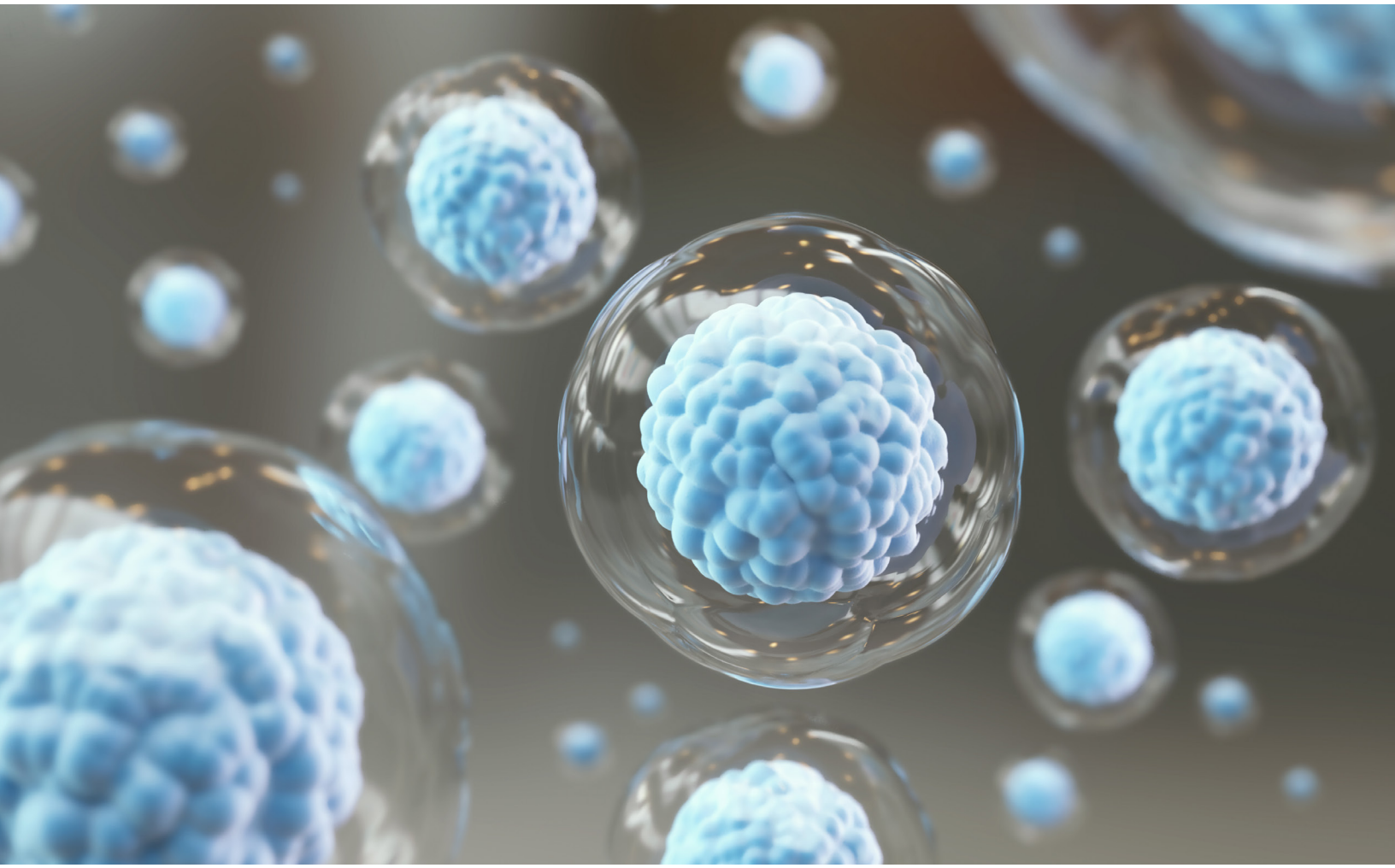
# Helping to accelerate cures: Regulating the rapidly evolving field of cell and gene therapies

In this interview, Peter Marks of the US Food and Drug Administration discusses how the organization has contributed to the broader ecosystem of innovation.



JANUARY 2019 • PHARMACEUTICALS & MEDICAL PRODUCTS PRACTICE

The drug-development landscape has been evolving, and there is a coming surge of products based on new modalities. Both cell therapy (the transfer of intact, live cells into a patient to help lessen or cure a disease[1]) and gene therapy (a technique that modifies a person's genes to treat or cure disease[2]) are expected to experience rapid growth in the next five to ten years.

