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IN FOCUS

October 25, 2024

Novel Gene Therapies for Blood Disorders

During the past few years, the U.S. Food and Drug Administration (FDA) has approved gene therapy products designed to treat blood disorders. Gene therapy works by modifying a person's genes to treat or prevent diseases. While the potential of gene therapy products to treat certain diseases has been established, their long-term risks are unclear. Gene therapy products are considered biologics (biological products) by FDA and regulated by FDA's Center for Biologics Evaluation and Research (CBER).

CBER has approved three novel gene therapy products since 2023 that treat blood disorders. Casgevy is used to treat sickle cell disease (SCD) and thalassemia, Lyfgenia is used to treat SCD, and Roctavian is used to treat hemophilia A. Casgevy and Lyfgenia are the first cell-based gene therapies for SCD. Casgevy is the first treatment to use a novel genome editing technology approved by the FDA. Roctavian is the first gene therapy for adults with severe hemophilia A.

These three gene therapy products were approved by FDA utilizing authority in Section 351(a) of the Public Health Service (PHS) Act. FDA has issued several guidance documents pertaining to gene therapy products. This In Focus provides a brief overview of the select blood disorders, the opportunity gene therapy products provide to improve care for individuals with these particular blood disorders, and the approvals required by FDA.

Blood Disorders Treated by Gene Therapy Products

One in 76 people in the United States are affected every year by blood disorders, which can be inherited or acquired. Common blood disorders include anemia (inability to supply oxygen throughout body), hemophilia (a bleeding disorder), and leukemia (a type of blood cancer). These conditions can cause blood cells to function abnormally, thereby affecting the health of an individual.

Sickle cell disease (SCD)

SCD, the most common inherited blood disorder, affects approximately 100,000 people in the United States. Although SCD is most prevalent in African Americans (90% of overall SCD patients), it also affects, to a lesser extent, Hispanic Americans (3%-9%). The life expectancy of those with SCD is 20 years shorter than the average U.S. life expectancy. SCD occurs because of a mutation in hemoglobin, a protein present in red blood cells that delivers oxygen to the body. The mutation causes the red blood cells to form a crescent or "sickle" shape. These sickled cells block the flow of blood in the blood vessels and reduce oxygen delivery to the body, leading to severe pain and organ damage, vaso-occlusive events (VOE), and vaso-occlusive crisis (VOC). VOE represent a group of acute complications that are associated with SCD. VOE include episodes of acute severe pain, infection, stroke, acute coronary syndrome, and spleen damage. VOC occurs when sickled red blood cells block blood flow to the point that tissue becomes deprived of oxygen. VOC can lead to health complications such as arthritis, kidney failure, and stroke. VOC is the most common cause of hospitalizations associated with SCD. VOE and VOC can lead to changes in patterns of daily activities, severe disabilities, or early death.

Thalassemia

Thalassemia is a form of hereditary anemia. It is caused by an altered synthesis of one of the two globin chains in hemoglobin. Hemoglobin is the iron-containing protein in red blood cells that carries oxygen to the body. Beta thalassemia is a type of thalassemia that reduces the production of hemoglobin. About 1.5% of the global population are carriers of beta thalassemia. For patients with beta thalassemia, reduced hemoglobin can lead to a lack of oxygen in many parts of the body. These patients are typically treated with lifelong regimens of blood transfusions. These transfusion-dependent beta thalassemia (TDT) patients are at risk of developing abnormal blood clots. Abnormal blood clots could lead to severe diseases such as heart attack, stroke, and kidney failure.

Hemophilia

Hemophilia is an inherited blood disorder that stops blood from clotting properly. According to the Centers for Disease Control and Prevention (CDC), approximately 33,000 people in the United States assigned as male at birth are living with hemophilia. As genes involved in hemophilia are present in X chromosomes and males have only one copy of X chromosome, males with hemophilia are much more likely to have serious bleeding symptoms than females with hemophilia. Females have two copies of X chromosomes and tends to have less serious symptoms from hemophilia. Due to deficient clotting factors, people with hemophilia take longer to stop bleeding after injury or surgery. Hemophilia A is a bleeding disorder that occurs due to a mutation in the gene that produces clotting factor VIII (FVIII), a protein that enables blood to clot. Severe hemophilia A is identified by especially low levels of FVIII (less than 1% of blood) and composes 60% of all hemophilia A cases.

