Hot Topics in Cardiovascular Devices: A Conversation with Michael John

Michael John, who is leading MCRA's new Cardio division, speaks out on the latest trends and challenges in the cardiovascular device arena, including the outlook for transcatheter valves; the current paclitaxel controversy in the periphery; and the potential impact of wearable, remote CV monitoring technologies.

by
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MCRA LLC is a contract research organization (CRO) and consulting firm that provides services to the medical device and biologics industries in the areas of clinical research, US and International regulatory, healthcare compliance, quality, and reimbursement. The company is owned by Viscogliosi Brothers LLC (VB), a highly successful family office/private equity firm that invests in the neuro-musculoskeletal/orthopedics/spine arena. The name MCRA was originally an acronym for Musculoskeletal Clinical and Regulatory Advisors LLC; however, the company recently decided to expand into new therapeutic areas. Its first foray outside of neuro-musculoskeletal takes MCRA into the cardiovascular (CV) market, where the firm sees significant innovation and growth ahead.

To that end, MCRA recently welcomed Michael John as its new Vice President of Cardiovascular Regulatory Affairs. Michael has extensive experience in interventional cardiology, both on the regulatory and the research sides, and thus brings with him a deep knowledge base in cardiovascular device technology. Immediately prior to joining MCRA, Michael served as Chief of the Interventional Cardiology Devices Branch within FDA's Division of Cardiovascular Devices, heading the group responsible for reviewing all of the regulatory submissions for new interventional devices intended for use in the coronary arteries, including drug-eluting stents (DES), drug-coated balloons, atherectomy devices, and various accessory devices used in the cardiac catheterization lab. Prior to that he was an animal testing reviewer within the same division, specializing in drug-eluting stents, transcatheter heart valves, and circulatory support devices. His earlier experience includes stints as a cardiovascular researcher at Massachusetts General Hospital, and at CVPath Institute Inc. under the direction of cardiovascular pathologist Renu Virmani, MD, who is well known for her work on DES-related tissue inflammatory processes.

During his time at FDA, Michael presided over a rapidly evolving CV device landscape; thus he brings a unique perspective on the opportunities and challenges facing the industry today. *MedTech Strategist* recently spoke at length with Michael, along with David Lown, President of MCRA. In the following Q&A, Michael shares his thoughts on everything from FDA's ongoing efforts to foster innovation in the US to the controversy now surrounding paclitaxel-coated balloons and stents in the periphery and the future of wearable, remote monitoring technologies. The CV market continues to innovate and evolve, he points out, and not just in terms of technology advances, but also with regards to where technology innovation is being nurtured.

MedTech Strategist: ***Can you provide some background on MCRA and the company's decision to branch into cardiovascular devices?***


DAVID LOWN

David Lown: MCRA is owned by a private equity/family office, called Viscogliosi Bros. LLC [VB] in New York City. VB has focused their entire career in the neuromusculoskeletal/orthopedics/spine space. Their strategy, beginning with the founding of their own company in New York City twenty years ago, was to discover, finance, and operate companies with innovative technology, particularly those with more of a PMA background. This was extremely unique, and is today as well, since the orthopedic industry has been mostly born out of the 510(k) regulatory process.

[*Editor's Note: since its founding in 1999, VB has invested in more than 20 companies and achieved many successful exits, including Spine Solutions, acquired by Synthes in 2003, now part of* ***Johnson & Johnson****; Spine Next, acquired by* ***Abbott Laboratories Inc.*** *in 2004, now part of* ***Zimmer Biomet****; Ascent Healthcare Solutions, acquired by* ***Stryker Corp.*** *in 2009; Soteira, acquired by* ***Globus Medical Inc.*** *in 2012; Knee Creations, acquired by Zimmer Biomet in 2013; Small Bone Innovations, acquired by Stryker in 2014; and Paradigm Spine, acquired by* ***RTI Surgical Holdings Inc.*** *in 2019.*]

The problem, and solution, was that when VB sold their device companies, the people involved in creating institutional knowledge and cumulative know-how left with the acquirer. VB was not happy, and subsequently the clinical, reimbursement, quality, and regulatory personnel were not really happy with this, as they didn't like going back into the totem pole of big company structure. VB decided to start a service business by hiring the FDA's Branch Chief of Orthopedics and Spine, Glenn Stiegman, who happened to work in the cardio branch for a while as well, and right away a few big companies called and asked if they could utilize MCRA.

