

Regulation and Oversight of Gene Therapy in the US

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This article discusses the evolution, potential uses and regulatory aspects of gene therapy and includes funding, delivery mechanisms, bioethics and steps toward clinical trial implementation.

Introduction

Sponsors and investigators need to be prepared to take specific steps to satisfy FDA and NIH requirements before, during and after clinical trial implementation. There are a significant number of guidance documents and internal procedures aimed at helping to prepare sponsors of gene therapy products to adhere to all product regulations, expectations and unique considerations. It is important to understand the process, standards, oversight, published expectations and internal procedures of current gene therapy regulation, as well as keep up to date with all regulatory resources to more efficiently navigate the regulatory framework.

Gene therapy is defined as the coordinated modification of genetic material within tissues, cells or organs of patient to cure or mitigate the effects of a disease.^{1} Gene therapy has been used to alter genetic mutations, deletions, repeats, polymorphisms, make insertions, replacements or modify an otherwise undesirable segment of genetic material. Increased understanding and expansion of various delivery mechanisms, cellular biology and disease states also has led to the use of genetic modification for expression of non-native, prophylactic products which can be used to combat or prevent disease at the molecular level.^{2}

As research and increased experimentation with gene therapies continues, diversifies and becomes more common, it will be critical for manufacturers or sponsors engaged in gene therapy product development to understand the regulatory framework and potential areas of extra oversight during all phases of the product lifecycle. Companies engaged in developing and commercializing gene therapy products will be subject to the legal

provisions and regulation applicable to all biological products as overseen by the US Food and Drug Administration (FDA) and will be obligated to operate under the direct and indirect oversight of the Office of Biotechnology Activities (OBA) at the National Institutes of Health (NIH). By understanding the process, standards, oversight, published expectations and internal procedures of current gene therapy regulation, a sponsor can be prepared to more efficiently demonstrate adherence to obligations required by all governing bodies involved.

Current Status of Gene Therapy

Gene therapy products are complex and can be administered in various direct or indirect methods using a range of delivery mechanics and techniques which can be performed in an *in vivo* or *ex vivo* procedure.^{3} An *ex vivo* therapy involves taking a sample of cells or tissues from a patient, genetically modifying the sample outside of the body, then reintroducing the genetically modified sample into the patient for therapeutic effect. *In vivo* therapy involves the direct administration of a genetic vector and a delivery vehicle to the patient. Viral-mediated vectors are commonly used in *in vivo* therapy wherein a modified virus carrying a desired genetic construct is used to deliver and infect a specific cell.^{4,5} Once at the target cell, the intra-viral proteins aid in the integration of the desired genetic vector into the host genome or promote the expression of the intra-viral genetic construct.

Several common tools for genetic modification at the molecular level include: enzymatic cleavage and recombinant reintegration of a desired gene construct or the use of guided endonuclease techniques, such as Zinc-Finger Nuclease (ZFN), Transcription Activator-Like Effector Nucleases (TALENs) and more recently, the innate bacterial based immune system CRISPER/Cas9 for identification and manipulation of specific genetic sequences in a genome.^{6}

As of 2012, FDA approved the clinical investigation of more than 1,100 different gene therapy trials.^{7} However, while FDA has approved gene therapy products for clinical phase investigations in humans as part of an Investigational New Drug (IND) application, the agency has not yet approved a Biological License Application (BLA) allowing for commercial distribution of a human gene therapy product.^{8,9}

Legal Foundation, Jurisdiction and Oversight—FDA

Pursuant to the final rule published in the Federal Register in 1993, FDA certified its jurisdiction and provided clarification on the regulation of somatic cell and gene therapy products.^{10} FDA has determined that characteristics of gene therapy products may be regulated as either a drug, device or biologic product depending on the constituents of the final product to be administered and the intended use(s). Manufacturers are responsible for analyzing all components of the gene therapy product to determine which regulations apply in the event their final gene therapy product constitutes a combination. For example, a gene therapy product employing a naturally-derived component (such as the CRISPR/Cas9 family of proteins for cleavage), but using synthetic gene constructs in the final product (to guide the CRISPR/Cas9 protein or as a gene for insertion), would constitute a final combination product and subject to the regulations applicable to a drug and biologic product. This would include pre-clinical, manufacturing, licensing and post-approval requirements in addition to any extracurricular oversight applicable to specific product or manufacturing components, such as regulations involving cell lines and adherence to current Good Tissue Practices (cGTPs). When it is undecided or in dispute over which part of the gene therapy product is the primary mode of action (drug, device, biologic), a manufacturer may submit a Request for Designation (RFD) to the Office of Combination Products (OCP). The designated agency will use a codified decision algorithm to determine the primary mode of action and subsequent center for review of the product.^{11,12}

