US FDA Perspective: preparing for a bright and busy future for cell & gene therapy

Peter Marks

As a year marked with more ground-breaking advanced therapy product approvals and new guidance from regulators comes to an end, David McCall, Senior Editor of Cell & Gene Therapy Insights, talks to Peter Marks, Director of the Center for Biologics Evaluation and Research at the US FDA, about his reflections on talking points and progress made in cell and gene therapy over the course of 2023, and his plans and priorities for the agency’s future activities through 2024 and beyond.

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Q How would you sum up 2023, both for Center for Biologics Evaluation and Research (CBER) and for the cell and gene therapy space as a whole?

PM: Although there has been concern in the community about contraction of investment in the rare disease gene therapy space, it has really been a remarkable year for CBER in the area of cell and gene therapy. We approved our first gene therapies for hemophilia A and Duchenne muscular dystrophy, as well as a gene therapy for certain types of dystrophic
epidermolysis bullosa. We have also approved innovative cell therapy products, including modified cord blood cells for use in stem cell transplantation to reduce the risk of infection, and allogeneic pancreatic eyelet cells to treat patients with type 1 diabetes who have hypoglycemic unawareness.

Overall, we see the pace of progress in the field accelerating. We hope that our actions in leaning into gene therapy and cell therapy development and approvals will address some of the issues that have led some to exit the area, particularly in the area of rare disease gene therapy.

Q How have the twin challenges for CBER around rapidly increasing workload in the cell and gene therapy space and staff sourcing, development, and retention evolved over the past 12 months?

PM: Indeed, we continue to see the number of submissions of investigational new drug applications, Biologics License Applications (BLAs), and supplements all increasing. Plus, the desire for people to have meetings with the agency continues to grow. However, we did anticipate this, and have been on a hiring mission to get sufficient new people on board. Some of this activity has been helped by the fact that the contraction that has occurred recently in the gene therapy space has made it easier to attract people with CMC expertise to the agency. So, I think we have been able to make some headway there, and we will continue to focus on staffing up. We also are benefitting from the reorganization of the Office of Tissues and Advanced Therapies into the Office of Therapeutic Products—a ‘super office’ in which we now have an office entirely devoted to gene therapy CMC as well as one completely focused on cell therapy CMC. That allows us to be more attractive to those who may want to work with a group of like-minded individuals. It also helps us with having better supervisory to staff ratios, better consistency, and improved responsiveness. I think this has all worked well so far—we will aim to keep it up as we move into 2024.

Q Can you comment on an issue that is currently being felt by regulatory agencies around the world: the loss of key staff members with decades of experience in the cell and gene therapy field?

PM: It is normal to have people with a great deal of experience retire. They do leave a hole when they depart the agency, but that said, we are lucky in that we have many people at the mid-career stage who are ready to move into more senior roles. I think some of those people bring with them a different vision. Perhaps because of their own experiences in this field, they may have a different idea of how to drive cell and gene therapy forward, and I think we can build off that. I also think that the opportunity is there for us to recruit for more people who are both genuinely interested in the field and in coming to work at a regulatory agency.

And although it is hard to see colleagues who have been at the agency for a long time retiring or moving on, it does present us with an opportunity to essentially rejuvenate ourselves with people, some of whom have come of age in a different era. For example, we are now recruiting people who have come of age during a molecular biology-focused period. I straddled two eras—I began my training in the biochemistry era prior to the genetic revolution,
and then had to retool to become a molecular biologist. Molecular biology was around then, of course, and I am not saying I am a dinosaur, but there are now people coming in for whom gene therapy is something that they trained in specifically. I believe it is an exciting time to be recruiting people because many of them have grown up seeing cell and gene therapy as a field of enormous promise.

Q: The FDA Office of Therapeutic Products Town Hall on Nonclinical Assessment of Cell and Gene Therapy Products is a recent example of the FDA's ongoing efforts to help sponsors by expediting the pathway to first in human clinical trials. What would you pick out as the key ‘take-homes’ for cell and gene therapy developers from that meeting?

PM: I have to acknowledge my CBER colleagues here, who have helped me pick out a few key take homes. These include first, that animal model and species selection for the nonclinical studies that are performed should be based on the biological relevance of the intended patient population, and the ability of those models to detect potential toxicity for a given cell and gene therapy product. A second item is that, in cases where the evaluation of the intended clinical product would not be informative in the selected species, testing of an analogous product to the clinical product may be a suitable alternative. In other words, sometimes you might not be able to test the clinical product because you would get a meaningless result, so an analogous product that could provide you with a meaningful result would be appropriate. A third is that specific toxicology and biodistribution study design elements, and things such as study duration, will depend on the persistence and safety profile of the specific cell and gene therapy product in question. These elements are ideally discussed with the agency at a pre-investigational new drug applications meeting.

Finally, we would encourage product developers to explore opportunities to develop alternative testing methods or leverage existing data from related products that can reduce the use of animal studies. Again, these are proposals that sponsors should ideally discuss with us in the early stages of development.

Q: There is much anticipation around the new guideline on comparability for cell and gene therapies that is due to come out in the summer of 2024—what are your expectations in terms of how it will help therapeutic developers and manufacturers meet CMC requirements moving forward?