MCRA spent the first six or seven years figuring out the right system, and since 2014 the entire business started to click. Today MCRA works with about 170 companies and 600 projects annually, and our CRO runs about 20 of the industry's most important clinical studies.

When we were looking to branch out from ortho, we performed significant analysis and cardio came out on top because the materials, the FDA processes, and the clinical trials are all similar to what MCRA currently does. Most importantly, I searched incessantly for the best talent in cardio to run this side of the business, and Michael's name kept coming up. So after significant discussion, Michael joined us in March 2019 and we officially changed our name from Musculoskeletal Clinical and Regulatory Advisors to simply MCRA, and we couldn't be happier. We also so far have brought on a further clinical team, including Lisa Beck [MD], who has run many of the industry's most important clinical trials.

Michael, what's your background and experience?

Michael John: Prior to joining MCRA, I was chief of the interventional cardiology devices branch at the FDA in the division of cardiovascular devices. I was in that role for about five years. We reviewed all of the coronary drug-eluting stents, coronary drug-coated balloons, atherectomy devices, guidewires, pretty much anything that went into the coronary arteries of the heart to treat myocardial infarction or other forms of vascular disease.

Given the burden of coronary disease we were probably one of the busier branches in the division. We certainly had more drug-coated combination products than anyone else, due in large part to how effective the drugs have become. Coronary drug-eluting stents were a really exciting product area to be involved in, and while it was a challenge to manage such a high-profile product area, it was incredibly rewarding to see outcomes improve in those devices year after year. I feel very fortunate to have played a part in where that technology is today. Prior to that I was an animal testing reviewer, also in that division. I reviewed the animal studies across all eight branches at the time—so everything from electrical devices, such as pacemakers, to ventricular assist devices and many of the transcatheter heart valves. Patients with significant cardiovascular disease have, or have been considered for, multiple devices and it's difficult to thrive in this industry unless you have a strong command of all of them. I was exposed to pretty much everything that comes through the division during that time, and for me that was an invaluable experience.

Prior to that I worked at Massachusetts General Hospital in Boston, where we had essentially an independent animal research lab, all for cardiovascular disease. We focused

on interventional cardiology—again, devices such as drug-eluting stents, atherectomy devices, etc.—and had a fully functioning preclinical catheterization lab. While I was there, I performed the interventional procedures as well as the pathological analyses, so looking at the tissue after explant under the microscope, seeing how much inflammation or other vascular responses had occurred, and then taking it on from there, writing papers, etc. Prior to that I was at the Armed Forces Institute of Pathology which later became CVPath, which is a big pathology center in the area—and one of the most renowned now in the country, if not the world—doing much the same for about five years.

"The Early Feasibility program greatly benefitted the TAVR space, and signaled a general embrace of the concept of the innovation ecosystem at the FDA."

What are your goals with MCRA in the cardiovascular area?

MJ: Well, I think first and foremost you have to appreciate that there's a lot happening in cardiovascular innovation at the moment. I think this is one of the most exciting times that I can recall in the development of devices intended to treat heart disease. I was involved in some of the reviews in the transcatheter heart valve space, and to think that in only a few short years the field has evolved so rapidly—from 2011 when the first TAVR [transcatheter aortic valve replacement] device was approved for patients who were inoperable, to now, as we saw recently at ACC, where the outcomes with TAVR are now remarkably favorable in low-risk patients. The pace of innovation is really shocking.

[*Editor's Note: results of* ***Edwards Lifesciences Corp.****'s PARTNER 3 trial, presented at ACC in March, showed that the company's Sapien 3 TAVR device was superior to surgery in low-risk patients with respect to the primary endpoint of death, stroke, and rehospitalization at one year. In press reports, physicians called the outcomes "practice changing" and noted they would usher in a "new era of valve replacement." FDA is expected to approve a low-risk indication for the device in the next few months.*]

And it's not just the pace of innovation, it's also the location of the innovation. Previously, the regulatory process was maligned for not being conducive enough to keeping innovation in the United States, and a lot of it went to Europe or Asia. I think the FDA has done a tremendous job in streamlining the process and embracing the concept of the innovation ecosystem, and as a consequence, bringing all that device development, especially in the cardiac space, back to the US. For some time, all of these start-ups were moving to Europe for their first-in-human trials. But that's all changed.