McKinsey partners Jeff Smith and Tara Azimi, along with consultant Kate Chavez, recently sat down for a discussion with Peter Marks, director of the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration (FDA). Among its various regulatory responsibilities, CBER regulates cell and gene therapies in the United States. The discussion provides interesting insights into how the FDA has approached regulating the rapidly evolving field of cell and gene therapies, and how it has played an important role in the broader innovation ecosystem.

**McKinsey:** *It's an exciting time for patients with the development of many new cell and gene therapies. From your viewpoint, what have been the drivers of success to date?*

**Peter Marks:** We have seen a quantum leap in gene therapy over the past decade. The ability to advance the technology has been driven because the scientific community has settled on certain vectors with promising characteristics. Focusing on these has allowed a deeper understanding of the science, which in turn has helped accelerate clinical applications.

For cell therapy, an important driver has been the development of improved manufacturing capabilities. One challenge historically has been that we could make some interesting things and test them in the lab and then in small numbers of individuals, but we weren't able to scale up production and replicate the results in larger trials because of variations in manufacturing. This is now being addressed with the application of more advanced production technologies. However, even with recent advances in manufacturing, there still can be significant challenges to the reproducible production of cellular products. Only when the process is well controlled can there be a successful product made at commercial scale.

**McKinsey:** *What are some of the critical factors for continued innovation in cell and gene therapies in the future? What are potential bottlenecks to continued innovation?*

**Peter Marks:** For gene therapy, the quantum leap that I would expect in the next five or so years is solving the issue of manufacturing vectors in a scalable fashion. This is needed to continue advancement of the field and to allow it to reach a broader range of patients. On the cell-therapy side, there is a group of people who have figured out how to manufacture certain autologous cell therapies with a consistent and highly controlled process. There is also a significant effort under way to produce allogenic cell lines that could safely reproduce the effects of these autologous products. If and when this breakthrough happens, it will have significant impact on the field of cell therapy.

As challenges are addressed, such as scaling the manufacturing of vectors for gene therapy and producing allogeneic lines for use in cell therapy, I think that there is significant potential that these technologies will find much broader application for a wide variety of different diseases. Currently, a substantial proportion of time and significant resources are spent on manufacturing and technical issues. As the technical challenges are addressed and as manufacturing capabilities expand, I would hope the balance could shift over time to more focus on innovation on product concepts that will drive the next wave of innovative therapies.

**McKinsey:** *From a regulatory standpoint, how does the FDA think differently about cell and gene therapies*

*than, say, traditional modalities (for example, small molecules or monoclonals)?*

**Peter Marks:** From a longer-term standpoint, I think we have an important role in providing regulatory clarity to innovators. Our job as regulators is to set the bar in accordance with statutory authorities for the degree of uncertainty that we are comfortable accepting for our society in reaching product-approval decisions.

For cell and gene therapies, we have products that utilize a common set of technologies, for example, some of the vectors that I mentioned earlier. So, once we have established precedent and greater postmarket experience with the safety of these products, we may feel more comfortable with additional products that make use of the same underlying technologies. We don't think it is reasonable or that it provides any greater level of risk mitigation to expect innovators to reinvent the wheel with each new product when the underlying technologies are nearly identical.

In some ways, this can be likened to a razor-and-razorblade model. In instances where there is something that we have seen before—the razor—we might have an established set of expectations. We could then focus our attention on the razorblade: the unique and different aspects of a particular product compared to all the others that we have seen.

Just to be clear, this is a long-term vision, and I think we can get there over time. We can be flexible once we get experience, and of course this must come without compromising patient safety. However, once we can achieve this, it will help avoid work that takes resources and capital that could go to more meaningful research. In the end, this is good for patients and for public health as it will help to expand existing approaches to more diseases and allow for additional attention to novel product concepts.

**McKinsey:** *How is the FDA thinking about surrogate endpoints for the diseases that cell and gene therapies treat?*

**Peter Marks:** It truly depends on the disease in question. In some cases, surrogate endpoints will be very useful and in other cases they could be potentially irrelevant or even misleading if they are not adequately validated. For example, in some of the genetic diseases that are the focus of gene therapies, the assays to understand protein-production levels are not yet reproducible. Unless the assay reflects reality, the surrogate endpoint is not helpful.

