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AN AUDIENCE WITH...

# John Jenkins


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When John Jenkins started working at the FDA in 1992, the agency had just created its accelerated approval pathway, had only approved a single monoclonal antibody and did not have a stand-alone oncology division. Over the subsequent 25 years, he has helped transform the agency, shaping Prescription Drug User Fee Acts, building more flexibility into the regulatory system, getting grilled by Congress about controversial approvals and navigating the way through difficult safety decisions. Last month, he resigned from his role as Director of the FDA's Office of New Drugs to take on new challenges. He spoke with **Asher Mullard** about approvals standards, breakthrough therapy designation and regulatory science hurdles.

***Why are you leaving now?***

I've been at the FDA almost 25 years, and I've been director of the Office of New Drugs for almost 15 years. I think it's time for a change for me, and time for a change for the organization. Also, I recently hired a deputy director, all my office and divisional director positions are filled on a permanent basis and we've completed our user fee negotiations for prescription drugs and biosimilars. Although there is no perfect time to retire from a job like this, this feels like as good a time as any.

***It doesn't have anything to do with your recent disagreement of the approval of Sarepta's eteplirsen or the potential for regulatory change under a new Trump-nominated FDA commissioner?***

I've been considering a move for a couple of years, and actually originally planned to retire in the summer of 2015. I decided that probably wasn't a good time from the organization's perspective, so I pushed that back until the spring of 2016. That didn't feel like it was a good time to go organizationally either, so I pushed it back again.

I know that people would like to point to particular events that occurred, but it wasn't any one event. I felt like I had completed the career I wanted to have here, and wanted an opportunity to do something different with the rest of my career before I fully retire.

***Do you have concerns that approval standards at the FDA are changing, given the eteplirsen precedent, the recent passage of the 21st Century Cures Act and the introduction of a new commissioner?***

We still have the same law on the standards for drug approval as we did before. And although some things change under the 21st Century Cures Act, I think Congress went out of its way to say in several places in the Act that this does not change the standards under which drugs are evaluated for approval. I think there is room for flexibility, for new ways of looking at data. But fundamentally the laws and regulations that govern new drug approvals will stay unchanged. Those are what we operate against as an agency, and I don't really see them changing dramatically in the near term unless the laws are changed.

***How do you feel about conflicting calls for the FDA to raise and lower its approval standards?***

It can be frustrating at times, because there seems to be a pendulum that swings to different extremes. We go from being criticized roundly about drug safety issues, with people complaining that we are approving drugs too quickly and not taking drug safety seriously, to being accused of holding back innovative therapies, with people complaining that patients are dying because the agency is too conservative. We are often criticized for being too fast and too slow at the same time. What I've learned is that you have to stay focused on having a balanced approach. There are no safe drugs, and I think it's easy for people to lose sight of safety issues if there haven't been any major safety issues in a while.

I also think that we are always grounded in the statutory requirements for approval, so I would say we are pretty steady in how we look at products. Of course, we are also a public health agency and have to be responsive to changing societal expectations, for example, during the AIDS crisis, when there was a real cry for the agency to be more flexible. And we responded to that with the accelerated approval programme in the early 1990s. We are now seeing some rapid development of oncology drugs because we developed ways to be flexible and innovative on how to get those to the market. But at the end of the day, every time we approve a drug we have to be able to justify in our minds, and in writing, how we met the statutory standards. This keeps us grounded in the science and the data, even as expectations and pressures evolve over time.

***The new flexibility you've described includes the recently created breakthrough therapy designation, which lets the FDA and companies work together to expedite development. Do you think the bar for this designation has been set too low?***

In the standard in the law for breakthrough therapy designation, the key word is 'substantial'. Drugs have to provide substantial improvements over available therapies for serious and life threatening disease. There is no absolute way to quantitatively describe what is meant by substantial. I think the agency has worked hard, and has struggled internally, to decide what this means and where to set the bar.

I've questioned whether we set the bar at the right level. When the law was being discussed in 2012, people thought that the FDA would grant breakthrough therapy designation to only a handful of products every year. We are now 4 years into the programme, and have designated around 150 products as breakthrough therapies. That either means that we've set the bar differently from where people thought it would be, or that the science is providing a lot more advances than were anticipated.

If I were the one in charge, I might have set the bar a little bit higher. But whether that

is right or wrong is an unanswerable question. To some degree this is a philosophical question. So, we've tried to be consistent in how we've applied that standard.

**Q** ***Could that standard change in the future?***
I think it's hard to substantially change where the bar has been set without some change in the legislative framework that the programme operates under.

**Q** ***What are the biggest regulatory science issues that your successor will have to address?***
The regulatory science area of patient engagement is one that the agency needs to continue to focus on. We need to develop a road map for how to navigate through that area, because patient engagement means a lot of different things to a lot of different people. It can help us to understand the impact of disease on the patients, so that we can understand what end points we should be measuring in clinical trials to make sure that drugs that are approved will provide the most benefit for patients. But we also need to figure out how to interface with patient communities beyond that, for instance, when they are encouraging the FDA to take a particular action on a particular drug. This is an area that is still very challenging to navigate. How do you hear the patient voice, and how do you factor input from patients into benefit–risk decisions that must meet statutory standards? How do you manage situations where individual patients are clamouring for drugs that haven't yet been shown to be effective? That's a regulatory science area that still needs to grow and develop. We can't approve a drug just because patients want a drug.

A second area that I would highlight is that as science advances, we are realizing that diseases that used to be thought of as one condition can be broken down into lots of different conditions. A disease that has a genetic basis can be caused by not just one genetic defect, but by hundreds of genetic defects that all produce the same phenotype. We are often not sure whether drugs that are being studied in these settings actually work the same way in all those different subsets of the disease. We are struggling in terms of how we should manage the application of a substantial evidence standard across increasingly smaller subsets of diseases, and how to extrapolate data between those subsets.

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**Q** ***What's next for you?***
You really can't look for a job when you are in this position. So I really haven't had specific discussions with companies outside of the agency. But I expect I'll stay in the pharmaceutical arena.