious journey to consolidate external information with their own internal expertise. The goal was to generate a operational playbook that would serve AAV drug developers of all backgrounds, but primarily those who could benefit from simplified language, guidelines, and templates for this complex process (e.g., family groups, non-profits, patient foundations, academic research labs, small biotechs, but not necessarily large pharmaceutical companies.

The process for developing this playbook started with collating source documents, such as FDA regulatory guidances, publications, and other publicly available resources. These foundational guidelines were supplemented with the BGTC's extensive expertise and experience in gene therapy regulatory processes. The initial playbook structure, reflected in the Table of Contents, was framed around key milestones common to a sponsor's typical regulatory journey from research and development (R&D) to pre-clinical through clinical development. The BGTC intends to continue enrichment of the playbook in subsequent versions by incorporating learnings from through standardize output – leveraging BGTC subject matter expertise (SMEs), defining efficiencies, platform strategies and from accrued knowledge based on FDA interactions. These invaluable insights formed the bedrock of the playbook, ensuring that it would encapsulate the latest advancements and emerging best practices.

As the playbook took shape, it became evident that this collaborative endeavor had the potential to revolutionize the field of gene therapy, particularly through continued evolution capturing learnings from the BGTC projects and advances across healthcare and drug development. Not only would it provide researchers and developers a unified resource to navigate the intricate regulatory landscape of AAV gene therapies, but it would also facilitate harmonization and streamlining among various stakeholders, including researchers, regulatory bodies, clinicians, and ultimately, benefiting patients with these rare diseases.

The BGTC Regulatory Playbook is a collective effort of the BGTC SMEs and it sets the stage for a paradigm shift in rare disease gene therapy development. With the BGTC leading the charge and drawing upon the collective experience, expertise, and passion of the scientific community, this playbook aims to serve as a guiding light, enabling researchers and developers to bring safe, effective, and transformative gene therapies to patients in need.

Acknowledgements

We would like to thank all BGTC consortium members and contractors for their valuable review and contributions to the playbook.

BGTC Regulatory Playbook Contact

For questions, email Brad Garrison, FNIH Sr. Project Manager, at bgarrison@fnih.org.

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Chapter 1: Introduction to the BGTC Regulatory Playbook

1.1. BGTC Vision and Philosophy

What is the BGTC?

Launched in October 2021, the Bespoke Gene Therapy Consortium (BGTC) is the first initiative of the Accelerating Medicines Partnerships® (AMP®) program with a mission-driven focus for rare diseases. The AMP® is a public-private partnership among the NIH, the U.S. Food and Drug Administration (FDA), multiple pharmaceutical and life sciences companies, nonprofits, and other organizations.

Coordinated by the FNIH, AMP BGTC brings together partners from across the healthcare ecosystem to foster development of gene therapies for rare diseases that currently have no commercial interest.

Why BGTC?

There are over 10,000 rare diseases that are caused by genetic defects with over 30 million people in the United States living with the devastating effects of these rare diseases. These patients often lack access to effective treatment, as knowledge and research funding for many rare diseases often lags compared to more prevalent diseases. With the current approach of targeting one-rare-disease-at-a-time, there are no effective business models to return the investments needed to bring a single rare disease therapy for a small population to market. [1] A gene therapy frequently treats a disease by replacing the malfunctioning gene responsible for the condition with a "working version" of the gene by using a delivery system often called a "vector." Adeno-associated virus (AAV) gene therapies have been successfully used as interventions to treat genetic disorders and have received U.S. Food and Drug Administration (FDA) approval for human use.

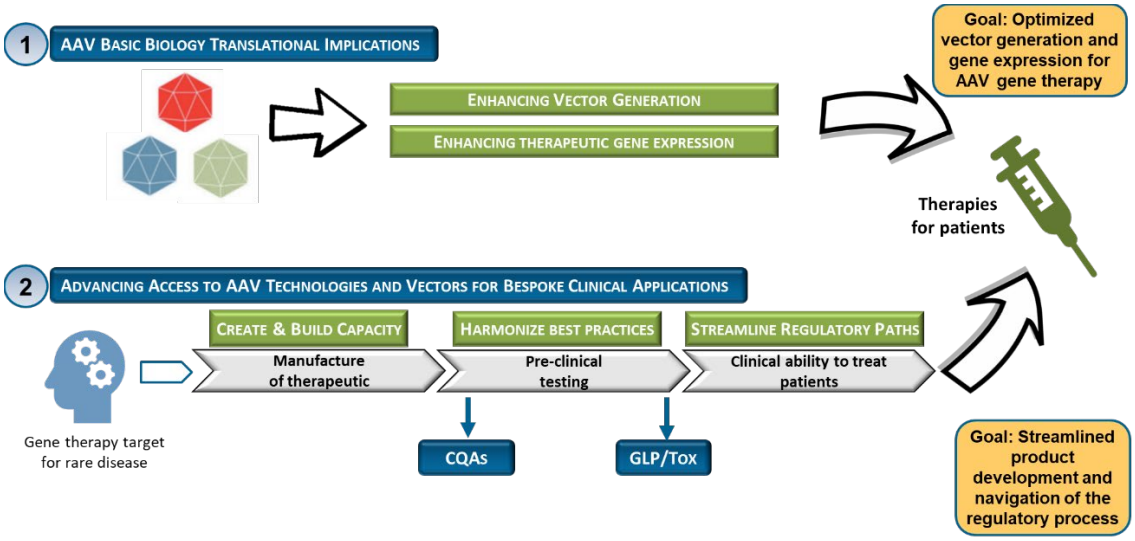
The good news is that these gene therapies can be tailor-made for a very small population or even a single individual. However, the development process for these "bespoke" therapies is complex, expensive, and hampered by a lack of common biologic, manufacturing, and regulatory standards.

This is where the BGTC comes in.

Utilizing the successful AMP® model for public-private partnerships, the BGTC aims to streamline product development and the navigation of the regulatory process, making AAV gene therapies for rare diseases more accessible to patients who need them. The solution .involves two areas of focus, as shown in **Figure 1** below:

1. Exploring AAV Basic Biology and Translational Implications
2. Advancing Access to AAV Technologies & Vectors for Bespoke Clinical Applications

Figure 1: The BGTC's two critical pathways for AAV gene therapy research [1]



By leveraging up to eight clinical trial test cases and the unparalleled combined expertise of the Consortium partners, we have developed a "**playbook**" for streamlining product development and navigation of the regulatory pathway for AAV gene therapies.

The BGTC Regulatory Playbook highlights the second objective, Advancing Access to AAV Technologies, acting as **operational guide** with the tools to embark on the regulatory process. In future versions of the playbook BGTC plans to decode efficiencies that streamline development and provide standards such as **minimum requirements (e.g., manufacturing, pre-clinical testing, etc.)** derived from our work to enable future investigations with AAV gene therapies for various genetic disorders.

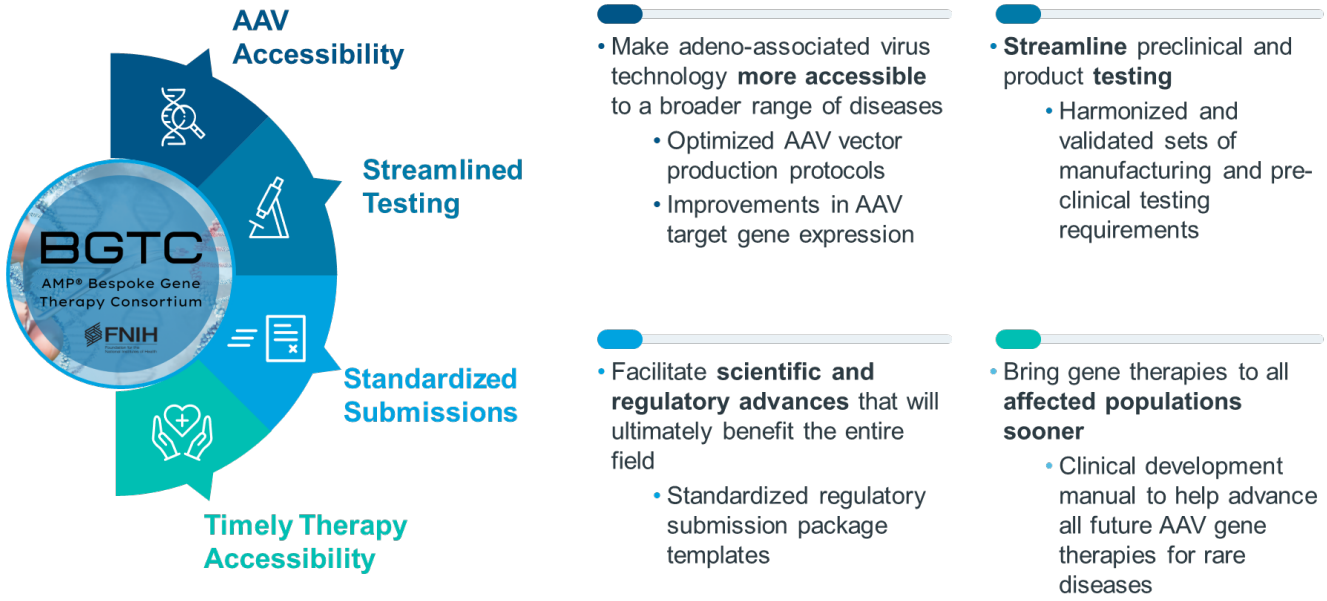
1.2. Streamlined Approaches to Bespoke Gene Therapy Development

The BGTC seeks to overcome the current obstacles faced during the development of gene therapies by streamlining approaches in four different sectors:

1) **Basic Research**
2) **Clinical Research**
3) **Manufacturing and Production**
4) **Regulatory Requirements**

See **Figure 2** below for an overview of the BGTC's specific goals. [1]

Figure 2: BGTC goals for streamlining processes for the development of bespoke gene therapies

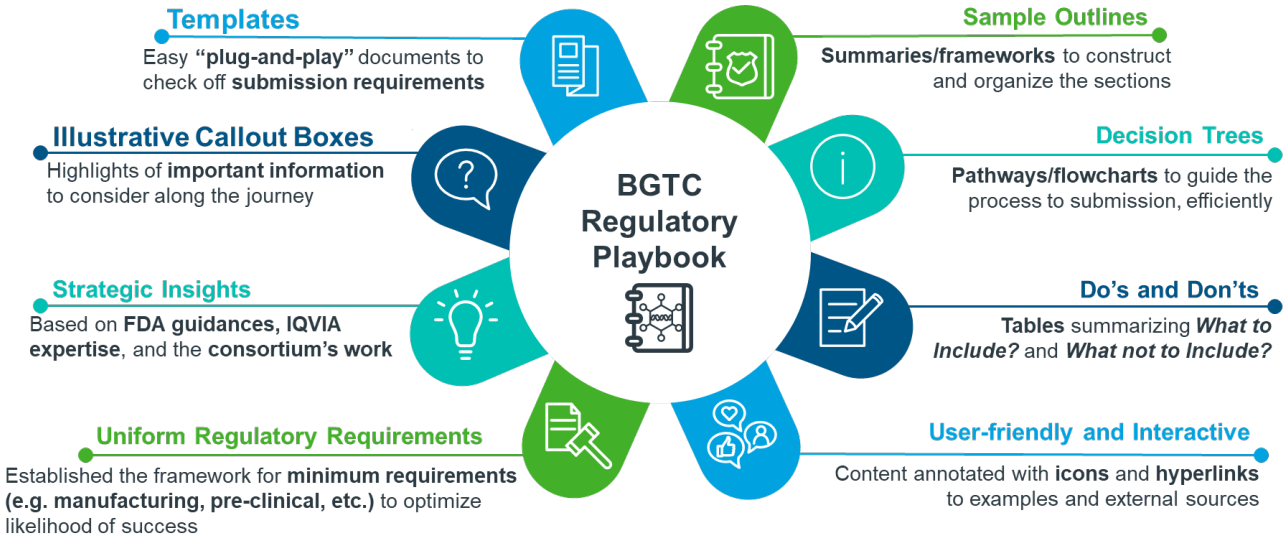


This playbook is a manifestation of “streamlined testing” and “standardized submissions,” taking a comprehensive and systematic approach to AAV gene therapy development. It covers all aspects of the development process up to IND submission and first-in-human studies.

Supplementing future iterations of the playbook, we plan to also include templates and minimum requirements (e.g., manufacturing, pre-clinical testing, etc.) to distill a more repeatable regulatory process for AAV gene therapies (see **Figure 3** below). The minimum requirements as they apply to the BGTC approach will get to the core of what is considered necessary and sufficient for a safety and efficacy evidence package in your regulatory submission to the FDA. This means reducing redundancies and leveraging available information to increase efficiencies in a typically complex and inefficient process.

The BGTC approach highlights best practices and recommendations to enable you to *strike the right balance* between **meeting FDA data requirements** and **accelerating your submission** as much as possible. You may refer to the Chapter 2: Platform-based Approach for AAV Gene Therapies for more information on how this approach further supports and defines what we collectively call “minimum requirements”.

Figure 3: Overview of BGTC Regulatory Playbook contents



This playbook helps you prepare for each stage of development, as well as answer the question "Am I ready?" each step of the way. At key milestones, we've provided Readiness Assessments and guidance for applying the BGTC approach in preparing for the INTERACT and Pre-IND meetings (see Chapter 4: INTERACT Meeting and Chapter 5: Pre-IND Meeting). This is intended to support you in reaching the **optimal state of preparation** at these milestones. We will guide you in applying one or more elements of the BGTC approach at critical timepoints throughout your regulatory journey.

Please read on to understand more about the BGTC approach as it relates to minimum Chemistry, Manufacturing, and Controls (CMC), pre-clinical, and other requirements.

1.3. Minimum CMC CQAs and Analytic Methods

What are CQAs?

Critical Quality Attributes (CQAs) are essential components in the development and manufacturing of pharmaceutical products. CQAs are the physical, chemical, biological, or microbiological characteristics that must be controlled within specific limits to ensure the safety, efficacy, and consistency of a product. Analytic methods are the tools used to measure and monitor these CQAs. The development and validation of these analytic methods are critical steps in the drug development process, and the FDA places significant emphasis on their accuracy, precision, and reproducibility.

The FDA requires that all pharmaceutical products meet specific CQAs to ensure their safety and efficacy. Establishing a **minimum set** of CQAs is necessary to streamline the manufacturing of gene therapies for rare genetic diseases. With the rarity of the diseases in

question, the number of anticipated patients in clinical trials may limit manufactured drug substance and drug product batches. In some cases, the pre-clinical and clinical lot may be the same. [2]

Keeping in mind these limitations on batch production and material availability, it is simply not feasible to perform extensive testing to ensure appropriate characteristics and specifications for these assets. Therefore, the BGTC Manufacturing Sub-team is actively working to establish a set of CQAs applicable across the current portfolio of selected indications, and generally applicable to AAV gene therapies in rare diseases. This minimum set of CQAs will be made available in future iterations of the BGTC Regulatory Playbook.

Even though a CQA can never truly be considered “non-critical,” because of AAV gene therapies being a platform modality and involving very well-controlled, highly similar processes, the BGTC can state with high confidence that certain attributes are unlikely to drift out of safe or efficacious ranges. If there is sufficient prior data that can be leveraged, an attribute may not be critical.

With this assumption, the BGTC has focused on a minimum set of CQAs scored on a Risk Priority Scale. Such a minimum set of CQAs would also provide uniformity across different qualified manufacturers and different gene therapy products, thereby benefitting the AAV gene therapy field more broadly.

The BGTC Manufacturing Sub-team continuously coordinates with the other Sub-teams on vector manufacturing for pre-clinical and clinical testing, and continues to develop proposals for optimized lot release assays, harmonized and validated vector quality tests, advanced product manufacturing capability, and standardized regulatory submission packages.

1.4. Minimum Pre-clinical Testing

Pre-clinical/ non-clinical testing refers to the *in vitro* and *in vivo* animal testing conducted to evaluate the safety and efficacy of a therapy. Under the FDA requirements, you as a sponsor are to submit data showing the toxicity and pharmacologic effects of your therapy.

The BGTC’s goal for pre-clinical testing is to streamline the process of going from proof-of-concept studies to a first-in-human trial. To that end, the BGTC Pre-clinical Sub-team has been developing a minimum set of animal toxicology studies that meet the threshold of adequate safety data for IND submissions while reducing the use of non-human primates (NHPs) as much as possible. These toxicology minimum packages will be based on route of administration – e.g., systemic AAV gene therapies administered intravenously (IV) will have different considerations compared to ocular (subretinal/intracorneal) or central nervous system via cerebrospinal fluid (intrathecal/intracerebroventricular/intracisterna magna). These minimum set of animal toxicology studies will be made available in future iterations of the BGTC Regulatory Playbook.

These minimum pre-clinical testing requirements we intend to include in the next version of the playbook are limited to toxicology at the moment and address animal species, dose, and length without including details such as number of animals to be used in each study. From here, the BGTC intends to integrate pharmacology and toxicology plans into an overall broader strategy

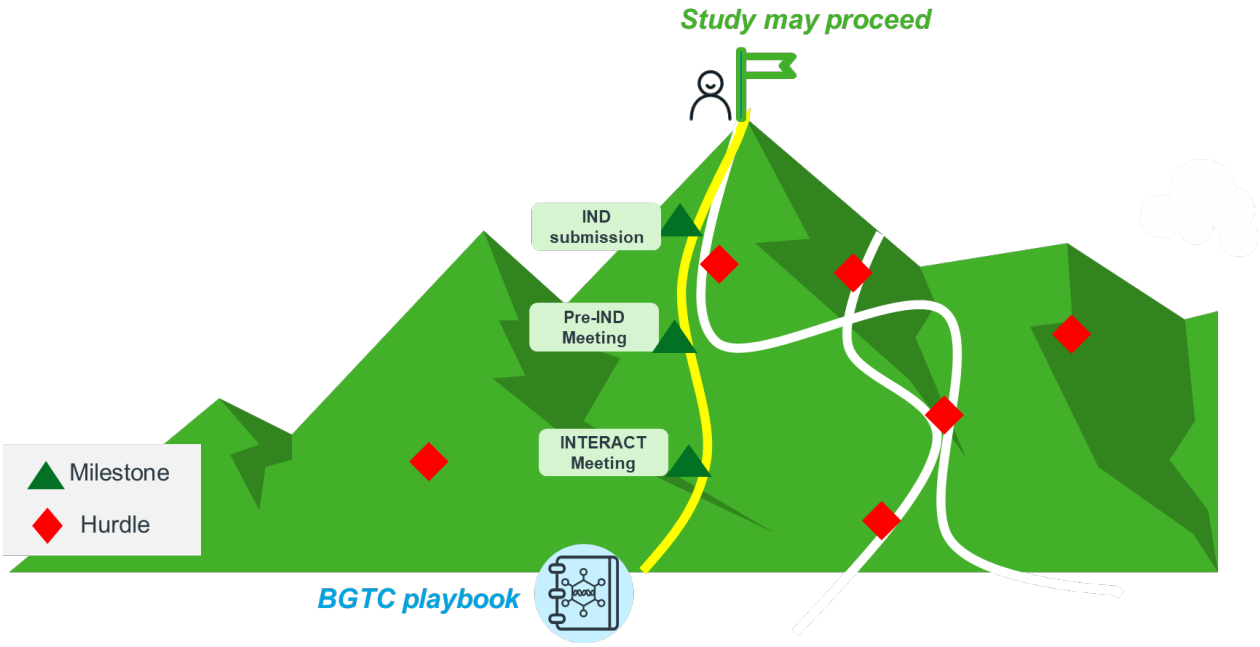
to define a standard clinical dosing strategy that can be applied for AAV gene therapies. It is important to note that in addition to the parameters listed above, there are other product development considerations a sponsor will encounter that are equally important, such as the delivery device, age and disease severity of the target population, prospect of direct benefit for pediatric target populations, etc.

1.5. How To Use This Playbook

The BGTC Regulatory Playbook is designed with usability in mind to ensure it is easy to navigate regardless of your level of expertise. It is organized into sections that cover specific aspects of AAV gene therapy development to take you from your first preclinical studies all the way through to IND submission. The BGTC's goal is to provide you with a workflow and guidance for your regulatory submissions to ensure seamless execution and increase your candidate's likelihood of IND acceptance.

Now, consider the regulatory process as a "mountain," and this playbook as your most trusted "navigator" to get you to the summit – "Study may proceed". See **Figure 4** below.

Figure 4: Role of the BGTC Regulatory Playbook



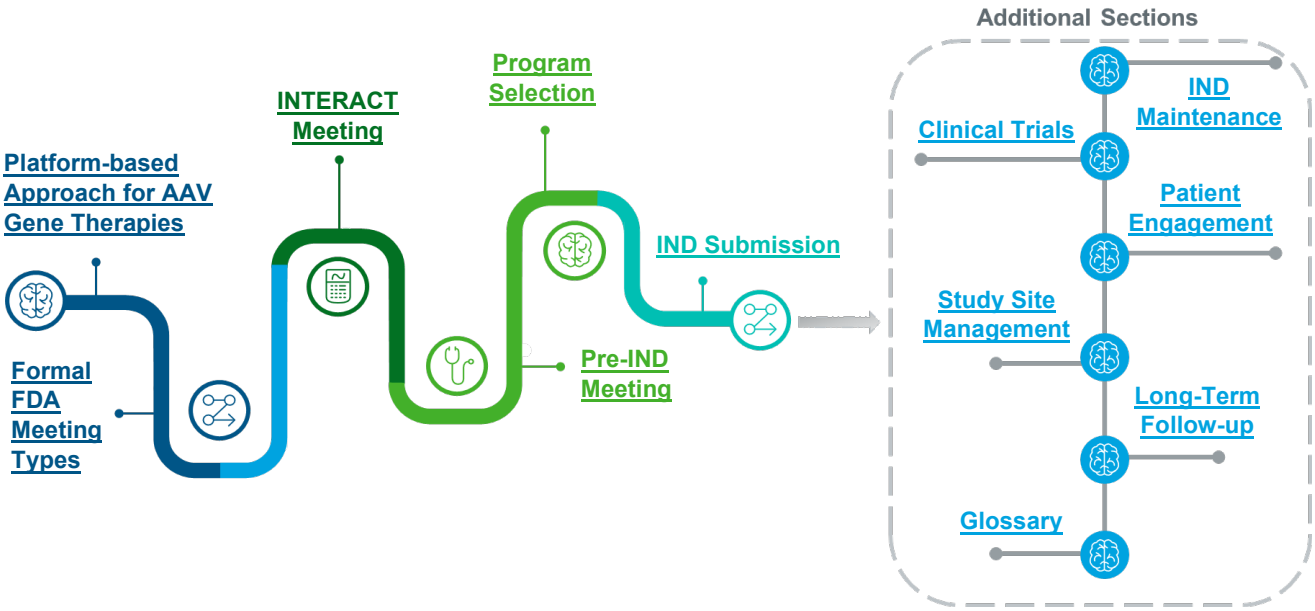
This playbook provides detailed guidance on the FDA's regulatory requirements, best practices, and key considerations for successful AAV gene therapy development. You will find tips for preparing and conducting various FDA meetings, as these are key milestones in your development path.

We have also included considerations to inform your clinical trial design, rare disease patient engagement, as well as study site management, IND maintenance and long-term follow-up. These aspects are particularly challenging when pursuing ultra-rare diseases and so we have included some industry considerations to support your planning of these components.

For easier filing, we have created a portfolio of templates focused on AAV gene therapies which are annotated with industry expertise and SME guidance from members across the BGTC. These templates will be plug-and-play, and you will be able to utilize them for the different sections as we will highlight throughout this playbook. Don't worry, we will tell you when to use which template, and link these templates within the playbook as well.

Now, we'll get into a high-level overview of what you can expect in each section of this playbook. Click on the chapters in **Figure 5** below to skip to the specific content and choose your own adventure.

Figure 5: Playbook drilldown



Overall, this playbook is designed to be an essential tool for the AAV gene therapy community in streamlining the navigation of the US regulatory landscape. Please note, while the playbook is focused on a successful submission to the US FDA, sponsors should also communicate with regulatory agencies besides the US, where they consider conducting their clinical trial(s). We have designed the playbook to be flexible and adaptable to the specific needs of your asset. By following the guidance and best practices outlined in the playbook, you can address the safety, efficacy, and regulatory compliance of your gene therapies in development, while also doing your part to help advance the field of bespoke gene therapy.

References

1. *AMP® Bespoke Gene Therapy Consortium (BGTC)*. FNIH. (2023, May 31). https://fnih.org/our-programs/AMP/BGTC

Chapter 2: Platform-based Approach for AAV Gene Therapies

What is a "platform-based" approach?

There is no standard definition for "platform-based" technology as this is something that has yet to be officially defined by the FDA in the context of gene therapies. There have however, been developments on a conceptual definition for this phrase in the US:

a) Janet Woodcock, the former FDA Principal Deputy Commissioner, has alluded to the concept previously: "may be large number of related drugs using a 'platform technology,' i.e., small modifications needed to address different mutations within the same gene. [1, 2]

b) The FDA has described continuous manufacturing as a "platform" – in the FDA guidance on "Continuous Manufacturing of Drug Substances and Drug Products", a "platform approach" was described in the context of process validation, considering elements such as prior facility experience in implementing a similar process and control system, availability of product-specific data arising from late-stage product development, etc. [3]

On the other hand, the EMA describes "platform technology" as a "technology that has already been approved for another medicinal product and has therefore been (at least partly) characterized previously." [3]

Within the context of the BGTC Regulatory Playbook, at this stage we describe a "platform-based approach" as an overall concept rather than a specific definition when it comes to AAV gene therapies with the mission of progressing use cases as part of the BGTC work.

The idea of a platform-based approach is centered on streamlining pre-clinical product development and navigation of the regulatory requirements by:

1) leveraging **existing data and information or prior** knowledge based on similar elements with approved/developed AAV gene therapy products
2) developing **minimum requirements** based on this platform-based approach to increase efficiency of development and regulatory submissions

These concepts are pursued while still prioritizing meeting the threshold for safety.

A platform-based approach uses the principle that various aspects of gene therapies can be sufficiently similar to the ones used in prior approved therapies, especially specific components which require product-specific testing. Thus, leveraging prior knowledge, learnings, and data about specific components and addressing key questions can pave the way for you to adopt the platform-based approach effectively.

Some **key questions** to consider in your rationale for leveraging the platform approach:

- ☐ **What are the similar components/aspects between the approved product and your therapy?**

If certain components are sufficiently similar, specific evidence requirements related to those components may be waived or referenced. If there are differences, consider the downstream effects expected and how that might affect your approach.

- ☐ **What sources of data can you leverage for these components? What is the level or nature of prior information that exists?**

The quality, completeness, rigor, etc. of available data directly determines what you may be able to leverage. For example, the BGTC approach focuses on referencing prior data that has been at least submitted in an approved IND. It is also important to note that data sources may differ on a case-by-case basis – for example, a prior data source that you may refer to for one therapy may not work for another.

Why pursue a platform-based approach for rare disease?

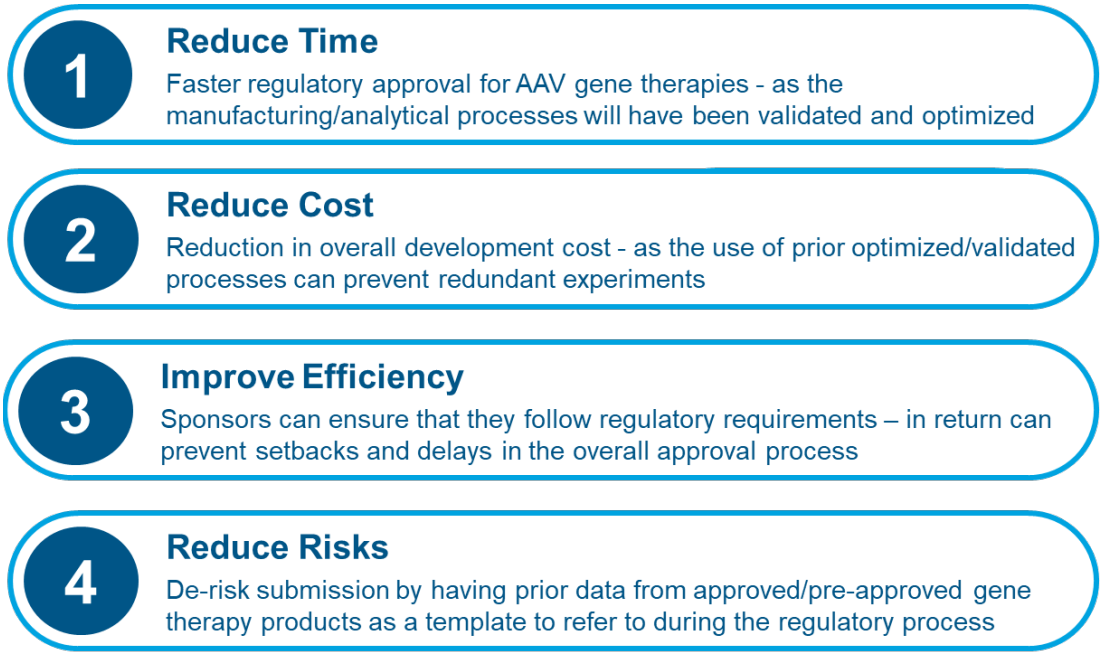
There are over 10,000 different rare diseases impacting the human population, of which around 85% are thought to be monogenic disorders.

> Monogenic disorders are ones caused by mutations in a single gene and are responsible for about 200 newly identified diseases each year

Even though recent advances in the medical and biotech field have allowed for approval of novel therapies, only 5% of the rare diseases have a specific regulatory approved treatment. With the current pace of only 3-5 rare diseases getting their first specific treatment approved each year, ~2000 years will be needed until specific treatments have been developed and approved for all rare monogenetic disorders. Additionally, the traditional one-disease-at-a-time approach s too inefficient to address the needs of the large number of patients with rare diseases, and too costly with limited return on investment for commercial interest [4].

To address the operations problems that currently lie with gene therapies, various departments of the NIH collaborated to initiate the platform vector gene therapy (PaVe-GT) pilot project in 2019. PaVe-GT aims to increase the efficiency of clinical trial startup by using the same gene delivery system and common manufacturing methods for multiple rare disease gene therapies. PaVe-GT will identify redundancies and leverage data from one product to the other, with the overall aim to increase the efficiency in preclinical testing and clinical trial start up from one disease to the next. The experience and learnings from the project, in the form of templates, regulatory packages and program results, are being made publicly available on the PaVe-GT website: https://pave-gt.ncats.nih.gov/. [4]

Through the use of a platform approach, sponsors may not only see reduction in time, cost, and risks but also an improvement in efficiency and submission process, as shown below.



Thus, to effect meaningful change in the current trajectory of rare disease therapeutic development, a platform-based approach which focuses on biological and modality-relevant commonalities across different diseases, rather than a one-disease-at-a-time approach, is needed.

How does the platform-based approach apply to AAV gene therapies?

