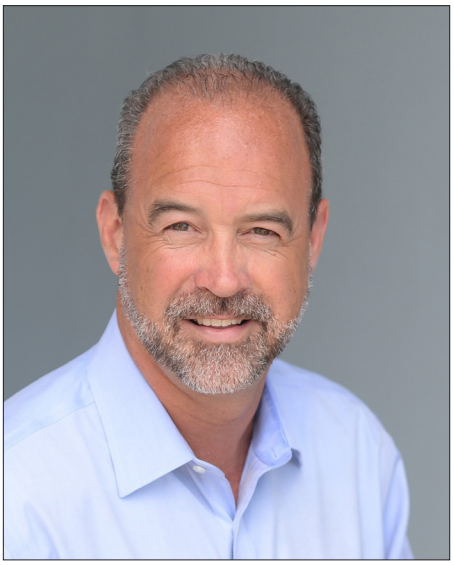
A Discussion with Cyrano Therapeutics CEO Rick Geoffrion About the Early Feasibility Studies Program



Wilson Sonsini attorney Charles Andres recently sat down with Rick Geoffrion, a medical device and life sciences entrepreneur who is currently the founder, president, and CEO of Cyrano Therapeutics, to discuss the importance of the Early Feasibility Studies Program for medical device manufacturers.

Charles: Rick, thanks for being here. Can you tell our readers a little bit about your background?

Rick: I have been in the medical device and life sciences industry for the last 35 years, founded or co-founded eight private venture-backed companies, mostly in the cardiovascular sector, and experienced a number of transactions. My current company, Cyrano Therapeutics, is developing a treatment for chronic smell and flavor loss. I also serve as the vice chairman of The Mullings Group Companies and sit on the executive committee and board of directors of the Medical Device Innovation Consortium, where I co-chair the Cardiovascular Early Feasibility Study (EFS) initiative. I consider the EFS Program, established by the U.S. Food and Drug Administration (FDA) in 2013, to be one of the hallmark advancements in U.S. regulatory policy over the last 20 years. For that reason, I am excited to be here today to discuss its merits.

What is the Early Feasibility Studies (EFS) Program?

The FDA issued guidance in 2013 for an Early Feasibility Study Investigational Device Exemption (IDE) pathway, effectively devising an early-stage clinical trial process that could go through an FDA review with more appropriate pre-clinical and engineering data suitable for an early-stage device. Before that, all IDE approvals were based on the clinical requirements of a full-blown Premarket Approval (PMA), disincentivizing most companies from considering clinical research in the U.S. until well proven in outside-the-U.S. clinical studies.

How did EFS come about?

To understand the background for the creation of EFS, you have to go back to a watershed moment in the history of medical device innovation in the United States—the approval of the first percutaneous aortic valve in the U.S., the Edwards Sapien valve. This transformative, life-saving valve was approved in November 2011, more than four years after CE Mark (Europe) and nearly 10 years after the first-in-human clinical experience. At that time, many clinicians, industry, the FDA, and even Congress realized there was a disconnect in getting novel, life-saving devices to U.S. patients. And the four-year gap in approval between U.S. and Europe became a rallying cry for process improvement to improve access for highly innovative medical devices.

So, before EFS, device clinical trials and approvals would often occur in Europe years before the devices were studied or cleared in the U.S.?

Yes. When the EFS Program was established by the FDA in 2013, virtually all early-stage clinical research in medtech was being conducted outside the U.S., primarily in Europe. U.S. patients were getting access to new medical innovations approximately four years after patients in Europe would access them. That was despite the fact that the majority of the world's medtech companies were housed in the U.S. The majority of medtech innovation was happening here in the U.S. and the majority of funding available for medtech innovation was here in the U.S. It was being created here, but only being tested there. It made no sense.

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For example, if you were an early-stage medtech company before 2013, not only did you perform your first-in-man study outside of the U.S., but if you were a Class III significant risk device, you would perform your entire CE Mark study for approval in Europe, outside the U.S., then use that data to finally start a study here in the U.S. Sometimes that was only a feasibility study, not even a pivotal study. As a consequence, patients in the U.S. would wait four years longer to gain access to a medtech innovation that was invented right here in the U.S.

Once U.S. patients did get access, they were often stuck with a first-generation device that was inherently inferior to second- and third-generation devices being used at the same time in Europe and elsewhere in the world. So, from a patient standpoint, the most important standpoint, it was suboptimal, to say the least. There were real human costs. In addition, devices were starting to be developed specifically for non-U.S. markets. The U.S. was falling behind, the quality of healthcare delivery was impacted, and the FDA started to take notice.

What kinds of medical devices are eligible for EFS?

Per the FDA, the EFS Program is open to devices subject to Premarket Approval, Premarket Notification [510(k)], De Novo classification, or Humanitarian Device Exemption (HDE). EFS may be applicable when clinical experience is necessary because non-clinical testing is unavailable or inadequate to provide the information needed to advance device development. Therefore, EFS may be conducted on new devices without prior clinical experience, and in some cases, EFS may also be conducted on devices with limited prior clinical experience.