When you look at the pace of innovation and the fact that a lot of it is coming back to the US, and you consider the scope of products that are showing better outcomes than they ever have in the past, it is a tremendous opportunity for a company like MCRA Cardio to play a central role in getting these devices to patients. And that's ultimately our objective. It's one thing to have a great idea. It's another to surround yourself with a team that is able to bring that idea to the public and to make that idea something concrete that everyone has access to. So that's what excites me about this initiative.

Michael, I'd like to get your perspective on some of the important trends and issues facing the medtech industry today, and specifically in cardiovascular. You mentioned that FDA has done a really good job of bringing early clinical studies back to the US. Can you remind us—where was that turning point? Did it correspond with what was going on with TAVR at the time?

MJ: Well, it was an interesting convergence of a number of different initiatives, and somewhat serendipitous in that regard. First, one can't underestimate the impact of [FDA's] Early Feasibility Studies program and having a structured mechanism to invite studies to be undertaken in the US, with a more pragmatic assessment of the requirements to do so. That happened at around the same time that a lot of innovation was occurring in the transcatheter heart valve space. So you have a more streamlined pathway to first-in-man studies—a shifting of the bar for US trial initiation—that occurred at a time when TAVR devices were iterating quickly and rapidly and were ready for US investigation. So the Early Feasibility program greatly benefitted the TAVR space, and again, signaled a general embrace of the concept of the innovation ecosystem at the FDA. And that is particularly true in the Division of Cardiovascular Devices, which in my view really

sees itself as a collaborator in the process and embraces the concept of shared risk. What I mean by that is obviously the Agency has a mandate to proceed responsibly in a way that protects patients, but it also has a responsibility to think very carefully about what is need-to-know and what is nice-to-know, and ensure that the latter doesn't impede the process of getting good devices to patients who are suffering from life-threatening diseases. I think that philosophy helped spur a lot of innovation, and not surprisingly, it's been a very popular program.

What was the impetus for that shift at FDA?

MJ: It primarily grew out of questions about the fact that many of these devices were CE marked prior to gaining approval in the US. The agency really should be commended for taking a hard look at whether we could improve the process to more responsibly and efficiently get these devices to patients in the US. And I think they definitely succeeded there.

Obviously TAVR has been immensely successful—do you think we'll be able to achieve the same type of success in the mitral valve arena?

MJ: Mitral valve repair and replacement technology has taken off much more quickly than anyone anticipated. If you look back just a few years ago, in 2015-2016, there were three acquisitions in the mitral space totaling almost a billion dollars on the basis of, I believe, three early feasibility studies that involved a very limited number of patients. But we have to temper the enthusiasm in the mitral space a bit, given that the biology of the mitral valve is so much different than the aortic valve. And the disease is very different as well, with primary and secondary mitral regurgitation having unique pathologies. Also, in terms of implanting a device, the aortic annulus is much different than the mitral annulus in that it's circular, making it much easier to orient the valve during implantation than in the mitral annulus, which is D-shaped and non-planar, like a saddle. The subannular apparatus is also very complex in the mitral valve and certain devices can get tangled up in the chordae tendineae, making it difficult to even navigate these devices to that site. So I think we have to be patient with our expectations for mitral technologies compared to the aortic space since the technical and anatomical challenges are different.

All of that being said, if you look at the results of the COAPT trial with [Abbott's] *MitraClip*, for the investigators to show a mortality benefit in a mitral repair device is remarkable. It's almost unheard of in the interventional cardiology arena, even for a trial that was as large as that one. I was sitting in the arena at TCT when those results were reported, and I can tell you, and I'm saying this as someone who has seen a lot of trial results, it was a powerful moment. To know that there are devices that are being developed in the cardiovascular space that can directly impact whether a person survives or not is pretty special. And I think it's one of the reasons that the mitral valve space is so exciting.

[*Editor's Note: The COAPT trial, presented at the 2018 TCT meeting, found that heart failure (HF) patients with moderate-to-severe functional mitral regurgitation (FMR) who were treated with the MitraClip were 47% less likely to have a HF hospitalization within two years and 38% less likely to die compared to patients treated with optimal medical therapy alone (numbers needed to treat were astonishingly low: 3.1 and 6, respectively). The results were surprising, given that some previous studies of MitraClip in FMR had not shown a benefit. In March, based on the COAPT results, FDA expanded MitraClip's approved indication to include secondary functional MR (MitraClip was previously approved only for use in primary degenerative MR). Although only about 10% of HF patients meet the strict COAPT treatment criteria, the study has already had a positive impact on MitraClip volumes at some US centers, analysts say, and is expected to continue to drive growth in this market.*]

I also wanted to get your perspective on what's going on right now with the paclitaxel-coated devices in the periphery. As you know, a recent meta-analysis found a significantly higher long-term death rate in people with peripheral vascular disease who were treated with paclitaxel-coated balloons and paclitaxel-eluting stents (see Box). I think the mystery there—at least with the coated balloons— is why there would be a higher rate of death related to this treatment when, presumably, the vessel is exposed to the paclitaxel for only a very short period of time. What's your take on this issue?