Based on the required expertise and risks associated with the complex nature of gene therapy products, the Office of Cell Tissue and Gene Therapies (OCTGT) at Center for Biologics Evaluation and Research (CBER) oversees gene therapy products (including medical device gene therapy products) and reviews applications concerning the use of gene therapies under or intended for clinical investigation or licensure.^{13} All gene therapy products intended for clinical investigation in humans for eventual commercial use in the US require submission of an IND application. Such products are subject to standard

federal regulations concerning INDs, such as those pertaining to patient safety, informed consent, use of an Institutional Review Board (IRB) for trial oversight, good clinical practices and adverse event reporting. Sponsors also must register and engage in adverse event reporting with the Genetic Modification Clinical Research Information System (GeMCRIS), an agency devoted exclusively to gene therapy clinical trials and gene therapy clinical information as part of an FDA and NIH collaborative effort to institute a Gene Therapy Patient Tracking System.{14}

CBER has released several guidance documents through the OCTGT to express its current thinking on the development of preclinical studies, potency testing, Chemical Manufacturing and Control (CMC) and other issues relating specifically to gene therapy products. The aim is to help manufacturers, sponsors and investigators with the preclinical and investigational phases of gene therapy since industry and scientific-standard methods of evaluation (i.e., a core battery of tests or appropriate animal disease model) and what may not always be practical, feasible or effective at providing a clear risk evaluation or indication of efficacy of the gene therapy product. FDA guidance suggests gene therapy products may rely more heavily on a scientific rationale and/or Proof-of-Concept (POC) testing as opposed to a more traditional core series of tests applicable to non-gene therapy biologics. This is valuable when initially substantiating an investigational application provided safety and other germane information is supplemented in the application throughout the clinical trials as learned.

NIH, OBA and the RAC

Sponsors of gene therapy products also are subject to oversight by the Office of Biotechnology Activities (OBA) and the Recombinant DNA Advisory Committee (RAC) at the NIH. This is true if their product is 1. investigated at a facility that accepts grant funding from the NIH for recombinant or synthetic nucleic acid research or 2. uses an investigational agent developed at least in part in a facility that accepts NIH funding for recombinant or synthetic nucleic acid research.{15} Given the specialized nature of gene therapy, most clinical trials are conducted at research institutes or with an investigational agent funded in some capacity by the NIH and as such, are subject to protocol submission to the RAC, review and adherence to the *NIH Guidelines for Research Involving Recombinant Synthetic Nucleic Acid Molecules*.{16} Failure to follow NIH guidelines may result in the loss of grant funding.

NIH Guidelines for Research Involving Recombinant Synthetic Nucleic Acid Molecules contain responsibilities and procedures for conducting clinical investigations and an index of points to consider for the design of a clinical protocol (Appendix M.) Specifically, Section IV-B-2-a-(1) of the guidelines calls for the use of an Institutional Biosafety Committee (IBC) to oversee the trial. This is in addition to the expectation of an Institutional Review Board (IRB) as required by federal regulations. The IBC is comprised of at least five members who have expertise with the types of recombinant, viral or specific molecular technology under clinical investigation. IBC also provides patient and environmental safety oversight to evaluate the risk and safety associated with the use of the investigational agent and clinical trial conduct.{17,18}

