COALITION FOR INNOVATION

HealthTech Blueprint for the Future

Coalition for Innovation, supported by LG NOVA

Jami Diaz, Director Ecosystem Community & Startup Experience
William Barkis, Head of Grand Challenges & Ecosystem Development
Sokwoo Rhee., Executive Vice President, LG Electronics, Head, LG NOVA

Blueprint Chairs

Alex Fang, CleanTech Chair
Sarah Ennis, AI Chair
Alfred Poor, HealthTech Chair

Authors

John Barton, Victor L. Brown, H. Timothy Hsiao, John Hsu, Sylwana Kaźmierska, Ricardo Machado, Ann M. Marcus, Nicholas Matias, Qiana Martin, Alfred Poor, Refael Shamir, Mark Wesson

The views and opinions expressed in the chapters and case studies that follow are those of the authors and do not necessarily reflect the views or positions of any entities they represent.

Senior Editor, Alfred Poor

October 2025

Preamble

The Coalition for Innovation is an initiative hosted by LG NOVA that creates the opportunity for innovators, entrepreneurs, and business leaders across sectors to come together to collaborate on important topics in technology to drive impact. The end goal: together we can leverage our collective knowledge to advance important work that drives positive impact in our communities and the world. The simple vision is that we can be stronger together and increase our individual and collective impact on the world through collaboration.

This "Blueprint for the Future" document (henceforth: "Blueprint") defines a vision for the future through which technology innovation can improve the lives of people, their communities, and the planet. The goal is to lay out a vision and potentially provide the framework to start taking action in the areas of interest for the members of the Coalition. The chapters in this Blueprint are intended to be a "Big Tent" in which many diverse perspectives and interests and different approaches to impact can come together. Hence, the structure of the Blueprint is intended to be as inclusive as possible in which different chapters of the Blueprint focus on different topic areas, written by different authors with individual perspectives that may be less widely supported by the group.

Participation in the Coalition at large and authorship of the overall Blueprint document does not imply endorsement of the ideas of any specific chapter but rather acknowledges a contribution to the discussion and general engagement in the Coalition process that led to the publication of this Blueprint.

All contributors will be listed as "Authors" of the Blueprint in alphabetical order. The Co-Chairs for each Coalition will be listed as "Editors" also in alphabetical order. Authorship will include each individual author's name along with optional title and optional organization at the author's discretion.

Each chapter will list only the subset of participants that meaningfully contributed to that chapter. Authorship for chapters will be in rank order based on contribution: the first author(s) will have contributed the most, second author(s) second most, and so on. Equal contributions at each level will be listed as "Co-Authors"; if two or more authors contributed the most and contributed equally, they will be noted with an asterisk as "Co-First Authors". If two authors contributed second-most and equally, they will be listed as "Co-Second Authors" and so on.

The Blueprint document itself, as the work of the group, is licensed under the Creative Commons Attribution 4.0 (aka "BY") International License: https://creativecommons.org/licenses/by/4.0/. Because of our commitment to openness, you are free to share and adapt the Blueprint with attribution (as more fully described in the CC BY 4.0 license).

The Coalition is intended to be a community-driven activity and where possible governance will be by majority vote of each domain group. Specifically, each Coalition will decide which topics are included as chapters by majority vote of the group. The approach is intended to be inclusive so we will ask that topics be included unless they are considered by the majority to be significantly out of scope.

We intend for the document to reach a broad, international audience, including:

- People involved in the three technology domains: CleanTech, AI, and HealthTech
- Researchers from academic and private institutions
- Investors
- Students
- Policy creators at the corporate level and all levels of government

Chapter 10: The Role of Regulation in HealthTech Innovation

Author: Alfred Poor

Introduction

Many people can look at the same scene, and each one will see something different. We see our realities through the lens of our own education, training, and experience.

We often can gain a better understanding of what a scene actually looks like by hearing the different points of view from various observers. This approach can be particularly helpful when considering complex settings that contain lots of different details.