Gene Therapy Products

Casgevy

Casgevy is a cell-based gene therapy for SCD patients 12 years old and above with recurrent VOC and TDT. Casgevy uses CRISPR/Cas9, a type of genome-editing technology. The technology can be directed to cut DNA in targeted

areas, providing the ability to accurately edit (remove, add, or replace) DNA where it was cut. A patient's blood stem cells are collected, modified, and then transplanted back into the patient, where they attach and multiply within bone marrow. This modification increases the production of fetal hemoglobin (HbF), which facilitates oxygen delivery. In patients with SCD, increased levels of HbF prevent VOC. In TDT patients, improved oxygen delivery decreases the severity of anemia and reduces the need for red blood cell transfusions.

Lyfegenia

Lyfgenia is a cell-based gene therapy for SCD patients, 12 years old and above, with a history of VOE. It uses a lentiviral vector (gene delivery vehicle) to modify blood stem cells, which are transplanted back into the patient. Modified cells with the corrected hemoglobin gene produce the hemoglobin protein that functions similar to normal hemoglobin A. Red blood cells containing the newly created hemoglobin have a lower risk of sickling and occluding (slowing or stopping) blood flow, thus preventing occurrence and reducing severity of VOE.

Roctavian

Roctavian is a gene therapy product for patients with hemophilia A. It contains an adeno-associated viral vector (a type of virus, used to transfer genes) carrying a gene for FVIII. After the gene is expressed in the liver of patients with hemophilia A, the gene increases the levels of FVIII in the blood, reducing the risk of uncontrolled bleeding.

Regulatory Activity, Guidance Documents, and Legislative Activity

Regulatory Activity by FDA

Gene therapy products are regulated under Section 351(a) of the PHS Act. In 1999, FDA amended the biologics section in the PHS Act to implement new biologics license application (BLA) requirements. This amendment applied to certain therapeutic products: deoxy ribonucleic acid (DNA) products, synthetic peptide products of 40 or fewer amino acids, monoclonal antibody products, and recombinant DNA-derived products. BLA approval gives applicants a license to market biological products in interstate commerce. These initiatives were intended to reduce burdens for industry while maintaining important public health protections.

FDA Guidance Documents

FDA guidance documents communicate FDA expectations over a product's lifecycle to the manufacturers of a particular product type. For manufacturers of gene therapy products, one FDA guidance document recommends that the manufacturers evaluate multiple versions of a gene therapy product and consider alternative approaches. These are intended to decrease animal use during drug development and expedite the process. In a separate FDA guidance, FDA provides information to assist sponsors in managing manufacturing changes and associated regulatory reporting for their gene therapy products. FDA regulators encourage prospective discussions during the product lifecycle. In addition, another FDA guidance specifies what information FDA expected to be provided in an investigational new drug (IND) application and a BLA to evaluate the safety and quality of the gene-editing product for human somatic cells.

Legislative Activity

In recent years, several pieces of legislation have been introduced that address gene therapy products. These bills sough to reduce the risks associated with gene synthesis products and their potential misuse, assess differences between approaches to approve interchangeable biological products (biosimilars), and address issues of market exclusivity for gene therapy products.

Considerations for Congress

The following are potential considerations for Congress with respect to gene therapies for blood disorders or gene therapies in a broader context:

- Congress may consider directing FDA to better assess the benefits and risks associated with gene therapy products over a prolonged period of time and the regulatory apparatus that exists to monitor and mitigate those risks.
- Congress may look at the sponsor (manufacturer) reporting requirements for gene therapy products, such as product safety, efficacy, and adverse events monitoring, and whether they provide sufficient information and feedback to FDA, policy makers, prospective patients, and providers to inform the need for potential changes in the future.
- Congress may consider directing FDA, or another entity such as the National Academy of Medicine, to assess the benefits and risks associated with gene therapy products for patients.

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IF12796

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