When a sponsor subject to NIH oversight intends to engage in clinical investigations, they must first submit their clinical trial protocol to the OBA. The protocol will be reviewed by RAC to determine if the clinical investigation employs a novel protocol or includes any particular aspects that could raise new questions regarding the safety or risk associated with the gene therapy. RAC also decides if public review is necessary. If RAC determines public review is necessary, the protocol will be reviewed at the next quarterly meeting. All final suggestions regarding the modification for the trial protocol will be summarized and sent to the sponsor, Principle Investigators (PIs), FDA, IRB, IBC and the Office of Human Research Protection (OHRP). If the protocol is determined to be adequate and does not require review, the same stakeholders receive notification that the protocol is sufficient.{19}

OBA releases the *Human Gene Transfer Protocols* list, a rolling compilation of all approved gene therapy trial protocols updated periodically.{20} Investigators and sponsors can cross-reference the protocol list and points to consider within NIH guidelines when developing a trial protocol, (particularly if the investigational agent and/or target

populations are similar), to identify specific characteristics or model a trial protocol design. This minimizes the chance of prolonged review by the RAC.

FDA and NIH Oversight and Correspondence

FDA is the only institution with the authority to approve or deny a protocol for a trial in an IND application. FDA also is the only entity able to make any legally binding decisions relating to legal product identification, applications or review determination of material submitted in product applications, including clinical investigations and supplemental materials. While RAC at OBA review protocols, suggestions proposed are not legally binding for the sponsor and NIH cannot institute a clinical hold or require a protocol change.

However, given that the notification phase of the RAC review process includes FDA notification, among other parties, the agency is conscious of all recommendations made by the committee and may place a clinical hold or require modifications of the clinical protocol if it determines that RAC recommendations were legitimate and should be implemented. If the sponsor changes the clinical protocol after receiving RAC recommendations or anytime during the investigational phase of development, FDA will notify OBA of such changes.

While OBA and RAC are not part of FDA, the lines of communication remain open and active between parties to provide coordinated oversight of gene therapy activities. Biologics internal procedure SOPP 9150.1 (Notification of National Institutes of Health (NIH)/Office of Biotechnology (OBA) of Changes in a Gene Therapy Protocol) requires CBER notify OBA every two weeks of any changes to current IND gene therapy protocols based on an internal bi-weekly 'Gene Therapy IND Protocol Amendments' report summarizing recent INDs with protocol supplements or changes.{21} Furthermore, it is CBER policy to notify OBA of any new IND involving a gene therapy product.{22} CBER also takes additional steps to make the sponsor aware that if they are subject to NIH oversight, all significant trial protocol modifications should be reported to OBA in addition to FDA. Additional internal procedures dictate CBER also will notify the OBA of any serious and unexpected adverse event in an IND safety report.{23} As such, sponsors or investigators are not discharged of their NIH obligations upon initial protocol submission. They must remain compliant and engaged with the additional guidelines concerning gene therapy given the inter-agency communication or risk losing potential grant monies.

Product and Lifecycle Impact

In response to industry inquiry, FDA has released several guidance documents detailing current thinking and expectations on preclinical and clinical activities key to the regulatory oversight and review of gene therapy products. Such guidance documents clarify expectations, recommendations for sufficient documentation, decision making or substantiation of a process or concept and in certain documents, indicate recommended internal agency procedures or policy for review.

Preclinical Development and Testing

IND preclinical information is crucial to demonstrating therapeutic effect and anticipated risks associated with a gene therapy product. In addition to recommended *in vitro* genotoxicity and suggested animal (or transgenic animal) model, the vector construct for delivery, delivery vehicle, active molecular agents and any excipients used in the final product should be characterized to create a product risk profile. Depending on the nature of the delivery vehicle, the investigator should anticipate and document risks associated with the delivery mechanism. For example, Adeno-Associated Viruses (AAVs) are known to potentially induce inflammatory responses; lentiviral vectors have the potential for mutagenesis; replication competent viruses introduce a higher risk of off target infection of cells; and non-viral endonucleases present a higher risk for gene deletion. All characteristics which may impact toxicity, expression and molecular behavior should be described.{24}

Gene therapy products should undergo biodistribution testing to determine the expression of the vector and products in both on and off-target cells and tissues as well as the dosing regimen required to achieve the desired level of expression.{25}

Chemical, Manufacturing and Control (CMC)

