MEDTECH INSIGHT
CITELINE COMMERCIAL

16 Feb 2021 | **Analysis**

Securing FDA Approval For Novel OPRA Prosthetic Wasn't A 'Slam Dunk.' Here's How Start-Up Integrum Made It Through The PMA Maze

by Shawn M. Schmitt

In this case study, experts at the law firm Hogan Lovells and device maker Integrum AB tell *Medtech Insight* about some hurdles the Swedish start-up jumped when trying to win premarket approval from the US FDA for its Osseoanchored Prostheses for the Rehabilitation of Amputees (OPRA) Implant System.

When medtech industry attorney Jonathan Kahan began working with Swedish start-up Integrum AB to secure premarket approval (PMA) from the US Food and Drug Administration for the company's novel OPRA prosthetic, he wasn't sure the agency would ultimately approve the device.

"When we started this project, this was not necessarily a slam dunk," Kahan, a partner with the law firm Hogan Lovells, told *Medtech Insight*. "This actually, in my experience – and I've been doing this for about 40 years – was a very difficult project."

That's because decades' worth of data on OPRA, a lot of it located outside the US, had to be rounded up in support of the prosthetic's PMA.

"Usually with a PMA, you start out with FDA from the very beginning, working with them and deciding from the very beginning of the discussions with FDA what they're going to need. You don't usually go to them with existing data that you have to tailor to what FDA is requiring," Kahan said.

The Osseoanchored Prostheses for the Rehabilitation of Amputees (OPRA) Implant System was cleared for use in the US roughly two months ago; Integrum had previously secured a humanitarian device exemption (HDE) for the prosthetic from the FDA in 2015. OPRA is the first implant system available in the US intended for use by adults with above-the-knee amputations who cannot use – or who are anticipated to have problems with – a conventional socket prosthesis. (Also see "*New Hope For Amputees: OPRA Prosthetic Gets FDA Nod*" - Medtech Insight, 22 Dec, 2020.)

> ***"Some of the data that was requested [by the agency] was more than 20 years old. …It was a little crazy. It was really challenging." – Rickard Brånemark***

That's a lot of data that Kahan – working alongside other Hogan Lovells experts and officials from Integrum – had to dig up, sift through, and send to FDA product reviewers.

"Some of the data that was requested [by the agency] was more than 20 years old, and now there are digitalized medical records, and those have been through some different iterations over the years," Integrum founder and owner Rickard Brånemark said in an interview. "And we found some old, scanned X-rays archived in an isolated place in Sweden that could be used to fully support the efficacy questions raised by FDA.

"It was a little crazy. It was really challenging. There was a lot of detective work that went on to find this data for the FDA, just like Sherlock Holmes," added Brånemark, who was the company's CEO from 1998 to 2015.

Kahan added more context: "FDA asked for a lot of data in this PMA with regard to adverse events and long-term follow-up. And Rickard turned over every rock possible to get that data from the previous investigational centers and commercial centers that had used the device, and that was critical to FDA approval."

The bottom line? "We didn't want to do a full, new, multicenter study if existing data would suffice," he said. "The challenge was to take the existing data, and the existing studies and ongoing studies, and submit that cumulative data to FDA for PMA approval."

The agency wanted that retrospective data, Kahan
said, because patients who are fitted with OPRA will use the device for a very long time.

"These are very, very difficult patients to treat in many ways. So you're going to have failures, and you have to explain those to FDA and explain the benefit-risk analysis," Kahan said. Hogan Lovells "worked with the company to gather that data and analyze it, and get it to FDA in a format that convinced [the agency] that based on 65 patients, they could grant a premarket approval application."

THE OPRA IMPLANT SYSTEM *Source: Source: Integrum AB*

The PMA filing was primarily supported by a total of 65 people using OPRA who completed a questionnaire for lower-leg amputees that asked about frequency of prosthetic use, mobility, problems with the device, and overall health. Their responses were then compared to surveys gathered while the patients were using conventional prosthetics. Their scores on the hundred-point scale rose 35.1 points after two years and 39.6 points after five years.

"There were some at FDA who were very concerned about expanding an HDE into a PMA based on 65 patients," Kahan said. "There are not many PMAs that are approved based on 65 patients. Almost none. And so, convincing FDA [to grant a PMA] based on a 65-patient population was a great regulatory challenge."

He said some FDA officials weren't optimistic the PMA would be granted based on the number of study participants and the use of older clinical data.

"But we also had some angels within FDA as well," Kahan said. "We had to get over the hump of FDA accepting the fact that this dataset, which was retrospectively reviewed and gathered, was not originally put together for a PMA. Those studies were not done for a PMA.

"Getting over that hump on benefit-risk and having FDA finally agree that the benefit far outweighed any risk for this patient population, which was key – that was the challenge we were able to overcome with Integrum."

Although OPRA has a history that spans more than three decades, Brånemark says the device hasn't changed much since the first patient used the prosthetic in 1990.

"This is a very new technology, and is still considered a new technology because there is nothing else like it," he said.

Kahan chimed in: "To say it's 'new' really means that the theory of osseointegration for this type of device is still, to some extent, a new technology because it was not widely embraced by the medical community.

"And now that it has PMA approval, that really adds more to the acceptance in the medical community and allows the more widespread, distributed use of the product," he said.

From HDE To PMA

But before there was a PMA for OPRA, there was the device's 2015 HDE, which was limited at first to 4,000 patients but was expanded to 8,000 as part of the 21st Century Cures Act.