And "complex" certainly describes the role of regulation in the healthtech industry. Different countries have different procedures. Within a single government, different products may face different requirements based on their intended use or how they are to be marketed. And within that, there can be multiple paths to approval; choosing the wrong path for your product can add years and millions of dollars to the project.

What does it take to bring a new healthtech product or service to market? What are the pitfalls to be avoided, and what strategic choices can a company — large or small — make in order to increase their chances of success?

Rather than address this issue from the viewpoint of one subject matter expert, I interviewed seven different experts who have different perspectives on the regulatory process. While there is naturally some overlap, each has their own piece of the puzzle to contribute.

Taken together, these interviews present valuable insights into the role that government regulation plays in the healthtech industry, and how companies can best navigate the complexities of the approval process.

[NOTE: These interviews were recorded and transcribed, then edited for length and clarity. The experts were given their edited interviews to review and offer corrections and edits. Those suggestions were included in this published version.]

Pathways to approval

Ashkon Rasooli, Principal Founder, EnGenius Solutions

Q: Tell me a little bit about your background, what's brought you into contact with FDA, I assume FDA clearance, and those kinds of issues.

Ashkon Rasooli: I've been in the medical device industry for about 15 years at this point, working with companies that had to interact with the FDA to get either clearance or approval of the product, or to make sure they stayed out of the zone where they needed clearance of a product, one way or another in that FDA-regulated space.

I've also had a few direct interactions with the FDA, in terms of the initiatives that the agency has had to develop for next stage regulatory frameworks.

Q: Can you say more about that?

Ashkon Rasooli: Back in 2018, I was engaged with the FDA's pre-certification initiative. I was part of one of the nine companies that they chose to pilot the program with. I was engaged in their mock audit; it was called an excellence assessment. They did not call it an audit.

Later on, I was part of a group sponsored by two public-private partnerships. We worked with the representatives from the FDA on coming up with what AI regulations might look like. The FDA doesn't currently have any official guidance or regulations on AI. They do have a good machine learning practices document, which is a set of principles.

When you look at the actual clearance reports of AI enabled devices, there is a heavy concentration in radiology. This typically looks like a back-end product that might have a web interface.

The products highlight certain details to assist radiologists in reading images to identify patterns. We call this CAD-X or CAD-E, which is “clinician-assisted diagnostics”.

So that's where the bulk of FDA-cleared devices are going. I believe you specifically mentioned LLMs in your original post, if I remember correctly.

Q: What sort of AI is being used. Is this based on LLMs, large language models?

Ashkon Rasooli: I think that it is important is we get our terminology right. AI as an umbrella term, that refers to a bunch of technical solutions. In theory, much of our standard software that we've had for the past 20 years could fit the definition of AI.

What most people talk about when they say “AI” is machine learning, which has been around for 10 or 15 years. For example, there’s Google's image processing that can identify a cat in an image. You start with a giant data set and learn from that data, then you can carry out the task.

But then a subset to that is now what ChatGPT brought to our attention in 2022, which is generative AI and LLMs.

Even though they're called large language models, for the most part, the industry has decided when we say “language”, we mean everything.

Q: It's not just text. It's images, video, and more.

Ashkon Rasooli: Right. The reason that I think the terminology is important is that the FDA has yet to clear anything with LLMs and generative AI.

When I talk about AI-enabled medical devices, they're really the classic machine learning kind of devices that are trained on a narrow task.

When I refer to classic machine learning, I’m talking about models that are trained for one particular task. We call those narrow models

Then there are foundation models that we call broad models. These can do a variety of tasks, within limitations. But the ones that are cleared by the FDA so far are only narrow machine learning models.

Q: It's easier to test the boundary conditions on those, I would think.

Ashkon Rasooli: Honestly, the idea of boundary conditions doesn't even mean anything in the machine learning world. The criteria depend simply on adequate quality assurance, and the FDA is just a little more comfortable with narrow models at this point.

Ultimately, the goal of the FDA is to ensure safety and effectiveness of devices. Their north star is safety and effectiveness.

Currently, the FDA is not comfortable with generative AI. I'm not either, to be honest. The entire industry is kind of uncomfortable and is unsure how you can validate an LLM? Nobody knows.

