Is 'bespoke' therapy the future of genomic medicine?

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September 25, 2020 -- Gene therapies hold extremely exciting promise for meeting the unmet needs of many individuals with genetic diseases, as discussed in a session of the second annual American Society of Gene & Cell Therapy (ASGCT) Policy Summit on September 24.

However, the development of these therapies is highly complex, and the research and regulatory communities are only beginning to get a grasp on what it will take to make these medicines commercially available, as explained by Dr. Peter Marks, PhD, director of the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER).

There are over 7,000 rare diseases that affect approximately 30 million Americans, according to the Genetic and Rare Diseases Information Center, a program of the National Center for Advancing Translational Sciences. Of these diseases, around 80% are genetic in origin and nearly half affect children. Many rare diseases are life-threatening conditions.

Gene therapy has the potential to make a significant impact in the rare disease space by targeting the underlying pathophysiology of each disease, the genetic mutation.
Although gene therapies may offer a transformative treatment option, there are currently only five gene therapies approved for use in the U.S. There are several unique challenges associated with the development of therapies for rare diseases, notably the small patient populations which can range from only a few dozen to hundreds of patients.

To begin, Marks addressed the differences between personalized medicine, which when the concept was developed in the 1990s indicated finding the right preapproved drug to treat a patient and the recent transition to the idea of individualized medicine, which involves creating a new product based on a genetic indication.

Entering the 'bespoke' era

Individualized therapies can be further broken down into two classes: customized products and created products. To help explain this concept, Marks uses the analogy of a buying a suit. He compares personalized medicine to a ready-to-wear suit, which is an option that someone might purchase off a rack. Here, there are several options to choose from, but nothing is designed specifically for any particular customer/patient.

The next step up in the tailoring experience is a made-to-measure suit, which is analogous to a customized therapy. A made-to-measure suit is premade, but the seams are left open to allow for certain modifications to personalize for the customer. Similarly, the idea of a customized therapy involves developing a set of products that target the same indications with the same mode of action but can incorporate patient genetic information to provide a customized, targeted therapy.

Lastly, a made-from-scratch, made-to-measure suit, or a bespoke suit, is the most precise and personalized garment option. These are custom made by a tailor and are the best fit for a customer. The bespoke suit corresponds to a created therapy, or bespoke therapy, as Marks refers to it. For these therapies, each product treats a different indication (genetic mutation) and can have vastly varying modes of action. As the development and regulatory mechanisms stand currently, the industry is reinventing the wheel every single time for these therapies.

"It's just not possible to reinvent the wheel every time if you're going to deal with thousands of rare disorders," explained Marks, referring to work of his colleagues at the National Center for Advancing Translational Sciences. "In fact, unless we do something fundamentally different, it's likely that to get to 100 rare disease [therapies], it's going to take 600 years."

Technology transfer is problematic

As it stands right now, manufacturing is the real "spoke in the wheel" when it comes to gene therapies. As a rate-limiting factor, technology transfer and process scale-ups create a significant bottleneck. Marks explained that many gene therapies produce great phase I/II clinical trial data but have serious problems when they try to transfer and scale technologies out of academic and research labs to larger contract manufacturers or in-house commercial facilities.

The issue may come from technology developed in academic labs, where therapies are developed with available resources which may not be optimized for transfer. To overcome these challenges, Marks suggests that the FDA develop a "bespoke gene therapy cookbook." Defining certain reproducible principles required for transfer will help move products through the development system.

Moreover, commercial pharmaceutical manufacturing is not set up to support the small batches needed for gene therapies. There are significant limitations in information transfer among manufacturers that decrease efficiency on top of the inherent inefficient and costly production of adenoviral and lentiviral vectors. Overall, there needs to be a transition away from manufacturing large batches to smaller (less than 100 batches per year) scale in a commercially viable process.

Marks insists that these genomic medicines can be implemented if manufacturing processes can be streamlined and efficiencies found that offer commercially viable pathways. However, we need new models for evaluating genome editing and assessing off-target effects in more effective preclinical models, and nifty statistical methods to account for small patient populations.

Dr. Marks closed his discussion by detailing the FDA's efforts to generate gene therapy master files for standard vector production, from vector generation to manufacturing therapeutics and delivering a clinical therapy to patients. This pilot program would be developed and managed by the Bespoke Gene Therapy Consortium, a nonprofit, umbrella organization. This group would help develop the regulatory framework needed to make gene therapies a reality.

"Hopefully we will see a streamlining of the time and the cost associated with developing these products," said Marks.