FDA Statement on Efforts to Advance Development of Gene Therapies

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Statement from FDA Commissioner Scott Gottlieb, M.D. on agency's efforts to advance development of gene therapies

Once just a theory, gene therapies are now a therapeutic reality for some patients. These platforms may have the potential to treat and cure some of our most intractable and vexing diseases. The policy framework we construct for how these products should be developed, reviewed by regulators, and reimbursed, will help set the stage for the continued advancement of this new market. Last year, we announced our comprehensive policy framework for regenerative medicine, including a draft guidance that describes the expedited programs, such as the breakthrough therapy designation, and the regenerative medicine advanced therapy (RMAT) designation, that may be available to sponsors of these therapies. Today, we're unveiling a complementary framework for the development, review and approval of gene therapies.

In the past 12 months, we've seen three separate gene therapy products approved by the FDA. This reflects the rapid advancements in this field. An inflection point was reached with the development of vectors that could reliably deliver gene cassettes in vivo, into cells and human tissue. In the future, we expect this field to continue to expand, with the potential approval of new treatments for many debilitating diseases. These therapies hold great promise. Our new steps are aimed at fostering developments in this innovative field.

Gene therapies are being studied in many areas, including genetic disorders, autoimmune diseases, heart disease, cancer and HIV/AIDS. We look forward to working with the academic and research communities to make safe and effective products a reality for more patients. But we know that we still have much to learn about how these products work, how to administer them safely, and whether they will continue to work properly in the body without causing adverse side effects over long periods of time. In contrast to traditional drug review, some of the more challenging questions when it comes to gene therapy relate to product manufacturing and quality, or questions about the durability of response, which often can't be fully answered in any reasonably sized pre-market trial. For some of these products, we may need to accept some level of uncertainty around these questions at the time of approval. For example, in some cases the

long-term durability of the effect won't be fully understood at the time of approval. Effective tools for reliable post-market follow up, such as required post-market clinical trials, are going to be one key to advancing this field and helping to ensure that our approach fosters safe and innovative treatments.

Even when there may be uncertainty about some questions, we need to make certain we assure patient safety and adequately characterize the potential risks and demonstrated benefits of these products. In part because of the added questions that often surround a new technology like gene therapy, these products are initially being aimed at devastating diseases, many of which lack available therapies, including some diseases that are fatal. In such cases of devastating diseases without available therapies, we've traditionally been willing to accept more uncertainty to facilitate timely access to promising therapies. In such cases, drug sponsors are generally required to conduct post-marketing clinical trials, known as phase 4 confirmatory trials, to confirm clinical benefit of the drug. This is the direction Congress gave the FDA by creating vehicles like the accelerated approval pathway.

When it comes to novel technologies like gene therapy, the FDA is steadfastly committed to a regulatory path that maintains the agency's gold standard for assuring safety and efficacy. As we develop this evidence-based framework, we're going to have to modernize how we approach certain aspects of these products in order to make sure our approach is tailored to the unique challenges created by these new platforms.

Today, we're taking a step toward shaping this modern structure for the regulation of gene therapy. The agency is issuing a suite of six scientific guidance documents intended to serve as the building blocks of a modern, comprehensive framework for how we'll help advance the field of gene therapy while making sure new products meet the FDA's gold standard for safety and effectiveness.

These policies are part of our efforts to communicate the steps we're taking to provide clear recommendations to sponsors and researchers, so that we can better support innovation. The documents are being issued in draft form so that we can solicit public input on these new policies. As with all draft guidances, all of the comments we receive will be carefully considered prior to finalizing these documents. We're committed to working with stakeholders to bring novel treatments to the market while ensuring the safety of patients.

Disease Specific Gene Therapy Guidances

Today we're issuing three new draft guidance documents on the development of gene therapy products for specific disease categories. These are the first three disease-specific guidances that the agency is issuing for gene therapy products. Our new commitment to develop disease-specific guidance documents reflects the increasing activity in this field, and its growing importance to advancing public health.

Human Gene Therapy for Hemophilia: Gene therapy products for hemophilia are now being developed as single-dose treatments that may enable long-term production of the missing or

abnormal coagulation factor in patients. This may reduce or eliminate the need for coagulation factor replacement. To define the proper development pathway for such products, we're issuing a new draft guidance on gene therapy products that are targeted to the treatment of hemophilia. Once finalized, this new guidance will provide recommendations on the FDA's current thinking on clinical trial design and preclinical considerations to support the development of these gene therapy products. Among other elements, the draft guidance provides recommendations regarding surrogate endpoints that could be used by sponsors pursuing accelerated approval of gene therapy products that are intended for treatment of hemophilia.