Q: You mentioned pre-cert. FDA also has the de novo clearance process and breakthrough designation. Have you dealt with either of those channels?

Ashkon Rasooli: I have not directly engaged with them, but I can tell you the feedback I've gotten from colleagues. The breakthrough pathway has been great, A, for publicity, but also B, for getting reimbursement. But if neither of those things are important in your business model, then the breakthrough pathways have been a little bit of a disadvantage for some companies. The idea with breakthrough designation is that we have identified your technology as worth accelerating the approval process, but we're not going to compromise safety and effectiveness, obviously.

The FDA will allocate additional resources to your project, and you're not going to be in the standard review process. You're going to get prioritized review.

Now, this also means that the company will have a lot more contact with the FDA to make sure that they get their buy-ins on the company strategy and other details.

It's kind of a pros and cons kind of a situation. And for some business models, it is definitely a way to go. For others, it's not.

Q: I've heard from some cases that a breakthrough designation is not necessarily a speedier path.

Ashkon Rasooli: Correct, but again it depends on your business model. It may not be the speedier path to market, but it may be the speedier path to reimbursement.

In medical device development, there's a thing we call "the Valley of Death". A lot of the medical devices get the FDA clearance and then they die.

And the reason they die is because they don't have reimbursement. The process of getting reimbursement is often far more arduous than the process of getting FDA clearance. This is why I say that you need to think about reimbursement early on.

I would say the same about the de novo pathway. A lot of companies are afraid of the de novo pathway. They try to position their products such that it fits within a standard traditional 510k pathway, so that it matches up with an already approved product. And that kind of ends up being their objective.

At the same time, while it is true that the de novo pathway is a longer pathway to market, sometimes it is the better decision for the business because it also becomes a moat around your castle.

You are creating a new regulation by the agency. You are given additional special controls. You become first to market under that regulation with that specific clearance. This means that your product is unique, the first of a kind. Anyone else who wants to compete with you on those exact same levels, on that exact same playfield, is going to have follow the example you set.

So again, is that of value to the business? Not all the time. Sometimes it is, sometimes the better approach is get to market fast.

Other times, I may choose to water down my technology and water down my claims in order to fit within a traditional 510K so that I can start making money sooner as a non-differentiated product.

Q: Maybe that's the better approach for the business, but I see products that are releasing a certain set of features now and shipping the product, but the roadmap is clear that they're planning to add more features in the future, you know, so rather than wait until they're ready. They

launch with the 510k features, and then they'll tack on the de novo features later when they're ready.

Ashkon Rasooli: And this is where the art of having a good regulatory strategist comes in. You need someone who understands the regulatory landscape comprehensively and can strategize around it so that you can build on that.

Q: Obviously, we're in a global economy. If you're coming out with a medical device, you've got CE, you've got Korea, you've got Japan, you've got the FDA: all these different agencies with their own hoops that you have to jump through.

How can companies strategize for an international product?

Ashkon Rasooli: I see two parts to that question. First, you have medical device-specific regulations, but then there's also non-medical device-specific regulations in general.

For example, if you've got AI in your product, the European Union passed the AI Act. It does not matter if it's a medical device application or not. You're going to have to comply with the AI Act. For that, you need to go beyond just a medical device regulatory quality management system framework.

For the medical device-specific items, though, what you're going to find is, yes, there are multiple agencies governing the introduction of medical devices to their markets.

However, there are initiatives working towards harmonizing these regulatory frameworks. One of the best-known ones is the MDSAP, the "single audit program" framework.

If you're a member of the MDSAP program, then instead of, you know, for example,

Brazil is a notable signatory to MDSAP. Classically, if you want to get into the Brazilian market, you must get ANVISA approval. And then you have regular audits every six months or so. But once you have MDSAP, countries including Brazil, Japan, and Canada will all recognize a single audit.

There are also committees such as the IMDRF that are focused on harmonizing the regulatory frameworks. But for many companies, by the time you've covered the U.S. and the E.U., the rest becomes marginal effort. That's been my experience.