The AAV as a vector is fundamentally a platform modality – a programmable multipurpose vehicle that delivers a variety of different therapeutic payloads to disease-specific target cells.

> AAV vectors are “intrinsically disease-agnostic because their applicability for a particular disease is governed more by their biodistribution as a function of capsid serotype, route of administration and dose, the genetic mechanism to address (for instance, loss of function versus gain of function), and the expression cassette used, rather than by pathophysiological specifics of the disease under consideration.” [4]

We can leverage the fact that AAV modularity of functions facilitates the swapping of transgenes, selection of regulatory elements (enhancer, promoter, etc.), and other alterations of the capsid, lending itself as a modality that is very amenable to the platform-based approach. This can lead to optimized AAV vector production protocols, improvements in AAV target gene expression, and other standardized and harmonized minimum sets of requirements (please refer to Chapter 1: Introduction to the BGTC Regulatory Playbook for more information on minimum requirements).

Where the BGTC approach comes in

The BGTC Regulatory Playbook expands on PaVe-GT's valuable pilot work initiated in 2019 and its dissemination goals, thus bringing the platform-based approach to life. Future versions of this playbook will identify recommended minimum requirements for pre-clinical and CMC sections and streamlining considerations for various sections of the product development process.

The aim is to utilize the learnings gained with each asset, translate the information into a continually enhanced and validated set of minimum requirements, and apply this knowledge into future versions of the BGTC Regulatory Playbook and overall program – with opportunities for increased specificity based on serotypes, routes of administration, affected organ/tissue, etc.

The evolution of the platform-based approach through the BGTC Regulatory Playbook highlights further opportunities for FDA interaction and a subsequent positive feedback loop for the success of future AAV gene therapies.

References

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2. Future of Drug Development, Janet Woodcock – https://www.fda.gov/media/104048/download Future of Drug Development, Janet Woodcock – https://www.fda.gov/media/104048/download
3. Continuous Manufacturing of Drug Substances and Drug Products – https://www.fda.gov/media/165775/download Continuous Manufacturing of Drug Substances and Drug Products – https://www.fda.gov/media/165775/download
4. The Platform Vector Gene Therapies Project: Increasing the Efficiency of Adeno-Associated Virus Gene Therapy Clinical Trial Startup. Brooks et al., (2020) – https://www.liebertpub.com/doi/10.1089/hum.2020.259 (2020) – https://www.liebertpub.com/doi/10.1089/hum.2020.259

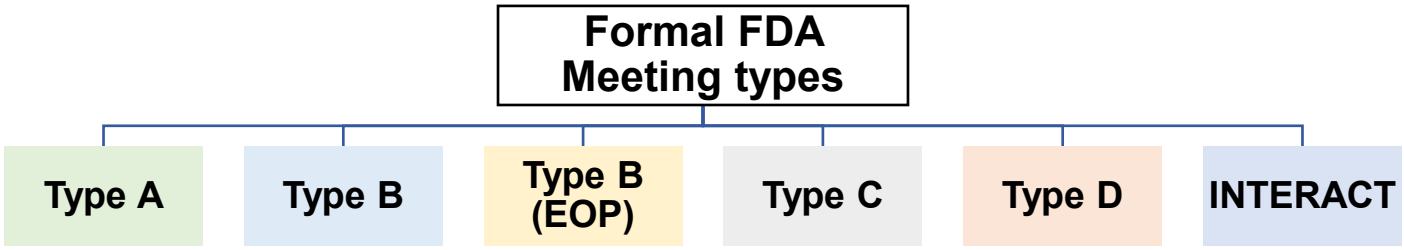
Chapter 3: Formal FDA Meeting Types

The FDA holds various meetings to facilitate collaboration among sponsors, health care professionals, and other key stakeholders involved in the drug development and regulatory processes [2]. With a shared public health goal of providing safe, effective, and high-quality drugs to the public as early as possible, engaging in meetings with the FDA at critical junctures in the drug development process expedites the evaluation process and minimizes time and resources spent. These formal FDA meetings serve as opportunities to address questions and issues, to receive valuable scientific and regulatory advice, and ultimately to enhance the efficiency and effectiveness of the development program [1,2].

While the pertinent meetings for early investigations will be focused on FDA feedback from pre-IND Meeting (Type B Meeting in the list below) and potentially INTERACT, the playbook provides for context, the types of meetings that are available to the sponsor as a program advances throughout development.

There are six types of formal meetings under the prescription drug user fee act (PDUFA) that occur between the FDA and the requesters, as shown in the **Figure 1** below.

Figure 1: The six types of formal FDA meetings: Type A, Type B, Type B (End of Phase (EOP)), Type C, Type D, and INTERACT



Now that you know what the different formal FDA meetings are, let's proceed and briefly discuss each of the different meeting types [1-3].

Type A

Before submitting a **Type A** meeting request, consider contacting the review division or office to discuss the appropriateness

Type A meetings are held for currently stalled product development programs that are either looking to proceed or address an important safety issue. Some examples of Type A meeting types, as included in the FDA guidance, are:

- Dispute resolution meetings as described in the Code of Federal Regulations (CFR) (21 CFR 10.74, 312.48, and 314.103) and in the guidance for industry and review staff Formal Dispute Resolution [4]: Sponsor Appeals
- Meetings to discuss clinical holds where:
    - The requester can seek input on how to address the hold
      Or
    - The FDA and requester have agreed that the development is stalled, and a new path forward is needed
- Special protocol assessment meetings after receipt of FDA Nonagreement Special Protocol Assessment letter in response to the protocols submitted under the special protocol assessment procedures
- Post-action meetings requested within 3 months by the sponsor after an FDA regulatory action other than an approval
- Meetings requested within 30 days of FDA issuance of a refuse-to-file letter. In order to file an application over protest, applicants must avail themselves for this meeting (21 CFR 88 314.101(a)(3))

Type B

Examples of Type B meetings as included in the FDA guidance, are:

- **Pre-investigational new drug application (Pre-IND) meetings**
- Pre-emergency use authorization meetings
- Pre-new drug application (pre-NDA) / Pre-biologics license application (pre-BLA) meetings
- Post-action meetings requested by the sponsor 3 months or more after an FDA regulatory action other than an approval
- Meetings regarding risk evaluation and mitigation strategies (REMS) or post-marketing requirements that occur outside the context of the review of a marketing application
- Meetings held to discuss the overall development program for products granted break through designation status. A follow-up meeting can be considered either Type A or B, depending on which criteria it meets

Type B (EOP)

Examples of Type B end of phase (EOP) meetings, as included in the FDA guidance, are:

- Certain End-of-Phase 1 meetings for products in consideration for marketing approval under 21 CFR part 312 subpart E, or 21 CFR part 314 subpart H, or similar products)
- End-of-phase 2 / Pre-phase 3 meetings

Type C

Type C meetings are any other meeting than a Type A, Type B, Type B (EOP), Type D, or INTERACT meeting regarding the development and review of a product. An example of a Type C meeting, as included in the FDA guidance, is:

- A meeting to facilitate early consultations on novel use of biomarkers as surrogate endpoints as the primary basis for product approval in the proposed context of use.

Type D

Type D meetings are focused on a narrow set of issues (should be limited to no more than two focused topics) and should not require input from more than 3 disciplines or Divisions. Some examples of a Type D meeting are:

- A follow-up question that raises a new issue after a formal meeting (i.e., more than just a clarifying question about an FDA response from a prior meeting)
- A narrow issue on which the sponsor is seeking Agency input with only a few associated questions
- A general question about an innovative development approach that does not require extensive, detailed advice [3]

INTERACT

INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) [3]

INTERACT meetings are for novel questions and unique challenges in early development (i.e., prior to filing of an IND) intended to facilitate IND-enabling efforts where the sponsor is facing a novel, challenging issue that might otherwise delay progress of the product towards entry into the clinic in the absence of this early FDA input. The sponsor must have selected a specific investigational product or a product-derivation strategy to evaluate in a clinical study before requesting an INTERACT meeting. These meetings are intended to provide FDA input on issues that a sponsor needs to address early in a development program prior to a Pre-IND meeting. Some examples of INTERACT meeting questions include:

- Novel questions for all CBER products (i.e., questions where there is no existing guidance or other information in writing the company could reference from FDA)
- Choice of appropriate pre-clinical models or necessary toxicology studies for novel drug platforms or drug candidates
- CMC issues or testing strategies aimed to demonstrate product safety, adequate to support first-in-human study
- Overall advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of an investigational product in a first-in-human clinical trial
- General recommendations regarding a future first-in-human trial in a target clinical population where the population is novel and there is no prior precedent or guidance

- Recommendations on approach for further development of an early-stage product with limited CMC, pharmacology/toxicology, and/or clinical data that were collected outside of a US IND

For more information, please refer to Chapter 4: INTERACT Meeting.

What are the different formal FDA meeting formats?

There are three meeting formats for the formal FDA meeting types. They include:

1. Face-to Face Interactions
2. Teleconference Meetings
3. Written Response Only

Note: The FDA now considers "face-to-face" meetings to include "in-person meetings and virtual meetings on IT platforms that allow for both audio and visual communication." Therefore, for the INTERACT and Pre-IND chapters in this playbook, we focus on teleconference and written response options. Please refer to the latest Update on In-Person Face-to-Face Formal Meetings with the FDA for more information.

How to request a formal FDA meeting?

When requesting a meeting, a written request must be submitted to the FDA through the appropriate pathway (electronic or paper submission) and to the respective review division or office. To get more information around eCTD requirements and exceptions, please refer to the FDA guidance: Guidance for Industry: Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications.

It is important to ensure that the meeting request includes adequate information for the FDA to assess the objective of the meeting and identify the appropriate members needed to discuss the proposed agenda items. Key items that the meeting request must include are:

- The proposed meeting format
- The date you anticipate sending the meeting background package to the FDA by
- Brief statement showcasing the purpose of the meeting

Pro tip: In the statement you can include a summary of completed or upcoming studies and/or data that you intend to discuss at the meeting. Additionally, it is recommended that you include a small table highlighting the major results, enough to facilitate the discussion while not including details of the study design.

- List of specific objectives and areas of input, and outcomes expected from the meeting
- Proposed agenda with the estimated time needed for each discussion item
- List of planned attendees from the sponsors' side – including their names and titles

- List of requested FDA attendees and/or discipline representatives

Pro tip: Requesting for the FDA staff who are not essential to the review process can affect the ability to hold the meeting within the proposed time frame of the meeting type. Thus, while requesting the attendance of a nonessential FDA staff, you should provide justification for their attendance and state whether a later meeting will be acceptable to accommodate the attendees.

Some of the other things that a meeting request can include are:

- Application number
- Product name
- Chemical name, established name, and/or structure
- Proposed regulatory pathway
- Proposed indications
- Dosage form, route of administration (ROA)
- Pediatric study plans or human factors engineering plans (if any)
- List of proposed questions, grouped by the FDA discipline, and a brief explanation for the purpose of each question.

Overall, it is important for you to define the specific areas of input needed from the FDA. In case there is a change in the planned attendees between the request and the meeting, please provide the FDA with an updated list of attendees (names, titles, and affiliations).

How to prepare the meeting package?

Sponsors need to submit a meeting package for each meeting type. Please refer to **Table 1** for a summary of meeting package timelines for each of the meeting types. The purpose of the meeting package is to provide the FDA with a summary of relevant product information that may be needed in response to the issues raised. The contents of the meeting package are intended to be aligned with the meeting objectives and organized. It is recommended that the package is a numbered document with a table of contents, appropriate indices, appendices, and cross references. Some of the information that it should include are:

- Application number
- Product name
- Chemical name, established name, and/or structure
- Proposed regulatory pathway
- Proposed indications
- Dosage form, route of administration (ROA)
- Pediatric study plans or human factors engineering plans (if any)
- List of attendees
- Background section including a brief history of the development program and its current status
- List of proposed questions, grouped by the FDA discipline, and a brief explanation for each

For a list of additional things you can include, please refer to the FDA guidance: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (guidance for industry).

How the FDA assesses and responds to meeting requests

Even though you as a sponsor, can request any meeting format for the formal FDA meeting types, ultimately the FDA assesses each meeting request and determines whether the request should be granted and its appropriate format. You can find a summary of the response and scheduling time frame for each meeting in **Table 1**.

If a meeting is **granted**:

The FDA will notify the sponsor in writing regarding the meeting type and format. For (written responses only) WRO requests, the FDA's letter will include the date that they intend to send their responses by. For face-to-face and other meeting formats, the FDA will schedule the meeting on the next available date within the scheduling time frame for each meeting type. If the meeting date is past the specified time frame for each meeting type, it is important to ensure that the date is within 14 calendar days of the requested day.

If a meeting is **denied**:

The FDA will notify the sponsor and include a letter explaining the reason for denial. It is important to note that the denials will be based on a substantive reason and not due to absence of a minor element in the request or package. These are examples of why a meeting request can be denied:

- Premature for the stage of product development
- Meeting package does not provide adequate information for a discussion

A follow up request to schedule a meeting will be considered a new request.

In case of **rescheduling** or **cancelling** a meeting:

At times, circumstances arise that may lead to rescheduling or cancelling of a formal FDA meeting. In the case that the meeting needs to be rescheduled, appropriate steps must be taken to ensure the meeting is rescheduled as soon as possible after the original date. Some examples of when a meeting can be rescheduled, as per the FDA guidance, include:

- The FDA review team determines that the meeting package submitted is inadequate or needs additional information or needs further discussion with the sponsor and foresees the sponsor providing the additional information needed within the submission time frame
- The sponsor provided insufficient time to the FDA review committee to look through the materials sent, despite submission within the specified time frames and appropriateness of context
- If the sponsor sends additional questions to the FDA intended for discussion at the meeting, after the submission of the meeting package, which requires additional review time

- The essential attendees are not available for the scheduled time and date

However, if the meeting is cancelled, the FDA will consider the follow up request to schedule a meeting as a new request. As per the FDA guidance, here are some examples of when a meeting can be cancelled:

- If a meeting package is not received by the FDA within the specified time frame of the meeting type or is inadequate
- If the sponsor determines that the preliminary FDA responses to their questions from the meeting package are sufficient and additional discussion is not needed

Thus, it's important that both you, the sponsor, and the FDA take reasonable steps to avoid rescheduling or cancelling of a meeting, unless necessary [1].

Preliminary responses are communications that occur between the FDA and the sponsor prior to the requested meeting. They should not be considered as final until agreed upon by both the sponsor and the FDA. Usually, the FDA holds an internal meeting to review the meeting package. Following this, the FDA sends the preliminary responses within 5 calendar days before the meeting type (for Type B (EOP) and Type C). After this, the sponsor will have 3 days to decide whether a meeting is still needed. If the meeting is not needed, the sponsor will reach out to the FDA project manager for a request of cancellation. Following this, the FDA will consider whether it agrees with the cancellation or not [1].

It is highly encouraged to continue to hold a meeting with the FDA, if granted, to ensure that you and the Agency are completely aligned on all topics/recommendations.

For more information on how to respond to the FDA regarding the meeting request, please refer to the FDA guidance: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (guidance for industry).

Steps to take while conducting a meeting

The formal FDA meetings will be chaired by an FDA staff member. It is important to note that no audio or visual recordings of the discussions at the meetings are allowed. Presentations are not needed as the topics of discussion have already been shared in the meeting package. However, if you plan on making a presentation, please discuss it with the FDA project manager in advance. Additionally, it is recommended that at the end of the meeting, either a representative from the FDA or from the sponsors summarize the key discussion points, agreements, and action items, to ensure mutual understanding.

You can find more detailed information and guidance (agendas, outlines, dos and don'ts, etc.) on conducting the formal FDA meetings in the respective chapters of this playbook.

Meeting Minutes

FDA meeting minutes are official records of the meetings documenting the meeting outcomes, agreements, disagreements, and action items. The FDA will issue the official finalized minutes to the sponsor within 30 days, after the meeting has been conducted. For more information of what will be included within the FDA meeting minutes, please refer to the FDA guidance: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (guidance for industry).

Even though the minutes issued by the FDA are generally considered final, the sponsor has the option of sending their meeting minutes to the FDA prior to the release of the final minutes. This additional step can provide a nuanced perspective on the sponsor's position. However, please note that the minutes should be a report of the topic(s) discussed and not include any new information.

Summary of the different meeting management procedural goals

The table below provides a comprehensive timeline for each of the meeting types.

Table 1. Summary of timelines for FDA meeting types [1,3]

Meeting Type	FDA Response to sponsor (days)	FDA Receipt of Meeting Package	FDA Preliminary Reponses due to sponsor (if applicable)	Sponsor response to the FDA's preliminary responses (if applicable)	FDA Scheduled Meeting date (days from receipt of request)	FDA Meeting Minutes to sponsor (if applicable)
A	14	With meeting request	Latest - 2 days before the meeting		Within 30 days	30 days after meeting. With WRO, the WRO will serve as meeting minutes from FDA.
B	21	Latest - 30 days before meeting	Latest - 2 days before the meeting		Within 60 days	
B (EOP*)	14	Latest - 50 days before meeting	Latest - 5 days before the meeting	Latest - 3 days after receiving preliminary responses	Within 70 days	

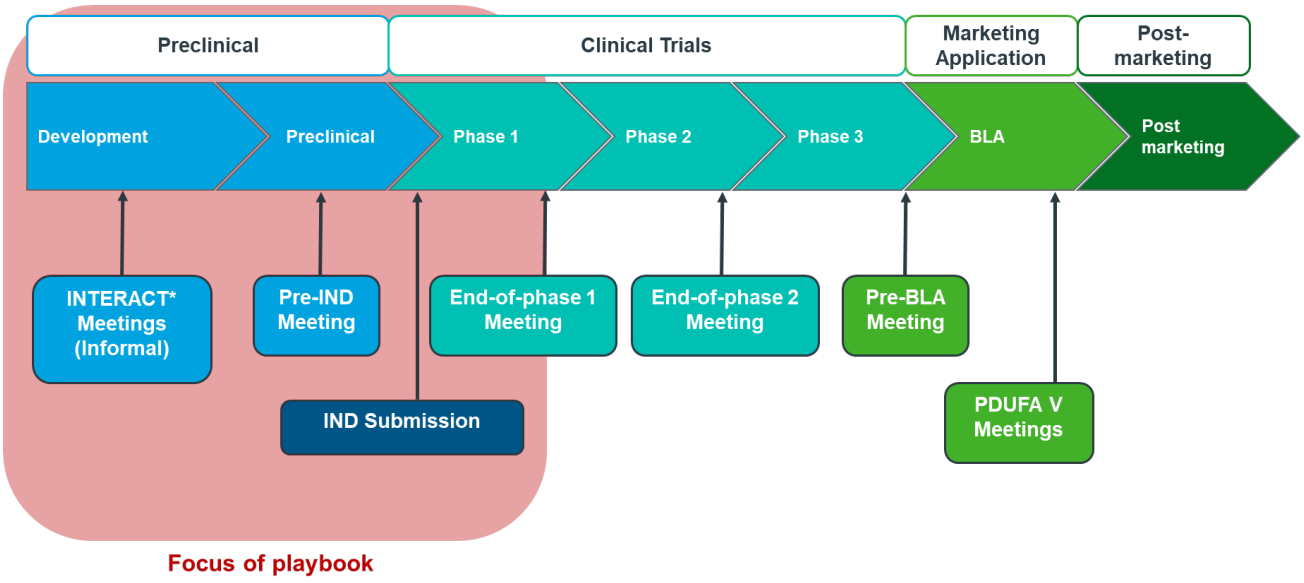
C	21	Latest - 47 days before meeting	Latest - 5 days before the meeting	Latest - 3 days after receiving preliminary responses		
D	14	With meeting request	No later than 5 days before meeting	Latest - 3 days after receiving preliminary responses	Within 50 days	
INTERACT	21	With meeting request	No later than 5 days before meeting	Latest - 3 days after receiving preliminary responses	Within 75 days	Preliminary responses will be annotated and resent within 30 calendar days if advice provided changes as a result of the meeting. With WRO, the WRO will serve as meeting minutes from FDA.

*EOP = End of Phase [1,3]

What does this playbook focus on?

For this playbook, we are focusing on the INTERACT, Pre-IND, and IND submissions and meeting types.

Figure 2: Schematic representing the focus of the playbook



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1. Research, C. f. (2023, September). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry. Retrieved from U.S. Food and Drug Administration: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry
2. Roule, J. (n.d.). Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. (2023, September). Retrieved from https://www.fda.gov/media/172311/download
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Chapter 4: INTERACT Meeting

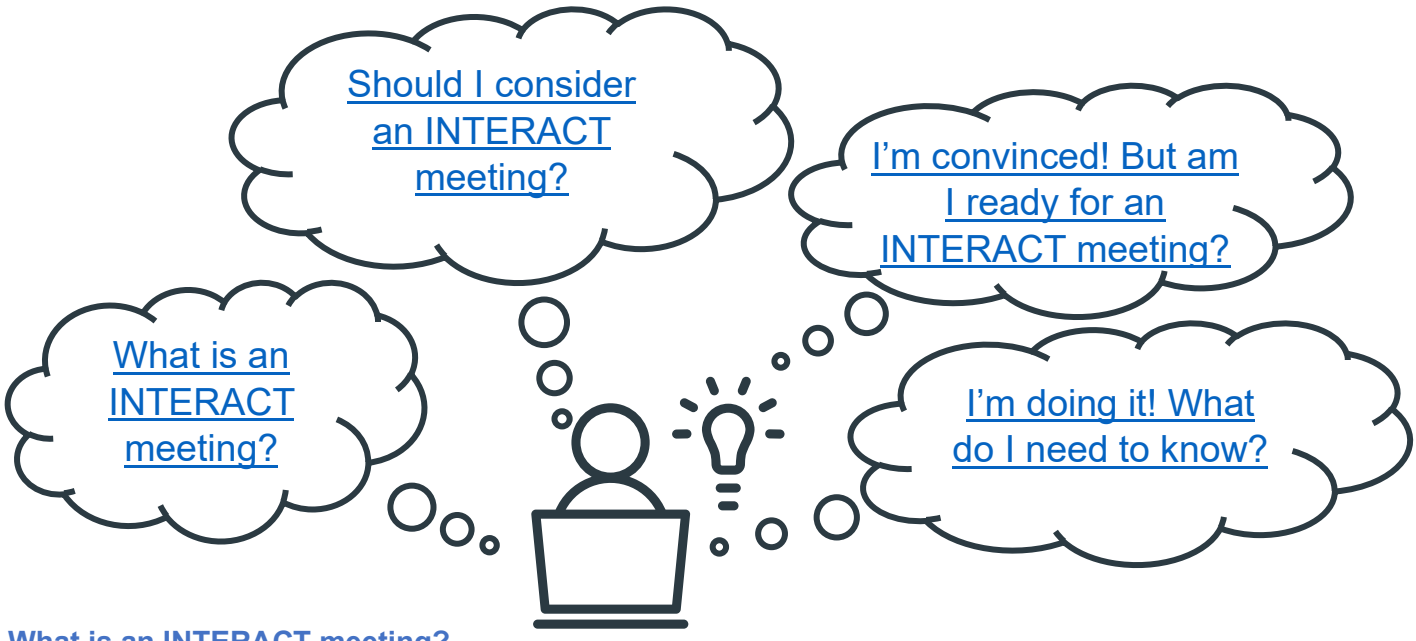
4.1. Readiness Assessment

Welcome to the chapter on the FDA INTERACT meeting for AAV gene therapies, a potentially beneficial step in the BGTC Regulatory Playbook for companies developing these innovative treatments. INTERACT stands for INitial Targeted Engagement for Regulatory Advice on CBER producTs, and it is one of two early engagement meetings (besides the Pre-IND) that you can have with the FDA Center for Biologics Evaluation and Research (CBER) prior to submitting your IND. [1]

The INTERACT meeting provides a unique opportunity for sponsors like yourself to engage with the FDA in a pre-submission setting, to discuss key aspects of your development plan and receive early and non-binding feedback on your program. This early feedback can be invaluable in guiding you towards a successful regulatory submission using the BGTC approach and can help to avoid potential delays in the IND process.

In this chapter, we will provide an overview of the INTERACT meeting, its role in the regulatory process for AAV gene therapies, and how it differs from the Pre-IND meeting. We will also discuss the benefits of participating in this meeting and provide guidance on how to prepare for a successful interaction with the FDA.

Before embarking on this journey, it will be helpful for you to do a readiness assessment. This assessment is designed to ensure you are at an appropriate stage to request a meeting, which can reduce the chances of rejection of the meeting and maximize success.



What is an INTERACT meeting?

INTERACT meetings are formal meetings held between sponsors of innovative investigational biological products and CBER to obtain **early advice** from the FDA on chemistry, manufacturing, and controls (CMC), pharmacology/toxicology, and/or clinical aspects of their AAV gene therapy development program. [1]

How is this different from a Pre-IND meeting?

An INTERACT meeting is not intended to take the place of Pre-IND meeting nor is it a prerequisite to requesting a Pre-IND meeting and is considered when early nonbinding feedback would be important to shape investigational plans. Like Pre-IND meetings, they are not a required FDA meeting.

The main difference for the INTERACT meeting is the phase of development and therefore, the types of questions you will be asking the FDA. The INTERACT meeting allows you to obtain preliminary feedback on your investigational product earlier in development than the Pre-IND stage, thus the background content in the request and package effects a much earlier stage of development.

Another difference is that you need to submit your meeting package together with your INTERACT meeting request letter (whereas you can submit together or separately for Pre-IND).

Should I consider an INTERACT meeting?

CBER recognizes that the development of AAV gene therapies in rare disease can introduce unique challenges related to unknown safety profiles, complex manufacturing processes, new technologies and equipment, incorporation of innovative devices, and the use of cutting-edge testing methodologies that can benefit from early FDA input.

An INTERACT meeting can provide great value for you in:

- Assisting your early product characterization and design of pre-clinical proof-of-concept studies
- Identifying critical issues around proof-of-concept studies, manufacturing-related questions, or other deficiencies you can address early in development, before approaching the Pre-IND

This feedback is a step toward o de-risk and accelerate your drug development process. [1]

Am I ready for an INTERACT meeting?

Overall, you can consider an INTERACT meeting if you have begun the development process for your asset but not yet reached the stage of Pre-IND meeting readiness.

You should have proof-of-concept data from *in vitro* and *in vivo* pre-clinical studies to demonstrate preliminary evidence of efficacy and safety for discussion at the INTERACT meeting – it would be premature to request a meeting if you do not – but you should not be as far along as having conducted your pivotal pre-clinical studies (e.g., definitive toxicology studies) – in fact, this would be considered too advanced for INTERACT. [2]

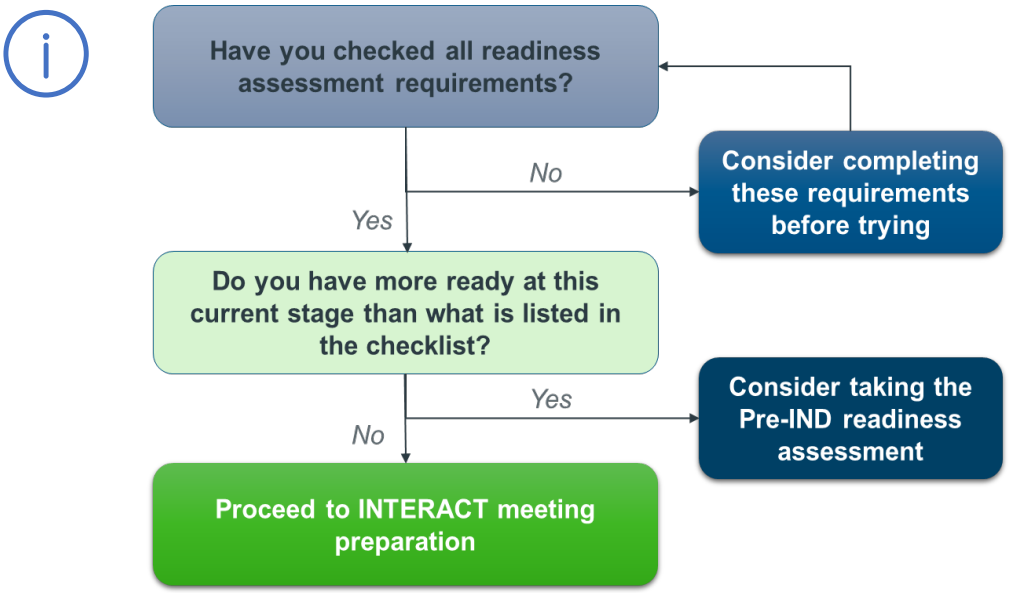
Please see below for a checklist to guide you in assessing if you are at the appropriate timing for an INTERACT meeting.

Pro tip: Note that these are **best practice recommendations** for when an INTERACT meeting would be most useful to a sponsor. The FDA denies about **two-thirds of all INTERACT meeting requests**, with the most common reason being that the meeting request is submitted too early or too late in development. In order to increase the likelihood of securing a meeting, do your best to check off as many items on this list to ensure you are at the **optimal stage of readiness**!

Table 1: Readiness Assessment for INTERACT meeting: Check to confirm completion of these tasks for optimal stage of readiness

	Readiness Assessment
Pre-clinical	☐ A defined investigational product and formulation, or product-derivation strategy ☐ A defined indication ☐ Proof of concept data (*in vitro* and/or *in vivo*) ☐ An identified animal model for pharmacology studies (if applicable)
CMC	☐ A defined "bench top" manufacturing process, working towards defined GMP process ☐ Ideas for/preliminary purity and potency testing
Clinical	☐ Preliminary dose range working towards a definitive dose range
Patient Engagement	☐ Preliminary engagement with patients and/or patient advocacy groups ☐ Understanding of patient journey, primary symptoms/endpoints, and major unmet needs

Prior to proceeding, let us do one final check to ensure you are ready to initiate the INTERACT meeting preparation.



Things to be aware of before continuing

Not all product development programs qualify for an INTERACT meeting – in fact, as mentioned before, a majority of these meetings are denied mostly due to stage of development. You should be able to avoid this using our checklist above.