FDA requires manufacturers of investigational gene therapy products to submit a Quality Control Plan (QC Plan) with the Chemical, Manufacturing and Control (CMC) portion of the IND explicitly designed for the oversight of the production methods in addition to standard quality control processes associated with good manufacturing practices. A QC Plan should document methods of production and identify specific points where adventitious agents are likely to infect the production materials (e.g., cell lines or effluent reservoirs). There also should be clearly defined methods for determining the existence of adventitious agents and the potential source, asking if the non-native agent was a dormant, undetected product of gene expression or was contamination from outside the cell. It is recommended that inspections are to be conducted on at least an annual basis by an independent group not part of the quality control unit. The QC Plan also should incorporate a strategy in the event an adventitious agent is detected. This would include a corrective plan for product production as well as a plan related to notification and mitigation of affected patients if possible.{26}

When reviewing CMC data for an IND application, FDA reviewers will document if the manufacturing facility has a QC Plan specifically for production of the gene therapy product and will record the most recent audit dates and results. Reviewers also expect the QC Plan will highlight essential duties and titles of individuals critical to executing the QC Plan. Depending on the nature of the gene product, reviewers also will document production methods and determine if the QC Plan is appropriate. For example, a QC Plan for a gene therapy product using *ex vivo* delivery of the gene product is expected to identify—and be designed to prevent—adventitious infection and cross-contamination of cell or tissue samples during the sample modification period. Because reviewers must document and review the QC Plan of a gene therapy product, manufacturers must submit a QC Plan in the CMC data associated with an IND application.{27}

Subject Monitoring and Delayed Adverse Events

Because certain gene therapy products may modify the genome of a host or otherwise alter the pre-therapy expression of a target through genetic intervention or manipulation, the potential for long-term risks must be carefully assessed. Patients receiving certain therapies should be monitored closely for delayed adverse effects not evident during or soon after clinical testing.

FDA guidance in response to collaborative concerns raised by the gene therapy community noted that not all gene therapies pose potential risks for long-term adverse effects. FDA does not generally require long-term follow-up studies; however, manufacturers should review all preclinical and clinical data to determine if there are any indications of latent expression, activation or risk indicating the need for long-term follow-up. To aid in deciding when a long-term study with risk assessment may be appropriate, FDA provides a Boolean decision algorithm based on the characteristics of the therapy. FDA suggests any investigation involving product with integrated vector sequences or a vector that has the potential for latency and reactivation should be considered for long-term follow-up. FDA also has provided a reference table of viral-based vectors warranting using long-term follow-up by nature of their molecular action, including the herpesvirus, gammaretrovirus and lentivirus.{28}

Expedited Review Programs and Orphan Designation

Gene therapies are commonly explored as treatment for diseases where there is no current therapy, when sub-populations are not responsive to currently available therapies, when current treatment options may only provide temporary relief or when available therapies are associated with high risks and serious adverse effects. Gene therapies are considered high risk; therefore, any disease currently under investigation for treatment using gene therapy is likely considered to be a serious condition.

Depending on the targeted disease and currently available therapies, a particular gene therapy product may be eligible for expedited review including: fast track designation, breakthrough designation, priority review or accelerated approval.{29} Expedited review programs are non-typical designations for drug or biologic products intended to treat

serious conditions. They are requested and implemented to allow patients suffering from serious conditions to gain access to new treatments as soon as possible.

Sponsors intending to treat disease where there is no current therapy may apply for fast track designation of their product through a request submitted within the IND. The request should be submitted no later than a pre-BLA meeting. Gene therapy products demonstrating significant clinical efficacy as compared to current 'gold-standard' treatment(s) may be considered for breakthrough designation. This type of designation is requested during clinical investigations by the end of Phase II meeting.{30,31} Similarly, therapeutics showing evidence for increased safety or efficacy compared to a current treatment may request priority review when applying for a BLA.{32} Therapeutics offering advantages over current therapies and those demonstrating clinical effect on defined surrogate endpoints or clinical endpoints other than irreversible morbidity and mortality are eligible for an accelerated approval pathway.{33,34}