Still, not all countries are created equal. Japan is notorious for being difficult. Brazil and China are also notorious for being difficult. They have their own specific requirements for certain things. This leads to a need for a case-by-case analysis.

Q: Is there anything that we didn't touch on that you think is important for companies entering the healthtech, med tech space?

Ashkon Rasooli: I think it's important to understand the intent behind the regulations. As expected, approval is slower and more reactive than for AI products for the consumer space. As a result, you're going to see the consumer market flooded with AI: especially generative AI and agentic AI.

On the regulatory side for medical devices, though, the potential failure of these models has far greater consequences and higher stakes. We're talking about actual misdiagnoses; we're talking about harm to patients; we're talking about fatalities. As a result, the adoption process understandably is going to be slow.

With that said, the application of AI in medical devices is going to be different from application of AI in the clinic in general. For example, we are already hearing about clinicians using LLMs such as ChatGPT to diagnose patients, which falls under the practice of medicine. It is scary, but it's happening. The hope is that you've got a trained clinician verifying everything that comes out of these systems. Ideally, it then becomes an assistant tool, but the current risks are real.

Q: I really appreciate your being so generous with your time. This has been very helpful.

Bringing a product to market

John Hsu, MD, CEO and Co-Founder, iPill Dispenser

Q: Please share a little about your background and what has brought you into contact – good or bad – with federal regulations for your products.

John Hsu: As an anesthesiologist and a chronic pain management addiction medicine physician, I'm supposed to make sure that patients take their medications as prescribed.

One day was actually late to my clinic and I saw my patients moving from car to car and I didn't know why. I asked one of them and they said, "You have a consent form for us for opioid use disorder treatment and pain treatment. Whenever our pill counts are incorrect, you kind of get angry and you always question us. So, from that point on, I stopped doing pill counts."

Later that day, I went to get something to eat and went to a bank ATM and couldn't get money out, so I opened my bank's mobile app, and that's when it hit me. Let's do a mobile app with a secure pill dispenser that we can send to patients' homes to reduce barriers to care.

I went home and built a model in my garage, wrote the app, and began some market test information. I found that there was a great deal of interest because of the opioid epidemic. The FDA really liked it and we won a position in the FDA Innovation Challenge program.

Then we received a breakthrough designation, and then from then on, we have been focused on commercialization. We're just about ready to launch product with Foxconn, the makers of the iPhone, and we have a pharmacy license in all 50 states.

We're now mailing dispensers to patients' homes with the drugs already installed, so patients don't have to go to the doctor. We actually treat the whole person; we combine psychosocial support for the mind and physical support with medications to prevent relapse and accidental overdose deaths. Only about 10% of people get treatment for opioid abuse disorder and I think we can make a difference.

Q: How does this differ from some of the other automated pill dispensers that have been tried?

John Hsu: Currently, this device has just one pill for opioid use disorder medications. It is designed to hold almost any size and shape of pill.

The National Health Service in the UK has asked us for it. Some Caribbean countries want to use it for chronic heart failure and hypertensive drugs.

We're developing a lineup of products: one for multiple medications, one for solutions, and one for sublingual films.

Q: How are medications loaded into the device? Does it come with a preloaded cassette of some sort?

John Hsu: We actually preload the drugs in the machine itself. If someone tries to break into it or tamper with it, we actually dissolve the medications within 20 seconds. That prevents abuse, diversion, and accidental overdose.

Q: So, you have to send out a whole new unit each time?

John Hsu: Yes, but we recycle the returned units. We have to take out parts that need to be destroyed in order to comply with the Drug Supply Chain Securities Act. Parts such as the pill tank get incinerated, and the remainder is recycled.

Q: Tell me more about your breakthrough designation. Did that make it easier to deal with the FDA? Did it make faster to receive clearance for your product?

John Hsu: Breakthrough designation supposed to make it faster, but it doesn't. We started the process in 2018 and now it's 2025. Also, it doesn't come with any money. It just puts us on the top of the list. And that's about it. Also, it didn't help the process when COVID hit.

Q: Was there a 510k path even available when you started this? Was there an equivalent device?

John Hsu: There is a predicate device, so we just elected to pursue a Class 1 registration, which means that it's 510k exempt.