The stage of your product development program may be **premature** if: [1]

- You do specify the investigational clinical product
- You do not provide pre-clinical proof-of-concept or other pilot data
- You have not conducted any pre-clinical studies proof-of-concept studies with your asset

On the other hand, a request may be **too advanced** for an INTERACT meeting and more appropriate for a Pre-IND meeting if: [1]

- You have indeed completed proof-of-concept and some safety studies
- You are at the point of design and conduct of definitive toxicology studies
- You have defined the manufacturing process to be used for the clinical studies and developed assays and preliminary lot release criteria
- The pre-clinical testing and manufacturing process for your product uses the same or a similar platform as for other product(s) you have previously submitted to the Office of Therapeutic Products (OTP)
- Clinical data exists from previous studies for the same product and clinical indication

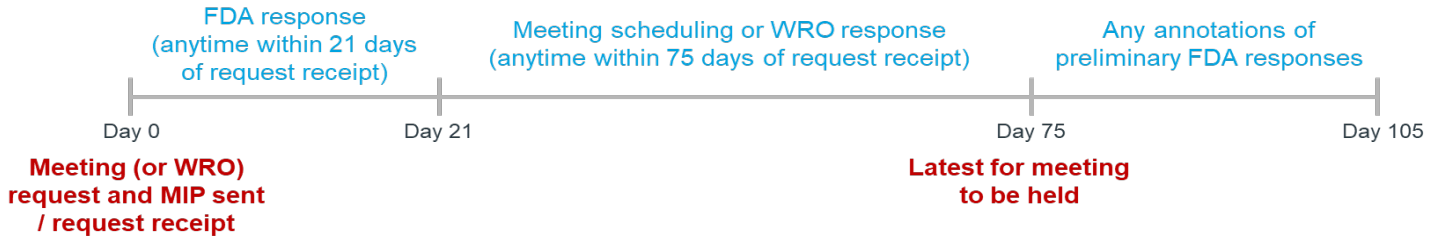
Some other reasons for INTERACT meeting denials include: [1]

- A meeting was previously held for the same asset, and no substantially new information has been added
- Missing meeting package in the meeting request
- Meeting package is deficient or has too many gaps, limiting the ability for constructive feedback during the meeting
- The feedback requested is outside the scope of the INTERACT meeting. For instance, if questions included in the package are solely focused on jurisdiction or regulatory pathway. OTP does not use INTERACT meetings to answer questions about:
    - Whether a product is appropriately regulated as a drug, device, and/or biological product or combination product, or what Center or Office should be the lead in review. For these questions, contact the OTP Policy Group at OTP_ADP@fda.hhs.gov or submit a Request for Designation (RFD) (see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd).
    - Whether it is appropriately regulated solely under Section 361 of the PHS Act and regulations in 21 CFR Part 1271. For these questions, visit the Tissue Reference Group website at https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group or contact the Tissue Reference Group in OTP at TissueReferenceGroup@fda.hhs.gov

Now that you know the most common causes for concern, you can proceed to your INTERACT meeting planning with the necessary information.

4.2. Meeting Request

Figure 1: Meeting Request and Written Response Only (WRO) Timeline



As of the date of this playbook, INTERACT Meetings are requested via email with the request and meeting information package (MIP) submitted to: cberdcc_emailsub@fda.hhs.gov, with OTPRPMS@fda.hhs.gov in cc line for Regulatory Management Staff awareness. [1]

The OTP will send an acknowledgment email following receipt of request, followed by a a decision to grant or deny the meeting through email communication. If you are granted a meeting, it will generally be scheduled within approximately 21 calendar days of request receipt, or reasons for denial will be sent also by Day 21. The meeting will be held via teleconference within approximately 75 calendar days of the request receipt and will usually be 1 hour in duration (see **Figure 1** for timeline). [2]

Now that you know what to expect with the meeting request process, let's get into the guidelines for the meeting package which you need to prepare **before** requesting an INTERACT meeting.

4.3. Meeting Information Package Preparation

For the INTERACT meeting, you must include your MIP together with your request. This package must be no more than 50 pages (average length 20-30 pages) and much less substantial than what is expected for the Pre-IND MIP. Although the content of an INTERACT briefing package is fairly limited relatively speaking, you must include sufficiently detailed information for the FDA to be able to provide substantive feedback on your questions.

Please refer to the guidance below on how to prepare your package using the INTERACT Meeting Request/Meeting Information Package template provided.

So, what should you include in your MIP?

You should generally include information on Chemistry, Manufacturing, and Controls (CMC), pharmacology/toxicology, clinical information, and any other specific information that will enable the FDA to respond to your questions.

It is important to include detailed questions with the briefing document, which will help the FDA focus on addressing your specific issues. As specified by the Readiness Assessment above, these questions will be high-level and reflect your early stage of development. According to the

FDA guidance, the questions and topics that fall within the scope of the INTERACT meeting include: [2]

- Novel questions for all CBER products in general (i.e., questions where there is no existing guidance or other information in writing you can easily reference from the FDA)
- Choice of appropriate pre-clinical models or necessary toxicology studies
- CMC issues or testing strategies aimed at demonstrating product safety
- Overall advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of your product in a first-in-human clinical trial
- General recommendations regarding a future first-in-human trial in your target clinical population where the population is novel and there is no prior precedent or guidance
- Recommendations on approach for further development of your product with limited CMC, pharmacology/toxicology, and/or clinical data that were collected outside of a US IND

Some example questions you may consider including in your MIP are:

- Chemistry, Manufacturing and Controls (CMC)
    - Innovative technologies for the qualification of new cell substrates.
    - Product-manufacturing (e.g., cell sources, donor eligibility determination for allogenic cellular products and qualification of international donors).
    - Product dependent and manufacturing process dependent reagents, starting materials and critical product components.
    - Qualification of a novel delivery device related to a specific investigational product.
    - Discussion of complex software issues and strategies to support device use in clinical studies.

- Pharmacology/Toxicology
    - Overall advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of an investigational product in a first-in-human clinical trial.
    - Specific questions on the adequacy of the selected animal models; study design (e.g., endpoints, dose levels, route of administration, dosing regimen); and acceptability of innovative preclinical testing strategies, products and/or delivery modalities.
    - Advice on modification of a preclinical program or study design, as applicable, to ensure judicious use of animals.

You can also provide a high-level overview of the proposed target product profile and an outline of your clinical development plan (e.g., clinical protocol synopsis) so that the FDA can view the CMC and pre-clinical data you provide in the context of the clinical trial and ascertain if the data provided adequately supports the proposed clinical trial plan.

Next, let’s dive into each of the different sections of the INTERACT package and what’s important to note in each of them.

4.3.1. Chemistry, Manufacturing, and Controls (CMC)

In this section you will introduce your product to the FDA by providing a summary of your investigational product and the proposed indication. To simplify the process, consider breaking this out into:

1. A high-level description of your product, manufacturing process, and proposed characterization and lot release tests
2. Your position and justification for your questions
3. References to published information related to your drug, with copies of the publications

You may find that the manufacturing details of your critical material suppliers (e.g., vector supplier) are proprietary and it may be challenging to provide that information, even at a high level, in the INTERACT package. In this case, we suggest working with those suppliers to understand if a drug master file (DMF) is on file with the FDA (see IND Section 7.3.3 Drug Master File (DMF)) and only providing high-level descriptions, per INTERACT expectations.

Drug master files (DMF) provide the FDA with confidential, detailed information about the facilities, processes, or articles that you may have used in the manufacturing, processing, and storage of your products. For more information on the different types of DMFs and what to include in each, please refer to Drug Master File (DMF) Submission Resources | FDA.

Pro tip: If you are working with a commercial AAV, it is possible that the supplier has a **Drug Master File (DMF) on file with the FDA**, which describes the characteristics and production of the AAV vector. The supplier may be able to assist you in providing these details in the MIP and should they have a DMF, it may **be possible to refer to it** when you submit the INTERACT meeting package, and later Pre-IND and IND.

4.3.2. Pharmacology/toxicology

At the INTERACT meeting stage, the main focus of pre-clinical studies is proof-of-concept pharmacology/toxicology conducted *in vitro* and *in vivo* with your product. You should provide:

- **Proof of Concept Studies**

A comprehensive summary of all pre-clinical *in vitro* and *in vivo* studies conducted thus far using your drug and the results obtained. Don't forget to include publications relevant to your development program, and copies as well, similar to the CMC section.

- **Protocol Outlines**

In this section, you want to showcase a detailed discussion, with protocol outlines regarding the additional pre-clinical proof-of-concept studies you think you need to conduct to adequately support administration of the intended clinical product in the target patient population. The goal of this meeting is to validate this with the FDA.

At this stage, you do not have to include questions on the acceptability of definitive pre-clinical safety studies – those are more appropriate for the Pre-IND meeting.

4.3.3. Clinical

Since this is early-stage, clinical comments are generally kept at high-level recommendations to guide the overall clinical development program rather than focusing on details of a specific protocol. Please note, it is not uncommon for the FDA to defer to Pre-IND for a discussion on clinical topics.

To prepare you for the Pre-IND and IND submission, you can include:

- Your disease of interest
- The target study population
- Any available natural history information/data on the condition
- Available treatment options for the condition, and
- A brief outline of first-in-human study

Once you've submitted the request and package, it's time to prepare for the actual meeting.

4.4. Preparation for the INTERACT meeting

If you are granted an INTERACT meeting, congratulations. The OTP will try to inform you in advance if any specific review discipline will not be able to participate (e.g., if any review team is not available due to workload/competing priorities). [1]

In the case of a teleconference, the FDA will send written responses to your questions in the meeting package no later than 1 day before the meeting to facilitate the discussion. For WRO meetings, the response is provided on the committed date. Please note that no additional questions will be accepted, but if you find the written responses provided by CBER sufficient and not warranting further discussion, you may cancel the meeting. [2]

If managed wisely and well prepared for, the INTERACT meeting can prove important for getting the right early input from the FDA. Below are some guidelines to make the most of a teleconference INTERACT meeting.

Dos	Don'ts
✓ As your MIP will be relatively limited (compared to Pre-IND), include sufficient detail for questions ✓ Highlight most important questions for discussion that have no substantive references or have not been addressed by any initial FDA feedback ✓ Take advantage of the INTERACT meeting setting to get early advice ✓ Summarize important points, agreements, clarifications, and action items to take into Pre-IND preparation ✓ Listen closely, be objective, and have your team also take excellent notes as official meeting minutes are not issued	X Approach the INTERACT meeting process when you are too advanced or premature – consider the alternatives X Be discouraged by a F2F meeting denial – you can still get valuable FDA feedback from the written response X Be overwhelmingly detailed or include new material or questions that were not part of the MIP– FDA may not be able to provide commentary in this setting X Attempt to answer every question from the MIP – time will be limited so organize questions in order of priority X Hide any concerns. Open dialogue is the purpose of this early interaction

4.5. Post-meeting follow-up

For INTERACT meetings, official meeting minutes will not be issued to sponsors. Additionally, any meeting minutes prepared and sent to CBER by the sponsor will not be reviewed or evaluated for accuracy.

In rare cases of INTERACT meeting resulting in changes to the initial advice provided, preliminary responses will be annotated and re-sent to you within 30 calendar days. In the case of a WRO, the WRO will serve as meeting minutes from FDA. [1]

If you've taken advantage of the INTERACT meeting, you're may have gained some direction that helps your continued regulatory journey towards the Pre-IND meeting.

Templates

- INTERACT Meeting Request/Meeting Information Package template

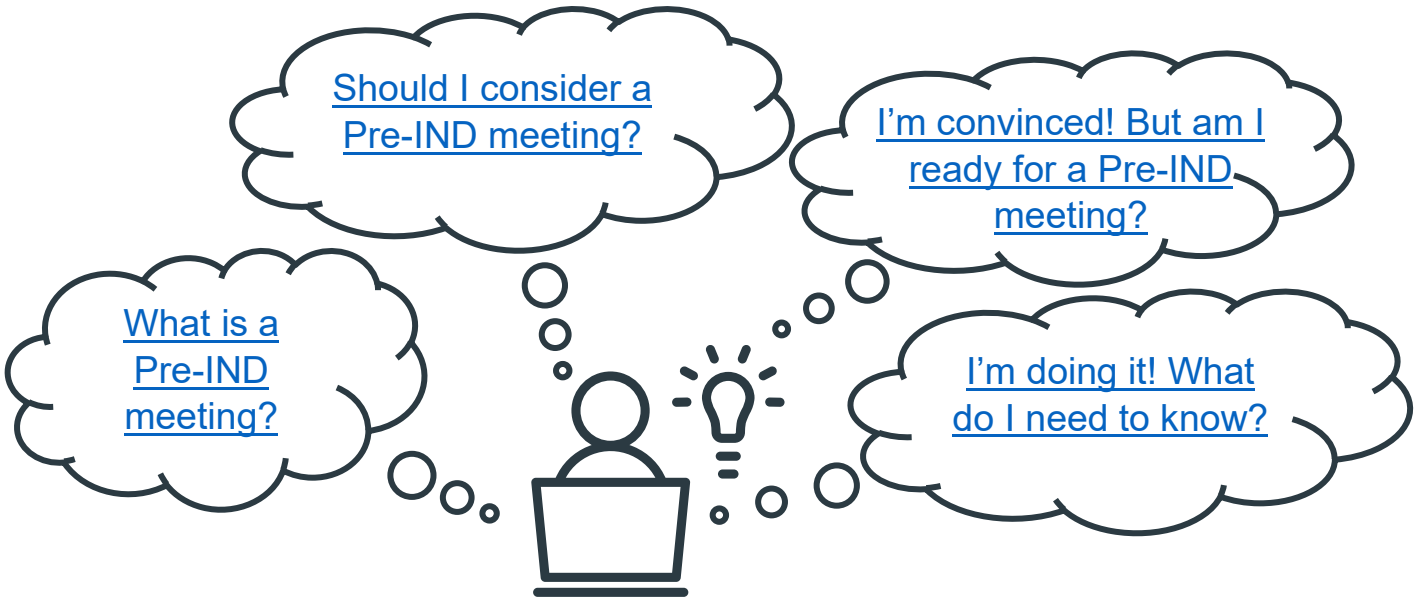
References

1. Center for Biologics Evaluation and Research. (n.d.). OTP Interact meeting. U.S. Food and Drug Administration. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meeting
2. Center for Biologics Evaluation and Research. SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products. https://www.fda.gov/media/84040/download

Chapter 5: Pre-IND Meeting

5.1. Readiness Assessment

Before embarking on the Pre-IND meeting and IND submission journey, it is essential for a sponsor (the entity responsible for a drug's development) to conduct a thorough readiness assessment. This assessment is designed to ensure that the data and information to be presented to the FDA at this stage of your drug's development are complete, accurate, and high quality, which can improve the chances of success for the Pre-IND meeting and IND submission.



What is a Pre-IND meeting?

A Pre-IND meeting is a Type B FDA meeting intended to obtain Agency feedback to guide your first-in-human/Phase 1/2 clinical strategy and IND submission. It is typically a sponsor's first **formal** meeting with the FDA (the INTERACT meeting is technically the first formal FDA meeting, but meetings are often denied). The purpose of the Pre-IND meeting is to provide an opportunity for the sponsor to ask questions, prior to IND submission, related to pre-clinical and CMC plans as well as the initial clinical study design.

The pre-IND meeting is more than just a productive exchange of information, it is also an avenue to obtain meaningful FDA agreement or advice on specific areas to address given the proposed plan.

Should I consider a Pre-IND meeting?

While a Pre-IND meeting is not required prior to submission of an IND, it offers many advantages and is therefore, highly recommended. [1]

Accelerate

The Pre-IND meeting will facilitate IND review by:

- Recognizing and avoiding unnecessary pre-clinical studies and instead, identifying the necessary safety and pharmacology pre-clinical studies appropriate for your AAV gene therapy asset and disease of interest. This also minimizes wasted time and costs in your overall program.
- Identifying inadequate or missing required CMC tests in the manufacturing process that could lead to IND clinical hold (*an order issued by a regulatory agency, such as the FDA, which stops or suspends clinical trials for your investigational drug*). For more information on grounds and procedures for clinical holds, refer to this guidance by the FDA. [5]
- Confirming that the Phase 1 clinical study is designed to meet its intended objectives while maintaining subject safety.
- Discussing any concerns or potential IND hold ups prior to submission of the IND. Addressing these with the FDA gives you an opportunity to correct these when you have time on your side.
- Identifying possible designations that will advance the clinical trial or marketing application review process. Through this meeting, you may wish to discuss the proposed designations with the FDA.

These suggestions will expedite the IND preparation process and reduce the time in which your therapeutic candidate or AAV product will get to clinical trials.

Close gaps

Your organization may be new to drug development, and it is likely that your product is intended to treat a serious or life-threatening disease, and/or is intended to treat a population with a currently unmet medical need. The Pre-IND meeting will assist you in resolving any unique development aspects in your IND and answer any questions you may have with time to resolve them before submission. Alternately, it would also be where you put forth proposals to the FDA and agree to a common plan forward given the unique and tailored development process for AAV products.

This may help avoid clinical holds or FDA requests for change due to gaps in your submission.

Build a relationship with the FDA

The Pre-IND meeting is an important opportunity to introduce your organization and investigational therapy to the FDA. The regulatory process should be viewed as a collaborative approach between the sponsor and the FDA. This meeting will serve both introductory and informational purposes, particularly with regards to scientific strategies, which will benefit future product development – data-driven rationale should be utilized to gain feedback on plans to accelerate product development.

Gaining early Agency insight and ensuring the endpoints and goals of your program are well-defined and complete will go a long way in your regulatory journey.

Although the FDA may be open to some communication (requests for advice) post Pre-IND meeting/before IND submission, only one Pre-IND meeting is granted per IND, so make it count. [1]

Am I ready for a Pre-IND meeting?

Now that you know the value of a Pre-IND meeting, it is important to consider if you are at the right stage to request one.

A readiness assessment can help identify any gaps or areas of concern in the development of your AAV gene therapy product and enable your team to address these issues proactively.

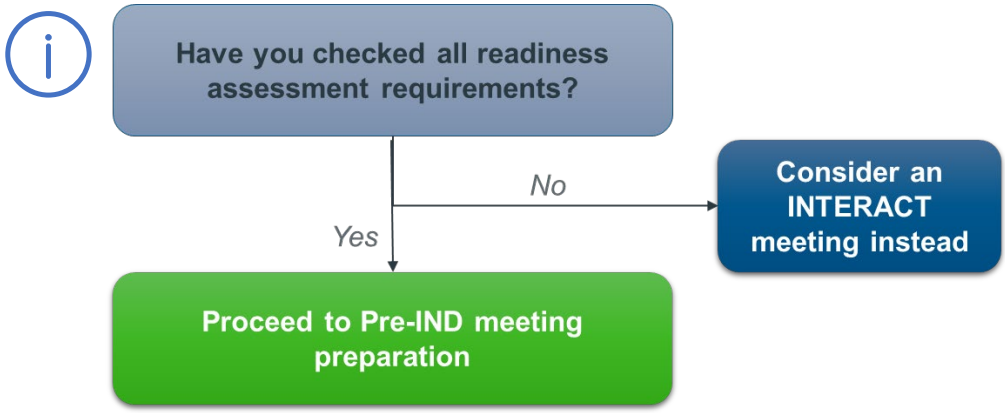
Please see below for a checklist to guide you in assessing if you are ready for a Pre-IND meeting. Completing the elements in the checklist is the first step to increasing the likelihood of a successful meeting and eventual IND submission.

Pro tip: Note that these are **best practice recommendations** for when a Pre-IND meeting would be most useful to a sponsor. You may have completed or not yet completed many of the tasks in the stages listed below and still be granted a Pre-IND meeting, so do your best to check off as many items on this list to ensure you are at the **optimal stage of readiness** for the Pre-IND!

Table 1: Readiness Assessment for Pre-IND meeting: Check to confirm completion of these tasks for optimal stage of readiness

	Readiness Assessment
pre-clinical	☐ Completed dose range finding studies and planning confirmatory GLP dose range studies ☐ Completed pilot *in vivo* pharmacology and toxicology studies and planning GLP pivotal pharmacology/toxicology studies ☐ Planning GLP biodistribution studies
CMC	☐ Preliminary defined processes, testing and specifications for Master Cell Bank (MCB), Working Cell Bank (WCB) and Drug Substance (DS) and Drug Product (DP) manufacturing ☐ Specifically, tests for safety should be identified and qualification/validation are in process. Potency tests are typically not expected to be completed at Pre-IND, but ideas on these types of tests should be presented ☐ Near completion or completion of GMP lots. At a minimum, engineering runs representative of GMP production should be in process ☐ Preliminary testing and design of stability studies for DS, DP, and Point of Care (POC) delivery (e.g., reconstitution of frozen product and administration through syringe)
Clinical	☐ Ideally, a completed clinical study synopsis should be prepared and included in the Pre-IND meeting package. If a final synopsis is not ready, at a minimum, a clinical study concept sheet which includes details on the population, inclusion/exclusion criteria, endpoints, dosing and dose escalation regimen, dose rationale, safety, and efficacy (if applicable) measurements and analysis, study time points and overall duration
Patient Engagement	☐ Engagement with patients/patient advocacy groups to capture patient voice and ensure representation throughout the journey

Prior to proceeding, let us do one final check to ensure you are ready to initiate the Pre-IND meeting preparation.



Things to be aware of before continuing

Some examples of recurrent problems that present themselves in Pre-IND meetings include [2]:

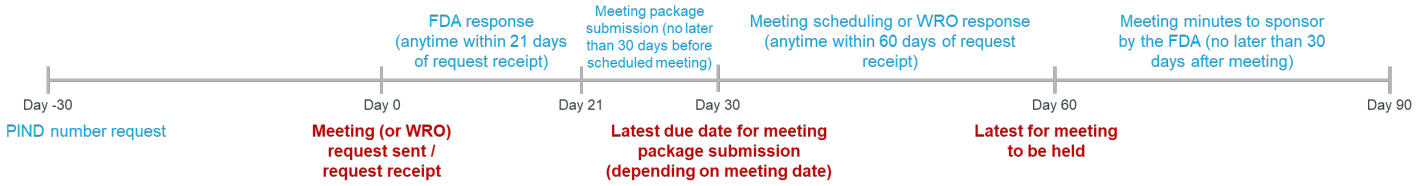
- Clinical trial design elements in the study synopsis – e.g., unsupported or lacking rationale for starting dose, missing specific safety assessments or time points, missing data safety monitoring board review

- Anything less than the minimal chemical, manufacturing, and controls (CMC) information. Refer to Section 5.3.6 for recommendations
- Anything less than the minimal toxicology and pharmacology studies to support the proof-of-concept (POC). Refer to Section 5.3.7 for recommendations
- A study design that does not comply with Good Clinical Practices (GCPs)
- Limited data supporting dose range

Now that you know the most common causes for concern, you can proceed to your Pre-IND meeting planning with the necessary information.

5.2. Meeting Request

Figure 1: Meeting Request and Written Response Only (WRO) Timeline



Before requesting a Pre-IND meeting, it is highly recommended that you have a solid draft of your meeting information package (MIP) before you send the meeting request, as often decisions/questions are worked out as the MIP is being drafted. It is also possible to have a Written Response Only (WRO) in lieu of a meeting – you may request one, or the FDA might determine a WRO is more appropriate for providing feedback and advice.

So, what is the Pre-IND meeting information package (MIP)?

The MIP, sometimes known as a briefing package, is a detailed document sent to the FDA in support of the Pre-IND meeting request. The goal of the MIP is to provide information, relevant to the discussion topics of the meeting request, to not only enable the FDA to prepare adequately for the meeting but also to achieve a focused and productive exchange of information.

Additionally, the timely submission of the MIP is crucial to provide sufficient time for meeting preparation and for accommodating adjustments within the meeting agenda and pre-meeting communications. The FDA requires that the MIP be submitted 30 days prior to the scheduled meeting date (See **Figure 1** for a recommended timeline for Pre-IND meeting).

A Pre-Submission Tracking Number (PSTN) should be requested 30 days prior to the planned meeting request submission date. To do this, send an email to 'cberrims@fda.hhs.gov' and

request this number. The emails should contain: Sponsor Name, Sponsor Address, Authorized Regulatory Contact, Name, Description, Code of Investigational Therapy, Indication and Anticipated Submission Date. CBER will respond with a unique PSTN that should be referenced in your paperwork when you are ready to submit the Meeting Request through the FDA Electronic Submission Gateway (FDA ESG). The timing for all this should occur approximately two months prior to your desired meeting time frame.

It is important to include enough information in order for the FDA to accept the Pre-IND meeting request and also identify the proper staff to discuss your proposed agenda items. Fortunately, the meeting request can be thought of as a summary version of your MIP – a lot of content may eventually go into the MIP and will set your team up well for the meeting.

Use the Pre-IND Meeting Request template to prepare your meeting request.

Pro tip: Similar to the INTERACT meeting, you have the option of preparing and submitting your complete MIP as a **"combined meeting request/MIP"** at this stage. The meeting request can be thought of as a way to stagger the information preparation by submitting an abbreviated version while using the additional time to prepare the MIP, but a combined submission will save 30 days since at the time of submission the FDA has all the information they need.

Consider including the following details about your program in the meeting request [3]:

1. The application number
2. The product name
3. The chemical name, established name, and/or structure
4. The proposed indication(s)
5. The meeting type being requested (i.e., Pre-IND is a Type B meeting)
6. Any proposed designations and general discussion about whether or not they are a value-added for acceleration or market access for rare gene therapies

The meeting request should also include key information about the meeting itself, such as:

7. Suggested dates and times (e.g., morning or afternoon) for the meeting that are consistent with the appropriate scheduling time frame (see timeline) as well as dates and times when you/your team are not available
8. A list of proposed questions, grouped by FDA discipline, with some brief explanation for each question
9. The proposed meeting format - teleconference/videoconference, or WRO
10. The date you will send the MIP (see **Figure 1** for the range of time you can do this)
11. A brief statement of the purpose of the meeting. This statement should include a brief background of the issues you are facing with your program or outstanding concerns. It can include a summary of completed or planned studies or data that you intend to discuss at the meeting. You can also highlight the general nature of the questions to be asked, and where the meeting fits in the overall development plans. You don't have to provide details of trial designs or completed studies – that should be included in the MIP

– but you should provide enough information to facilitate the FDA's understanding of the issues
12. A list of the specific objectives or outcomes you expect from the meeting
13. A proposed agenda, including estimated times needed for discussion of each agenda item
14. A list of planned attendees from your organization, including titles and affiliations
15. A list of requested FDA attendees and/or discipline representative(s)

Once you have submitted the request, the clock starts. If you are granted a meeting, you can expect to have it scheduled approximately 60 days from the request, and you may proceed to the next step.

If you are denied a meeting, the FDA will notify you according to the timeline described and provide reasoning for denial. For WRO requests or if the FDA determines a WRO would suffice, the FDA's letter will include the date the FDA intends to send the written responses. See **Figure 4** below for more information on these options for FDA responses.

For additional information please visit OTAT Pre-IND Meetings | FDA [10]

5.3. Meeting Information Package Preparation

Now that you know about meeting requests, it is important for you to ensure that all the content provided in the request and the MIP is up to date, accurate, and supports the intended objectives of the meeting.

So, what should you include in your MIP?

Although the contents of the MIP will vary, they generally include product information, questions for the FDA *(grouped by discipline – CMC, Pre-clinical, Clinical)*, and any specific information that will enable the FDA to respond to your questions.

For additional information, please follow the FDA guidance: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products [7]

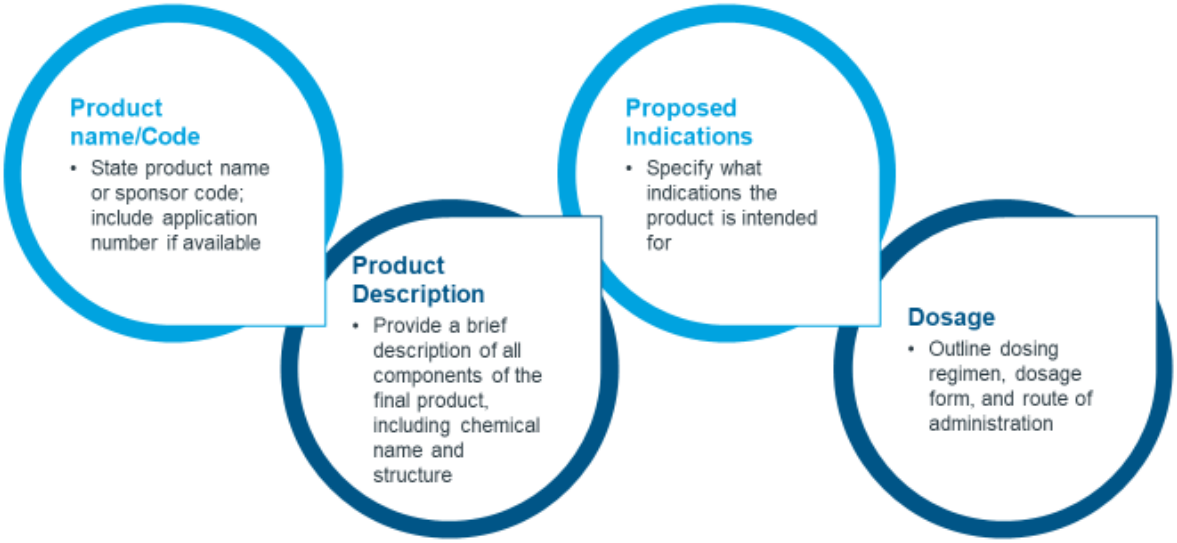
Next, let's dive into each of the different sections of the Pre-IND MIP and what's important to note in each of them as you fill out the template. We have also provided you with a template for the MIP, that you can find here.

5.3.1. Introduction, Purpose, and Objective of the Meeting

Introduction

In this section, you will introduce your product to the FDA by providing a summary of your investigational product and the proposed indication. To simplify the process, consider breaking your introduction into four sections as shown in **Figure 2** below. Additionally, a description of what information you should consider adding under each section is provided.