Gene therapies intended to treat diseases that affect fewer than 200,000 individuals in the US or gene therapies unable to recover the cost of development are eligible to apply for an Orphan Drug Designation through FDA's Office of Orphan Products Development (OOPD).{35} Orphan designation provides several advantages, such as a period of marketing exclusivity and tax credits for specific clinical testing.{36}

Ethical Considerations and Policy Implications

Bioethics

The controversial nature of genetic modification for treating disease has been a gradual evolution. The ethical bounds defining acceptable clinical, research and moral limitations can vary greatly between the perspectives of scientists, public opinion and political representatives who can impact regulation of the field. Genetic intervention in somatic cells for the cure of diseases is generally recognized as an acceptable practice,{37} particularly in cases of serious or life-threatening diseases where no other options exist or where current standards of treatment are ineffective. Presently, the majority of gene therapies aim at treating various cancers, cardiovascular disease, infectious diseases or monogenic diseases.{38}

In its infancy, gene therapy protocols and therapies were not (and still are not) without serious potential repercussions. There are legitimate patient-safety concerns associated with the use of a genetic based therapy, including potential mutagenesis of genes, off-target replication, deletions or unintended insertions of which may be severely difficult to rectify at the molecular level and phenotypic expression causes severe harm.{39} Such was the case in a gene therapy trial where patients were cured of an X-linked immunodeficiency, but subsequently developed leukemia.{40} Other forms of gene therapy, such as *ex vivo* transplantation using genetically enhanced, modified cells or expression products, introduce unique patient safety concerns for immunogenicity activation, destruction or disruption of natural cell processes or organelle functions. Latent activation, random replication or unknown sex-linked modifiers may be hard to detect and dependent on the mechanism and location of alteration. These effects may only be noticed in future progeny. As understanding and customization of the various targeted delivery vehicles, modification mechanisms and gene vectors are more intimately understood, these risks are minimized through the design of therapeutic products and protocols. The National Gene Vector Biorepository (NGVB) is a primary resource for ordering and cataloging cellular, molecular and therapeutic tools, pharmacological/toxicological data, informatics sequencing tools and a library of compiled resources which can be used to modify or analyze an innovator product or therapy.{41,42}

Therapy of this sort also may present ethical implications conflicting with or raising philosophical and social concerns. Certain practices are considered to be less-acceptable or beyond the current scope of acceptable research or clinical investigation. For example, while somatic cell therapy is considered acceptable for treatment of disease, the use of Human Embryonic Stem Cell (HESC) modification has been rejected. Current legislation prohibits gene therapy of germ-line gene therapies.{43} This often raises ethical questions about using gene therapy for non-disease related, but personally desirable procedures. Similarly, gene therapy for non-disease related ailments (i.e., cosmetic enhancement) are not accepted nor are they funded by NIH.

Bioethics Effect on Legislation and Policy Decisions

The ethical acceptability of gene therapy research has a direct impact on future technologies available for the researcher, investigator and product developer. For those involved in a gene-therapy venture or related pipeline, it is critical to monitor the political environment and resulting legislation or policy that may influence product research and development.

The oscillating nature of laws and regulations pertaining to controversial research in gene therapy product design can inhibit or promote product development. For example, in 2001, president George W. Bush instituted policy provisions limiting NIH funding for stem cell research to stem cell lines already in use; these limitations on cell lines restricted the number of disease states which could be modeled and minimized the genetic diversity that could be seen to those lines already in use.^{44} In 2009, president Barack Obama signed Executive Order 13505 (Removing Barriers to Responsible Scientific Research Involving Human Stem Cells).^{45} This order allowed researchers to receive NIH funding and engage in research in several formerly prohibited cell lines, provided such stem cell lines satisfy applicable standards and criteria set forth in the concurrently then-revised NIH guidelines. However, after challenging the NIH funding of embryonic stem cell research in court (Sherley V. Sebelius),^{46} researchers were allowed to receive NIH funding for stem cell research provided no public money was used to create a new stem cell line.^{47} Gene therapy products which may be conceived from or are undergoing further development based on active NIH sponsored stem-cell research are particularly vulnerable to political influence and policy reversal. To avoid such issues, sponsors working closely with a research group should consider private sources of funding as even state-level funding is susceptible to political influence. Various private groups and research institutions have secured the use of private research funding allowing them to have more control over experimental parameters and research exploration, especially in more controversial areas of research.^{48}