PM: We are excited about comparability guidance because we feel that it is addressing a very important issue in the cell and gene therapy area. The issue is that often, early in development, people use generation one processes that are highly suitable and appropriate based on our current guidance in order to get started and obtain some data on their cell or gene therapy. Then, later on, they have to move to a commercial process. Sometimes bridging that gap and demonstrating comparability is a challenge.
It is our hope that by providing robust guidance in this area, we can help sponsors make plans for how they will move forward from the outset, so that ultimately, we avoid delays at the end of development as people try to catch up and show that the products with which they have completed their pivotal studies are the same as those with which they originally started. I think this will be a really important guidance for industry—we view it as one of the most important things that we see in manufacturing at this point.

Q What will be some other key areas of focus for the FDA in terms of developing new guidance for the cell and gene therapy field over the next 12 months?

PM: We will be spending a fair amount of time and effort on trying to accelerate rare disease gene therapy, including potentially providing guidance on how best to apply our accelerated approval provisions to that space. One aspect of this is leveraging the ability to use biomarkers to help in rare disease gene therapy development. I think there might also be some discussion of how novel study designs may best support advancement in this area.

We will also see continued regulatory policy work in the area of genome editing. That is clearly a very rapidly evolving field, not just with CRISPR/Cas9, but now moving into base and prime editors. It is an area of innovation that we will essentially be looking to stay in step with.

Q Where are you seeing artificial intelligence (AI) starting to impact the regulatory application and review processes, and with what outcomes to date? Where can we expect to see further leveraging of AI in this context moving forward?

PM: I actually wonder whether the question is, where aren't we starting to see AI affecting things? AI is beginning to come into play for everything from helping to assemble submissions, to how people look at manufacturing process optimization, to sorting out adverse events in terms of the signal-to-noise ratio. I think our great challenge right now is to become educated about all the different ways in which AI may be applied in our particular set of circumstances, and to work out how to do so in the most thoughtful manner.

The latter part is key, because we believe there are some things that AI does well and others that AI will not do well for us. I think that over the coming year or two, you will see CBER trying to rise to this occasion, in part through an internal AI working group within the Center that will host lectures and aim to keep up with this field. Again, we anticipate seeing AI permeate all aspects of drug development from manufacturing through to helping understand the ideal nonclinical studies to perform, and from potentially helping in the assembly and interpretation of clinical data to analyzing adverse events. We are not yet sure how far this will go, but we are certain that AI is here to stay, and that we need to learn the extent to which it will come to be incorporated into the various applications that come to us.
What are the key points of focus for you as we move into 2024, in terms of fostering international regulatory harmony, particularly related to guidance for advanced therapies?

**PM:** I am really glad you asked this question because this is actually on my personal list of areas where I would like to see a breakthrough in 2024. I think we have made a lot of important advances in 2023: we have announced some of our internal programs that are moving ahead to help us review things more efficiently; we have announced some external programs to help us give advice to sponsors in a more timely manner. Overall, we are trying to take action that really leans into moving cell and gene therapies forward more rapidly here in the US.

I do think that 2024 really needs to be the breakthrough year in the rare disease space—in particular, in terms of making real progress towards global regulatory convergence in this area of rare disease gene therapy. It is very clear to me that all our different patient populations around the world suffer from minor regulatory differences between jurisdictions. These differences can serve as impediments to rare disease gene therapies developed in one country from being submitted and approved in others.

In my ideal world, in 2024, we would start to pilot some programs whereby we can mutually accept a submission—a common technical document at different agencies across several different countries at least—and then potentially review the submission collaboratively in much the same way as is already happening in the oncology space, through our Oncology Center of Excellence at the FDA.

As you mentioned at the start, it has been a year of significant progress in terms of BLA filings and new product approvals across a range of advanced therapy modalities and indications—what will be some specific areas to watch for you over the next 12 months in this regard?

**PM:** I am hoping that we continue to see a good pace of BLA submissions and see more products making it through the R&D pipeline. We will be looking closely now at how we conduct pharmacovigilance on the wealth of products that are starting to come to market. We need to make sure we are comfortable that we are doing all the requisite safety monitoring that needs to get done.

We will also be keeping an eye on how these products actually get deployed. That is not our primary business, but nevertheless, it will be something that we will be watching and working on with our partners at the Centers for Medicare and Medicaid Services at least, to ensure that approved cell and gene therapy products are able to get to the patients who need them.

As we have discussed, it has been a year of real progress. I think next year promises continued growth in this area. More so than I would have said in previous years, I feel that gene therapy is now coming around the corner from being in its infancy to starting to really grow up a bit. We understand now where its limits are, but we also understand where its possibilities are and where we can potentially go with it. I think it is a tremendously exciting time to be in this area and I am really looking forward to what the next 12 months will bring.
BIOGRAPHY

PETER MARKS is the Director of the Center for Biologics Evaluation and Research (CBER) at the US FDA. The center is responsible for assuring the safety and effectiveness of biological products, including vaccines, allergenic products, blood and blood products, and cellular, tissue, and gene therapies. Marks and center staff are committed to facilitating the development of biological products and providing oversight throughout the product life cycle.

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