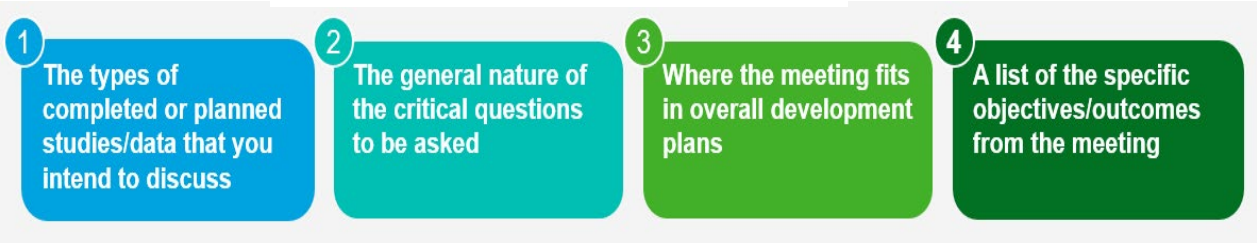
Figure 2: Investigational Product Summary



Purpose and objective of the meeting

In this section, you will be providing a brief statement summarizing what you intend to discuss with the FDA. Consider including the following in your statement:

Figure 3: Key Discussion Points

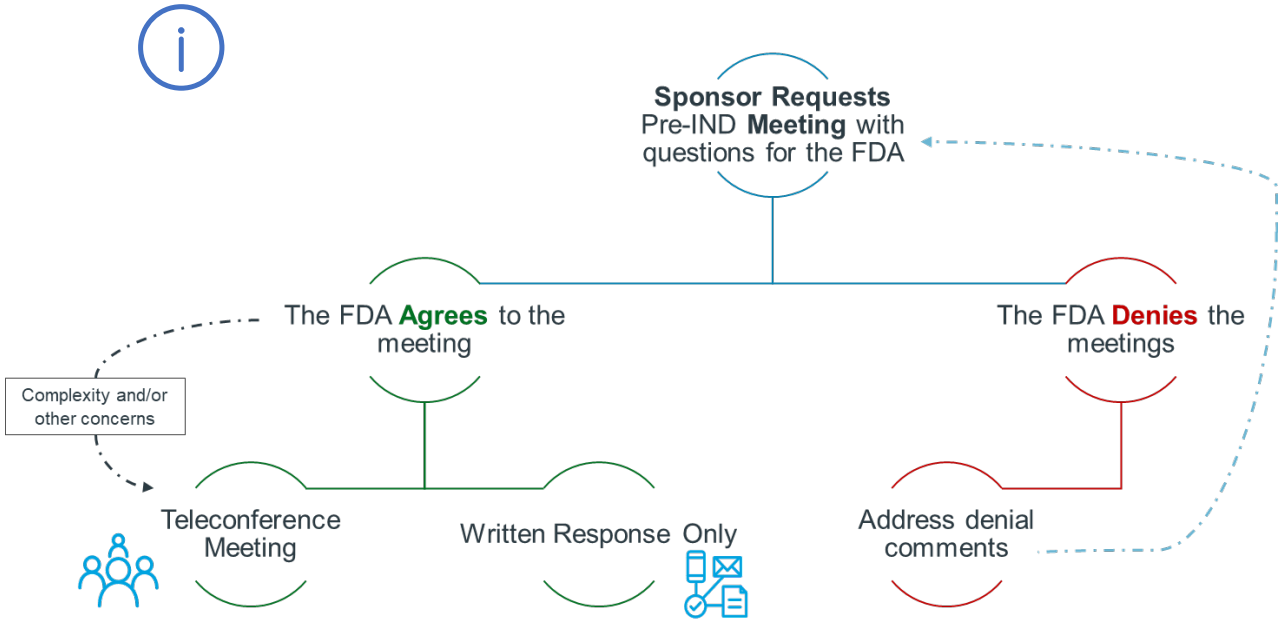


5.3.2. Proposed Agenda of the Meeting and Attendees

Proposed agenda of the meeting

Follow the decision tree to understand how to approach this section of your Pre-IND MIP preparation based on your meeting logistics. *(Each of the routes were designed based on FDA guidances and experiences from prior candidate submissions.)*

Figure 4: Pre-IND Meeting Request Potential Outcomes



In the event that the FDA denies your pre-IND meeting request, you will need to address the gaps/concerns described in the meeting denial. There are a variety of reasons why a meeting can be denied, with the most common reason being that the applicant's development plan is not yet ready for pre-IND feedback. Further development and data may need to be collected and summarized in an updated pre-IND package before requesting a pre-IND meeting a second time."

Option 1- Planning a Teleconference Meeting:

If you are requesting a teleconference for the Pre-IND meeting, it will be important to include the following (Note that a teleconference is not always granted. However, written feedback from the FDA will always be provided, whether a teleconference is requested/granted or not):

1. A clear and concise list of the specific agenda items that will be covered during the meeting
    a. Here you can include a list of specific questions you have for the agency along with a brief statement about the background and purpose for each
2. An estimated amount of time needed for each agenda item

The following is an example of the "Proposed Agenda Template" in Table 2:

Table 2: Proposed Agenda Template

Proposed Agenda	Estimated Time (minutes)
Introductions and Objectives	X
(E.g., Agenda Item 1: Specific questions raised by sponsor)	XX
(E.g., Agenda Item 2: Meeting Summary)	XXX

This way you can ensure that the meeting is focused and productive.

Option 2 –Written Response Only:

On the other hand, if you requested a WRO from the FDA, or if the FDA decides that a WRO is more appropriate, then no proposed agenda is needed. Even if you requested a teleconference, the Agency may determine that a written response to your questions would be the most appropriate means for providing feedback and advice.

When it is determined that the meeting request can be appropriately addressed through a WRO, the FDA will respond with the date they intend on sending the written response to you, which is usually 60 days from the meeting request receipt date.

The FDA will take requests for clarification to the responses they have provided after receipt of the WRO. If you believe a Pre-IND teleconference meeting is valuable and warranted, and your needs may not be addressed through a WRO, then you may provide a rationale in a follow-up correspondence explaining why a meeting is valuable and warranted. The FDA will convert where possible, WRO to a teleconference meeting for requests that include novel approaches to development and/or where precedents are not well established.

You may refer to the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027 or any latest PDUFA guidance for more information.

The FDA may deny the request for a teleconference meeting and choose the WRO or deny the request altogether for several reasons (and the FDA's letter will include an explanation of the reason for any denial). For instance, a meeting can be denied because the application is at too premature of a stage in development, or the request/MIP does not provide an adequate basis for the meeting discussion.

The FDA may also choose the WRO option due to resource issues. However, this option is not preferred as it limits the opportunity for discussion or clarification, so denials are usually based on a substantive reason, e.g., not merely on the absence of a minor element of the meeting request or meeting package items. [7]

Attendees

In this section you will be providing the FDA with a list of individuals from your organization who will attend the meeting. List their names along with their respective disciplines including affiliations and titles. Usually, the FDA provides preliminary advice a few days prior to the meeting date, after which the team should triage and decide the questions, they intend on bringing up at the actual meeting. To improve productivity, we recommend that you first short-list the questions you want to focus on and then match subject matter experts (SMEs) with disciplines based on those question(s) to attend the meeting.

The FDA also encourages that you consider including patient representatives in the meeting (either the patients themselves and/or their family members/caregivers) where topics would benefit from

By doing so you will not only provide the FDA with an overview of whom to expect at the meeting but also ensure that all key stakeholders are included for a productive discussion.

The following is an example of the "List of Attendees Template" in Table 3:

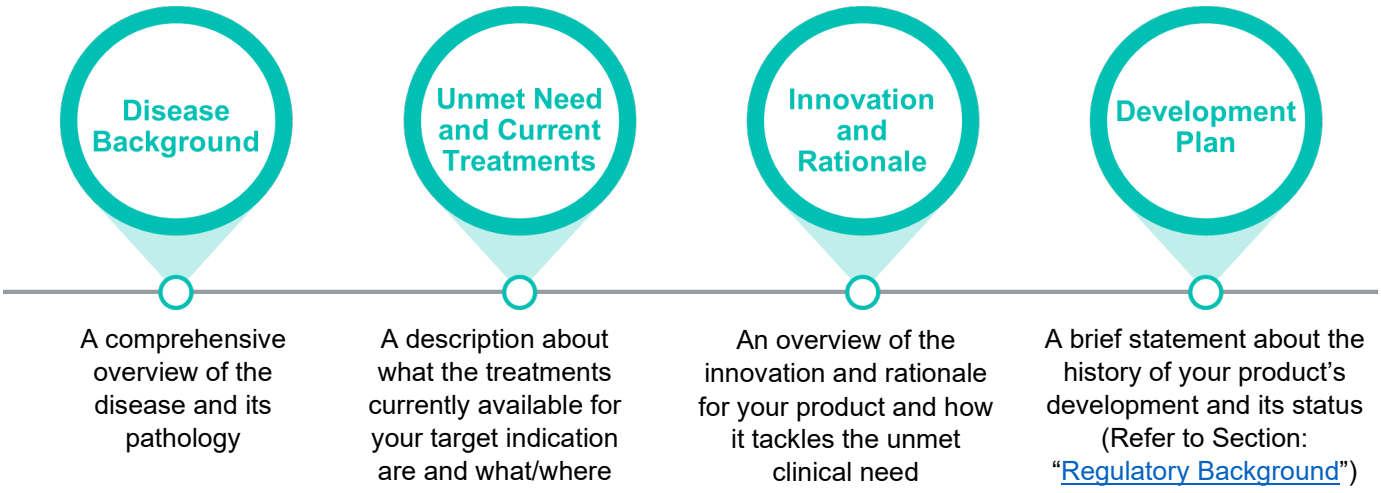
Table 3: List of Attendees Template

Name of Sponsor's Attendee/Investigator	Affiliation / Collaborative Institute	Role/Contribution
Attendee 1	X	CMC/Pharmacology/Toxicology/Clinical/ Biostatistics/ Principal Investigator etc.
Attendee 2	XX	CMC/Pharmacology/Toxicology/Clinical/ Biostatistics/ Principal Investigator etc.
Attendee 3	XXX	CMC/Pharmacology/Toxicology/Clinical/ Biostatistics/ Principal Investigator etc.

5.3.3. Product Background

In this section you will be providing the FDA with an overview of your product's background, rationale, and development plan. Key topics that you should consider highlighting in this section, along with a brief description of what can be included under each section, are shown in the **Figure 5** below.

Figure 5: Key Categories for Product Background



5.3.4. Questions for the Agency Grouped by Discipline

This is the 'meat' of the Pre-IND MIP. In this section, your goal is to provide the FDA with a list of the key questions for discussion grouped by discipline (CMC, Pre-clinical, Clinical) and a summary of background and need for each. Since the FDA recommends limiting your questions to less than 12, you should use this opportunity to ask critical questions related to your specific development program; also refer to available FDA guidances applicable to your product.

For maximum efficiency, it is important to pose clear, focused questions, so that the FDA can provide advice targeted to your specific product development program. If questions are too broad or general, the response you get may also be general.

Another thing to keep in mind is that you should refrain from asking single multi-topic, all-encompassing questions such as '*are the starting material selection, manufacturing process and analytical testing acceptable?'* Rather, you should ask specific and clear questions like the following directional examples (tailored to your specific product, of course):

- Does the FDA agree that the proposed CMC package supports the intended clinical investigation
- Does the FDA agree with the proposed release specifications and testing strategy?
- Does the FDA agree with the stability testing of the drug substance and drug product?
- Is the assay qualification plan sufficient?
- Is the delivery device compatibility plan sufficient [if a device is integral to your product deliver]?

5.3.5. Regulatory Background

A Regulatory Background section may not be applicable in all cases. Include this section if the investigational product has been approved in other countries or has been approved by the FDA

for another indication. Also, include whether prior meetings have taken place with the FDA on the investigational product. Other types of questions not fitting in pre-clinical, CMC or clinical topics may be presented in this section.

5.3.6. Chemistry, Manufacturing, and Controls Information Summary

The Chemistry, Manufacturing, and Controls (CMC) information summary describes the manufacturing processes, controls, and analytical methods used for your investigational product and is intended to provide an end-to-end view of the entire workflow and quality control involved. This is an important part of the MIP that needs to be prepared with particularly great care to demonstrate without a doubt to the FDA that you will have an efficacious and most importantly, safe product to administer in humans.

You may find that the manufacturing details of your critical material suppliers (e.g., vector supplier) are proprietary and it may be challenging to provide that information in the Pre-IND. In this case, we suggest working with those suppliers to understand if a drug master file (DMF) is on file with the FDA (see IND Section 7.3.3 Drug Master File (DMF)) and only providing high-level descriptions for the Pre-IND.

Drug master files (DMF) provides the FDA with confidential, detailed information about the facilities, processes, or articles that you may have used in the manufacturing, processing, and storage of your products. For more information on the different types of DMFs and what to include in each, please refer to Drug Master File (DMF) Submission Resources | FDA.

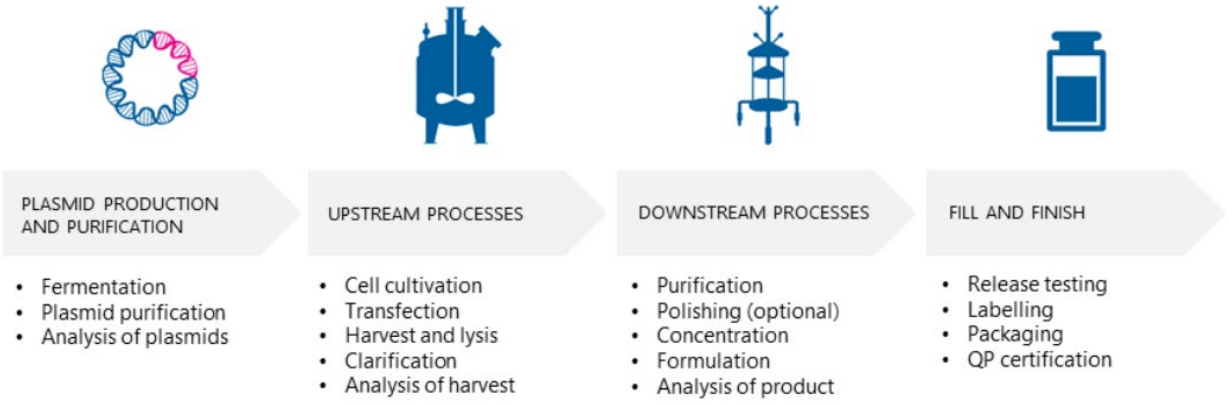
At this point in your program's development stage, you can include a high-level manufacturing plan up to first-in-human / Phase 1/2 studies. Consider asking yourself the following questions:

- ? Where is my organization sourcing all the different components of our drug product?
- ? What is the current clinical trial plan in terms of regions? Is development conducted in one country? Or primarily in one and secondarily in another/other countries?

You can then plan how to structure and lay out the CMC summary.

You may want to start with an overview of manufacturing plans from your current stage of development until your first-in-human / Phase 1/2 studies (see **Figure 6** below for an example).

Figure 6: Manufacturing Plan Overview



To best demonstrate your data and gain the confidence of the FDA in your process validation, consider categorizing data you include in your CMC summary into the broad sections below.

- **Drug substance and drug product: Vector production process**

In this section, you can provide a summary description of your AAV vector gene therapy, including its physical and chemical properties, composition, and manufacturing process. This should include the method of production, purification, and characterization of the vector. As noted previously, some of this information may be proprietary to your vector supplier, however a summary description, or cross-reference to DMF or other documentation at most is expected for the Pre-IND.

Describe your drug product and list out the components. Include cloning and sequencing information on plasmids, sources for cells, e.g., bacteria cell banks for *E. coli*, American Type Culture Collection (ATCC) or other sources for HEK293 cells, including an analysis of possible contaminants from HEK293 cells.

- **Quality characterization of the vector, cells, and all components used in the process**

The CMC information summary for the Pre-IND can provide information on the physicochemical properties of the AAV vector, such as its size, shape, and purity. The stability of the AAV vector is an essential factor that needs to be addressed as this demonstrates the long-term stability of the vector under various conditions, such as temperature, pH, and storage time. Overall, quality control measures that will be implemented to ensure the consistency and purity of the AAV vector should be described – this includes osmolality, sterility, in-process testing, release testing, and others. [6]

Pro tip: If you are working with a commercial AAV, it is possible that the supplier has a **Drug Master File (DMF) on file with FDA**, which describes the characteristics and production of the AAV vector. The supplier may be able to assist you in providing these details in the MIP and should they have a DMF, it may **be possible to refer to it** when you submit the Pre-IND meeting package and later, IND.

Pre-Clinical Data Summaries

What are Pre-Clinical Data Summaries?

Pre-clinical studies are investigations that test the drug in a non-clinical setting with cells and/or animal models to determine potential adverse/toxic effects before clinical trials. The pre-clinical data summaries for AAV gene therapies would include information about the AAV vector used,

Can I 'bypass' some CMC summaries with a platform-based approach?

Since a platform approach may use similar upstream and downstream processes, cell lines, raw materials, etc., testing related to the vector/capsid specifications for components kept the same across, purification, shipping/compatibility, stability and potentially other CQAs or evidence requirements might be exempt if that data/information already exists. [8]

transgene expression, biodistribution, shedding, and reports of any adverse effects and/or immune response. [4]

The goal for all non-clinical studies is to support Phase 1/2 safety and tolerability studies and comply with good laboratory practice (GLP). The GLP regulations can be found in 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies.[8]

These regulations can provide you with the minimum requirements needed for your non-clinical investigations, specifically on:

- Information regarding studies conducted – including protocols, operating procedures, and study reports
- Personnel involved
- Facilities and equipment
- A system of quality assurance oversight for each study to help assure the safety of the FDA-regulated product

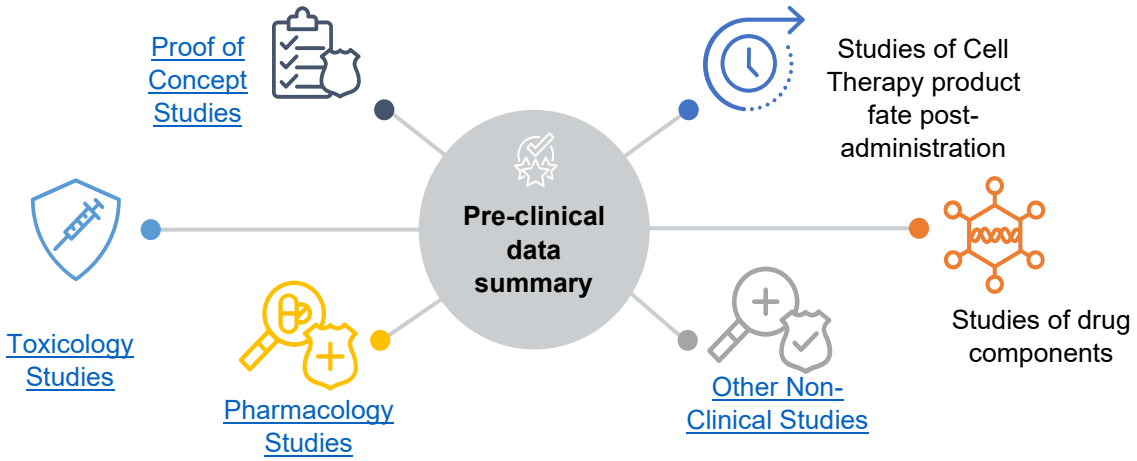
Data about a drug's activities and effects in animals helps establish boundaries for safe use of the drug in subsequent human testing (clinical trials).

Before testing your product clinically, you must determine its toxicity. Usually, pre-clinical studies will be animal studies foundational to the planned clinical investigations, but will provide detailed information on pharmacology, biodistribution, safety exposure, dosing, and toxicity levels.

Additionally, it is recommended that you provide summarized results of your completed pre-clinical studies along with information on any planned studies. Providing this information will help the FDA with background information and context to be able to answer any pre-clinical questions you may have. To best convey your data, consider categorizing it into the broad sections shown in **Figure 7** below.

Click on each bubble to get a brief description on what each section entails. *For the FDA guidance on specific details that go into each category, refer to the guidance titled Preclinical Assessment of Investigational Cellular and Gene Therapy Products | FDA.* [4]

Figure 7: Pre-clinical Data Summary Topics



- **Proof of Concept Studies**

In this section your goal is to provide the FDA with the feasibility and efficacy of your product in a pre-clinical setting, such as *in vitro* models or animals. It is important for you to ensure that the summarized results you provide in this section are well organized and include sections on study design, methods and materials, statistics, etc., for ease of review by the FDA reviewers. Furthermore, you can develop these summaries into study reports for the IND submission.

- **Toxicology Studies**

In this section your goal is to provide the FDA with data sets from your toxicology studies showcasing the safety and risk assessment of your product, prior to advancing to clinical setting.

- **Pharmacology Studies**

Here, your goal is to provide the FDA with the key data sets that highlight the pharmacological properties of your product including its interaction with the target site, absorption, metabolism, elimination, and potential adverse effects. Additionally, if the intended target population or the initial clinical trials are to be conducted in children, it is important that pre-clinical studies demonstrate a prospect of “direct benefit" to the child.

- **Studies of ROA devices (if applicable)**

In this section your goal is to provide the FDA with studies showing the efficacy and biocompatibility of your product’s device component. In addition, you should provide detailed information about your device, the device description and the regulatory status of such device in

the US.{if device delivery is a critical component of your product delivery, as in intrathecal injection]

- **Other Non-clinical studies (if applicable**)

In this section you can provide the FDA with any other non-clinical data sets that support the efficacy and feasibility of your product.

What are the consequences or considerations of a platform-based approach for pre-clinical studies?

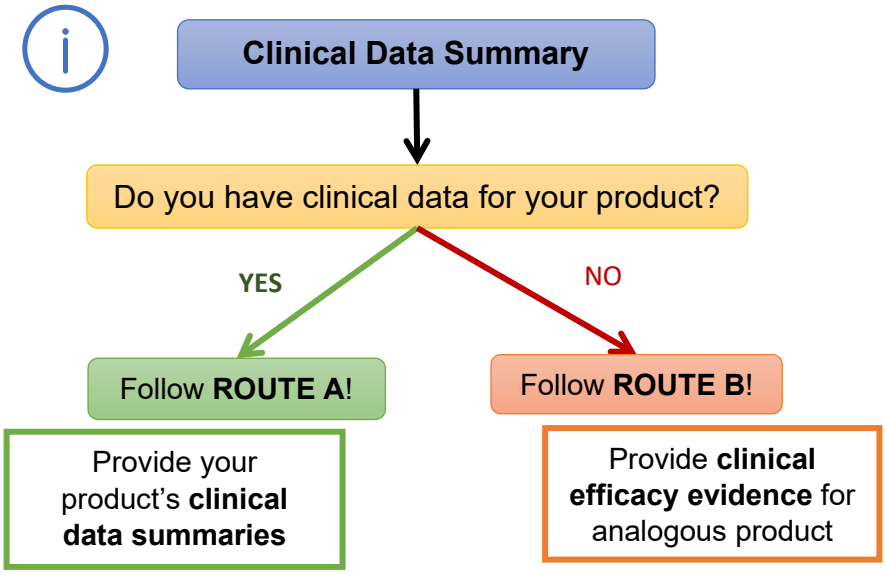
With a platform-based approach, your product may have similar components as other products – e.g., use the same vector, regulatory elements, route of administration – but use a different transgene. Therefore, there may be opportunities to streamline here as well. Some pre-clinical studies may be waived based on existing data/information for elements that are the same as previously manufactured clinical grade AAV vectors that have been used under INDs approved by FDA-CBER.

Additional pre-clinical studies may be needed for assessment of toxicity due to the transgene itself, and if different regulatory elements are included (e.g., promoter), then you should still be able to streamline studies to address any residual uncertainty, e.g., impact of different promoters on biodistribution or other attributes.[2] The BGTC is developing a minimal set of animal toxicology studies to reduce use of non-human primates (NHPs) for IND submissions – please refer to Chapter 2 for more information on the platform-based approach.

5.3.7. Clinical Data Summaries

In this section your goal is to provide the FDA with a summary of any clinical data that has been accrued (only in the case that there have been prior use in patients). Additionally, you can also use this section to disclose key findings from prior and/or ongoing human trials and information regarding upcoming/planned ones as well. Long-term follow-up is another important piece of data to provide to the FDA – you will need to provide the FDA with any data that may suggest long-term performance of the product post-administration. Consider following the decision tree below to determine the best approach, based on your development plan, you should use for tackling this section.

If you don't have natural history studies or prior clinical data for your product (which is typical for BGTC candidates), then please skip directly to planned/upcoming clinical studies



Route A

If you have clinical data for your product, then your goal for this sub-section is to provide the FDA with concise data summaries along with key learnings and findings from your studies.

Remember, full study reports or detailed data sets are generally not appropriate for Pre-IND meeting information packages. Consider dividing your information into the following 3 sub-sections

- ☐ Natural history studies
- ☐ Prior clinical experience
- ☐ Planned/Upcoming clinical studies

Click through each topic or scroll through them to learn more about what you can include under each:

- **Natural history studies**

  It may be helpful to include natural history studies to provide the scientific foundation upon which your product development program can be built.

Additionally, the data from the studies can be more informative in the Pre-IND phase to help design efficacy trials.

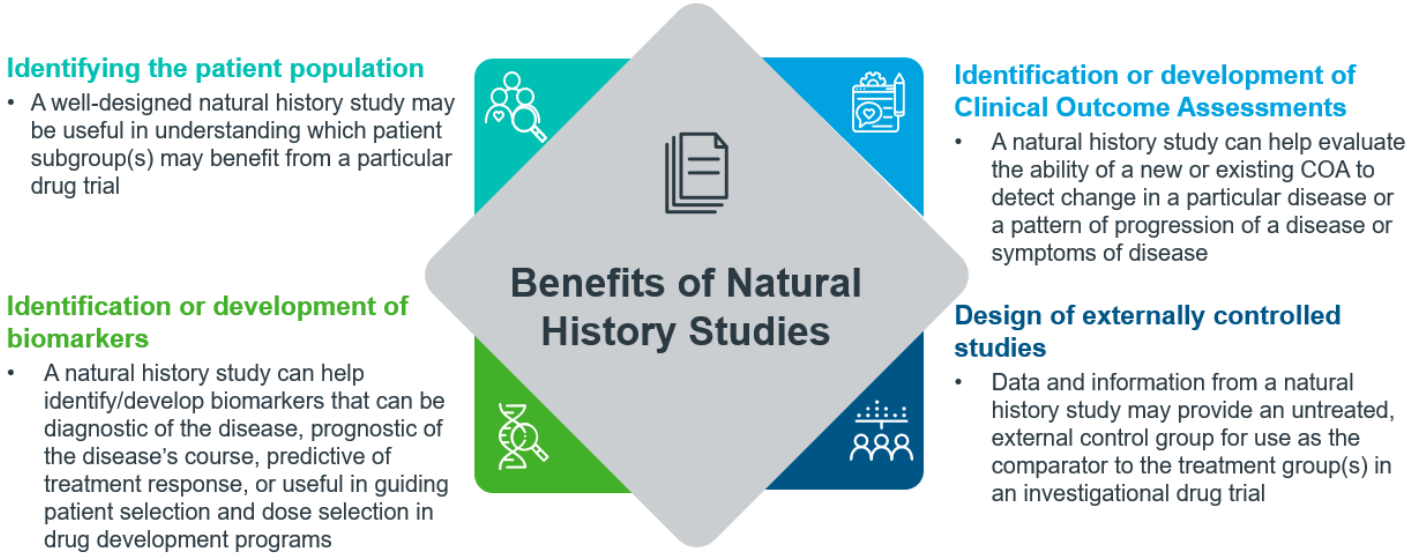
What is a natural history study?

A natural history study collects information about the natural history of a disease in the absence of an intervention, from the disease's onset until either its resolution or the individual's death. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes.

Although the knowledge of a disease's natural history can benefit drug development for many disorders and conditions, natural history information is usually not available or is incomplete for most rare diseases; therefore, natural history information is particularly needed for these diseases.

In addition to natural history studies being highly encouraged for rare disease by the FDA, there are ways in which they can help you in your clinical development plan. These have been summarized into four sections below. (*If you are curious to know more about natural history studies and how exactly they tie into your clinical development plan, the FDA has specific guidance you can find here: Rare Diseases: Natural History Studies for Drug Development | FDA.)* [11]

Figure 7: Benefits of Natural History Studies



- **Prior clinical experience**

In the case that there is clinical data from your product, then it is recommended for you to include a summary of the key learnings and findings along with key data sets under this sub-section. If more than one study has been conducted, separate the section out by each study. To ensure you are effectively communicating all aspects of the study conducted, consider following the outline below for each:

- ☐ Study title
- ☐ Study objectives and criteria for evaluation
- ☐ Methodology
- ☐ Diagnosis and main inclusion criteria
- ☐ Treatment arms and dosing regimen
- ☐ Study results *(For easier visualization of your data, consider having it in a tabular or graphical format)*
- ☐ Study site/s
- ☐ Drug manufacturing site

You can include your study reports in the appendix section of your Pre-IND MIP.

- **Planned/Upcoming clinical studies**

Before moving on, it is recommended that you conclude the sub-section with a summary of any planned/upcoming IND opening clinical study. This will be the critical part of the clinical section. This includes providing the FDA with clinical study synopsis or draft outline for the studies that you plan to conduct in your clinical development plan. Consider a tabular description of all study-related events and assessments, including, but not limited to:

- ☐ Investigator/study center
- ☐ Trial design
- ☐ Subject screening and enrollment (e.g., patient population or healthy normal controls, inclusion, and exclusion criteria)
- ☐ Safety assessments
- ☐ Efficacy evaluations
- ☐ Pharmacokinetics sampling (e.g., immunogenicity markers, viral vector shedding, other laboratory detectable metabolites, biomarkers if applicable)
- ☐ Route of administration
- ☐ Proposed treatment regimen
- ☐ Stopping rules *(a set of criteria that specify when dosing an individual subject, cohort and/or trial should be suspended)*

Route B

At the time of Pre-IND, you may not have clinical data for your product yet. In this case, your goal for this section is to provide the FDA with relevant clinical data from analogues and a brief overview of the clinical investigational plan for your product. You may be able to leverage similar data based on serology, capsid type, disease, biomarker, endpoint, route of administration, etc. (refer to Chapter 2: Platform-based Approach). Please remember to keep your data and summaries accurate, concise, and relevant to your product.

To ensure you are providing the FDA with the key information needed, consider breaking this section into the following sub-sections while filing your Pre-IND meeting information package:

- **Prior data from analogues**

Please note that analogues aren't always available. Therefore, please consider this section only in the case when they are available and you are confident in the comparison between the analogues and your product, which should be highlighted in this section.

What is an analogue?

The use of analogues, therapies that work in a similar way or target similar diseases, can help strengthen our understanding of how well an upcoming therapies will work over a period of time. Analogues help define specific parameters including safety profile, dose range, and tissue tropism, which is the viral vector type (e.g., AAV, LV, Ad, etc.) and their subcategories (e.g., AAV serotype/capsid). In cases where you have used novel capsids or modified an existing one enough that it may generate variations in the expected parameters, new studies will be required by the FDA. [4,9]

Under this sub-section, your goal is to provide the FDA with a hypothesis of what to expect from clinical studies. This section may be limited if your investigational therapy is unique and novel. However, there is typically precedence for similar therapeutics in clinical trials. It may be helpful to present a summary of this research and any learnings from such studies. If analogues are available, it will be helpful to summarize why you consider them analogues (i.e., vector features, indication, etc.), aspects of the analogues' clinical studies that may apply to your study design as well as in any safety or efficacy results, key findings and learnings from the analogue cases and draw a hypothesis of what the clinical experience with your product may look like. Sources of publicly available data include peer-reviewed publications, clinicaltrials.gov, product labeling and Summary Basis of Approval issued by the FDA. If other sponsor data is intended to be relied on to support the safety of your product, you will be required to obtain a Right of Reference Letter from that sponsor and include this information in the IND.

- **General Investigational Plan**

Here, your goal is to provide the FDA with an overview of the clinical investigational plan for your drug. Consider including the following topics discussed in the "Planned/Upcoming clinical studies" sub-section including the goal and status around the clinical development of your product.

5.4. Preparation for the Pre-IND meeting

Once you have sent the MIP, it is time to prepare for conducting the actual meeting itself. The FDA will send you written comments back, usually 2 days before the planned meeting. This time is an intensive stage as you review and carefully digest the FDA's comments. During this time, you will also need to work on prioritizing which questions you will discuss in the meeting itself and communicating this to the FDA, as well as finalizing any preparations for presentation. Sometimes the FDA's written comments are sufficient enough that you can decide to cancel the teleconference meeting.