In 2016, NIH instituted a policy change allowing sanctioned research wherein Human Pluripotent Stem Cells (HPSCs) are implanted in animal embryos (with species-crossing limitations).^{49} Despite ethical implications associated with the development of a potential humanoid exhibiting qualities of both an animal and a human, NIH has determined allowances could lead to medical developments ultimately beneficial to the scientific community. Gene therapy products using hybrid animal expressions, gene constructs or cells from hybrid gestation may provide unique combinations of disease modeling and genetic tools that may be more easily translated to human somatic cell therapies based on the partial human specificity of the maturing embryo. Sponsors looking to develop an innovator requiring more unique modeling for vector quantification or unique manufacturing challenges, such as the need for specific animal cell types to more efficiently produce viral expression products with human-integrated gene segments, may be more likely to find ongoing research or a research group that has already undertaken foundational development, which may expedite product development.

Future Considerations

Private product development often results from publicly sponsored foundational research which, in recent years, has seen relaxed constraints and expanded scope. Social and technological advancements may move gene therapy to a standard of care to where gene-based protocols are more commonly used for treatment. China and some countries within the European Union have already approved commercial gene therapy products for sale.^{50,51} With the number of active, ongoing trials, gene therapy is inevitable in medicine in the US and other countries. While it may take decades for gene therapy to replace some current therapies, gene therapy offers several potential corrective solutions at the molecular level and may even evolve for use in less-traditional methods over time. These possibilities include pre-therapy to induce genetic polymorphisms to increase a patient's pharmacogenetic specificity for a particular drug product to ensure that drug therapy is more efficacious.

Furthermore, the role of informed consent and oversight committees may evolve as gene therapy becomes more routine. Patients in a clinical investigation are expected to be informed about the risks of participation and the basic scientific premise for the clinical

investigation. However, the complex and extremely detailed technical nature of gene therapy products raises concerns that patients may not fully comprehend the risks when agreeing to participate in a gene therapy clinical trial. This issue is further compounded by the notion that potential patient candidates are usually in dire health or financial situations and there are few to no alternative treatments. Thus, the high-risk experimental treatment may appear as their only choice. While the role of ethics committees will always deal with patient safety and oversight, committees also may need to acknowledge the lack of comprehension on the part of patients, but still allow more participants in the future as product safety can be more assured from sponsors through repeated use of similar technologies.

Strategies for Product Development and Application Pathways

Suggested Order of Approach to FDA and OBA for Initial Protocol Review

Manufacturers should consult FDA for a pre-IND meeting to answer initial questions regarding preclinical materials and trial design. After the pre-IND meeting, the sponsor should submit the clinical trial protocol to RAC at OBA for review to determine if modifications are necessary. The sponsor should implement recommendations to the trial protocol before submitting the initial IND package to the FDA.^{52} Therefore, FDA will receive a revised version of the protocol incorporating RAC recommendations, as opposed to applying for RAC review after IND submission and having to implement changes to satisfy RAC recommendations at the request of FDA, potentially stalling initiation of the clinical investigation.

Using Human Gene Transfer Protocols as a Trial Template

In the event the sponsor is using a gene therapy product that has been clinically investigated in a similar form (e.g., modified lentiviral vector for delivery of a gene construct), the sponsor should cross-reference and base the design on previous trial protocols compiled in the OBA *Human Gene Transfer Protocols* reference.^{53} Submitting a modified or tailored version of gene therapy protocol previously or currently used for investigational studies will lessen the chances the protocol appears novel or introduces new issues of safety. This could minimize the delay for public comment and review in addition to minimizing the likelihood of recommendations or requirements from any entity (RAC or FDA) that the trial should be modified.