Now, we're going for a Class 2 clearance and working to make sure that everything is going pass muster with the FDA.

One of the reasons why we're doing that is because we're using photoplethysmography to capture vital signs without a blood pressure cuff or EKG contacts. You take a picture with your phone, and you get vital sign data.

We're also putting a transmitter in each individual pill so that when the pill hits the stomach, we can tell who's taking it where and when. This way we can distinguish between medication adherence and medication diversion or medication abuse.

Q: Does this system require that the user has a smartphone?

John Hsu: It does. 98% of the United States population has a smartphone, according to Pew Research. If you don't have a smartphone attached to this, there's no good way to remind people to take their pills.

Q: But you're also using the phone for identification and presumably for the pill tracking to confirm that the patient took it.

John Hsu: Correct. This technology can also help make the family, friends, and the caregiver a part of the team. When the patient forgets to take their drugs, their contacts can be notified via text or email or a phone call or a telehealth session. We use telehealth plus medications to really treat the body and the mind.

Q: What's your take on the future of telehealth? Currently in the U.S. many telehealth services rely on emergency regulations, not all of which have been renewed. It would seem to me that there's a fair amount of uncertainty about what the regulations are going to be around telehealth.

John Hsu: I think that the need for urgent care facilities is permanent, but there's also an important role for telehealth.

As a physician, a patient's history is the most important part of the exam, and I can get that in a telehealth session. But if I need to examine the patient, I need to see them in person.

The problem with opioid abuse is that pain is subjective. A physical exam is crucial because I actually need to look at and feel the patient. It's also part of the medical board requirement that I do a physical exam of some sort within 30 days.

Q: That seems reasonable. We're still a long way away from just being able to do it by phone call.

John Hsu: I think it's getting closer. And, you know, I'm a fan of technology. Elon Musk's Optimus and the DaVinci robotic operating system are giving us new tools for remote patient monitoring. Soon, we're going to get to a point where we can do telehealth and actually feel and be able to push on different parts of the body so that we more information for a diagnosis.

There's still something to be said about interacting with someone to see micro-expressions and so forth.

Q: Where does iPill stand in the FDA clearance process at this point?

John Hsu: We're FDA Class 1 registered. We're FDA Class 2 submitted. We think we will probably get a de novo approval for the Class 2 device. The contactless vital sign capture is already Class 2 approved. The small little transmitter on each pill is already approved.

But just because you get FDA clearance, that doesn't mean you can get reimbursement from the payers, such as Medicare or other insurers. If you don't have reimbursement structure, you do not have a company.

You have to go to Health and Human Services; a breakthrough designation is supposed to be helpful with that.

But one of the most intricate things and innovative things that we're doing with iPill is that we're not to going after insurance.

Instead, we're going after companies that will pay us ahead of time because they feel that our product can save lives and save money, which is way beyond getting insurance reimbursement.

Q: For a new company setting out to navigate these waters, any words of advice for people who think they've got a medical product?

John Hsu: Yes; you need to have a good engineer, a good attorney for IP, and a consultant for FDA.

You need to have a good fundraising consultant, or you need a lot of know-how of your own. Patience and perseverance are the two most important qualities.

Q: What about working with the FDA?

John Hsu: The easiest thing to do is to get to them first and see what needs to be done. Treat them as a collaborator, not as a competitor. That's the most important thing that I learned, even though I fought tooth and nail with them at times.

I think one problem is that the insurance companies haven't embraced some of the innovation that the FDA is pushing forward, and it's holding back patient care, honestly.

Q: Is there anything else that we didn't cover that you think is important?

John Hsu: Yes; as a founder, you need to have thick skin. You know how many pitches I gave before I raised money? Everyone was telling me that I was wasting my time, that no one's going to pay for the device, that no one's going to want you. They said that I was a doctor, and that no one's going to believe that I am going to be a good businessman, even though I had already created five successful companies.

You can't let that discourage you. Just focus on building relationships based on mutual respect. Learn from your mistakes and stay humble.

Q: That's sound advice. Thank you for being so generous with your time and knowledge.