MJ: This is one of the more interesting developments in interventional cardiology in quite some time. As you know, there are two drugs primarily used on all drug-coated stents and balloons, the first being analogs of rapamycin such as sirolimus; the other being paclitaxel. One of the key characteristics of paclitaxel is that it's more lipophilic

than sirolimus and has an easier time getting into the vascular wall, which is important on a drug-coated balloon since it is only inflated in the artery for a short time. The recent meta-analysis, as you know, showed a dramatically increased risk in the rate of observed death—much higher than was expected—out to two and three years [following treatment]. What is interesting about this observation is that the paclitaxel, when it's delivered via the balloon catheter, has a very transient exposure in the blood vessel, say 60 to 90 seconds. What I think people are struggling with is establishing a biological correlation between a very rapid and transient drug exposure and death out that far after the treatment procedure. Despite the fact that the [mortality] signal is rather strong, without a clear biological mechanism to explain the signal, it's difficult to discount the possibility that there was something in the meta-analysis itself that needs to be scrutinized, and ultimately whether we have enough data to trust that we are assessing this outcome in the right way.

What is quite remarkable, is that the FDA recently submitted a letter to healthcare providers on the paclitaxel signal, and based on FDA's own internal analysis felt that they should send a notification to the public advising them to consider using alternative treatments other than those coated with paclitaxel. And that's for balloons and stents, products that the interventional community has grown

The Paclitaxel Controversy, In Brief

Last December, the *Journal of the American Heart Association* published a study by Katsanos, et al, detailing a pooled meta-analysis of 28 randomized, controlled drug-eluting stent and drug-coated balloon trials involving patients with femoropopliteal disease. The analysis included a limited amount of five-year data, although the majority of the studies did not follow patients beyond two years. At one-year, the analysis showed no difference in all-cause mortality between patients treated with paclitaxel balloons and stents and those treated with uncoated balloons or bare-metal stents. However, at two years, patients treated with paclitaxel devices had a 68% greater relative risk of death, and at five years, that risk grew to 93%, with a number need to treat of only 14. Although the results of a pooled analysis should be interpreted with caution, and more details are needed to reach a definitive conclusion (in fact, most of the studies in the analysis did not even report the actual cause of death), the results raised alarm bells among both clinicians and regulators.

Initially, FDA told physicians that it believed the benefits of these devices outweighed the risks; however, upon further evaluation, the agency changed its position, and in March of this year, FDA sent a Dear Doctor letter recommending that clinicians use alternative devices whenever possible while the issue is further evaluated. (Also in March, **BD/Bard** revealed that five year data from its randomized Levant 2 trial showed a slightly higher, but statistically significant, mortality with the *Lutonix* paclitaxel-coated balloon versus uncoated balloons.) According to FDA's March letter, the agency is conducting an analysis of long-term follow-up data from the pivotal premarket randomized trials for these devices and the preliminary findings show "a potentially concerning signal of increased long-term mortality… with paclitaxel-coated products." The agency looked at three trials with five-year follow-up data and "each showed higher mortality in subjects treated with paclitaxel-coated products." Of the 975 subjects in these three trials "there was an approximately 50% increased risk of mortality in subjects treated with paclitaxel-coated devices versus those treated with control devices (20.1% versus 13.4% crude risk of death at five years)," FDA noted in the letter.