Use a Master File in the IND for the Therapeutic Product Used by Multiple Groups

When a sponsor or principal investigator of a therapeutic agent intends to use the same product in multiple trials (e.g., multiple trials with different patient populations), they should consider submitting a master file with all associated CMC information to allow for consistent documentation across all clinical investigational applications.^{54} Any change to the master file will be reflected in all dependent applications; sponsors will only have to reassess how changes in manufacturing affect the risk-benefit factor to determine if continued investigation is justified for each trial. This method provides more consistent, coordinated documentation across all dependent application and can minimize the need for necessary redundant supplements.

Use Easily Scalable Manufacturing Techniques for Production of the Therapeutic Product

Applicability of current good manufacturing practice regulations allows manufacturers of drugs or biologics under Phase I investigation (including gene therapy products) to be exempt from the regulations for finished pharmaceuticals provided the agent has not been distributed or otherwise prepared for use in a Phase II or Phase III trial.^{55,56} Therefore, sponsors investigating a gene therapy product may use justifiable local or non-standard techniques for manufacture that may not be acceptable for later phase studies.^{57} Manufacturers should consider using methods that can be scaled for larger production to meet the standards of finished pharmaceuticals if feasible, thus minimizing changes in manufacturing and repeat subsequent re-evaluation and justification for risk-benefit, compliance and comparable product potency testing.

Develop a Product Regulatory Strategy With Anticipated Approval Pathway

A pre-development strategy defining the intended (if any) applicable expedited review program will promote better product preparedness and more efficient product development through investigational clinical phases. Trial protocols can be established with the appropriate surrogate endpoints to satisfy or suggest therapeutic efficacy or safety, which may provide the foundation for justification of an expedited review program upon request. The timing of a request for an expedited review implies the timetables required to demonstrate certain clinical safety or efficacy. As a result, sponsors should plan to compile all necessary clinical data to support a break through designation no later than Phase II.

Establishment of Concurrent Reporting Procedures to NIH and FDA

Sponsors should establish a standard internal procedure within the clinical trial protocol to ensure reporting to FDA through MedWatch and NIH through GeMCRIS are performed simultaneously in the event of a serious adverse event since FDA relays adverse event reporting notifications to the OBA, and the reporting schedules between both parties, have been harmonized.

Secure Private Funding for Areas of Related Research and Development

To avoid the potential 'ripple effect' of legislation or legal actions, sponsors basing innovator research, therapy development or manufacturing on more controversial areas of research, should consider privately funding an entire venture or replicating research in a privately funded environment. While public funding and publicly funded research may be more susceptible to changing guidelines and barriers, privately funded ventures have much more leeway.

Parallel Scientific Advice from FDA and EMA

Sponsors interested in exploring concurrent clinical investigation in the US and Europe should request Parallel Scientific Advice (PSA) during product development. CBER Biologics Internal Procedure, SOPP 8001.6 (Procedures for Parallel Scientific Advice with European Medicines Agency (EMA)) allows gene therapy product sponsors to request the use of PSA, wherein the sponsor may submit a single set of questions for response from both FDA and EMA.^{58} FDA and EMA coordinate review and discussion of questions and provide answers to the sponsor simultaneously. In the event of inconsistent answers from both parties regarding a specific question, an explanation is provided to the sponsor. A sponsor should write the PSA Product Office Lead at the Office of Cell Tissue and Gene Therapies to initiate the meeting request. If accepted, FDA will coordinate the meeting with appropriate EMA staff. If desired, sponsors should consider requesting PSA pre-IND or at the end of Phase II when FDA and EMA review activities are most closely aligned.^{59}

Conclusion

As gene therapy continues to evolve and novel protocols or production develop as a result of emerging technologies, sponsors and investigators should be prepared to satisfy all requirements of FDA regulations and NIH guidelines. There are a significant number of guidance documents and internal procedures to help prepare sponsors of gene therapy products to adhere to all product regulations, expectations and unique considerations. As this class of products becomes more common in the future, developers will receive more clarification on FDA thinking in regard to specific types of technologies and the most appropriate means of satisfying all governing requirements. Interested parties should remain current on all regulatory resources in order to more efficiently navigate the regulatory framework.

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Cite as: Ramina, G. "Regulation and Oversight of Gene Therapy in the US." *Regulatory Focus*. February 2017. Regulatory Affairs Professionals Society.

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