Interacting with the FDA

Steven LeBeouf, CEO and Co-Founder of Quellios

Q: If you would, please share a little background about your experience with the FDA clearance process.

Dr. LeBouef: My first exposure to FDA clearance was in my past company, Valencell, and it was literally not through a Valencell product directly, but through partner products.

With Valencell, a large part of our business was B2B licensing of our technology. I'm not going to say the name because there still could be some confidentiality there, but we had a customer that was pursuing FDA clearance. We had to make sure that our manufacturing of the sensor modules – as well as the software that we provided them – met the FDA's criteria for compliance. As a result, we witnessed their battles and how they went through the FDA.

Ultimately, they had to take the de novo pathway because there was nothing substantially equivalent to what they were doing.

Now, when I look at what they went through, if they had known to take the de novo approach right away, that would have been better for them, even though the de novo approach does take longer. If you know that and you just plow through the process, the timelines can be reasonable.

Q: Are we talking years?

Dr. LeBouef: Yes, maybe two years, which sounds like a lot, right? But let's say that you went with the 510k approach. When you submit a 510k to the FDA, nine times out of nine, they're going to reject it.

I mean, there's a few times where they won't. Maybe somebody's on vacation and so the intern's there and the intern stamps it.

But the reality is that you're not going to get a 510k approved the first time around. So, you need a budget for that delay.

You're talking about a minimum of six months, and it's longer than that because you're going to have to make some changes in between submissions. So, in reality, it's nine months. So now you're already a year into the process, and you may not even get it this next time.

And you're constantly trying to force feed your solution into a predicate device that came before.

If I were going to launch a new cuffed blood pressure device, for example, I would definitely just take the 510k route. The science is already there, so there are no new tests required; you use the same tests as before. In three months, you get a result, and it should pass.

But if it's something new, you really need to consider the de novo approach. My next experience I had with the FDA was when Valencell decided it was going to make its own product in blood pressure device that was worn on the ear. It was not as accurate as a cuff, but it could track your blood pressure rather than infer it from some other data.

The first thing we tried to do was get a general wellness exemption, because the FDA has a 513g provision for general wellness products.

For example, the heart rate on your wearable device, the breathing rate on your wearable device. And to some extent, even some versions of SpO2 on your wearable device are considered to be general wellness solutions. This means that you don't need to get a 510k clearance from those from the FDA because the FDA said that those things are generally understood to be used in wellness situations that don't necessarily lead to a medical diagnosis.

Rather than just launching our device, we approached the FDA about getting a 513g classification. Their response was that if you use the words "blood" and "pressure" together, they view that as giving someone a diagnostic reading.

They still hold that position to this day, and frankly, I agree with them. Their argument is that if you tell someone their blood pressure, it's different than telling someone their heart rate.

If your heart rate is 180, you're just exercising maybe, and so you're just trying to stay within a heart rate zone. It doesn't necessarily mean that you're going to die. But if your blood pressure is 180 over 100, that's getting close to where you could probably die soon.

And many consumers know that; they know those numbers mean hypertension and there's no way to unknow that. It's not like 180 over 100 is ever good in any normal situation where you're going to measure blood pressure. But blood pressure can vary a lot in the moment, such as when you exercise strenuously, even though it will drop back down to normal range when you stop.

As a result, we had to pursue a clearance. Now, in hindsight, I think we would have been better off taking a de novo pathway, but we decided to pursue the 510k approach.

And in that approach, we would compare ourselves to the cuff. The challenge is that the FDA has special tests that they demand on devices that aren't exactly the cuff if you want to get a 510k.

Q: The device that you were creating is one that looked like a pulse ox clamp on the end of your finger.

Dr. LeBouef: Exactly. We decided that we would pursue what we call the fingertip BP device. It's a pulse oximetry type device, but rather than providing you blood oxygenation, it provides you your blood pressure reading as a spot check.

And that solution we developed, and we decided to pursue a 510k. The challenge, though, is that the tests that you have to go through are still pretty rigorous, in order to claim substantial equivalence to a cuff.