FDA has planned a mid-June panel meeting to discuss the issue. Meanwhile, there has been a ripple effect across US health systems, with some taking these devices off the shelf altogether and others requiring patients to sign informed consent forms, according to Larry Biegelsen, an analyst with Wells Fargo Securities, who predicts that utilization of paclitaxel devices in the periphery could drop by as much as 50% initially. If the mortality trend proves out in FDA's ongoing analysis, some believe FDA will require manufacturers to jointly conduct a large, potentially years-long mortality trial. And that raises the question of whether or not such an endeavor would be worth the cost, given the relatively small size of this market at present (Biegelsen pegs total US sales of peripheral paclitaxel devices, excluding **Cook Medical**'s *Zilver* stent, at a mere $367 million in 2018, although pre-controversy growth expectations had been strong, with models predicting a near doubling of the US market by 2020). Industry leaders include BD/Bard, **Medtronic plc**, **Boston Scientific Corp.**, Cook, and **Philips**/Spectranetics.

very comfortable with given their long safety profile, which is a strong statement from the FDA. They of course have a responsibility to protect the public, and they felt that this signal was strong enough to do so. And, again, a death signal in a drug-coated balloon or stent is not something that any prudent regulatory agency should overlook. But they clearly made that decision out of an abundance of caution, and I think that industry should take notice.

How much weight should we give to data from a pooled meta-analysis?

MJ: Whenever you conduct a meta-analysis and you're trying to combine data from multiple trials, pool-ability is always an issue, and assuring that you're measuring apples to apples. And given that this was just one meta-analysis, it's surprising how strong and how swift the reaction from the cardiovascular community has been. A part of that may just be a consequence of outcomes in the interventional cardiology space being so good for so long. I mean, it's very rare to see any negative outcomes with these devices. So to see one that is this concerning caught a lot of people off guard.

The other interesting issue is that the companies who have these devices on the US market have not seen a mortality signal like this in either their pivotal trial data or even their real-world post-market registries, although BD/Bard did recently report a slight elevation in mortality at five years in its Lutonix pivotal trial.

MJ: No, not like this they haven't. It's unclear why the meta-analysis showed outcomes that are so dissimilar from what we've seen in the past. We have to spend more time analyzing those results to determine how the community should react to them.

It also seems odd that paclitaxel would be associated with a long-term death signal in the periphery, since paclitaxel-eluting stents have been used safely in the coronary arteries for a number of years. There was an issue at one point with late-stent thrombosis with some of the earlier-generation DES devices, but as far as I know there has never been a mortality signal with those devices like we're now seeing in the periphery.

MJ: That's correct. There was no death signal with those devices. But you have to remember that the only paclitaxel-coated coronary stent that was FDA approved was the *Taxus* stent [**Boston Scientific Corp.**], and that was a first-generation DES device. The current paclitaxel signal does remind me of a little bit of the late-stent thrombosis signal that occurred shortly after these first-generation stents were coming to the fore. In those devices there was an increase in clotting events in treated vessels much further out than people expected to see them. However, there were challenges with the interpretation of those data for many reasons, the main one being that the drug-elution polymer on the *Taxus* stent was not optimized in the way that the new polymers are [on the current generation of DES]. And there were a lot of concerns that it was the polymer itself that was causing the delayed healing [leading to late-stent thrombosis], and not the drug. Combine that with the fact that in a first-generation stent you have a much thicker strut, they're not as flexible, and the outcomes simply aren't as good as contemporary devices, and it's difficult to implicate paclitaxel alone as being the cause of the issues that were seen with the *Taxus* stent.

What I think is unique about that late-stent thrombosis signal compared to the mortality signal we're seeing now is that there was a very plausible mechanism for those adverse events with the first-generation DES. If you look at the animal studies and the animal data that was being developed around that time, there was evidence of delayed healing, inflammation, and impaired endothelial recovery, all of which pointed to the stent struts being exposed in the blood stream and therefore serving as a nidus for platelet adhesion and clot formation. With the paclitaxel signal we're seeing today in the periphery, it's unclear that the animal data showed any systemic or local vascular responses that were so pronounced that they could portend the possibility of late events. So, while one can point to a very plausible mechanism for the events that we saw many years ago with late-stent thrombosis, that doesn't seem to be the case with the paclitaxel signal.

Have researchers doing these analyses of the peripheral data outlined exactly what these people are dying of two, three or five years down the road?

MJ: Excellent question. So again, that has not been done with the level of granularity that I think we would all like to see. These are patients with multiple comorbidities. Many of them could have come back for a second procedure and the issue of how much paclitaxel

exposure they've had is unclear. We really have to unpack all the data on a patient level to get at the root cause of this issue. In the recent notification, FDA said they were looking into that.

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So it could be a while before we get to the bottom of this.