It is critical to keep in mind that the purpose of the Pre-IND meeting is to have a dialogue with the FDA. Therefore, there is no need to prepare for a long presentation of the MIP – the Pre-IND meeting is usually no longer than 1 hour, so it is crucial to use the time wisely and as effectively as possible. In fact, any presentation by you, the requester, is generally deemed unnecessary because all information for review and discussion should be part of the MIP, and attendees are assumed to have digested it in advance. The meeting will be chaired by an FDA staff member, so you can expect the meeting to be "driven" by them.

Generally, you will be asked to present a summary of your application to ensure that there is mutual understanding of meeting outcomes and action items. This is a good place to reiterate your objectives and concerns/challenges that you require their input on. The FDA staff can then add or further clarify any important points not covered and these items can be added to the meeting minutes.

Here are some guidelines for conducting an effective Pre-IND meeting:

Dos	Don'ts
✓ Discuss with the FDA project manager ahead of time thow you wish to prioritize the meeting agenda ✓ Keep any presentation brief to maximize time for discussion ✓ Ensure attendees have slide materials ahead of the meeting ✓ Summarize important points, agreements, clarifications, and action items (this can be done by you or the FDA chair, and at the end of the meeting or after each question ✓ Focus on questions that have not been addressed by any initial FDA feedback ✓ Listen closely, be objective, and have your team also take excellent notes (don't rely solely on the FDA minutes.)	X Record the meeting discussion – this is prohibited, as meeting minutes will be provided by the FDA X Increase the length of a meeting to accommodate a presentation X Include new material or questions that were not part of the MIP– the FDA may not be able to provide commentary, thus defeating the purpose of the meeting X Attempt to answer every question from the MIP – time will be limited so organize questions in order of priority. Stay focused on the agenda. X Hide any concerns. Transparency is key. X Be defensive or antagonistic especially upon disagreements with the FDA – any misunderstandings or additional input needed can be resolved in the follow-up

5.5. Post-meeting follow-up

In this section, your goal is to provide the FDA with information related to meeting minutes. After your Pre-IND meeting, the FDA will issue meeting minutes, summarizing the content discussed, 30 days after the meeting. The purpose of this is to give you the opportunity to review what was discussed. If there are any aspects that you disagree with in the minutes, then you can request clarification or suggest changes (which the FDA may or may not agree with). It is important to note that responses to these minutes will have to be included in the IND submission, and the contents need to be addressed in the actual drug development period between Pre-IND and IND submission.

It is highly recommended that you also write your own meeting minutes and provide them to the FDA right after the meeting, as this is helpful to the Agency and can also further accelerate the process. It is also recommended to log your interaction minutes and develop a game plan for how you plan to address/modify plans as needed, or to prepare for the next interaction with the FDA on topics as warranted.

Templates

- Pre-IND Meeting Request Template
- Pre-IND Meeting Information Package Template

References

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Chapter 6: Program Selection

6.1. Summary

Supporting the development and evaluation of new treatments for rare diseases is a key priority for the FDA. As you conduct your IND preparations, it is important to consider and take advantage of the FDA's special programs/designations to speed up your approval. You can submit your application for a special designation at any stage of the drug development process. However, it is typically recommended that you apply early in the development process to maximize the benefits and incentives associated with the programs.

Pro tip: The FDA encourages sponsors to discuss their plans for special programs before they submit an Investigational New Drug (IND) application. This allows time for the FDA to review and grant the designation early on, providing important incentives and regulatory advantages throughout the drug development process.

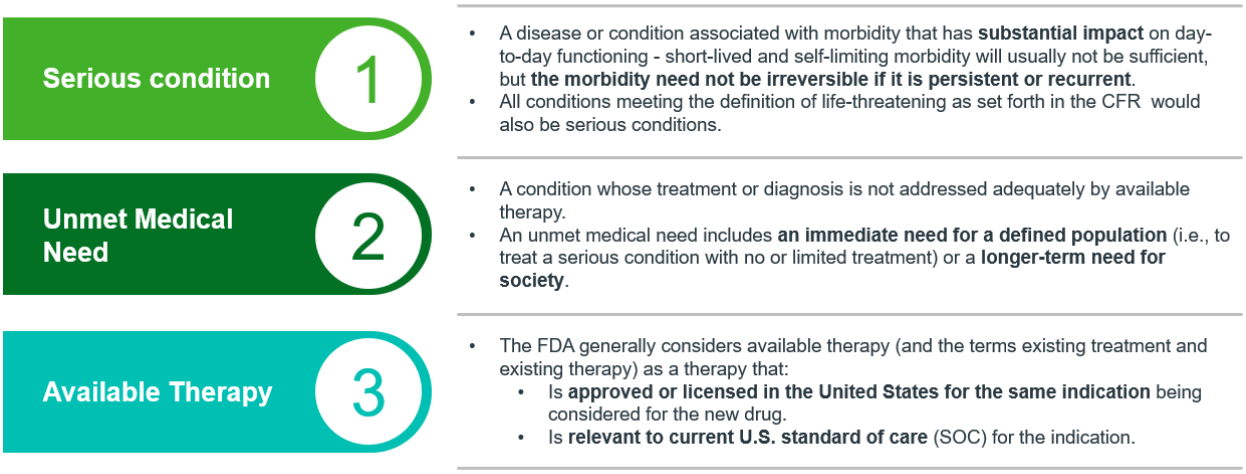
What are special designations/programs?

These are specific regulatory pathways and designations established by the U.S. Food and Drug Administration (FDA) to expedite the development, review, and approval of certain products. These designations are important because they **provide incentives and regulatory advantages** to encourage innovation in areas where treatment options are limited. By so doing, the FDA helps to advance treatments for serious or life-threatening conditions, expediting access to potentially life-saving treatments for patients in need.

Special designations are meant to address 21 CFR part 312 (intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. See **Figure 1** below for important definitions to note when it comes to special programs. [5]

If you are using this playbook, then chances are you are addressing an unmet need and qualify for at least one of the special designations – take advantage.

Figure 1: Important Definitions



Now that we have established the definitions and baseline, let us get into the details of each of the special programs and how you can take advantage of them.

6.2. Orphan Drug Designation

According to FDA guidance, Orphan Drug Designation (ODD) is a status granted by regulatory authorities to drugs or therapies that are meant to treat rare diseases or conditions. For some rare disease treatments, the low financial incentives to continue development or production led to them being “orphaned” or discontinued. To help with this, the Orphan Drug Act (a law passed by Congress in 1983) incentivizes drug development for rare diseases. [10]

What are Orphan Drugs?

These are drugs (including biologics) for the prevention, diagnosis, or treatment of diseases or conditions **affecting fewer than 200,000 persons** in the US, **OR** drugs that will **not be profitable** within 7 years following approval by the FDA

Companies and other drug developers can request orphan drug designation and the FDA will grant it if the drug meets the required criteria. An ODD provides financial incentives to make it easier to bring a drug or therapy to market. [14] These incentives include:

- ☐ Tax credits for qualified clinical (in humans) testing
- ☐ Waiver of the FDA New Drug Application or Biologics License Application – currently at almost $3 million for a new drug)
- ☐ Eligibility for 7-year marketing exclusivity ("orphan exclusivity") upon marketing approval

In addition, the Orphan Drug Act established the Orphan Product Grants Program to provide funding for developing products for rare diseases or conditions [10]

How do I apply for ODD?

Sponsors seeking orphan drug designation for a drug must submit a request for designation to the agency. Sponsors requesting designation of the same drug for the same rare disease or condition as a previously designated product must submit their own data and information to support their designation request. Designations for Orphan Drug and Rare Pediatric Disease are granted by the Office of Orphan Products Development (OOPD), and this is where you send your request. It is important to note that ODD is a separate process from seeking approval or licensing. Drugs for rare diseases go through the same rigorous scientific review process as any other drug for approval or licensing. [3]

OOPD evaluates information from product sponsors to determine if drugs, biologics, or medical devices meet the criteria for certain incentives and administers grants to provide funding for research on rare diseases. The office also works on rare disease issues with medical and research communities, professional organizations, academia, government agencies, industry, and rare disease patient groups. Together with the Office of Pediatric Therapeutics and product centers, the OOPD also determines Rare Pediatric Disease Designation for drugs or biologics that meet certain criteria.

It is therefore important for you to ensure you are delivering correct information to meet application requirements when you apply for a potential orphan drug. We recommend that you ensure your request includes the following:

- ☐ Orphan Drug Designation request statement
- ☐ Administrative information
- ☐ Description of the rare disease or condition, proposed indication, and need for therapy
- ☐ Description of your investigational product and scientific rationale for use
- ☐ Orphan drug status
- ☐ Patient subset considerations and medical plausibility of the chosen subset
- ☐ Regulatory status and marketing history
- ☐ Documentation of patient population size

The FDA has a form designed to assist sponsors in providing the required content completely and succinctly for Orphan Drug Designation requests.[8] This can be found here Form FDA 4035. We have provided you with a template that you can use for the ODD request. This template was generated based on the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) Platform Vector Gene Therapy (PaVe-GT) team's experience preparing an Orphan Drug Designation (ODD) request to the FDA Office of Orphan Products Development. If you need an example for reference while you prepare your request, feel free to use PaVe-GT's lightly redacted example found on their website linked here.

How to submit ODD requests [8]

You may submit Orphan Drug Designation requests one of three ways:

1. Through the CDER NextGen portal
2. By emailing the required information to orphan@fda.hhs.gov
3. By mailing the required information to:

   Office of Orphan Products Development
   Attention: Orphan Drug Designation Program
   Food and Drug Administration
   WO32-5295
   10903 New Hampshire Avenue
   Silver Spring, MD 20993-0002

If you plan to email information to the FDA that is private, sensitive, proprietary, or commercial confidential, it is strongly encouraged to send it from an FDA-secured email address, so the transmission is encrypted. The agency will assume the addresses of emails received or email addresses provided as a point of contact are secure when responding to those email addresses.

Next, we will look at the Rare Pediatric Disease Designation.

6.3. Rare Pediatric Disease

The Rare Pediatric Disease program focuses on pediatric patients with rare diseases and unmet needs. Its purpose is to stimulate the development of new drugs for rare pediatric diseases by offering additional incentives for obtaining FDA approval of such products

What is a rare pediatric disease?

A rare pediatric disease is one that is **serious or life-threatening** in which the serious or life-threatening manifestations **primarily affect patients from birth to 18 years**, including neonates, infants, children, and adolescents. It must also be a rare disease or condition as described in the FD&C Act, with a **prevalence of fewer than 200,000** people in the United States.

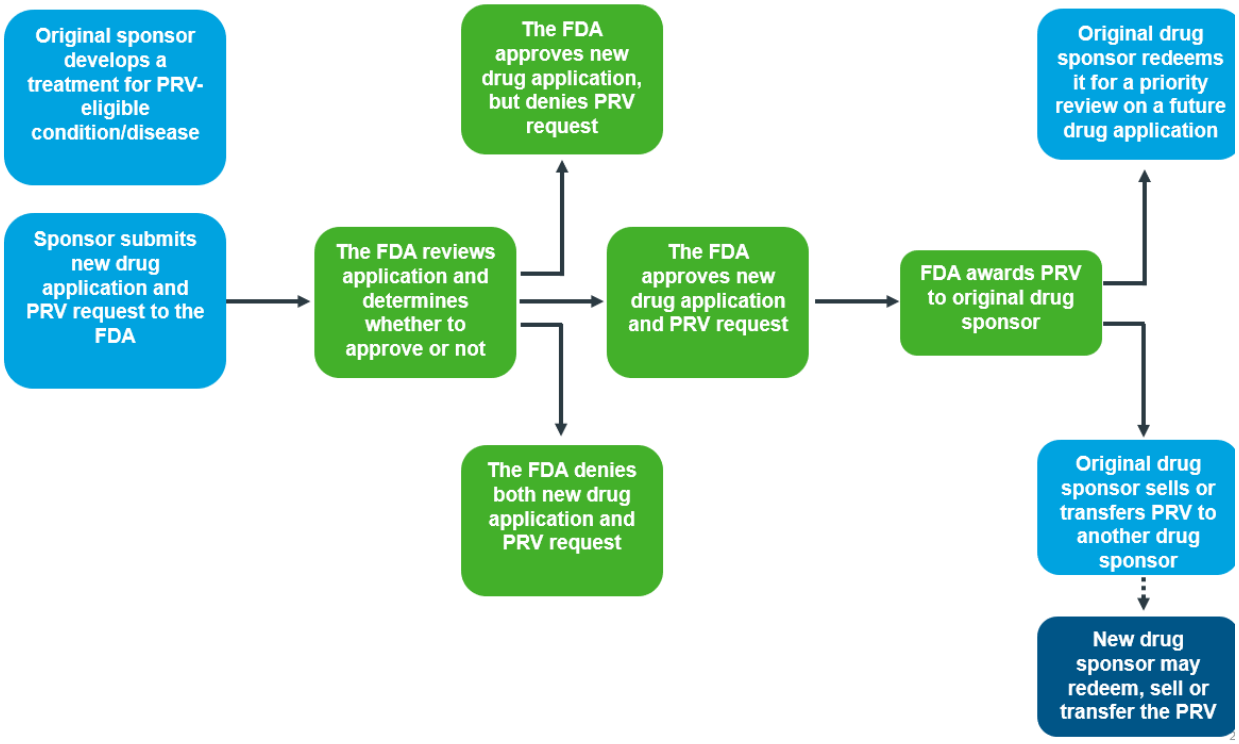
For your drug to obtain RPD Designation (RPDD), it must meet the following criteria:

- ☐ It must be intended for the prevention or treatment of a rare pediatric disease
- ☐ Adequate documentation or prevalence data must demonstrate that the intended pediatric disease or condition is rare
- ☐ Your application must not be for an active ingredient that is already approved for use
- ☐ There must be supportive data suggesting that your drug may be effective in the rare pediatric disease or condition [7]

Like the ODD, there are some advantages to applying for the RPDD. The FDA incentivizes sponsors with Priority Review Vouchers (PRV) to potentially help drug development companies recoup their expenses sooner. [12] The PRV can be used to receive a Priority Review designation of a later NDA or BLA for a different product – it can also be sold. See **Figure 2** below. [11]

Under the current statutory sunset provisions, after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease Priority Review vouchers.

Figure 2: Priority Review Voucher Process



Example of a template request form for the RPDD, as well as an example of RPDD application from the PaVe-GT program can be found on their website link here. Requests for RPDD are also sent to the Office of Orphan Drug Designations. This office works in collaborations with the Office of Pediatric Therapeutics to review and grant the RPDD designation. See the previous section on "How to submit ODD requests" for mailing addresses.

A white paper Successfully Navigating FDA Orphan Drug and Rare Pediatric Disease Designations for AAV9-hPCCA Gene Therapy: The NIH Pave-GT Experience that describes in detail the "how to" of creating ODD and RPDD applications was published by the PaVe-GT

team in Human Gene Therapy [14]. We encourage you to read the white paper prior to initiating your application preparation using the templates provided.

The ODD (and where applicable the Pediatric RD designation) are the main programs that you will be considering during the early stage of development. As your program accrues nonclinical data, consider whether criteria have been met for seeking Fast Track. As clinical data and progressing along the development continuum, there are additional programs that may apply, and these are provided below for completeness.

6.4. Expedited Programs

The FDA has five expedited designations for speeding up the availability of drugs for serious diseases. These are summarized in **Table 1** below. We will go into a bit more detail on each of the programs in the next few sub-chapters.

Therapies receiving special designations must meet the evidentiary standards for approval, including demonstrating effectiveness (regardless of whether the product receives accelerated or traditional approval). Fast track designation, Breakthrough Therapy designation, and Regenerative Medicine Advanced Therapy (RMAT) designation are distinct designation programs with different programmatic requirements. It is possible to apply for and receive more than one designation for a given product, but you should apply for each designation separately. Information that supports more than one designation may be submitted in each separate designation request. [5]

Table 1: Summary of Expedited Programs

	Type of data required	Qualifying criteria	Benefits
Fast Track	Preliminary non-clinical, mechanistic, or clinical data	A drug that is intended to treat a serious condition **AND** non-clinical or clinical data demonstrate the potential to address unmet medical need **OR** a drug that has been designated as a qualified infectious disease product	• More frequent meetings with the FDA • More frequent written communication from the FDA • Eligibility for Accelerated Approval and Priority Review if criteria are met • Rolling review
Breakthrough Therapy	Preliminary clinical data	A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• More frequent meetings with the FDA • More frequent written communication from the FDA • Rolling review • Intensive guidance on an efficient drug development program • Involvement of FDA senior managers to expedite development

Accelerated Approval*	Not specified; Sponsor should make justification of alternate endpoint based scientific support	A drug that treats a serious condition **AND** generally provides a meaningful advantage over available therapies **AND** demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	• Approval based on a surrogate or intermediate endpoint (often allows for shorter development time) ***Note:*** The FDA requires clinical trials to be conducted post approval to confirm clinical benefit
Priority Review	Data contained in the final NDA submission	An application (original or efficacy supplement) for a drug that treats a serious condition **AND**, if approved, would provide a significant improvement in safety or effectiveness **OR** any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505Ab **OR** an application for a drug that has been designated as a qualified infectious disease product **OR** any application or supplement for a drug submitted with a priority review voucher	• Review of application in 6 months
Regenerative Medicine Advanced Therapy (RMAT) Designation‡	Preliminary clinical evidence	A drug that is a regenerative medicine therapy intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, **AND** preliminary clinical evidence indicates that the drug has the potential to address unmet medical	• Early interactions with the FDA to discuss potential surrogate or intermediate endpoint • Eligibility for Priority Review • Eligibility for Accelerated Approval under current FDA preapproval standards but with new post-approval requirements

		needs for such disease or condition	
*Accelerated Approval is a pathway, unlike the other four which are designations ‡Still relatively new and not easy to get			

6.4.1. Fast Track

Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. An investigational new drug intended to treat a serious condition, and for which non-clinical or clinical data demonstrate the potential to address an unmet medical need in patients with such condition, can receive Fast Track designation. [4]

In addition, such a product could be eligible for Priority Review if supported by clinical data at the time of marketing application submission. Fast Track designation must be requested by the drug company/sponsor – the request can be initiated at any time during the drug development process. The FDA will review the request and decide within 60 days based on whether the drug fills an unmet medical need in a serious condition. [6]

6.4.2. Breakthrough Therapy

This designation is designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints. Clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- ☐ An effect on an established surrogate endpoint
- ☐ An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- ☐ An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- ☐ A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

Pro tip: Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested Breakthrough Therapy designation, the FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation.

The level of evidence required for Breakthrough Therapy designation is higher than for Fast Track designation. Specifically, Fast Track designation requires only that non-clinical or clinical

data demonstrate the potential to address an unmet medical need, whereas for Breakthrough Therapy designation, preliminary clinical evidence must indicate that the product may demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints. [2]

6.4.3. Accelerated Approval

When studying a new drug, it can sometimes take many years to learn whether the drug actually provides a real effect on how a patient survives, feels, or functions. A positive therapeutic effect that is clinically meaningful in the context of a given disease is known as "clinical benefit." Mindful of the fact that it may take an extended period to measure a drug's intended clinical benefit, in 1992 FDA instituted the Accelerated Approval regulations, allowing drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Using a surrogate endpoint enabled the FDA to approve these drugs faster. Accelerated approval has been used primarily in settings in which the disease course is long, and an extended period would be required to measure the intended clinical benefit of a drug. [1]

The FDA may grant accelerated approval to drugs which include regenerative medicine therapies, "for a serious or life-threatening disease or condition…upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

Sponsors of drugs that have been granted accelerated approval have been required to conduct post-approval confirmatory studies to verify and describe the anticipated effects of their products on irreversible morbidity and mortality or other clinical benefit.

6.4.4. Regenerative Medicine Advanced Therapy (RMAT)

. An investigational drug is eligible for RMAT designation if:

- ☐ It meets the definition of regenerative medicine therapy
- ☐ It is intended to treat, modify, reverse, or cure a serious condition; and
- ☐ Preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition. [13]

Regarding the preliminary clinical evidence to demonstrate the potential of a regenerative medicine therapy to address unmet medical needs, the FDA generally expects that such evidence would be obtained from clinical investigations specifically conducted to assess the effects of the therapy on a serious condition. When determining whether the preliminary clinical evidence is sufficient to support RMAT designation, CBER consider factors including but not limited to:

- ☐ The rigor of data collection
- ☐ The consistency and persuasiveness of the outcomes
- ☐ The number of patients or subjects
- ☐ The number of sites contributing to the data
- ☐ The severity, rarity, or prevalence of the condition

As opposed to Breakthrough Therapy designation, the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies. In order to apply for RMAT designation, a sponsor should submit a request to CBER either with an IND or in an IND amendment.

Pro tip: CBER will not accept requests for RMAT designation for INDs that are inactive or on clinical hold. Additionally, the FDA will not further process a pending RMAT designation request for an IND that is placed on inactive or hold status while the designation request is under review.

6.4.5. Priority Review

A Priority Review designation means FDA's goal is to act on an application within 6 months of filing by the FDA. A drug, including those that received Fast Track, Breakthrough Therapy, or RMAT designation, may be eligible for Priority Review, if it meets the criteria for Priority Review at the time the marketing application is submitted. A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. [9]

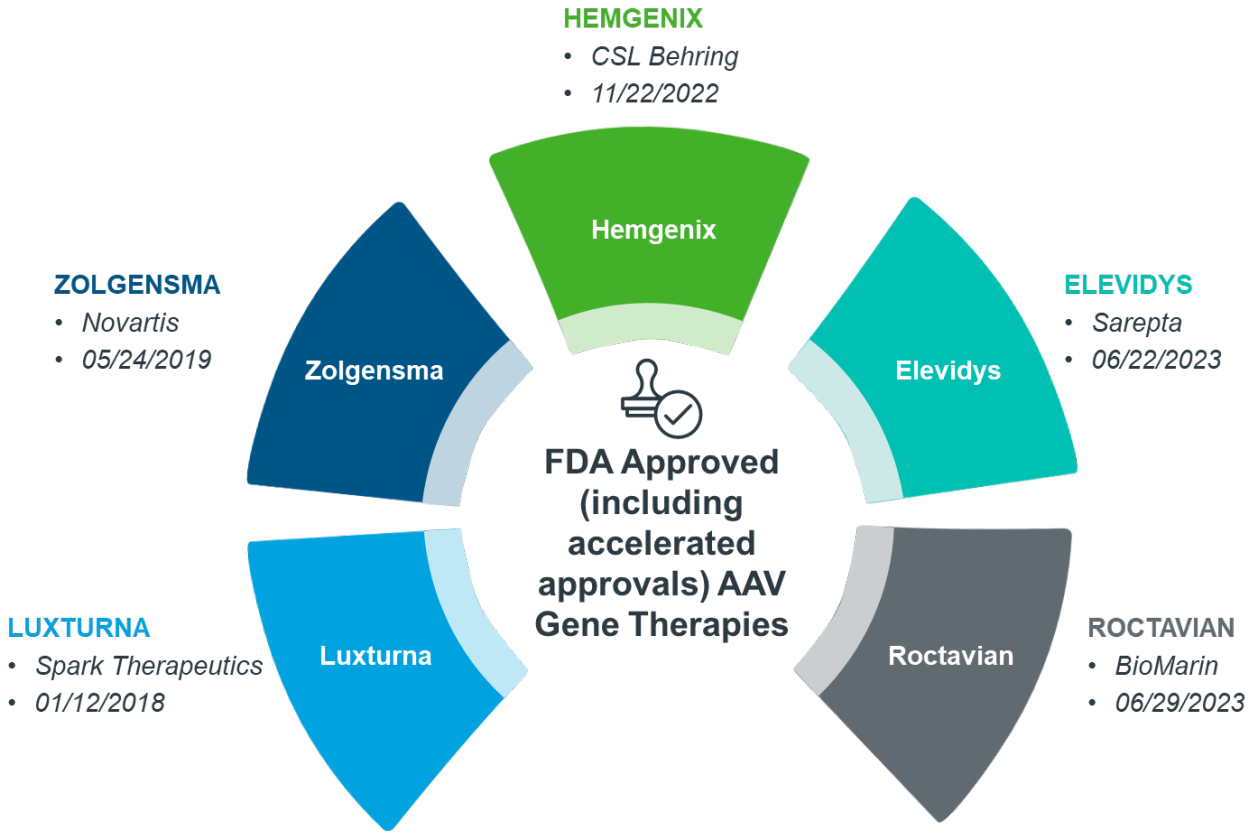
At the time of a pre-biologics license application (pre-BLA) meeting with CBER, sponsors of regenerative medicine therapies, including those under expedited development programs, should consider discussing their eligibility for Priority Review. A regenerative medicine therapy may receive Priority Review if it treats a serious condition, and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment of the condition.

6.5. Case Studies

To conclude this chapter, we will highlight the currently FDA-approved (including accelerated approvals) AAV gene therapies. There are five that fall in this category as of this version of the playbook, which are shown in **Figure 3** below.

From the 5 approved therapies, Zolgensma was awarded all the special designation programs (except for RMAT). We will highlight some of the important milestones for Zolgensma in the next section.

Figure 1: FDA Approved AAV Gene Therapies (in vivo gene replacement)



LUXTURNA

- **Approved Indication**: LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).
- Link to FDA approved package insert/labeling and other publicly available regulatory documents.

HEMGENIX

- **Approved Indication**: HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: Currently use Factor IX prophylaxis therapy, or Have current or historical life-threatening hemorrhage, or Have repeated, serious spontaneous bleeding episodes.

- Link to FDA approved package insert/labeling and other publicly available regulatory documents.

ELEVIDYS

- **Approved Indication**: ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. This indication is approved under accelerated approval based on expression of ELEVIDYS microdystrophin in skeletal muscle observed in patients treated with ELEVIDYS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Link to FDA approved package insert/labeling and other publicly available regulatory documents.

ROCTAVIAN

- **Approved Indication**: ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.
- Link to FDA approved package insert/labeling and other publicly available regulatory documents.

ZOLGENSMA

- **Approved Indication**: ZOLGENSMA is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.
- Link to FDA approved package insert/labeling and other publicly available regulatory documents.

You may refer to the FDA's Expedited Approval Mechanisms for New Drug Products as an additional resource on this topic.

Now that you have the overview of all special programs, including paths taken by previously approved AAV gene therapies, you're more prepared for your IND submission journey – in the next chapter.

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Chapter 7: IND Submission

What is an IND?

An Investigational New Drug application (IND) is a request from a pharmaceutical developer (also known as sponsor) to obtain authorization from the FDA to study their investigational product in humans. An IND is an exemption of the federal law that requires that any prescription drug transported across state borders must have a drug application approved by the FDA. Because most sponsors have manufacturing sites and clinical study sites across the United States, an IND is necessary to proceed with investigational trials of a new drug.

The FDA's primary objectives in reviewing an IND are to enforce the safety and rights of subjects and assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety. The FDA's review of Clinical Phase 2 and 3 data will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval, so it is important to set yourself up for success from your IND submission.

What should I include in my IND?

The IND must contain information in three broad areas [5]

- ☐ *In vitro* and Animal Pharmacology and Toxicology Studies (Non-Clinical)
- ☐ Chemistry, Manufacturing and Controls (CMC) Information
- ☐ Clinical Protocols and Investigator Information

The information you must submit in an IND to optimize successful review depends upon factors such as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

An important part of the IND preparation process includes the **general investigational plan** and the **protocols for specific human studies**. Subsequent IND amendments containing new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies, as appropriate. Annual Reports to the IND should focus on reporting the status of studies being conducted under the IND and update the general investigational plan for the coming year. This playbook will summarize the requirements for IND maintenance in Chapter 8.

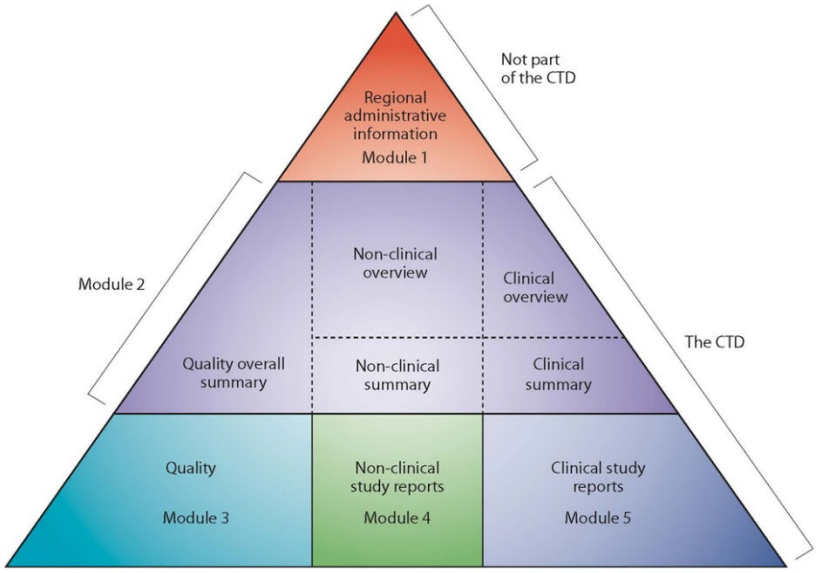
What format should I use for my IND submission?

Sponsors are required to follow the IND format set forth in CFR Title 21 Part 312.23 [2]. In the interest of fostering an efficient review of applications and harmonizing with global regulatory submissions, your IND should follow the eCTD format (electronic Common Technical Document – see **Figure 1** below) and should be submitted electronically through the FDA gateway.

The eCTD, which is divided into 5 sections, called modules, is the accepted standard format for submitting applications, amendments, supplements, and reports to the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). The eCTD process also includes technical requirements for electronic submissions. Please refer to FDA's eCTD Resource Page [3] for more information.

The technical aspects of electronic submissions will not be covered in this handbook; however, the outline and format of the eCTD structure is reflected in the templates and section headers of the IND to comply with electronic submission specifications. Sponsors following the outline presented in this handbook will meet electronic submission format requirements.

Figure 1: eCTD Modules



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Before electronic submission of your IND, you must obtain an IND number through CBER. Similar to the Pre-IND process (see Chapter 5.2: Meeting Requests), requests must be submitted via email to CBERRIMS@fda.hhs.gov and should contain the following information:

- Name of Applicant, Applicant Address, Applicant Contact
- Regulatory Contact (if different from Applicant contact)
- Drug Name and Description
- Indication
- Review Division within CBER
- Type of IND (commercial or research)

Once your IND is submitted, you will have to wait 30 calendar days before initiating any clinical trials. During this time, the FDA will review your IND for any safety concerns to ensure that research subjects will not be exposed to unreasonable risk.

Pro tip: In some cases, FDA may allow exceptions to electronic submissions by **submitting a waiver.** This may be appropriate, for example, for small non-profit organizations or research institutions. After you have requested and received the IND number, please send an email to esubprep@cber.fda.gov and formally request the waiver. Once your waiver request has been approved by the esubrep staff, you may submit the IND via DCC email at: cberdcc_emailsub@fda.hhs.gov

Now that you know what an IND is and how it is submitted, we will get into the details of each specific module and what you will need to include in each section.