You are fully free to pursue a de novo pathway instead, and I do believe that more companies need to view that as a possibility for things that aren't just blood pressure.

For example, Apple was able to pull off a de novo clearance with atrial fibrillation monitoring at the wrist. That worked out really well for them, and since then other companies have gotten a 510k based off Apple's de novo. But had Apple tried to get a 510k, they could have gone years trying to do that.

So, you do need to balance it out which is best for you. But if your business model depends on a quick launch for your medical device, you might want to find another business.

Now, some companies have tried to make a decision as whether or not just to launch without the FDA, and I do advise that approach in some situations. If you have a wearable tech health product that does not make a medical claim, then don't pursue the FDA clearance. This means definitely no blood sugar and no blood pressure devices; those are the two hot spots. But there are so many other things you could do.

For example, one of Valencell's customers was a company named GoGoBan. They were actually detecting childhood in enuresis. If a child is about to wet the bed, it was able to detect that and wake the child.

They weren't making a medical claim. They were not diagnosing whether your child had enuresis. They were just simply indicating that your child might wet the bed. In that case, they didn't pursue 510k. They never got an FDA letter. They never were pursued in that particular way.

And so, I do advise companies to think about ways to launch a product if it's in healthtech where you don't have to make a medical claim.

Q: Going back to the Valencell fingertip blood pressure device, as I understand it, there was a lot of data collecting and machine learning because you were going for a non-calibrated device.

Dr. LeBouef: That's right. You didn't have to calibrate with a cuff.

Q: Machine learning and AI in general are playing increasing roles in healthtech. What are your views about how these large data sets can play a role in the development of this new healthtech? And what's the appropriate role of regulation to make sure that the conclusions that machine learning comes up with are valid?

Dr. LeBouef: The FDA has been proactive in trying to give people a paradigm for what they need to report in the machine learning.

And everything they're talking about makes sense. Now, what I do hate about it is, you never get anything from the FDA that is just, boom, a one-page of what you've got to do.

Instead, you get mounds and mounds of information, but to get to the roux of the gumbo, they want to make sure that you understand what your training sets are, and your testing sets are.

The training and testing sets must never, ever overlap. You have to identify and isolate all the co-founding situations that potentially could change the output. There are some other things that they have a lot of concern about there, but that's the most important.

Where people really get into trouble with machine learning is when they develop a model and they test it on the same data that they trained it on. The problem with this is that all you've done is create a filter that's perfect at characterizing your training set. If you train a model on 10,000 people and then test it on those 10,000 people, it's going to work perfectly.

On the other hand, if you train a model on 10,000 people and then apply it to a completely different set of 10,000 people and it still works, then you have something that works.

However, it is disconcerting when you train a model on 10,000 people, in reality it's not going to work on 10,000 people perfectly. It will always be less than perfect. But the question becomes, "Does it work good enough still to be useful?"

With things like blood pressure, the FDA has very well-defined ranges of what useful is. In other things, such as diagnosing childhood enuresis, there's not a device that has been cleared to do that today so there's nothing to compare it to. You have to set up your own parameters and then present that to the FDA.

That's part of the de novo process, but the provisions for that are clear before you start. Then if you train on 10,000 people and test on 10,000 separate ones, and it's good enough, then it's good enough.

Q: But doesn't the makeup of training and testing populations matter?

Dr. LeBouef: The FDA has a provision for this; your training and test sets need to be broad enough to include the market for intended its use.

For example, if you want to get your cuffless blood pressure device cleared and you narrow it down to just people of a certain weight, the FDA will let you do that.

But if you're using machine learning, you need to show that your training and testing sets had those people.

There's nothing egregious in this policy. It's basic, good housekeeping of machine learning.

Q: So, in developing a product, you can put guardrails up. I've seen products that say that if you've got atrial fibrillation, you can't use their product.

Dr. LeBouef: Yes, and there are companies that have clearances for blood pressure of people only in certain age ranges, such as only infants, or people of only certain wrist sizes because the wrist size is critical to how their technology works.

The folks at the FDA are not unreasonable at all. What is unreasonable is that I still feel that a lot of what the FDA communicates is not clear enough to the average entrepreneur.