Human Gene Therapy for Retinal Disorders: Another area of fast-paced activity is gene therapy products targeted to the treatment of retinal disorders. The Human Gene Therapy for Retinal Disorders guidance, once finalized, will assist those developing gene therapy products for a wide variety of retinal disorders affecting both adult and pediatric patients. Gene therapy products currently undergoing clinical trials in the United States for retinal disorders are commonly delivered by intravitreal injections (into the fluid portion of the eye), or by subretinal injections (beneath the retina). In some cases, the gene therapy products are encapsulated in a device to be implanted within the eye. This new guidance document will focus on issues that are specific to gene therapies for retinal disorders. The document provides recommendations related to product development, preclinical testing, and clinical trial design for such products.

Human Gene Therapy for Rare Diseases: Rare diseases are those that affect fewer than 200,000 people in the United States. The National Institutes of Health reports that nearly 7,000 rare diseases affect more than 25 million Americans. About 80 percent of rare diseases are caused by a single-gene defect, and about half of all rare diseases affect children. Since most rare diseases have no approved therapies, there is a significant unmet need. The Human Gene Therapy for Rare Diseases guidance, once finalized, will provide recommendations on preclinical, manufacturing and clinical trial design for all phases of the clinical development program for these types of gene therapies. The information is intended to assist sponsors in the design of clinical development programs, where there may be limited study population size, potential feasibility and safety issues, as well as issues relating to the interpretation of effectiveness.

Guidances on Manufacturing Gene Therapies

Today, we're also providing new and comprehensive updates to three existing guidances that address manufacturing issues related to gene therapy. These updates reflect input from many stakeholders. We encourage additional feedback on these documents during the comment period.

The first draft guidance, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), provides sponsors with recommendations on how to provide sufficient CMC information to assure safety, identity, quality, purity and strength/potency of investigational gene therapy products. The guidance applies to human gene therapies and to combination products that contain a human gene therapy in combination with a drug or device. In addition, this guidance is organized to follow the structure of the FDA guidance on the Common Technical Document.

The second draft guidance, Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up, provides additional recommendations regarding the proper testing for RCR during the manufacture of retroviral vector-based gene therapy products, as well as during the follow-up monitoring of patients who've received retroviral vector-based gene therapy products. Specifically, the draft guidance recommends the identification and amount of material to be tested. The guidance also provides advice on general testing methods.

The third draft guidance, Long Term Follow-Up After Administration of Human Gene Therapy Products, provides recommendations regarding the design of long-term follow-up (LTFU) observational studies for the collection of data on delayed adverse events following administration of a gene therapy product. Because of some of the additional uncertainty intrinsic to a novel platform like gene therapy -- including questions related to the durability of the treatment effects as well as the theoretical potential for off-target effects if the genes do not insert correctly -- there's an increased need for robust long term follow-up of patients in the post-market period. This guidance describes product characteristics, patient-related factors, and the preclinical and clinical data that should be considered when assessing the need for LTFU observations and describes the features related to effective post-market follow up.

Once finalized, these draft guidances will replace previous guidances issued by the FDA in April 2008 (CMC) and November 2006 (RCR and LTFU).

The field of gene therapy has progressed rapidly since these guidances were first issued. Therefore, the FDA is updating these guidances to provide sponsors with the agency's most up-to-date thinking.

Our goal is to help promote safe and effective product development in this field. We'll continue to work with the product sponsors to help make the development and approval of these innovative gene therapies more efficient, while putting in place the regulatory controls needed to ensure that the resulting therapies are both safe and effective. We'll also make full use of our expedited programs such as breakthrough therapy designation and regenerative medicine advanced therapy designation whenever possible.

Gene therapy represents one of the most promising opportunities for developing highly effective and even curative treatments for many vexing disorders. Some of these products are almost certainly going to change the contours of medical practice, and the destiny of patients with some debilitating diseases.

Our goal is to help these innovations advance in a framework that assures the safety and effectiveness of these resulting treatments, and continues to build peoples' confidence in this novel area of medicine.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible

for the safety and security of our nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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