"The United States has a lot of wounded warriors who need this device because of the wars in Afghanistan and Iraq," Kahan said. "One of the very good things, and important things, for the PMA is that we had the full support of Walter Reed" National Military Medical Center.

"Dr. [Jonathan] Forsberg, a Navy captain who is one of the leading surgeons in this area and who worked with Rickard, was a real impetus to treating those patients," Kahan said. "Dr. Forsberg and Walter Reed were critical to assisting us."

After some time, Brånemark, Forsberg and even patients at Walter Reed saw that there were people who were in need of the novel prosthetic, but fell outside the narrow scope of the HDE.

Also, a company that holds an HDE can only keep that exemption as long as another manufacturer doesn't put a PMA-approved version of the same device on the market. Once that happens, the company's HDE is revoked.

What Makes OPRA So Different?

Typical leg prosthetics are secured with a cup-like shell called a socket that is fitted to the patient's remaining limb. But some amputees don't have enough residual limb to properly fit a socket, while others may have conditions like pain or scarring that may make it difficult or impossible for them to comfortably use a conventional prosthetic.

By contrast, OPRA uses an implanted surgical device anchored to the patient's remaining thigh bone to connect to an external prosthetic limb.

Implanting OPRA takes two surgical procedures roughly six months apart, the FDA says. In the first operation, a cylinder-shaped fixture is implanted into the central canal of the remaining thigh bone. Once tissue has grown to anchor the fixture and the skin has healed, OPRA's additional device components are attached to the fixture from the previous procedure via a second surgery.

Patients then undergo about six months of rehab and training with a physical therapist to learn how to bear weight on a prosthetic limb before they are fitted with a custom

"There are other companies in [the prosthesis] area that, if they did get approval, Integrum would actually have to file a PMA or take the product off the market under their HDE approval. So that was one impetus about two and a half years ago that we discussed with Integrum," Kahan said.

> prosthesis.
>
> – *Elizabeth Orr*

"And the other impetus was that there are very strict limitations for a humanitarian device, many of them very restrictive in terms of the ability to make a profit, who can get the device, Institutional Review Board approval, and limited informed consent," he said. "There were a lot of patients out there who needed this device that couldn't get it with an HDE approval."

That's when Integrum decided to take the PMA pathway. Hogan Lovells experts sat down with company officials and explained the difference between holding an HDE and going forth with the PMA process.

"Once we figured that out, we set up a pre-submission meeting with FDA. Dr. Forsberg came with us, and everybody [at the agency] knew him. He's extremely well respected and well known. And so, everybody at FDA, I think, was receptive to listening to us," Kahan said.

"Now, there were some people who were at FDA who were, I would say, more strict as to what they were going to require. So we had to work through that with them," he noted. "But once we had our FDA meeting and level set to some degree with FDA as to what was going to be required, we then started down the road of putting together the premarket approval application."

Device Center Reorg Made Interactions With FDA 'Bumpy'

Kahan said working with the FDA to get the PMA approved was "bumpy at the beginning" because the agency's Center for Devices and Radiological Health (CDRH) was in the middle of a massive reorganization.

Beginning in 2017 and lasting two years, the reorg essentially dissolved and replaced the Office of Compliance, the Office of Surveillance and Biometrics, and the Office of Device Evaluation with an

Why Integrum Didn't Take FDA's Breakthrough Pathway

Hogan Lovells' Kahan explains:

"The *Breakthrough Devices Program* is primarily designed to help you speed the product through the investigational process. But we were at the other side of the approval process with OPRA. We had gone through the

Office of Product Evaluation and Quality "super office." (Also see "*FDA Blames 'Super Office' Reorg For Falling Short On 2019 Review-Time Goals For Recalls, High-Risk Adverse Events*" - Medtech Insight, 11 Feb, 2020.)

"With 1,100 device clients, we saw the reorg across every area of CDRH. And in some divisions and offices, it was easier than others," Kahan said. The reorg "made it a little bit messier, but ultimately, we and FDA were moving in the same direction at the same time. The reorg, I didn't think, was helpful, but it really wasn't that high a hurdle. We overcame it pretty quickly."

HDE. We were at the PMA. So breakthrough really wouldn't help us that much.

"If Integrum was early in the process, getting breakthrough now would absolutely be part of the deal. And now with the new CMS [Centers for Medicare and Medicaid Services] *change in policy of allowing automatic reimbursement for breakthrough devices* after approval, yes, we would have gone for breakthrough.

"But OPRA was way too far down the road for breakthrough."

It took a few months before the FDA and Integrum/Hogan Lovells were on the same page.

"But once that ball started rolling, FDA was very responsive, very helpful. And our lead reviewer was terrific," Kahan said.

Hogan Lovells' director of regulatory sciences, Megana Sankaran, pointed out that the agency's review team was very communicative.

"They would ask us for a quick turnaround when they had questions, and we would get back to them, and if we ever wanted a call, they were open to it, even if it meant 9 at night, when our reviewer was on vacation," Sankaran told *Medtech Insight*.

"They were extremely responsive toward the end of the process," she added.

And communication is key, Kahan said.

"If you're in the PMA process, the No. 1 tip I would give is, plan out your strategy with FDA, and then the other key is to communicate, communicate, communicate," he said. "The more you and FDA communicate, the more you avoid stepping on landmines."