7.1. Module 1: Admin Information

The eCTD is the standardized format for marketing applications as established by the International Conference on Harmonization (ICH) and accepted by the EU, US, Japan, and many other countries. With minor exceptions, this enables consistent IND content and format requirements among ICH-adopting countries. Module 1, being the exception, does not follow the ICH format as the module is almost entirely comprised of local requirements and covers regional administrative information required by the applicable regulatory authority – in your case, the US FDA.

7.1.1. Module 1.1: Forms 1571 and 3674

Forms 1571 and 3674 should accompany your IND. You can find the most current version of these forms on the FDA website here: Forms | FDA. Each form serves a unique purpose in the IND application:

- ☐ Form FDA 1571 – general information on the sponsor, description of the drug, type of submission and submission contents
- ☐ Form 3674 – to certify compliance with ClinicalTrials.gov requirements

7.1.2. Module 1.2: Cover Letter

This is typically a summary of the IND and serves as an introduction to the drug and contents of the submission. The IND cover letter is an important component of the IND submission and should clearly and effectively communicate the key points of the submission to the FDA. Consider including the following:

- ☐ A description of the drug being studied
- ☐ The purpose of the study and an overview of the study design
- ☐ A statement indicating each study's compliance with all applicable FDA regulations and guidelines

7.1.3. Module 1.12.14: Environmental Analysis Waiver

What is an Environmental Analysis Waiver?

Environmental impact considerations are covered under CFR 21 Part 25 [1]. The Environmental Analysis Waiver (EAW) process is used by the FDA in compliance with the National Environmental Policy Act (NEPA), which requires federal agencies to consider the environmental effects of their proposed actions. The FDA may determine that an EAW is appropriate for certain actions, such as the approval of new drug applications or medical devices, or the issuance of certain guidance documents. The waiver allows the agency to forgo a formal environmental analysis if it determines that such an analysis is unnecessary.

So how does the waiver process work?

Most INDs will be exempt from a formal environmental analysis, so a statement must be included, for example: “A categorical exclusion from the requirements of preparing an environmental assessment is claimed for this Investigational New Drug application under 21 CFR 25.31 (e). The drug to be shipped under this notice is intended to be used for clinical studies and/or research programs in which waste disposal will be controlled, the amount of waste expected to enter the environment is reasonably expected to be nontoxic and in minimal quantities, and to the knowledge of the applicant no extraordinary circumstances exist (21 CFR 25.15 (d)).” Other similar language may be appropriate. The exemption may not apply to all drugs (e.g., radioactive drugs) so additional analysis on the environmental impact may be necessary.

Environmental Analysis Outside the United States

As previously noted, Module 1 will contain different regional requirements. The European Union and specific European countries will have different environmental assessment requirements specific to AAVs and other gene therapy-based drugs. These products are considered “genetically modified organisms” (GMO) and the Ministry of Environment for the relevant countries requires specific format and content for the Environmental Analysis to be reviewed. If your general investigational plan includes study sites in Europe, you may need to consider these requirements. Please refer to this link for more information. [4]

7.1.4. Module 1.12.1: Pre-IND Correspondence

The Pre-IND meeting minutes issued by the FDA should be provided in this section. Any data or information requested by the FDA in the Pre-IND meeting may also be referenced in this section pointing to the module where the information is provided.

7.1.5. Module 1.14.4.1: Investigator’s Brochure

The purpose of the investigator’s brochure (IB) is to provide the investigator with clinical and non-clinical information about the investigational drug relevant to the study of the drug in human subjects. The IB contains summaries of non-clinical, CMC, and clinical information regarding the investigational drug, which can be used by investigators to understand the scientific basis for the treatment and its safety profile. Please refer to the IB template to learn more about the information to include.

7.1.6. Module 1.14.4.2: Investigational Drug Label

The purpose of the investigational drug label is to provide a copy of all labels and labeling for the investigational product (both drug product and diluent, if applicable). A mock-up or printed representation of the proposed labeling for the investigator(s) is acceptable. The United States requires that investigational drug labels contain a "caution" statement that reads: "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

7.1.7. Module 1.20: General Investigational Plan [6]

For this section, you will provide an outline of the proposed clinical investigation plan of the drug. This includes both current and future studies. Your general investigational plan must summarize the following:

- ☐ Rationale supporting the proposed clinical trial (including the dose, schedule, and patient population)
- ☐ The planned trial duration
- ☐ Indication(s) to be investigated
- ☐ General approach for evaluation of the investigational drug
- ☐ Twelve-month clinical development plan
- ☐ Estimated number of subjects to be exposed in the trial
- ☐ Any serious risks anticipated

Now that you are done with Module 1, let's get into Module 2, which contains summary documents.

Templates

- Investigator's Brochure Template
- General Investigational Plan Template

References

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7.2. Module 2: Summary Documents

7.2.1. Module 2.2: Introduction

In this section, you will be providing the FDA with a summary of the development plans, non-clinical and any clinical data obtained on the investigational product. Ideally, the introduction should include basic information like proprietary, nonproprietary, and common names of your product, company name, formulation of the dosage form, strengths, route of administration, and proposed indications.

Consider following the sample outline below while structuring your introduction based on the information you have available.

- ☐ Product Name
- ☐ Product Description
  - o Active Ingredients
  - o Pharmacological Class
- ☐ Proposed Indication
- ☐ Formulation of the Dosage Form
- ☐ Route of Administration
- ☐ Clinical Program Objectives
- ☐ Planned Duration of the Proposed Clinical Study
- ☐ References

7.2.2. Module 2.3: Quality Overall Summary

This section is **OPTIONAL** at the IND stage as many sponsors are still in the early stages of CMC development. Should you still wish to include a QOS, consider the recommendations in the section below to understand what key information to present.

The overall goal of the QOS section is to provide the FDA with a summary of the scope and outline of the body of data you are showing in Module 3. A summary of the type of information you should consider including and not including within the QOS is shown in **Table 1** below:

Table 1: Information you should consider including in the QOS

QOS should include	QOS should not include
➢ **Sufficient information** to **provide** the **Quality Reviewer** with an **overview** of Module 3: Quality ➢ **Emphasis** of critical **key parameters** of the **Drug Substance and Drug Product – refer to Module 3 for further definition of DS and DP** ➢ **Justification** for cases where **guidances** were **not followed** ➢ **Discussion** of key **issues** that **integrate information from other modules,** particularly Module 3 ○ Cross-reference supporting information in other modules	✗ **Information**, data, or justification that was **not** already **included** in Module 3: Quality or in other parts of the CTD

Pro tip: Please make sure that the QOS is no longer than 40 pages of text, excluding tables and figures. Biotech products such as gene therapies, have more complex manufacturing processes so the document can be longer (but should not exceed 80 pages of text). Most of the information in QOS can be imported from Module 3: Quality (including tables, figures, or other items)

7.2.3. Module 2.4: Non-Clinical Overview

An Investigator Brochure containing a comprehensive summary of all non-clinical studies referenced in the IND may serve as a substitute for the **2.4 – Non-clinical Overview** and **2.6 – Non-clinical Written and Tabulated summaries**. Alternative approaches such as this may be considered on a case-by-case basis.

The overall goal of the non-clinical overview section is to provide the FDA with an integrated and critical assessment of the safety and efficacy of your product via **pharmacologic** and **toxicologic** evaluations. For more information on how to structure and what the key information to include in this section, check out the Module 2.4: Non-Clinical Overview template and consider the pro-tips below while building yours. [2]

Pro tip: Ensure the document length is no more than **30 pages (maximum)**.

Some points you should consider highlighting in the non-clinical overview section include:

- Relevant guidances on the conduct of studies and provide justification for any deviation made from the guidances
- Discussion and justification of the non-clinical testing strategy
- Good laboratory practice (GLP) status of the studies being submitted
- Any association between non-clinical findings and the quality characteristics of the human pharmaceutical, clinical trials results, or effects seen with related analogues
- Any literature which contains data or methods used to support the non-clinical information of the drug

You can cross-reference quality documents!

Can help justify proposed impurity in your drug substance and product

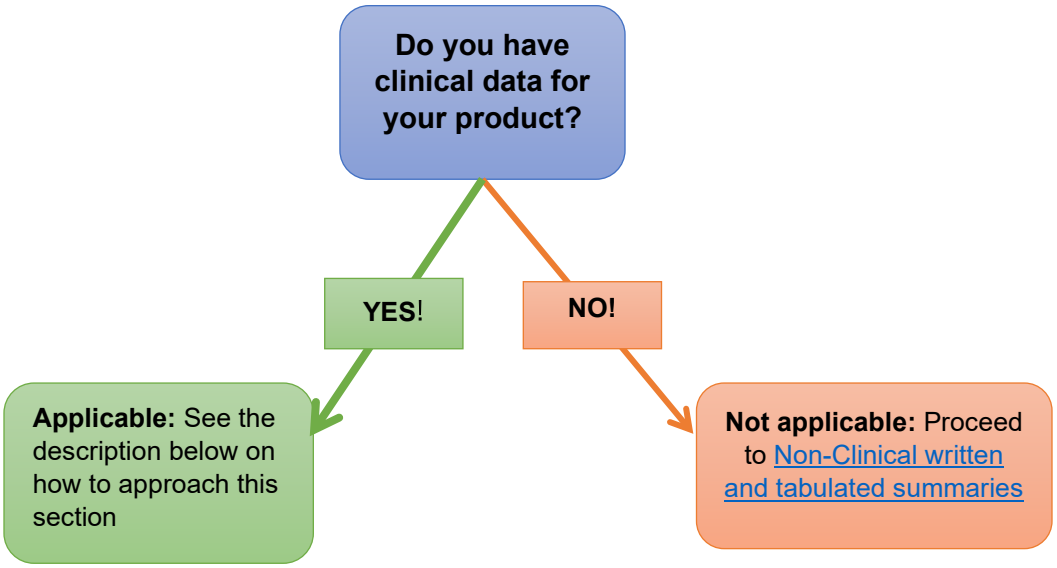
As AAV gene therapies are biotechnology-derived products, it is highly suggested that you:

- Provide an **assessment** of the **comparability** of material you used in the non-clinical and clinical studies and one you are proposing to market
- Provide relevant scientific literature and the properties of related products
- For scientific literature used in place of studies conducted include justification around the design of the studies and deviations from available guidances
- Provide information on the quality of batches for drug substance used in these referenced studies

If your drug product includes a novel excipient (i.e., an inactive substance that serves as the vehicle or medium for your AAV drug product, often to increase stability and thus shelf-life) then you should include excipient's safety information

7.2.4. Module 2.5: Clinical Overview – NOT APPLICABLE unless drug has clinical data

This section will not be required for the majority of original INDs. Most novel investigational drugs (such as the BGTC candidates) do not have prior clinical data unless the drug has been studied in other countries or otherwise tested in humans under other legal exemptions. Another exception would be if you have experience with your asset in another indication. Analogues may be used to help define specific parameters (e.g., safety profile, dose range, and tissue tropism) to use as a baseline comparison for clinical data for your product. Please see the Pre-IND chapter for more information on analogue selection.



The overall goal of the clinical overview section is to provide the FDA with a brief overview of your product's clinical data, key findings, and any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications). For more information on how to structure this section and what key information to include, check out the clinical overview template in **Table 2** and leverage the pro tips below.

Table 2: Clinical Overview Template

What you should include	Potential Table of contents
• Strengths and limitations of the development program and study results • Analysis of the benefits and risks for your product for its intended use Highlight how the findings support critical parts of the prescribing information	1. Product Development Rationale 2. Overview of Biopharmaceutics 3. Overview of Clinical Pharmacology 4. Overview of Efficacy 5. Overview of Safety 6. Benefits and Risks Conclusions 7. References

You can use graphs and tables in the body of the text for brevity and ease

Pro tip: Ensure the document length is no more than **30 pages** maximum, unless it contains complex data. Some other points you should consider highlighting in your clinical overview section include:

- Discussion and justification of the clinical development plan for your product (include critical study design decisions)
- Good clinical practice (GCP) status of the studies being submitted
- Provide benefits and risks evaluations based on the conclusions of the relevant clinical studies

Consider the **efficacy and safety findings** which support the proposed dose and target indication

Consider evaluation of how **prescribing information** and other approaches can optimize benefits and manage risks

- Address any issues (particular around efficacy or safety) that you may have encountered in your development and how you resolved them
- Disclose any unresolved issues and indicate what effect they may have on your program

7.2.5. Module 2.6: Non-Clinical Written and Tabulated Summaries

The overall goal of this section is to provide the FDA with a comprehensive, factual overview of your non-clinical data [2]. Click through the Module 2.6 Non-Clinical Written and tabulated summary template to learn more about how you can structure this section and convey all the key information needed for your product.

Share all the current **pharmacology** and **toxicology information** that supports translation of the study from **non-clinical to clinical** and **readiness** for this IND submission.

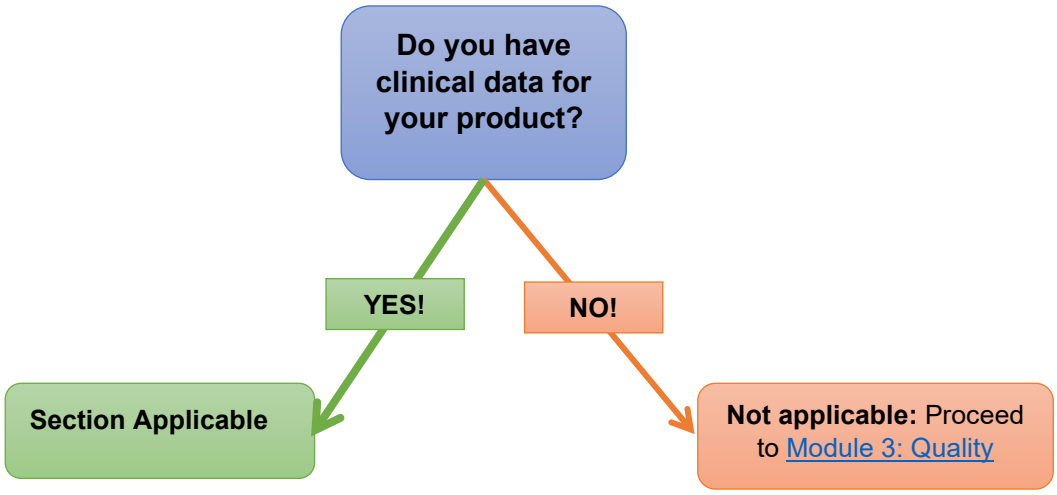
The Module 2 sections provided below reflect the most typical study types conducted for AAV therapies. Other factors such as indication, on-target vs. off-target sites may require additional pre-clinical testing (e.g., reproductive toxicity). For other study types not listed below, please refer to FDA Guidance*: The Comprehensive Table of Contents Headings and Hierarchy (fda.gov)*

Module 2	Summaries
2.6	Non-clinical Summary
2.6.1	Introduction
2.6.2	Pharmacology and Non-clinical Efficacy Written Summary
2.6.3	Pharmacology and Non-clinical Efficacy Tabulated Summary
2.6.4	Pharmacokinetics Written Summary*
2.6.5	Pharmacokinetics Tabulated Summary*
2.6.6	Toxicology Written Summary
2.6.7	Toxicology Tabulated Summary

*Traditional pharmacokinetics (absorption, distribution, metabolism, excretion) studies are not feasible with AAV gene therapies. However, these sections are noted here for completeness per eCTD structure. These sections may be left blank.

7.2.6. Module 2.7: Clinical Summary – NOT APPLICABLE unless drug has clinical data

Similar to Module 2.5, this section (Module 2.7) will not be required for the majority of original INDs for the same reasons.



The overall goal of this section is to provide the FDA with a comprehensive, factual overview of the clinical data for your product. You should consider including information about any prior investigations or marketing (US or globally) that has been done with your product, list the countries where your product has been marketed and whether it was withdrawn or state if there has been no prior human experience. Additionally, you need to ensure that this section is between 50-400 pages. [1]

To get more information about how you can structure this section and convey all the key information needed for your product, consider structuring this section based on the sample outline below:

Sample Outline for Clinical Summary

1. **Summary of Biopharmaceutic Studies and Associated Analytical Methods**
   In this section, your goal is to provide the FDA with an overview of the formulation development process, *in vitro* and *in vivo* dose determination information, the general approach, and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), *in vitro* dissolution profile database, and analytical methods used. Consider the following flow:

1.1. Background and Overview
1.2. Summary of results of individual studies
1.3. Comparison and analysis of results across studies

Avoid including detailed information about individual studies here

2. **Summary of Clinical Pharmacology Studies**
   In this section, your goal is to provide the FDA with a summary of the clinical pharmacology studies including pharmacokinetics (PK), pharmacodynamics (PD), and human biomaterial database. Consider the following flow:

   2.1. Background and Overview
   2.2. Summary of Results of Individual Studies
   2.3. Comparison and Analyses of Results Across Studies

Avoid including detailed information about individual studies here

3. **Summary of Clinical Efficacy**
   In this section, your goal is to provide the FDA with a description of the controlled studies that were conducted to test efficacy (including: dose-response, comparative efficacy, and long-term efficacy). Consider the following flow:

   3.1. Background and Overview
   3.2. Summary of Results of Individual Studies
   3.3. Comparison and Analyses of Results Across Studies
   3.4. Analysis of Clinical Information Relevant to Dosing Recommendations
   3.5. Persistence of Efficacy and/or Tolerance Effects

Avoid including detailed information about individual studies here

4. **Summary of Clinical Safety**
   In this section, your goal is to provide the FDA with a summary of any data relevant to safety in the intended patient population. You can also incorporate your findings from the individual clinical study reports and other relevant reports within this section. The safety profile of your product should be outlined clearly and in an objective manner. Consider the following flow:

   4.1. Exposure to the Drug
   4.2. Adverse Events
   4.3. Clinical Laboratory Evaluations
   4.4. Vital Signs, Physical Findings, and Other Observations Related to Safety
   4.5. Safety in Special Groups and Situations
   4.6. Post Marketing Data

5. **Literature References**
   In this section, your goal is to include all the publications cited in the clinical summary. Any references need to include their full copies in the literature section.

6. **Synopses of Individual Studies**
   In this section, it is recommended that you include a study synopsis of each relevant clinical study on the drug.

Templates

- Non-clinical Overview Template
- Non-clinical Written and Tabulated Summaries Template

References

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2. M4S: The CTD — Safety. Retrieved from U.S. Food & Drug Administration: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m4s-ctd-safety

7.3. Module 3: Quality

For this section of the IND, your goal is to describe the manufacturing processes, controls, and analytical methods used for your investigational product. It is essential that you provide an end-to-end view of the entire workflow and quality controls involved.

Module 3 is an important part of the IND submission that **needs to be prepared with detail and clarity** in order to demonstrate that you will have a product that **meets safety standards required** for the study in humans.

We will now dive into the details of what you need to cover in this section, starting with information on the drug substance. For a more detailed description of what to include in this section, see the guidelines and sample outline shown in **Figure 1.** [1]

7.3.1. Module 3.2S: Drug Substance

What is a Drug Substance?

A Drug Substance is the **active ingredient** that produces the **intended pharmacological effect** in the diagnosis, cure, mitigation, treatment, or prevention of a disease. This does not include intermediates used in the synthesis. For AAVs, the plasmid is often considered the drug substance.

In this section, you will provide the FDA with detailed information on the composition, quality, and manufacturing process of the drug substance. This will give the FDA assurance that the drug substance is manufactured and tested for purity and potency for use in clinical trials.

It is advisable that you cover the following:

- ☐ Physical, chemical, and biological characteristics
- ☐ Name and address of manufacturer
- ☐ General method of preparation (include a list of the reagents and solvents)
- ☐ Acceptable limits and analytical methods to assure identity, strength, quality, purity
- ☐ Stability information (appropriate to phase of investigation)

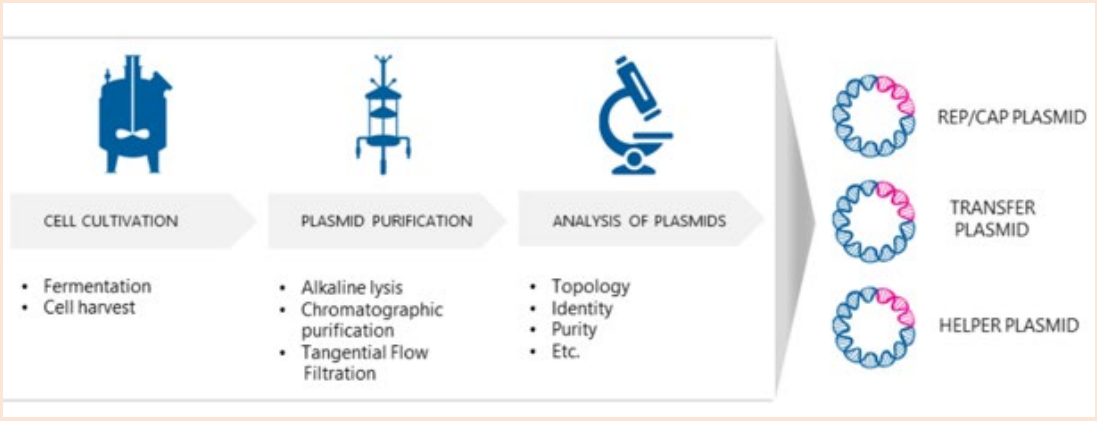
Consider the sample outline [1] below in **Figure 1**, for the specific contents to include.

Figure 1: Sample outline for Module 3.2S

- **General Information**
  - Nomenclature
  - Structure
  - General properties
- **Manufacture**
  - Manufacturer(s)
  - Description of Manufacturing Process and Process Controls
  - Control of Materials
  - Controls of Critical Steps and Intermediates
  - Process Validation and/or Evaluation
  - Manufacturing Process Development
- **Characterization**
  - Elucidation of Structure and other Characteristics
  - Impurities
- **Control of Drug Substance**
  - Specification
  - Analytical Procedures
  - Batch Analyses
  - Justification of Specification
- **Reference Standards or Materials**
- **Container Closure Systems**
- **Stability**
  - Stability Summary and Conclusions
  - Stability Data

Pro tip: For the general method of preparation, the FDA suggests a **detailed flow diagram** to complement a written description of the preparation. See **Figure 2** below.

Figure 2: AAV Plasmid Production



Additionally, more information may be needed for a comprehensive assessment of the safety of biotechnology-derived drugs or drugs extracted from human or animal sources.

It is recommended that you provide the FDA with:

- A brief description of the testing and analytical methods that were used to ensure the identity, strength, quality, and purity of your drug substance along with acceptable limits
- A brief description of your stability studies and methods you may have used to monitor the stability of your drug substance during toxicology studies
- Preliminary tabular data based on representative material may be submitted

Given that the list of tests and attributes can be quite extensive for an AAV gene therapy product, the BGTC is actively working on establishing a minimal set of Critical Quality Attributes (CQAs) that will be included in future iterations of the BGTC Regulatory Playbook. These CQAs are applicable to most AAV gene therapies and can be used as a guideline for what you can include in your IND submission. It is important to include certificates of analysis or compliance to show quality control acceptance.

Given process development is at an early stage, the FDA expects to see continued development and refinement of quality tests and specifications. These development plans should be discussed during Pre-IND interactions with the FDA.

7.3.2. Module 3.2P: Drug Product

What is a Drug Product?

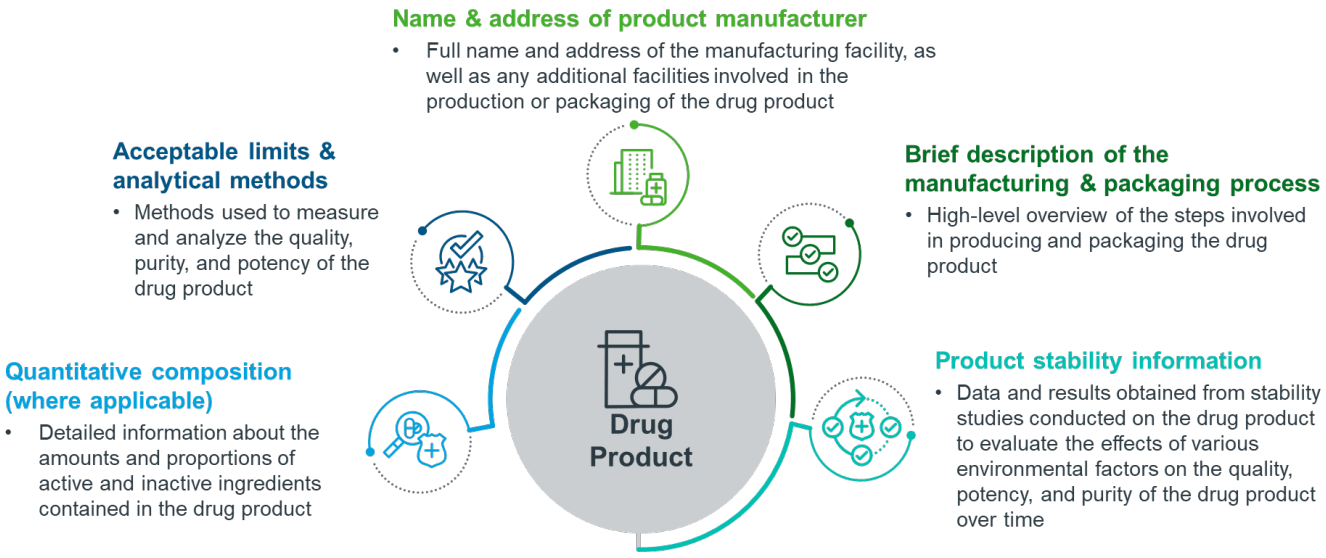
This is a finished dosage form, for example tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. For AAV gene therapy products, this usually means the final infusion or injectable solution, containing the vector and excipients (if any), in any final delivery device.

Similar to the drug substance sub-section, your aim here is to provide a detailed description of the drug product, including its composition, manufacturing process, and specifications. In this section, you should include information on the chemical structure and physical properties of your drug product, as well as its intended use and dosage form. You should also include a description of the formulation of the drug product, including the ingredients used and the manufacturing process, to provide assurance that the drug product is consistent in quality, purity, and strength. Additionally, you should include information on the stability of the drug

product and its packaging, as well as any known or potential interactions with other drugs or substances. This information is critical for safety in human trials.

Similar to the drug substance section, the drug product section will contain lots of information. It is recommended that you break it down into different categories – see **Figure 3** below for considerations.

Figure 3: Categories to consider for Drug Product



You should provide a list of all components which are used in the manufacturing process. This includes, but is not limited to the following:

- ☐ Cells
- ☐ Cell banking systems
- ☐ Viral banking systems
- ☐ Reagents
- ☐ Raw materials
- ☐ Culture bags
- ☐ Culture flasks
- ☐ Chromatography matrices
- ☐ Tubing
- ☐ Container closure system

Your list should include reasonable alternatives for inactive compounds used in the manufacturing of the investigational drug product, including both components intended to

appear in the drug product and those which may not appear, but which are used in the manufacturing process (also known as reagents).

A detailed flow diagram and a brief written description of the manufacturing process should be submitted, including sterilization process for sterile products. See **Figure 4** for a sample outline of the Drug Product section, showing the key topics to include in this section of the IND.

Figure 4: Sample Outline for Drug Product

- **Description and Composition of the Drug Product**
- **Pharmaceutical Development**
- **Manufacture**
  - Manufacturer(s)
  - Batch Formula
  - Description of Manufacturing Process and Process Controls
  - Controls of Critical Steps and Intermediates
  - Process Validation and/or Evaluation
- **Control of Excipients**
- **Control of Drug Product**
  - Specification(s)
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Batch Analyses
  - Characterization of Impurities
  - Justification of Specification(s)
- **Reference Standards or Materials**
- **Container Closure System**
- **Stability**
  - Stability Summary and Conclusion
  - Stability Data

You will most likely work with a contract development and manufacturing organization (CDMO) for manufacturing and testing of the drug substance and drug product. The CDMO may have a Drug Master File (DMF) in place which will facilitate preparation of your IND. In entering a partnership with your CDMO, a Quality Agreement will be established. This agreement will outline the roles and responsibilities between you and the CDMO. In most cases, the CDMO will manufacture, test, and release the drug substance and drug product batches per your specifications and will provide a signed Certificate of Analysis (COA) for each batch ensuring lot release testing criteria have been met. While this arrangement is typical and acceptable, as the drug developer, you are still ultimately responsible for ensuring your CDMO complies with all appropriate regulations and standard operating procedures, as outlined in your Quality Agreement. As for this section of the IND (Module 3.2P), be sure to include a copy of the COA for the clinical batch.

Given process development is at an early stage, the FDA expects to see continued development and refinement of quality tests and specifications. These development plans should be discussed during Pre-IND interactions with the FDA.

While AAV formulations are stable when frozen, stability studies are required to verify purity and potency in order to administer in human trials. Per the FDA's feedback on the stability requirements, a sponsor may not be required to provide real-time stability data provided stability data from comparable products (other AAVs with similar manufacturing and packaging) is presented. For Phase 1 clinical batches, a sponsor may also propose a stability study that deviates from ICH guidelines and timepoints, provided the study design evaluates stability indicating attributes. You should present your modified stability study design in your Pre-IND meeting to obtain the Agency's feedback, prior to submission in your IND.

7.3.3. Drug Master File (DMF)

Your CDMO may have a Drug Master File (DMF) submitted to the FDA. There are different types of DMFs which will contain different content depending on the type (see Drug Master File (DMF) Submission Resources | FDA). You must obtain approval from the DMF holder to refer to their DMF in your IND (this is commonly referred to as a Right of Reference Letter and is provided in Module 1.4.1 Letter of Authorization). If you rely on a DMF, you will need to ensure that it contains all the information necessary for the FDA to review your IND. **Table 3** provides information on what sections are typically covered in a DMF. The Drug Product section is almost always covered in the IND, rather than a DMF.