MJ: Indeed. And that obviously has a lot of impact on the companies with paclitaxel-coated devices because they are sort of in a holding pattern until FDA and the community at large come to grips with this signal and has confidence in paclitaxel-coated devices again. But this is a big deal, and I personally hope that the cardiovascular community doesn't abandon these drug-coated technologies prematurely. We owe it to the public to assess the paclitaxel issue methodically and ensure that we are making rigorous and evidence-based decisions about the future of this drug.

I know some companies are working on sirolimus-coated balloons—is that a potential alternative here?

MJ: The sirolimus-coated balloons remain an option for many patients, and there are a number of those devices in development. Outcomes with sirolimus-coated stents in the coronaries are excellent. So there are options available for patients. In the coronary arteries, the potential advantage of drug-coated balloons is that if you have a patient who comes back to the cath lab with in-stent restenosis, they can then receive another treatment without necessarily getting another layer of metal. And that, I think, underlies the interest in the drug-coated balloon technology. None of those are FDA approved at the moment. But since the mechanism for the mortality observations hasn't been elucidated, you hope that the community is still willing to move forward with the drug-coated balloon technologies, because as outcomes get better in stents and more stents are used, it stands to reason that there will be patients who need a treatment for in-stent restenosis, and we need to have a viable one.

If a company came to you today, in your current capacity, and wanted some advice on this—they either had a drug-coated balloon in development or maybe had one already on the market—what would you tell them? What is the best course of action at the moment for companies operating in this space?

MJ: Well, first and foremost we would look at all of the data together and assess whether the product is viable and whether it can be studied responsibly and in a way that gets to the key scientific questions, but obviously takes into account the FDA's heightened safety concerns about the drug. In this case, that might amount to modified animal studies and more robust follow-up for the patients in the trial and in the post-market. So for anyone who had a device who wanted to bring it to market, I would suggest that same sort of level-headed and systematic approach to assessing the device and moving it through the regulatory process. But I have tremendous faith in the collective ability of the cardiovascular community to figure this out, and I wouldn't advise anyone to rush to judgment on the paclitaxel signal until all of the facts are in.

Another big topic of interest right now is the future impact of digital wearables and artificial intelligence-based analytics in healthcare. It seems like FDA has made the regulatory process for technologies such as digital apps and AI-based algorithms a lot smoother and more predictable over the past couple of years, which has helped to bring some of that technology to the forefront. In the field of cardiology, for example, we now have smart watches that can monitor people for irregular heart rhythms and researchers are starting to use this technology, and other wearables, to design less burdensome, more real-world clinical trials. Where do you see all of this taking us in the years ahead?

MJ: The speed with which Apple's [**Apple Inc.**'s] new heart monitoring algorithms moved through the regulatory process speaks to the interest in these types of technologies. I was recently at the ACC late breaking trial session where results of the Apple Heart Study were presented, and to see a study with 400,000 subjects is almost unheard of.

A study like that could have a huge public health impact given that there are approximately six million people in the US who suffer from atrial fibrillation. And to think that our watches and phones, which are with us all the

time, are now capable of continually monitoring for potentially dangerous heart rhythms, provides the user with a sense of control over their own health status, which has definitely resonated with a lot of people.

What I was most concerned with in that study—and I think a lot of people were—was whether there would be a high rate of false positives. But only 0.5% of the people in that study received a notification of an irregular heartbeat, which put those fears to rest. Whether it's digital health technologies or artificial intelligence or machine learning, the technology component of medtech is absolutely exploding, so much so that every time you go to a conference you see another way that someone has figured out how to mine data to make more informed clinical decisions. And I think there's a potential for much more tailored and accurate medical prognoses to be made as a result.

Is this the future of clinical trials? Or will it take some time before we're really ready to embrace the concept of digitally enabled, remote studies for regulatory submissions?

MJ: If we get to a stage where physicians are comfortable with the concept of wearable technologies not just as a lifestyle modification tool but as an accurate and reliable diagnostic device, then they could absolutely lead to much more efficient and robust data collection. Any form of technology that we can use to simplify clinical investigations and also take some of the burden off of patients is a good thing. If you can avoid people having to come back into the clinic for office visits, but can instead transmit outcomes electronically, that offers huge savings, not just across healthcare, but for individual patients. There's a lot of upside there. But, again, we have to temper our enthusiasm for these technologies with the understanding that it's still very early in their development, and these are systems that have to be validated appropriately. If we are going to be making important clinical decisions, not just about regulatory approvals but about care of individual patients, based on data generated by those tools, we need to be confident they're sending the right signals and that they're being used responsibly by the end user.