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What are some key elements of an EFS?

- Small number of subjects; usually 10-15 to start.
- Can be a 510(k) (Class II) or a PMA (Class III) device.
- The study should be conducted early in the device's development.
- Does not have to involve the first clinical use of the device.
- An EFS can be approved on less non-clinical data.
- The company is allowed to pause the study and change design midstream in an EFS.
- The majority of EFS applications can be approved within a 30-day period.
- It is always important to have a pre-submission meeting with the FDA. They can tell you if you are ready to submit for an EFS.

How does an EFS translate into benefits for a medical device start-up company?

The most significant advantage is that a company is likely to have a faster pathway to approval in the U.S. by initiating the pathway to approval or clearance in the U.S. at an earlier stage. Let's assume the first 10-15 cases in an EFS are successful, safety looks good, and there appears to be an emerging signal on efficacy. The company can apply for an EFS extension to enroll more cases, until such time the company is ready to start a pivotal trial. So, the EFS can dovetail nicely into a definitive path to approval in the U.S. It is also data that can likely be leveraged toward a CE Mark application in Europe. And the EFS Program gives U.S. patients early access to the newest and most innovative therapy.

Are a reasonable number of EFS typically run in the U.S. each year?

More than 50 EFS are approved each year.

Can you provide more detail on how the Medical Device Innovation Consortium (MDIC) is working to make EFS better?

MDIC is working to make EFS better in several ways. First, we are creating attention and awareness around the EFS Program. Second, MDIC is working to engage the entire clinical research ecosystem to improve the time it takes to initiate and complete an EFS. We have a wonderful steering committee, chaired by Dr. David Holmes of Mayo Clinic, with participation from the FDA, senior clinicians, industry, and clinical sites. MDIC has dedicated staff for EFS, including a program director, and together we've worked on a number of projects and resources over the last few years to create meaningful improvements in the EFS ecosystem.

Next, after obtaining input from many stakeholders, we decided to start by

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collecting the facts, the analytics on how well the ecosystem was working. We reached out to industry sponsors and asked them to provide to MDIC on a confidential basis the start-up statistics for their Early Feasibility Studies. MDIC was uniquely equipped to bring these groups together and get them to share this data. This was a first for industry to share this kind of data, but we had good cooperation from many companies and were able to gather a snapshot of the performance of the clinical ecosystem. We measured the FDA review cycles, the Institutional Review Board (IRB) review cycles, the contracting and budgeting timing, and the time to first patient enrollment. The results were eye-opening to all the stakeholders and really quantified what to many had previously been anecdotal information.

Here are the results of that first analysis conducted on 2015-17 EFS in the U.S.:

- We found that FDA approval of the IDE was taking on average 68 days, well within expectations for a timely approval cycle.
- IRB review times were slightly longer at 72 days—not that bad.
- Contract approval, however, was taking a surprisingly long 133 days—nearly four months on average for a sponsor and site to work through a contract and budget.
    - The time to first patient enrollment once all the administrative activities were complete was then a surprisingly long 187 days—nearly six months.
    - Now some of these processes are done in parallel, like IRB and contracting, but it does objectively show that in the 2015-17 timeframe, it took nearly a year to get an EFS clinical site up and running in the United States—a very long time that had little to do with the actual study enrollment.

With the data in hand showing the issues and the current state of affairs, we set out to bring the stakeholders together to work on the common problems. Our first effort was a Best Practices Workshop held in Washington at the MDIC offices with 65 participants from leading industry players—both big companies and small companies, clinical site coordinators, principal investigators, the FDA, CMS, and MDIC. Over a day and a half, we discussed the key issues and openly shared best practices to achieve efficient processes. We published the findings and made the information available for everyone.

Then, with the help of all stakeholders and the use of tools developed by MDIC, by 2019 the average IDE approval time was reduced from 68 days to only 53 days, IRB approvals were shaved to 51 days, and the time to first subject enrollment was significantly reduced, from 187 days to only 88 days.

One metric that had not yet improved was the time to contract approval. Therefore, a further key step was to develop a Master Clinical Trial Agreement (MCTA) that streamlined the contract negotiating process between industry sponsors and sites with pre-agreed language on the thorniest issues. We believe that the use of the MCTA will significantly improve the time to contract approval once we have transitioned out of the current pandemic.

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Impressive! Any last thoughts on EFS and the Medical Device Innovation Consortium?

If you go to the MDIC website at www.MDIC.org and look under the Initiatives tab, you will find a list of wonderful free tools developed by MDIC to assist companies with the efficient execution of an EFS. The program director for EFS at MDIC is Liliana Rincon Gonzalez and she can be reached at lrincon-gonzalez@mdic.org. The team at MDIC has done a great job creating these tools and we would like to invite all companies to take advantage of it. Thank you.