Table 3: IND Sections Potentially Covered in a DMF (note these will depend on your CDMO)

	DMF (CDMO Responsibility)	**IND (Sponsor Responsibility)**
3.2.S – Drug Substance		
3.2.S.1 General information 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General properties		X
3.2.S.2 Manufacture 3.2.S.2.1 Manufacturer(s) 3.2.S.2.2 Description of Manufacturing Process and Process Controls 3.2.S.2.3 Control of Materials 3.2.S.2.4 Controls of Critical Steps and Intermediates 3.2.S.2.5 Process Validation and/or Evaluation 3.2.S.2.6 Manufacturing Process Development	X	
3.2.S.3 Characterization 3.2.S.3.1 Elucidation of Structure and other Characteristics 3.2.S.3.2 Impurities	X for those with *	X for all others

3.2.S.4 Control of drug substance 3.2.S.4.1 Specification 3.2.S.4.2 Analytical Procedures* 3.2.S.4.3 Validation of Analytical Procedures 3.2.S.4.4 Batch Analyses 3.2.S.4.5 Justification of Specification	X for those with *	X for all others
3.2.S.5 Reference standards or materials	X	
3.2.S.6 Container closure systems	X	
3.2.S.7 Stability 3.2.S.7.1 Stability Summary and Conclusions 3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment 3.2.S.7.3 Stability Data	X	
3.2.A - APPENDICES		
3.2.A.1 Facilities and Equipment [name, manufacturer]	X	
3.2.A.2 Adventitious agents safety evaluation [name, dosage form, manufacturer]		X
3.2.A.3 Novel excipients		X
3.2.R – REGIONAL INFORMATION		
Drug Substance and Drug Product Batch Records		X

7.3.4. Module 3.2A: Appendices (Facilities & Equipment, Adventitious Agents, Novel Excipients)

If you have supplemental information that may be helpful to the FDA in evaluating the safety, efficacy, and quality of your drug product, this is where you will want to include it. This information may include detailed descriptions of the analytical methods used to test the drug substance and drug product, additional data on stability testing, validation reports, and other relevant information. This section supplements the content of the main body of Module 3.

The appendices section of the IND Module 3 is not mandatory, but it is often included by sponsors to provide a more complete picture of the drug product and its manufacturing process. Including this additional information can help expedite the regulatory review process and increase the chances of approval for your IND application.

7.3.5. Module 3.2R: Regional Information

The goal of this section is to provide the FDA with details about the drug product manufacturing and control information for the specific region or country where you will be applying for approval of your AAV gene therapy product.

This section may include the following information:

- ☐ Description of the manufacturing site(s) for the drug product, including details about the facilities, equipment, and personnel involved in the manufacturing process
- ☐ Information on the quality control processes used during drug manufacturing, including specifications and testing procedures for raw materials, intermediates, and finished products
- ☐ Details on the packaging and labeling of the drug product, including any specific requirements or regulations in the region

- ☐ Information on the stability and storage conditions of the drug product during transportation and distribution
- ☐ Any relevant regulatory requirements for the region, such as GMP (Good Manufacturing Practice) guidelines or other quality standards

7.3.6. Module 3.3: Literature

In this section, your goal is to include all the publications cited. Any referenced literature needs to include their full copies in this section (as separate pdf files – include links).

References

1. Administration, U. F. (January 2020). Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs). Retrieved from https://www.fda.gov/media/113760/download

7.4. Module 4: Non-clinical Data

7.4.1. Module 4.2: Study Reports

The goal of this section is to provide the FDA with all non-clinical reports relevant to the safety and biological activity of your investigational product in the indications of interest. The study reports should be organized in the disciplines outlined in MODULES 4.2.1 through 4.2.3 which mirror Module 2.6 summaries. Please refer to FDA Guidance on the order of reports in this section: The Comprehensive Table of Contents Headings and Hierarchy (fda.gov). It is highly recommended to include a table of contents that showcases the list of all the non-clinical data study reports along with the location for each section. A sample template is provided here: Module 4 Template. A snapshot of what a TOC may look like along with the name of the study reports is provided in **Table 1**. You will note that the studies listed in **Table 1** are most likely what you will have for your gene therapy (Refer to discussion on Module 2.6).

Table 1: Snapshot of TOC for Module 4

Module 4: Nonclinical Study Reports and Literature References	
4.2.1	Pharmacology
4.2.1.1	Primary Pharmacodynamics
	Construct/delivery optimization in in-vitro and in-vivo, Platform biodistribution (optional)
	POC/DRF Efficacy and Safety in wild-type mice
	POC/DRF Efficacy and Safety in wild-type NHPs
	POC/DRF Efficacy and Safety in Disease Model if needed
4.2.1.2	Secondary Pharmacodynamics
4.2.1.3	Safety Pharmacology
4.2.2	Pharmacokinetics-biodistribution (reference to Primary PD&Tox)
4.2.2.1	Analytical Methods and Qualification/Validation Reports
	Method Validation Report for DNA Biodistribution in mice
	Bioanalytical Procedure for DNA Biodistribution in mice
	Method Qualification Report for DNA Biodistribution in Cyno Monkeys
	Bioanalytical Procedure for DNA Distribution in Cyno Monkeys
	Method Validation Report for mRNA Biodistribution in mice
	Bioanalytical Procedure for mRNA Biodistribution in mice
	Method Qualification Report for mRNA Biodistribution in Cyno Monkeys
	Bioanalytical Procedure for mRNA Biodistribution in Cyno Monkeys
	Method Validation Report for protein detection in mice
	Bioanalytical Procedure for protein detection in mice
	Method Qualification Report for protein detection in Cyno Monkeys
	Bioanalytical Procedure for protein detection in Cyno Monkeys
	Dose Formulation Analysis Validation Report
	Etc.
4.2.2.2	Absorption (do not complete – not appliable to gene therapies)
4.2.2.4	Metabolism (do not complete – not applicable to gene therapies)
4.2.3	Toxicology
	Single-dose Toxicity
	GLP Tox in wt mice
	Literature References Cited in the Nonclinical Summary

Some sponsors submit their non-clinical studies on the investigational product for publication in peer-reviewed journals. A copy of the published study may be included as a report in Module 4.

For non-clinical safety studies completed on or after December 17th, 2016, the FDA requires SEND data to be included with the IND. SEND was developed by the Clinical Data Interchange Standards Consortium (CDISC) to provide a standard format for the submission of non-clinical data, which facilitates the review and analysis of data by regulatory agencies. SEND data should be provided in Module 4 and prepared per electronic data technical requirements (see https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources#Catalog). Most CROs conducting non-clinical studies automatically generate data in SEND format – be sure to ask for it! [1]

7.4.1.1. Module 4.2.1: Pharmacology

Include a table of contents of the study reports included in this section. Note that these reports are summarized in *MODULE 2.4: NON-CLINICAL OVERVIEW and MODULE 2.6.2 and 2.6.3: NON-CLINICAL WRITTEN AND TABULATED SUMMARIES.*

7.4.1.2. Module 4.2.2: Pharmacokinetics

Include a table of contents of the study reports included in this section. Note that these reports are summarized in *MODULE 2.4: NON-CLINICAL OVERVIEW and MODULE 2.6.4 and 2.6.5: NON-CLINICAL WRITTEN AND TABULATED SUMMARIES.*

7.4.1.3. Module 4.2.3: Toxicology

Include a table of contents of the study reports included in this section. Note that these reports are summarized in *MODULE 2.4: NON-CLINICAL OVERVIEW and MODULE 2.6.6 and 2.6.7: NON-CLINICAL WRITTEN AND TABULATED SUMMARIES.*

7.4.2. Module 4.3: Literature

In this section, you must include all the publications cited either in your non-clinical study reports or in the *MODULE 2: NON-CLINICAL* section discussions. Any referenced literature needs to include their full copies in this section.

Template

- Module 4 template

References

1. Administration, U. F. (2022, November 08). Study Data for Submission to CDER and CBER. Retrieved from https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

7.5. Module 5: Clinical Study Reports

Clinical study reports relevant to the development of your investigational product that have been discussed in *MODULE 2.5: CLINICAL OVERVIEW* should be provided in *MODULE 5.3: PROTOCOL FOR INITIAL CLINICAL STUDY*. For novel therapies, there typically are no reports unless the product is approved for compassionate use and/or studied in a foreign jurisdiction. See *MODULE 2.5: CLINICAL OVERVIEW* guidelines on what clinical information to include.

7.5.1. Module 5.3: Protocol for Initial Clinical Study

In this section you should plan to provide complete protocols for each study you intend to conduct and include:

- ☐ Form FDA 1572 for each Investigator participating in the study [2]
- ☐ The CV of the Principal Investigator (primary doctor leading the study) and any sub-investigators
- ☐ The Informed Consent Form

Please refer to the sample outline below, **Figure 1**, for guidance on the Clinical Study Protocol. A template for a Clinical Study Protocol has been provided here. The template and sample outline are intended as guidelines and not all sections in either document may be applicable to your drug product or study design.

Figure 1: Clinical Study Protocol Example

1. Introduction
2. Trial Objectives and Purpose
3. Investigational Plan
4. Selection and Withdrawal of Subjects
5. Treatment of Subjects
6. Study Drug Materials and Management
7. Pharmacokinetic Assessments
8. Assessment of Safety
9. Statistical Analysis
10. Direct Access to Source Data/Documents
11. Quality Control and Quality Assurance
12. Ethics
13. Data Handling and Recordkeeping
14. Publication Policy

☐ **Introduction**

The purpose of the introduction is to provide an overview of the clinical trial, as well as the rationale for conducting the clinical trial. [1]

☐ **Trial Objectives and Purpose**

Here, you want to provide a detailed description of the specific objectives and the purpose of the trial. You may include primary and secondary objectives, as well as any exploratory or safety objectives. The objectives should be clearly defined and measurable.

☐ **Investigational Plan**

The investigational plan outlines the specific procedures, tests, and assessments that will be conducted during the course of the trial. It provides detailed information on how the investigational product (e.g., gene therapy) will be studied, including its administration, dosing, monitoring, and evaluation.

☐ **Selection and Withdrawal of Subjects**

For this section, you want to include detailed plans that outline how a clinical trial will be conducted in terms of candidate selection. You will need to include the inclusion/exclusion criteria and ensure that it's in accordance with good clinical practice (GCP) guidelines. You should also include the circumstances under which a subject may be withdrawn from the trial, as well as the procedures for handling withdrawals.

☐ **Treatment of Subjects**

This covers information on how the clinical trial participants will be managed and cared for throughout the duration of the study. It includes various aspects related to the intervention(s) being tested, as well as the overall management of participants' health and well-being.

☐ **Study Drug Materials and Management**

This section of the protocol outlines the specific requirements and procedures that need to be followed to ensure that your study drug is used safely, correctly, and in compliance with the study protocol and regulatory guidelines.

☐ **Pharmacokinetic Assessments**

All assessments involving measuring the time course and extent of drug absorption, distribution, metabolism, and excretion (ADME) in humans or animals go in this section. The purpose of these assessments is to help determine the pharmacokinetic profile of a drug, which in turn informs dosing recommendations, safety, and efficacy.

☐ **Assessment of Safety**

Here, you will have to outline the procedures for monitoring the safety of trial participants, including the collection and reporting of adverse events (AEs) or serious adverse events (SAEs), as well as any safety assessments or laboratory tests that will be conducted to monitor for potential safety concerns.

☐ **Statistical Analysis**

This includes details on the statistical methods that will be used to analyze the trial data, including the primary and secondary endpoints, sample size calculations, and any planned interim or final analyses.

☐ **Direct Access to Source Data/Documents**

You should ensure that it is specified in your protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents. [1]

☐ **Quality Control and Quality Assurance**

You (or study sponsor) are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted, and data are generated, documented, and reported in compliance with the protocol, good clinical practices (GCPs), and other regulatory requirements. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

☐ **Ethics**

Here, you will include a description of ethical considerations relating to the clinical trial, including the protection of human subjects, informed consent procedures, and any additional ethical requirements or considerations specific to the trial.

☐ **Data Handling and Recordkeeping**

This section will describe the overall process and responsibilities of parties involved in the management, recording, verification of data, including statistical analyses and preparation of trial reports. If you (or study sponsor) decide to use an independent data-monitoring committee (IDMC) to assess the progress, safety, endpoints, and study stop/start, this should be described in this section. If data is captured electronically, information on the tools, programs, and procedures for this should be provided in this section.

☐ **Publication Policy**

If not addressed in a separate agreement, the Publication policy goes here.

Long-Term Follow-Up Studies

For certain gene therapy products, the FDA expects to see long-term follow-up (LTFU) after administration of the investigational product in humans. The purpose of LTFU is to monitor subjects (patients) for any potential latent adverse events due to the investigational treatment. These studies are typically designed as extended clinical assessments and may include other methods for patient monitoring. The duration of LTFU studies depends on the type of gene therapy, so we recommend consulting the latest FDA Guidance on this topic: Long Term Follow-Up After Administration of Human Gene Therapy Products; Guidance for Industry (fda.gov). You can also refer to the Long-Term Follow-Up chapter.

7.5.2. Module 5.4: Literature

In this section you must include all publications cited in any clinical protocols, the Investigational Brochure, or the General Investigational Plan. Any referenced literature needs to include their full copies in this section (as separate pdf files – include links).

Templates

- Informed Consent Template
- Clinical Protocol Template

References

1. *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1)*. (2018, March). Retrieved from U.S. Food & Drug Administration: https://www.fda.gov/media/93884/download
2. *Forms*. (2023, 4 19). Retrieved from U.S. Food & Drug Administration: https://www.fda.gov/about-fda/reports-manuals-forms/forms

Chapter 8: IND Maintenance

8.1. IND Review Process

Once the IND has been successfully transmitted to the FDA, your organization's regulatory point of contact (POC) will receive via email an acknowledgment letter from the FDA's Regulatory Project Manager (RPM) assigned to your IND. At this point, the FDA's Pre-Clinical, CMC and Clinical subject matter experts will begin their review and the 30-day review clock starts. The FDA has adopted an interactive review process which allows reviewers to request clarification and additional information throughout the review process. Once the 30 days have passed, you will receive one of three letters through email:

- ☐ Study May Proceed
- ☐ Study May Proceed with Follow Up Comments, or a
- ☐ Clinical Hold Letter

A phone call from the FDA Regulatory Project Manager will accompany a Clinical Hold letter and is intended to notify you of the major concerns identified during review. For additional information on Clinical Holds, please refer to https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-clinical-hold.

8.2. IND Maintenance

Annual Reports

Once your IND is active, you will be required to notify the FDA of any critical updates on your drug product, on an annual basis. This update is referred to as an Annual Report (AR). The AR is due within 60 days of your IND anniversary date. For example, if you received your Study May Proceed letter on January 15, 2023, you must submit the AR every year thereafter between January 16 and March 16. The data collection (reporting period) for the first AR would be January 15, 2023 – January 14, 2024, and you would have until March 15 to submit the AR. For additional information on IND Annual Reporting, please refer to: https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-annual-reports**.**

Safety Reporting

Throughout the year, additional information is required to maintain the IND. The most important and time sensitive notifications are those involving clinical trial safety. These are known as safety reports and are to be documented and submitted to the FDA on Form 3500A (https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting).

Safety reporting involves two steps: an Initial Report and a Follow Up report. You are required to report any adverse reaction confirmed or suspected due to the investigational treatment (as identified in both animal and human studies), that is determined to be both serious and unexpected. You must submit the reports as soon as possible but no later than within 15 calendar days following initial receipt of the information. Unexpected fatal or life-threatening suspected adverse reactions are especially important and must be reported to the FDA as soon as possible but no later than 7 calendar days following receipt of the information. The Follow-up

report will include details of the investigation of the adverse experience and should be submitted no later than 15 calendar days after you receive the information. For additional information on safety reporting, please refer to: https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports

8.3. IND Amendments

Throughout the year, any critical changes or updates to your IND's CMC, Non-Clinical, Clinical information must be submitted as an IND amendment. Amendments will either be referred to as Information Amendments (pertaining to Non-Clinical and CMC changes) or Protocol Amendments (pertaining to your protocol(s) and study activities or information). The degree of risk the change may have on trial subjects will determine whether you need to obtain approval from the FDA prior to implementation. For example, if you plan to widen a lot release specification, such a change may pose a risk to purity and potency of the drug product. This type of change will require clearance from the FDA prior to implementation of the change. Similarly, any changes affecting the safety, design or scientific quality of an existing protocol must be submitted to the FDA prior to implementation. Any new protocols are also be cleared by the FDA in advance. All protocols open under your IND, such as a long-term follow-up study, fall within the scope of IND maintenance requirements. For additional information on IND amendments, please refer to: https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-protocol-amendments and https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-information-amendments

Chapter 9: Considerations and Best Practices for Clinical Trial Planning, Design and Execution

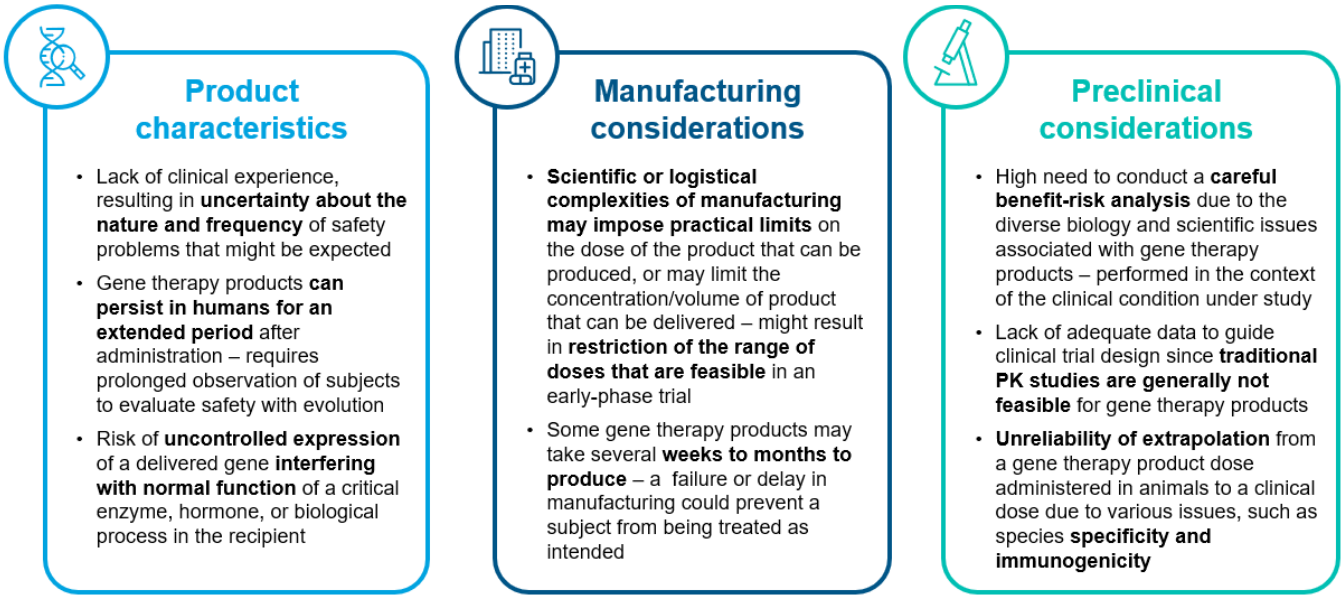
Introduction

The purpose of this chapter is to provide recommendations regarding selected aspects of the design of early phase clinical trials of gene therapy products, as covered by established FDA guidance for gene therapies. Such trials include most Phase 1 trials, including the initial introduction of an investigational new drug into humans (FIH), and some Phase 2 trials. Note, this section will not provide detailed information about the pre-clinical and CMC components of an IND, as we have previously discussed these in the appropriate IND modules.

The design of early-phase clinical trials of gene therapy products often differs from the design of clinical trials for other types of pharmaceutical products. Differences in trial design are necessitated by the distinctive features of these products and may also reflect previous clinical experience. Early experiences with gene therapy products indicate that some gene therapies may pose substantial risks to subjects. Risks could include multi-organ failure and death, as well as malignancies. These events illustrate that the nature of the risks of cell and gene therapy products can be different from those typically associated with other types of pharmaceuticals.

The design of early-phase clinical trials of gene therapy products often involves consideration of issues related to clinical safety, pre-clinical, and CMC that are more prevalent in gene therapy development compared to other therapies (e.g., biologics and small molecules). Such issues are more prominent in gene therapies because of factors such as novelty of the technology, complex mechanism of action, potential for long-term effects, and manufacturing challenges due to complex processes involving production and purification of viral vectors. Trial design is influenced by the many distinctive features of gene therapy products as it relates to product characteristics, manufacturing considerations, and pre-clinical design. Some of which are

Figure 1: Features of gene therapies influencing CT design



unique to gene therapy products and can dictate critical elements of the clinical trial design. **Figure 1** describes some of these special features.

It is important to ensure proper planning, design, and execution of clinical trials. This is essential for generating reliable, valid, and ethical results. Next, we will look at clinical trial design and the important elements to consider.

9.1. Clinical Trial Design

The randomized, concurrent-controlled (placebo) blinded trial is generally considered the ideal standard for establishing effectiveness and providing treatment-related safety data – randomization in early stages of development is encouraged. For your design, you should consider stratifying randomization across disease stage/severity. This improves the internal validity of the trial, enhances statistical power, increases generalizability, optimizes subgroup analyses, and promotes ethical allocation of interventions. It is also an effective strategy for minimizing bias, ensuring balanced treatment groups, and generating more reliable and informative results in clinical trials.

In certain situations when conducting a randomized, controlled trial is not feasible (e.g., small target population for rare diseases, ethical considerations withholding potentially effective treatment), a single-arm trial using historical controls may be considered. This approach may involve an initial observation period. However, it is crucial to have a good understanding of the natural history of the disease. If the natural history is well-known and it is not possible to conduct a randomized, concurrent-controlled trial, an available therapy can be used as a comparison to evaluate the clinical performance of the intervention being studied. Established biomarkers can be used to help guide the dose and estimate efficacy.

With advances in technology and the use of Real-World Data, “digital twin” technology can be another approach to utilize in your trial design. This technology allows you to create a digital control group of your study participants and more patients will receive the treatment. This would be particularly useful for gene therapy trials, given the ethical considerations around withholding a potentially life-saving treatment.

> Clinical trials need to get more personalized. Assuming that we’re talking about applications where handfuls of individuals — maybe 20, 30, 40 people — are available for a clinical trial, one has to start to really look on a very individualized basis. In a rapidly progressing rare disease, a trial can show a new treatment’s efficacy fairly quickly. With a gene therapy for Spinal Muscular Atrophy type 1, for example, you know within a year’s time if an intervention made a big difference – ***Peter Marks***

9.2. Early-Phase Trial Objectives

For early-phase clinical trials, especially first-in-human trials, the primary objective should be an evaluation of safety. Safety evaluation includes an assessment of the nature and frequency of potential adverse reactions and dose estimation. For gene therapy products, these early-phase trials often assess not only safety of specific dose regimens and routes of administration but may also include secondary objectives regarding feasibility of administration and pharmacologic activity. You should consider the design of early-phase studies in the context of the objectives of the overall development program – you can, therefore, include design elements to foster further

product development. Some Phase 1 studies include selected features of Phase 2 study design to gather preliminary evidence of effectiveness.

Secondary trial objectives for early phase studies include:

- ☐ Safety Assessment
- ☐ Pharmacokinetics and Pharmacodynamics
- ☐ Dose Finding and Optimization
- ☐ Preliminary Efficacy Assessment
- ☐ Feasibility and Proof of Concept
- ☐ Biomarker Identification
- ☐ Evaluation of Formulation or Delivery Methods
- ☐ Assessing Treatment Combination or Sequencing

9.3. Choosing a Study Population

Selection criteria for trial subjects depends on the expected risks and potential benefits, recognizing that there will be considerable uncertainty about those expectations in an early-phase trial. Expected risks may be estimated from the nonclinical data, an understanding of the biological mechanisms, and any previous relevant human experience, but the clinical significance of those risks can depend on the population that receives the product. Similarly, the potential for benefit might depend on the choice of study population. [1]

For rare diseases, limited sample size creates challenges around assessing feasibility, safety as well as interpreting the outcomes on bioactivity/efficacy. The objective is to select a trial population with an acceptable balance between the anticipated risks and potential benefits for the study subjects, while also achieving the study's scientific objectives

Choosing the appropriate study population is a critical aspect of trial design. The study population should reflect the target patient population for the gene therapy and align with the research objectives. Some rare diseases are more prevalent in low- and middle-income countries, where treatments are rarely tested. It's important to ensure that whenever trials are being conducted, there is a good representation of the real-world demographics of the population that would benefit from the intervention. Because of this, some experts have begun advocating for clinical trials to operate in the countries most affected by the disease being studied.

Some considerations when selecting participants are listed below.

- ☐ **Healthy volunteers**
  - Study of healthy volunteers may be reasonable for products with short duration of action with a well understood safety profile
  - The risks of most gene therapy products include the possibility of extended or permanent effects – the risk-benefit profile is therefore not acceptable for healthy volunteers

- ☐ **Disease stage or severity**

- Subjects with more severe or advanced disease may be more willing to accept the risks of an investigational gene therapy
- In some cases, however, selection of subjects with less advanced or more moderate disease may be appropriate – subjects with minimal reserve of physiological function due to severe or advanced disease may be less able than subjects with less severe disease to tolerate additional loss, which could leave them with no function

☐ **Lack of Other Treatment Options**

- Early-phase studies of gene therapies typically have significant risks and an uncertain potential for benefits. Therefore, early-phase trials sometimes enroll only the subset of subjects who have not had an adequate response to available medical treatment or who have no acceptable treatment options
- If a trial is designed to enroll only subjects for whom no other treatment options are available or acceptable, the trial should include procedures to ensure that each subject's treatment options have been adequately evaluated, and it should be designed to capture the pertinent information regarding that evaluation

☐ **Other Considerations**

- For certain gene therapies, pre-existing antibodies to either the vector or the transgene may influence the safety or effectiveness of the product – the study might therefore exclude subjects with such antibodies
- For products for indications (e.g., severe renal, hepatic, or cardiac disease) that might ultimately be amenable to organ transplantation, you should consider whether exposure to the investigational agent would cause sensitization that could compromise the prospect for future transplant success

☐ **Pediatric Subjects**

- If you are developing a gene therapy to treat pediatric diseases, you should consider how you will incorporate additional safeguards for pediatric subjects in clinical investigations into your overall development program
- Clinical development programs for pediatric indications usually obtain initial safety and tolerability data in adults before beginning studies in children
- Before a trial can proceed, the Institutional Review Board (IRB) is required to determine that the trial meets additional requirements applicable to studies in pediatric subjects

9.4. Control Group and Blinding

Early-phase trials usually focus on safety objectives and may not require a control or comparator placebo arm. Measures of efficacy or improvement in quality of life (e.g., mobility), if any are to be made, are usually exploratory. Therefore, in early-phase trials, a concurrent control group and blinding are generally not as critical as for a confirmatory efficacy trial (Phase 3 trial). However, in early phases of clinical development, a control group can be useful to interpret safety data and provide a comparator for any assessments of activity or efficacy.

Given the small number of patients with rare diseases, some experts advocate reducing the number of people who receive non-therapeutic doses in clinical trials. According to Peter Marks, even in phase 1 studies, you want to make sure that the doses of any therapy are optimized as quickly as possible. Skipping the very low doses could add a bit more risk to a clinical trial, but

such risk can be mitigated by detailed pre-clinical data from cell-based studies or animal models. [2]

If a new therapy is very promising, it might be unethical to have patients receive a placebo. You may also find yourself in a situation where patients do not want to enroll in the trial, because they fear ending up in the placebo arm. Consequently, some trials put all patient participants on the investigational treatment. Although this prevents comparisons with patients who do not get the treatment, efficacy could be determined in other ways, such as comparing a patient's status during and after the trial to a baseline determined at the start of the trial, or using a synthetic control arm, wherein a placebo group is modeled based on previously collected real-world data. [2]

Pro tip: An increasingly popular approach to aid enrollment of more patients with a rare disease in a trial is to conduct decentralized trials, in which patients participate at various sites scattered around the country, or even across the world. Virtual consultations and wearable technology, from a smartwatch or a designed-for-purpose device, could collect data on patients from their homes, reducing the need for in-person visits.

9.5. Dose and Regimen

If animal studies or *in vitro* data are available, there might be sufficient information to determine if a specific starting dose is considered low risk. However, conventional allometric scaling methods for gene therapies may be less precise than for small molecule drugs, and traditional pharmacokinetic and pharmacodynamic correlations might not be possible. Therefore, it may be difficult to establish an initial starting dose based on the considerations used for small molecule drugs. If available, previous clinical experience with the gene therapy or related products, even if by a different route of administration or for a different condition, might help to justify the clinical starting dose. [1]

For many gene therapy products, dose is based on vector titer. However, some vector types may have specific properties that necessitate dosing using alternative units. For example, viral particles that do not contain the therapeutic gene are unlikely to have therapeutic activity. These particles themselves might produce adverse reactions, such as an allergic response. If there are such safety considerations, the study dose(s) should be based on the total particle number, as is the case with adenoviral vectors. Other considerations for describing dosing may be related to the strengths and weaknesses of the methods available to accurately quantify specific attributes of the gene therapy products. For example, adeno-associated viral (AAV) vectors are typically dosed based on vector genomes, due to the strengths of the quantitative polymerase chain reaction (PCR) assay and the difficulties in quantitating transducing units.

Clinical development of gene therapies has often included dose escalation in half-log (approximately three-fold) increments. However, the dosing increments used for dose escalation should consider pre-clinical and any available clinical data regarding the risks and activity associated with changes in dose. Many gene therapy products can persist in the subject or have an extended duration of activity, so that repeated dosing might not be an acceptable risk until there is a preliminary understanding of the product's toxicity and duration of activity. Therefore, most first-in-human gene therapy trials use a single administration or one-time dosing regimen.

9.6. Treatment Plan

Here, we will briefly discuss procedures designed to evaluate the safety and efficacy of your drug product. Your treatment plan should outline the actions and guidelines that investigators and healthcare professionals will follow to administer the treatment to study participants. A few considerations for the treatment plan include the following. *(Please refer to Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry (fda.gov) for more detailed information.)*

- ☐ **Staggering administration**
  - Most first-in-human trials of gene therapies include staggered treatment to limit the number of subjects who might be exposed to an unanticipated safety risk
  - With staggered treatment, there is a specified follow-up interval between administration of the product to a subject, or small group of subjects, and administration to the next subject or group of subjects
- ☐ **Cohort size**
  - For trials that enroll sequential cohorts with dose-escalation between cohorts, the choice of cohort size should consider the amount of risk that is acceptable in the study population
  - For gene therapies, manufacturing capacity is often limited, which might place a practical limit on cohort size, particularly early in clinical development
- ☐ **Operator Training**
  - For product delivery that involves a complex administration procedure or a device requiring special training, such as subretinal injection, the skill of the individual administering the product can impact the product's safety and efficacy
  - When individual skill in administering a product may affect its safety or effectiveness, the trial should specify minimum requirements for the operator's training, experience, or level of proficiency

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Chapter 10: Considerations and Best Practices for Patient Engagement and Patient-Centricity

Introduction

The importance of involving patients throughout the trial process and ensuring their needs are at the forefront of drug development and clinical trial research cannot be stressed enough. In this chapter, we will explore the main challenges associated with patient engagement and provide strategies and best practices to actively engage and empower patients in your drug development. The goal is to help you enroll trials faster and promote a patient-centered approach that enhances the quality and success of your clinical trials.

10.1. Why engage patients

Rare disease patient communities are often great forces for progress. Informal groups may exist on social media platforms to share information. When patients and caregivers formally organize as nonprofits, these patient advocacy groups can become incredibly important and influential partners for gene therapy clinical trial developers. Depending on the size, mission, and scientific sophistication of the organization, patient advocacy programs can include websites, social media presence, webinars, support groups, patient educational conferences, medical and scientific conferences, patient registries, grantmaking, or even independent gene therapy program development.