That said, for diseases where there is a good correlation between protein-production levels and the clinical function, there is a sound basis for relying on a surrogate endpoint. We recognize that rigorous clinical endpoints can take much longer to measure. That's why we recently issued draft guidance that provides advice on potential accelerated approval on the basis of protein levels obtained using a validated assay and subsequent full approval based on an accepted clinical endpoint.

The other situation to consider is when the effect of the treatment is dramatic. For example, for some conditions, such as certain cancers, one can start to see dramatic improvement within weeks of treatment. We of course hope to see more of these types of breakthrough treatments in the future. These types of products can often be initially approved on an accelerated basis using an intermediate endpoint and then receive full approval based on an accepted clinical endpoint.

**McKinsey:** *Many stakeholders eagerly await data on long-term durability of cell and gene therapies—from patients to payers to regulators. How do you think about durability?*

**Peter Marks:** Indeed, one of the big questions for gene therapies is the durability of the treatments—

that is, will these treatments work for a few months, a few years, or provide a functional cure? Patients expect to know how long their treatment will work. Because it is relevant for benefit–risk considerations, from a regulatory perspective we want to know this information as well. We also understand that durability will be an important consideration for payers as they conduct their health economic analyses. So, I think the expectations are set that manufacturers will need to gather these data over the long term. However, this doesn't imply regulatory approvals will be delayed for decades until we have long-term durability data.

**McKinsey:** *There is increasing interest to combine a cell or gene therapy with a small molecule or monoclonal antibody. What are the regulatory implications and the implications for everything from discovery to pivotal trial design?*

**Peter Marks:** We will continue to work with manufacturers on a pathway forward. This requires that we look at each combination product uniquely and think about safety and efficacy. We do expect that there will be further innovation in a variety of things, including in clinical-trial design, and that will influence what we're looking for as regulators.

However, industry will also need to get out of the mode of "the combination just needs to work." Sometimes industry does not want to accept failures early on in development, when losses could be best mitigated. This is driven in part by anchoring bias that if you have two products in your portfolio, you are more likely to try to have them work together and embark on a large and comprehensive program. We are trying to pivot away from encouraging developers to study everything possible and instead allow them to move forward thoughtfully when it's appropriate and warranted by the data. Again, we don't want to encourage manufacturers to pursue research and studies that won't have any impact or provide us as regulators any greater certainty in decision making.

Also, there is potential for complex side effects with combination therapy—we are dealing with the unknown. For those of us who have seen such late side effects before, we are holding our breath—will there be evidence years in the future that some novel combinations cause safety issues? I'm optimistic that we have learned some from experience, but we need to be guided by the data.

**McKinsey:** *What has CBER done to be well prepared for the wave of cell and gene therapies in the pipeline, for example, from the standpoint of resources, capabilities, and regulatory science?*

**Peter Marks:** At CBER we have been working to develop additional capacity and expertise in cell and gene therapies. This is a trend that we have seen coming for a long time, and we have prepared accordingly. We firmly believe that doing regulatory reviews and mission-driven research allows us to keep pace with industry and academia. The research that we do allows us to be more effective regulators.

That said, there is always more to do—in this rapidly evolving field, it is never possible to be fully prepared. We try to keep a pulse on what is happening in industry. For example, understanding the progress of the overall portfolio across academia and industry, listening to what is happening in the space, and thinking about regulatory implications, such as how we can manage risk and provide regulatory certainty to manufacturers, where appropriate.

We also realize that we are operating in an environment where external expectations are very high—there are many people clamoring for even more advice from the FDA related to cell and gene therapies. This is due in large part to the expanded industry pipeline. CBER received more than 100 gene-therapy INDs [investigational new drug applications]

in 2017, and we're on track to grow significantly in 2018. For us, this has had major implications for our organization. We have leading experts in cell and gene therapy, but at the same time it is difficult to scale up at the rate needed. On top of this, there are foundational challenges that we face at the FDA and must address—hiring and information technology come to mind, and if these lag behind, they could pose a risk to our ability to expand our capabilities in the area of cell and gene therapies. ■

[1]"Gene and cell therapy FAQ's," American Society of Gene & Cell Therapy, asgct.org.

[2]"What is gene therapy?," US Food and Drug Administration, fda.gov.

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