A new paradigm for gene therapy

Peter Marks has a broad mandate. As director of the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration he oversees the regulation of biological products, including vaccines and cell and gene therapies. Dr Marks has worked in academic medicine, pharmaceutical medicine and is now a top regulator. He is also a frequent conference speaker where he shares some of the thinking of the FDA.

At a meeting of the International Society for Cell and Gene Therapy on 26 May, Dr Marks reviewed some current concepts and also gave more detail about the FDA's thinking on standardising the review of gene therapies.

A unique opportunity

The starting point is that gene therapies offer a unique opportunity to tackle or even cure rare diseases but their development needs to be modernised. "Increasingly it is really clear to us that very rare disorders are important in their own right because of the suffering that they cause. They are also important because they serve as potential paradigms that will help move us along towards treating less rare disorders. Conversely, many relatively common disorders may turn out to be really a host, or collection, of very rare disorders," he told the meeting.

Gene therapies represent an opportunity to understand and even redefine disease. But at the same time they face huge bottlenecks, especially in the manufacture of viral vectors, the vehicles that bring transgenes into cells. According to FDA data, the current capacity for manufacturing adeno-associated viral (AAV) vectors, one of the most common vector types, works well for populations of between 100 and 10,000 individuals. However for patient cohorts of fewer than 100 people, the cost of production is unsustainable. And for populations greater than 10,000, current technology is not viable.

Constraints also exist on the regulatory side, arising in part from the different way gene therapies are constructed compared with small molecule drugs and antibody therapeutics. Whereas small molecules are the basis for personalised medicines that can be taken off the shelf to treat specific diseases, gene therapies represent a different genre of medicine. Dr Marks said they might be described as individualised medicines falling into one of two categories: customised products and created products.

Customised products are products with the same indication and mode of action but which are administered differently from person to person. Examples include chimeric antigen receptor (CAR) T cell therapies and certain vaccines. An example of a customised vaccine would be a vaccine for pancreatic cancer using dendritic cells pulsed with an individualised peptide mixture.

Created products are those which have different indications and different modes of action. An example might be gene therapies for two different haemoglobin mutations using the same vector backbone. "You could imagine a smaller group of created products which might be centered around the re-use of a vector backbone," he told the meeting.

In an interview, Dr Marks explained what created products might look like. The disease might be mucopolysaccharidoses (MPS), a group of inherited lysosomal storage disorders where a deficiency or malfunction of specific enzymes can lead to progressive damage to cells, tissues and organs.

He described a hypothetical situation in which a company wants to develop gene therapies for seven MPS subtypes. The company starts by characterising a product for MPS1, called the originator product, and then prepares to move on to MPS2 and possibly other subtypes. The concept is to reuse data from the first development to streamline the development of subsequent created products in the same disease group. Under the paradigm, the company would present new data for the gene insert, but then reference its previous application for information about the vector.

"In terms of manufacturing information, I am just going to show characteristics of my insert, the gene that I used to make the product. Everything else about how I make the AAV [vector], the media, the growth process that controls that, I reference back to my prior application. What I am doing here is leveraging. That simplifies things tremendously because the chemistry, manufacturing and control section of the application suddenly go from being massive to being relatively [small]," he said.

Dr Marks said he envisions a suite of different vector backbones that would operate across the gene therapy industry. The scenario includes non-vector delivered gene therapies such as plasmid DNA. And it would cover proprietary vectors as well as public vectors. "You could imagine that there could be public vectors, in other words AAVs that don't have patent protection that would be on file for reference," he said. "We would be open to alternatives that perhaps would be more inviting to academic physicians."

The concept of a re-usable vector is part of a wider discussion that Dr Marks and others at the FDA are having with industry about standardising gene therapy production and regulation. This is taking place under a public-private partnership known as the Bespoke Gene Therapy Consortium. The consortium hasn't formally launched yet. But it has issued a statement of objectives which is to create an operational playbook for gene therapy production which would include streamlined templates, master regulatory files, and descriptions of uniform production processes. These procedures will be tested in four to six cases of gene therapies for very rare diseases sometime in the future.

At the ISCT meeting, Dr Marks said there is a clear link between these rare disorders and larger disease indications. "I think that this is really a good paradigm for us because if we can get it right for the very small, I think that ultimately we will be able to get it right for the larger indications," he said.

This article was written by Victoria English, the *MedNous* editor, with editing by Miguel Forte, a member of the *MedNous* Editorial Board.