Through these functions, patient advocacy groups or motivated individual advocates can contribute to the quality and success of your clinical trials in myriad ways. It can be valuable to engage members of the patient community to get feedback on enrollment materials prior to finalization. The patient community can be a crucial partner in trial recruitment, due to their trusted position in the patient community and established communication channels. Engage patient leaders early to learn about how they partner with researchers. For example, do they disseminate information about upcoming, newly open or ongoing clinical trials?

Many patient communities maintain their own patient registries. These registries can be extremely useful in finding eligible participants for trials. IRB-approved registries can also contain valuable data about the disease state.

Patients are the undisputed authority on the outcomes that matter to patients. At all stages in the research process, researchers should make efforts to ensure that their efforts are aligned with the needs of the patient community. Patient priorities should be major factors in the clinical outcomes that are tested and the design of potential interventions. Patients with extremely rare diseases and their caregivers often have a great deal of expertise on their disease condition, which is a precious source of disease information for diseases with limited published clinical research.

The patient community can also be an unexpectedly powerful ally in overcoming roadblocks to research. While this role should not be expected of patient communities, research teams that are candid with patient communities about the causes of delayed progress will sometimes find that the patient community can be a powerful partner in

identifying and enabling solutions. Sharing information about research progress is not only often ethical, but it also sometimes helpful to the research team.

First steps in patient engagement should ideally begin well in advance of trial recruitment. Research teams can begin with simple engagements like sharing copies of new papers with patient communities along with a plain language summary, scheduling an introduction with patient advocacy group leadership, or asking to attend a patient educational conference in order to learn more about patient needs and priorities. Patient communities are the single most affected stakeholder for research on their disease. Patient engagement empowers patients to partner, enables efficient recruitment, and yields better science. Every research team needs a patient engagement plan for ethical, logistical and scientific reasons.

10.2. Challenges – particularly for rare disease

Patient engagement and patient centricity in clinical trials face numerous challenges that impact the research process and hinder the inclusion of diverse patient populations. Several key factors contribute to these challenges, and we will briefly discuss some of these below.

10.2.1. Misdiagnosis and delayed diagnosis

Some rare diseases lack clear biomarkers, while some have rare biomarkers. Both scenarios make accurate diagnosis challenging. With most rare diseases requiring genomic testing for assessing biomarkers, the inaccessibility of testing and regional variations lead to misdiagnosis and delayed diagnosis. Non-standard diagnostic tests and limited data on genetic mutations further complicate patient screening and recruitment.

10.2.2. Lack of awareness among HCPS and patients

There is limited understanding and awareness about the clinical trial opportunities for most rare diseases. HCPs who are unaware of available clinical trials for rare diseases may not refer eligible patients to these trials. They may not have the necessary knowledge or resources to identify appropriate trials or may simply not consider clinical trials as a treatment option. This can result in a smaller pool of potential participants for these trials.

Without information about ongoing trials, patients may not actively seek out these opportunities or understand the potential benefits they could receive from participating. Lack of patient awareness can therefore result in missed opportunities for patient advocacy groups or organizations to promote clinical trials to their communities.

10.2.3. Lack of trust in the medical system

Given the novelty of gene therapies, there is some apprehension in patient communities around their use. Patients have concerns and misconceptions about the safety, efficacy, and ethical implications of gene therapies. Patient acceptance

and understanding of gene therapy mechanisms, as well as benefits versus risks, is an important milestone to ensuring successful engagement. There is also lack of knowledge and understanding among healthcare professionals (HCPs), contributing to a lack of trust between rare disease patients and HCPs. Sponsors typically face challenges in building collaboration and trust with patient communities, making it difficult to identify potential participants and address barriers to enrollment. Tailored communication approaches are therefore required to engage and involve patient communities effectively.

10.2.4. Patient Identification and Recruitment

Small and a hard-to-find patient populations create challenges in identifying and recruiting suitable participants. For some rare diseases, patients are required to have specific gene mutations or antigens for inclusion, resulting in limited sample sizes. Conducting statistically significant trials and drawing robust conclusions becomes challenging. Screening, testing, and diagnosis complexities also cause delays in patient recruitment.

Many of the rare diseases are under-diagnosed, and their true prevalence is not well understood. The resultant lack of reliable data hampers patient identification and recruitment for clinical trials.

10.2.5. Under-served Communities

Patients in under-served communities face additional barriers to healthcare access and clinical trial participation. It is therefore important for you to understand the demographic disparities for your proposed indication and to account for these disparities in your trials. Addressing these disparities is crucial for promoting patient engagement and inclusivity in clinical trials.

Overcoming these challenges in patient engagement and patient centricity is crucial to advancing clinical research and improving healthcare outcomes. By raising disease awareness, enhancing trust and education, fostering collaboration with patient communities, and addressing barriers to access, we can strive towards a more inclusive and patient-centric approach in clinical trials. In the next section, we will dive into potential strategies to address achieve this.

10.3. Considerations and best practices

Effective patient engagement is crucial for the success of clinical trials, as it ensures active participation, improves recruitment rates, and enhances overall trial outcomes. In this section, we will discuss some possible strategies you can implement to enhance patient engagement and recruitment.

10.3.1. Enhancing disease understanding

Empowering rare disease patients begins with education of the disease from the moment of diagnosis. You can leverage the expertise of patient advocacy groups to build educational resources and support your research efforts. Ensuring that patients stay informed about new innovations, such as biomarker partnerships and patient-mediated data, allows for tailored and personalized care. Sharing

accurate information through trusted sources, like physicians, will improve patient knowledge and acceptance of treatments.
Additionally, clear and frequent communication with patients, addressing their questions and explaining the risks and benefits, fosters an environment of trust. These strategies work together to empower patients, ensuring they are well-informed and engaged in their rare disease journey.

10.3.2. Raising awareness of studies

Raising awareness about clinical studies is crucial for advancing medical research and improving patient outcomes. To achieve this, you can consider the following recommendations:

☐ **Existing registries**
Existing registries serve as valuable resources for connecting patients with relevant clinical studies. By leveraging these registries, researchers can reach out to potential participants who have already expressed interest in contributing to medical research. It's important to note, however, that not all diseases will have an existing registry.

☐ **Awareness campaigns**
Patient advocacy group (PAG) awareness campaigns play a vital role in disseminating information about clinical trials. Collaborating with PAGs allows for targeted and impactful outreach to patient communities, raising awareness and fostering a sense of urgency regarding the need for participation in clinical studies. Consideration should be given to funding screening programs through PAGs (e.g., newborn screening supported by NORD). This enables the identification of potential candidates for clinical trials, streamlining the recruitment process and ensuring a more efficient enrollment of eligible participants.
Another strategy would be to utilize sibling/family programs. These provide an opportunity to engage not only the affected individual but also their caregivers. They offer support, education, and a sense of community, while also raising awareness about ongoing clinical studies and the importance of participation.

☐ **Healthcare Provider presentations**
Presentations by healthcare providers (HCPs) at conferences can be another way to effectively raise awareness among their peers and colleagues. Sharing knowledge about ongoing clinical studies, their objectives, and potential benefits encourages HCPs to refer eligible patients and collaborate with researchers.

☐ **Clinical Trial Educator deployment**
Deploying Clinical Trial Educators (CTEs) can alleviate the burden on clinical trial sites while actively engaging patients. CTEs serve as dedicated resources, providing education, addressing queries, and guiding patients through the study enrollment process.

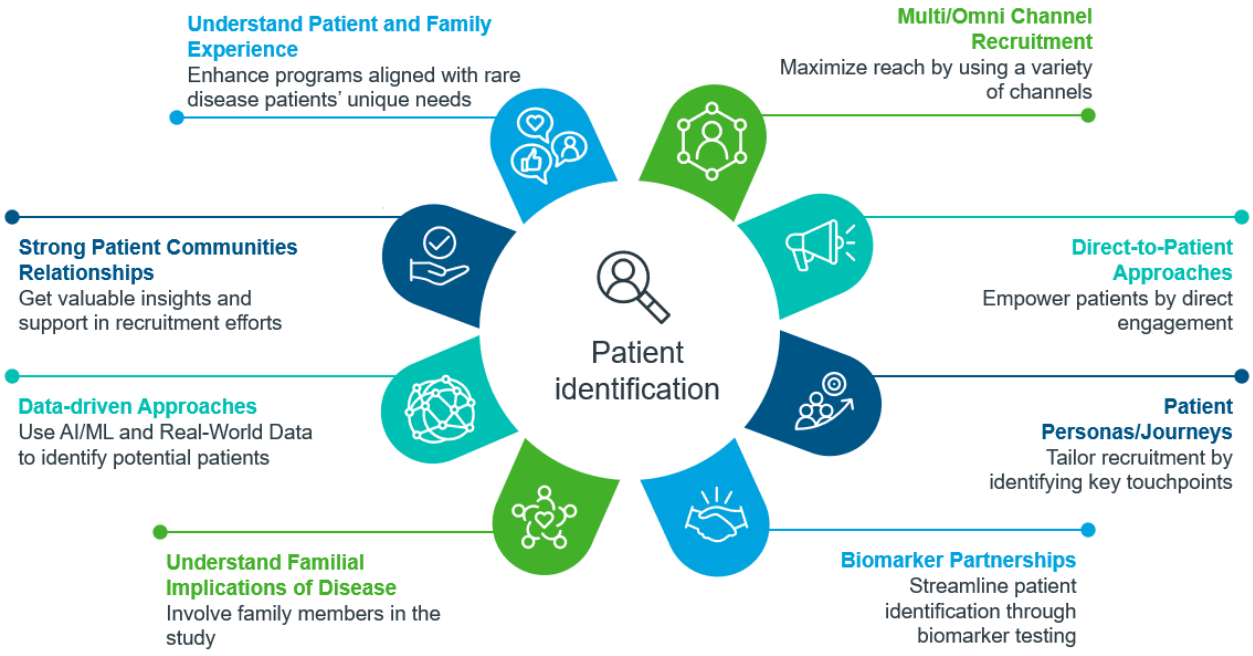
☐ **Launch platform**
Creating a platform for launch throughout the interventional program ensures continuous awareness and engagement among patients, HCPs, and other stakeholders. Regular updates, educational materials, and interactive resources

keep the community informed and foster a sense of involvement in the clinical study.

10.3.3. Identifying the right patients

Finding the right patients for a rare disease clinical study requires a comprehensive and patient-centric approach. See **Figure 1** for key strategies to consider.

Figure 1: Patient identification strategies



10.3.4. Refer and recruit

Streamlining the recruitment process is essential for identifying potential participants efficiently. Establishing physical referral hubs can facilitate seamless patient enrollment. Providing comprehensive recruitment support to patients, caregivers and healthcare providers can increase trial awareness and interest. Collaborating with specialists enables the understanding of current genetic testing protocols in both community and specialist practices.

Evaluating referral pathways helps identify suitable opportunities for introducing genetic testing and trial participation. It's important to enhance patient convenience through easily accessible forms, information, audio-visual tools, and electronic consent processes.

10.3.5. Continue engaging with clinical trial participants beyond enrollment

Sustaining patient engagement beyond enrollment is crucial for successful clinical trial completion. Implementing a patient portal facilitates ongoing communication, updates, and access to trial-related information. Collaborating with external organizations and patient communities is another way to enhance engagement

efforts and expand trial awareness.

10.4. Diversity and Inclusion

New requirements from the FDA (DEPICT Act) will necessitate changes in the way that industry approaches product development and study execution.[1] The concept of diversity and inclusion is a key focus especially in rare disease, where diagnosed populations do not account for the under-served populations, owing to the diagnosis/genetic testing challenges. Marginalized identities are not mutually exclusive and can intersect, where one patient can be marginalized by more of these dimensions. Diversity encompasses not only race and ethnicity but also gender, age, socioeconomic status, sexual orientation, and disability. These identities can intersect and compound to create unique experiences and highlight health disparities among certain populations. By understanding and addressing these intersectional challenges, you can foster a more comprehensive and equitable approach to clinical trial recruitment, engagement, and participation. Through targeted strategies, you can be intentional about this from the beginning of your trial lifecycle.

We have provided you with a sample checklist for operationalizing diversity below.

- ☐ Study Design – ensure that your D&I goals are established upfront and validated by real-world data
- ☐ Site Selection – consider site staffing augmentation by need, including cultural research specialists
- ☐ Site Activation
- ☐ Recruitment Planning
- ☐ Patient Recruitment
- ☐ Community Engagement – Site-led activities
- ☐ Community Engagement – Centralized activities
- ☐ Enrollment
- ☐ Engagement and Compliance

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Chapter 11: Study Site Management

Introduction

Clinical study site management plays a pivotal role in the successful execution of clinical trials. With rare diseases, traditional site identification and recruitment approaches may not work efficiently. This chapter aims to provide an overview of the key considerations and best practices for effectively managing study sites in the context of rare disease therapies. By understanding the complexities of rare diseases, their limited patient populations, and the need for tailored strategies, you can optimize trial outcomes, enhance patient engagement, and contribute to the advancement of therapeutic options for these underserved populations.

11.1. General Study Site Selection and Principal Investigator Engagement

Selecting appropriate study sites and establishing effective engagement with Principal Investigators (PIs) are critical for successful gene therapy trial execution. [3]

11.1.1. Study Site Selection

An established Center of Excellence Network can simplify the site selection process. Centers of Excellence are specialized programs within healthcare institutions which supply exceptionally high concentrations of expertise, experience, and related resources centered on a particular therapeutic area or disease field. If a network has not yet been established, we advise you to consider the following (see **Figure 1** for overview): [1].

Figure 1: Site Selection Considerations

11.1.1.1. Patient population density

Carefully evaluating population density allows you to identify study sites that are better suited to achieve the recruitment and research objectives for your gene therapy clinical trials. This will help maximize recruitment potential, enhance diversity, ensure timely enrollment, improve access to healthcare services, and increase operational efficiency. You can utilize real-world data (RWD) to identify the variability in patient populations by location to tailor your site selection [4]. Potential sources for RWD include:

- ☐ Epidemiological Studies
- ☐ Disease Registries
- ☐ Electronic Health Records
- ☐ Claims Databases
- ☐ Public Health Reports
- ☐ Census Data
- ☐ Work with CROS

11.1.1.2. Geographical accessibility

Geography plays a crucial role in patient participation and retention in clinical trials. Study sites that are geographically accessible to the target patient population may reduce the burden on participants in terms of travel time and expenses. This convenience can improve recruitment rates and help maintain participant engagement throughout the study duration. Having study sites in areas where the target population lives or often travel to may foster community engagement as residents and patient advocacy groups (PAGs) may have a greater sense of connection to nearby sites. [4]

Travel barriers can impact participant recruitment and retention, particularly for those with limited mobility or financial resources. They can hinder diversity and representation in your study population, compromising the generalizability of your findings. By selecting central locations, you can minimize travel challenges and encourage broader enrollment. PAGs and patient and family insights will help you anticipate the geographic challenges and develop proactive solutions for patients to participate in the study. Addressing travel barriers can enhance feasibility of your study and improve your resource allocations in the study operations.

If site selection presents challenges, you can also consider decentralized trials. Please refer to the Clinical Trial Design, Planning, and Execution chapter for more information on this.

11.1.1.3. Site capabilities

By considering site capabilities for rare disease research during study site selection, you can leverage existing expertise, access specialized facilities, foster collaborations, enhance patient support services, and navigate regulatory and ethical considerations effectively [4]. These factors contribute to the successful execution of clinical trials, enabling high-quality data collection, improved patient care, and advancements in rare disease research and treatment options. You can conduct site outreach through rare disease networks to identify sites with capabilities in your targeted rare disease.

11.1.1.4. Special accommodations that may be needed at participating sites

Participating trial sites may require special considerations to ensure smooth trial operations. Historical trial data (if prior studies have been performed in the indication) is a valuable tool to

assessing what special accommodations may be required for your selected sites. These can include the following:

- ☐ Training and education (e.g., logistics, cultural awareness, and rare disease training)
- ☐ Site-specific infrastructure (e.g., storage requirements, patient disability accommodations)
- ☐ Investigational product management (e.g., therapy delivery technology/mechanisms, route of administration, specialized devices, and equipment)
- ☐ Patient support services (e.g., cultural awareness, childcare for participants, and concierge services)

If the clinical study will involve long stays at a distant site, it may also be helpful for you to be aware of how this may affect an individual or their family, and therefore also affect patient participation and retention in the study. Developing a patient support program will be crucial in this case, to ease this burden on the patients and their caregivers [4].

11.1.2. Principal Investigator Engagement

Within the dynamic landscape of gene therapy clinical trials, effective Principal Investigator engagement plays a pivotal role in ensuring the success and integrity of your trial. One method you can use to ensure this process is seamless is to utilize vendors/Contract Research Organizations (CRO) who can provide this full-service offering for you. When selecting and engaging with PIs, there are certain things you can do to ensure that your trial goes smoothly. Key considerations include the following:

- ☐ **Specialized Expertise**
  It is important to engage skilled and motivated PIs who possess the necessary expertise and understanding of the unique challenges associated with rare diseases. They should have a deep understanding of the disease and the proposed therapy. As a sponsor, you can also identify and engage key opinion leaders (KOLs) who are renowned experts in your specific rare disease and AAV gene therapies. Their endorsement and involvement can significantly enhance the credibility and visibility of your trial.

- ☐ **Collaborative Approach**
  As a sponsor, you need to foster a collaborative relationship with your PIs. Involve the PIs in trial design, protocol development, and decision-making processes. We also recommend that you invite their input as they have valuable subject matter expertise that will also enhance their engagement and commitment to the trial.

- ☐ **Training and Education**
  It is essential that you provide comprehensive training and education to PIs regarding the specific gene therapy being used, including its mechanism of action, potential risks and benefits, administration techniques, and patient management strategies. This will ensure that they are well-prepared to handle the unique aspects of your AAV gene therapy.

- ☐ **Regular Communication**
  Maintain open lines of communication with your PIs throughout the trial, providing frequent updates on trial progress, regulatory changes, and any new information relevant to the

study. Encourage the PIs to share any concerns or challenges they encounter and try to address them promptly.

☐ **Investigator Meetings**
Organize regular investigator meetings or conferences where PIs can come together to discuss their experiences, share best practices, and learn from each other. These meetings also provide an opportunity to address common issues, refine study procedures, and build a sense of community among investigators.

☐ **Resource Support**
Ensure that PIs have access to necessary resources, including adequate funding, study coordinators, research staff, and specialized equipment. This support will enable them to effectively carry out their responsibilities and streamline the trial operations.

☐ **Regulatory Compliance**
Ensure that your PIs are well-informed about regulatory requirements and that they adhere to Good Clinical Practice (GCP) guidelines. Help them navigate the regulatory landscape, including ethics committee submissions, informed consent processes, and reporting of adverse events.

11.2. International Sites and Filings

The patient pool for rare disease clinical trials is often small and widely dispersed. Likewise, clinical sites with this specialized experience are rare. As a result, it may be beneficial to consider ex-US sites to meet your recruitment targets [2].

Investigators are responsible for complying with the applicable laws and regulations of the country in which the study is being conducted, regardless of whether the study is being conducted under an IND. It is recommended that you obtain signed, written statements from investigators acknowledging their commitment to comply with regional, national, or local laws and requirements. In addition, if a foreign clinical study is being conducted under an IND, the investigator must sign Form FDA 1572 (investigator statement) and ensure that the study is conducted in accordance with the investigator statement and all other applicable regulations under 21 CFR part 312. An exception to this requirement would be if you have requested, and FDA has granted, a waiver of the signature requirement. If a waiver is granted, you, together with the investigator, must ensure that the study is conducted in accordance with the terms of the waiver [2].

Some important things to note about foreign sites include the [2]:

- If a clinical study is conducted at a foreign site under an IND, all FDA IND regulations, including the requirement to obtain a signed 1572, must be met unless the sponsor requests and is granted a waiver that provides for specific exceptions.
- In the case where a foreign investigator cannot or will not sign Form FDA 1572 (e.g., because regional, national, or local laws or regulations prohibit its signing), the sponsor may submit a request for a waiver of the 1572 signature requirement; alternatively, the site may operate as a non-IND site, in which case the study would be conducted as a non-IND study.

- If a clinical study is conducted outside of the United States and the study is not under an IND, then the investigator need not sign a 1572.
- If the study data from a non-IND site is to be submitted to support a marketing application (e.g., a new drug application (NDA)), the study at the non-IND site must be conducted in compliance with federal regulations.

For more information, consider referring to the FDA guidance titled “Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions” linked here.

You may be faced with a situation where you would have to recruit outside the US and bring the study subjects to sites within the US. This is known as cross-border enrollment, and it can help reach recruitment targets for rare disease clinical trials. For such a scenario, refer to the following articles/whitepapers for more information:

- Cross-border enrollment of rare disease patients: Considerations for planning and conducting global rare disease clinical trials
- Reducing Barriers to Participation in Clinical Trials for Rare Diseases

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Chapter 12: Long-Term Follow-Up

What are LTFU studies?

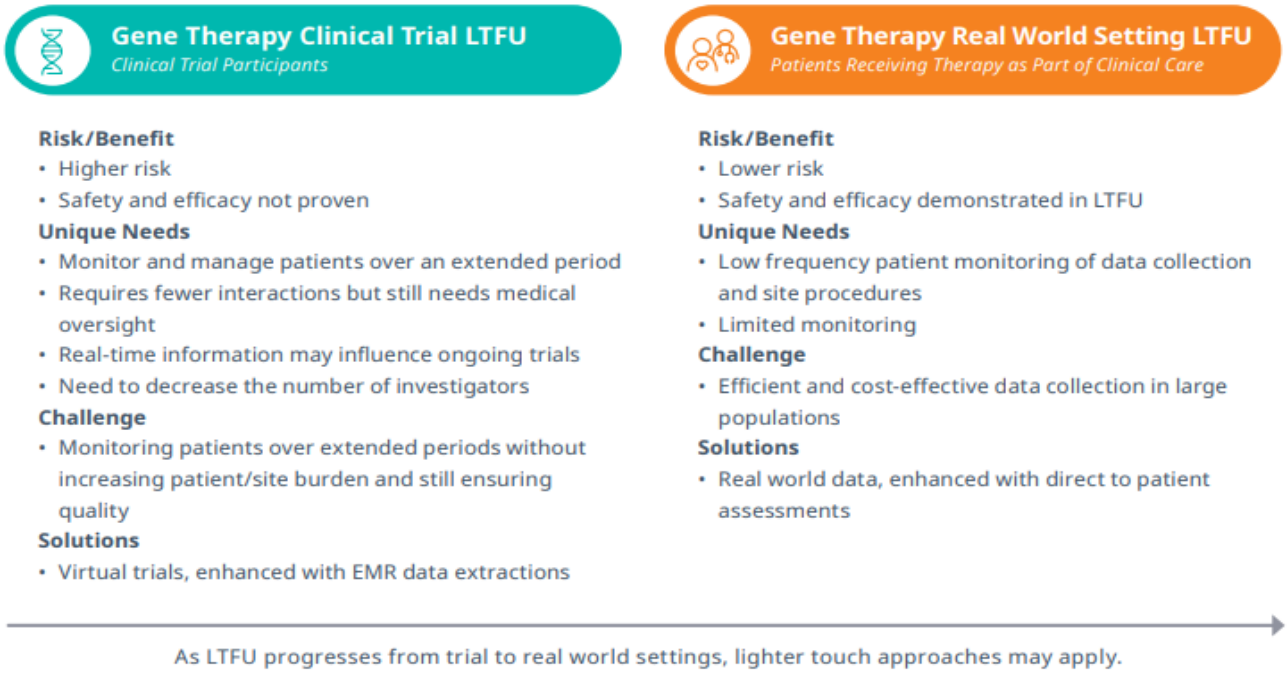
As the field of gene therapy continues to evolve with new trends and emerging developments, it is imperative to stay up to date with the latest news and FDA regulatory guidelines. Of the key trends, real world evidence has been a fast-evolving requirement from regulatory bodies across the life sciences industry and even more so for gene therapies. The current approved therapies have already transformed patients' lives, and with several more in the pipeline, gene therapy is expected to continue to transform the field as we know it. [4]

To fully understand the efficacy of a gene therapy product and long-term safety, it is important to monitor patients who are receiving therapy over an extended period of time. Regulatory agencies, including the FDA and EMA, have published guidelines highlighting the recommended study design and key data elements needed for the long-term follow-up (LTFU) studies generally. The current **minimum duration of LTFU studies needed** for AAV gene therapies is 5 years. [3]

For more information about the latest US regulatory guidelines please refer to the FDA guidance document here.

There are two types of LTFU studies associated with gene therapy clinical development. A brief overview of the two types along with the risks/benefits and challenges is shown in **Figure 1**. [3]

Figure 1: LTFU Studies for Gene Therapies [3]



What are the challenges of LTFU studies for AAV gene therapies? [1-4]

There are several challenges to LTFU studies that are even more difficult for gene therapies. The list below highlights challenges we face in LTFU studies for AAV gene therapies; this list is not exhaustive.

- **Burden of data collection:**
  - Collecting and managing large volumes of data over an extended period – in the case for AAV gene therapies, a minimum of five years – can be time and resource consuming. Additionally, factors like patient engagement, data quality/analysis, and compliance can impact the data collection process.

- **Limited patient population:**
  - The small and often sparse and scattered patient population for any given rare disease makes it challenging for studies to enroll an adequate number of participants. Additionally, patients may not follow up or lose contact with their HCP due to life changes (e.g., relocating), which can affect your ability to monitor patients and continue collecting the LTFU data by the physician practice or treatment center.

It is important to note that patients with positive clinical outcomes may reduce their engagement with the healthcare system, and are less likely to follow-up. This could result in LTFU that **biases towards patients with poorer outcomes** – something to keep in mind as you think about your LTFU needs.

- **Disease progression and study design:**
  - Variability of other genes across the patient sample may have an unknown impact on the natural progression of the disease. To address this, it is important to explore relevant biomarkers in the LTFU study and identify associations, if any, between genetic variations in the study population and their clinical outcomes. This analysis can help you better understand the disease course and potential impact of your gene therapy on certain sub-populations.
  - Additionally lack of knowledge, research, education on disease, biomarkers, etc. for rare diseases can make it hard to identify meaningful endpoints needed to measure safety and efficacy – the clinical end points may differ between patients, regulatory agencies, and payers.

- **Study execution/operations**
  - Monitoring patients over an extended period can pose challenges in terms of time, cost, and resources. The administrative burden associated with LTFU studies often leads to decreased interest from investigators. Consequently, lower incentive for participation and sustained engagement contributes to lost-to-follow-up of patients in the study.

- **Safety considerations**
    - Given how novel and innovative AAV gene therapies are, LTFU studies are a critical tool for monitoring long-term safety profiles due to uncertainties with dosing, potential for adverse events, and/or impact on patient's quality of life.

What are the considerations and best practices to follow for LTFU studies?

While the current FDA minimum requirement for AAV gene therapy LTFU studies is 5 years, the following considerations and best practices are also highly recommended to ensure robustness in your LTFU study for your AAV gene therapy product. [1-4]

- Have a well-defined study design and implementation plan with an optimized efficient, timely, and high-quality data collection and monitoring system
    - Prioritize a systematic approach that incorporates clinical perspectives, regulatory requirements, data collection efficiencies, flexibility, and patient centricity
- Align your methods, goals, and approach with that of the regulators – considering the prolonged study period, keep a pulse on evolving FDA guidances
- Prepare to adapt based on emerging technology, evolution in disease understanding (e.g., biomarker partners, patient-mediated data, and services), and regulatory changes
- Draw insights around the therapy's impact on the patient's quality of life (e.g., frequency of follow-ups, interactions with clinicians)
    - Additionally, capture insights on how findings from LTFU studies can impact the ongoing clinical program
- Develop a patient support plan to engage with patients for the duration of the LTFU to minimize risk of loss-to-follow-up. Some ways you can do this include:
    - Providing telemedicine services and digital engagement solutions
    - Having a 24/7 patient support line
    - Supporting patient advocacy groups
    - Creating an information sharing portal
- Develop a registry or leverage an existing disease registry to track patients through follow-up to reduce some of the challenges/risks associated with LTFU studies
- Incorporate elements of decentralized clinical trial (DCT) solutions in the LTFU design to minimize the patient burden by reducing onsite follow-up, testing, and data collection
- Include a contingency or back-up plan around redosing or product failure/discontinuation
- Maintain diversity and inclusion as a key focus of the LTFU studies to ensure the patient population is adequately represented

References

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Chapter 13: Glossary

Adeno-associated virus (AAV): A member of the parvovirus family of single-stranded small DNA viruses that require a helper virus such as adenovirus or herpes simplex virus for replication. AAV vectors are the leading platform for gene delivery for the treatment of a variety of human diseases.

Accelerating Medicines Partnership (AMP): A public-private partnership between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), multiple biopharmaceutical and life science companies, non-profit and other organizations to transform the current model for developing new diagnostics and treatments.

Bespoke Gene Therapy Consortium (BGTC): An AMP that aims to develop platforms and standards that will speed the development and delivery of customized or 'bespoke' gene therapies that could treat the millions of people affected by rare diseases.

Chemistry, Manufacturing, and Controls (CMC): Crucial activities when developing new pharmaceutical products. CMC involves defining manufacturing practices and product specifications that must be followed and met in order to ensure product safety and consistency between batches.

Drug Master File (DMF): Submissions to FDA that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products. DMFs can contain other types of information as well (e.g., toxicology information, shared system REMS (risk evaluation and mitigation strategy)).

Center for Biologics Evaluation and Research (CBER): The Center within FDA that regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products.

Center for Drug Evaluation and Research (CDER): The Center with the FDA that performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States. CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.

Clinical Hold: A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the

investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Electronic Common Technical Document (eCTD): The standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Formal dispute resolution: To promote rapid and fair resolution of scientific and/or medical disputes between a sponsor and CDER or CBER, FDA has established both formal and informal mechanisms to address instances where a sponsor may disagree with the Agency on a matter, and a dispute arises.

Natural history study: A preplanned, observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes.

Platform-based approach: An approach for streamlining R&D/pre-clinical development and navigation of the regulatory pathway by leveraging existing data and information or prior knowledge based on similar elements with approved/developed AAV gene therapy products, and developing minimum requirements based on this platform-based approach to increase efficiency of development and regulatory submissions.

Pre-clinical: Research or studies about a drug or treatment for a disease that occurs before it is tested by human volunteers. Used interchangeably with non-clinical.

Prescription Drug User Fee Act (PDUFA): A law passed by the United States Congress in 1992 which allowed the Food and Drug Administration (FDA) to collect fees from drug manufacturers to fund the new drug approval process.

Special Protocol Assessment: A process by which a sponsor asks FDA to evaluate a protocol to determine whether it adequately addresses scientific and regulatory requirements for the purpose identified by the sponsor.

Sponsor: a person or entity who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.