You know, entrepreneurs are not idiots. We're pretty smart, but when we struggle to understand what the FDA is communicating, that's a real problem, and they need to figure out how to improve that.

Q: One of the things I've heard is that if you start with conversations with the FDA early in your product development, you're kind of stuck going through that channel. It's hard to unring that bell.

Dr. LeBouef: That's a great point. It's a blessing and a curse. If you want to launch your product in a reasonable timeframe, then you need to start conversations with the FDA soon.

At the same time, if you start conversations with the FDA and they take you in a certain direction, that's the direction you're going to go down.

This means that you're forced to find good consultants early on to help you with that strategy and realize that when you start executing that strategy, it's going to be a challenge to veer away from it.

We fell under this at Valencell. Looking back, we probably shouldn't have had to agree to some of the provisions, but we had taken that path, so we were committed to them. Forget about trying to go backwards.

Q: On balance. Would you say that the de novo pathway encourages innovation.

Dr. LeBouef: Yes. Your product doesn't have to do it the way we've always done it. But if you decide to go a de novo route, it's critical to find a consultant who has experience on that pathway.

In any case, anything new with the FDA is going to be a long road, and you need to be prepared for that.

Q: Thanks! This has been great information. I appreciate your sharing your time and experience to support this project.

The challenges of novel devices

Robert Rose, Chief Officer, MD Remote Connect

Q: Please share a little context about your history with regulation in the med tech space.

Robert Rose: Most recently, we started development of MedWAND in 2014. And we were to start FDA clearance by about 2017 or 2018.

The device has multiple sensors. It has a pulse oximeter, an ECG, a high-resolution imaging system, a digital stethoscope, and an IR non-contact thermometer. And while the stethoscope and the camera were exempt from FDA clearance from 510K, the others were not. So, I had three different devices and one handheld device that had to be cleared, but they also required us to clear the entire device for safety. This was like doing at least four devices in parallel, each of the three that required 510k plus the entire device itself.

Some of the requirements were appropriate, but some were silly and forced us to do some major redesign work along the way. It ended up being a five-year journey -- across a pandemic as well -- to clear the device.

Some of the hurdles were regulatory requirements. For example, the device is tethered by a USB port to a tablet, and the tablet's plugged into the wall. They want to be sure that if you're using the ECG in a thunderstorm and lightning strikes your house, and the lightning comes through all the safety things in your house to the power supply, into the tablet, out of the tablet, up the USB port, into the device that you don't get shocked while doing an ECG.

That sounds a bit like the of Hound of Baskervilles not barking; how do you prove that's not going to happen? Well, you can't. You have to design a failsafe to cause it not to happen.

So, we had to design an isolation board for the power supply side of the device, which we then had to fit inside, which meant we also had to retool because once we had the board, it had to be mounted.

And I mean, it was very arduous and expensive. That was just one of those examples of where regulatory can be over the top, I think, in that case.

Q: Time to market can make or break a project because you're aiming at a certain price point in a competitive field that is changing rapidly. I know from the display industry, if you missed by six months, your project was dead.

Robert Rose: In this case, it didn't so much cause the project to be dead, but it did cause us to transition from having our clearance.

It was being issued during the pandemic where we could have had some substantial impact by keeping people home and out of clinical settings. Telemedicine wasn't cool when we started even though it is now. The time to market impact was significant and these are things sometimes you can't project when you're in the FDA cycle and regulatory space.

There's also the issue of the IRBs, the review boards, the protocols for various FDA clearances. These protocols are approved by the IRB before you even begin the study.

Q: You mentioned the retooling, redesigning, coming up with new manufacturing, but also there is just the cost of the new testing. And this can cost millions, right? A lot of startups don't have that financial shock absorber to be able to survive that.

Robert Rose: If you're in the hardware design business and medical equipment, yes, you've got to have the funding depth to be able to absorb those kinds of things. And you really can't predict them. Depending on what you read, the average cost to bring a product to market regardless of the size of the company is around $30 million for a simple, single-clearance type of a product. This would be for a new pulse oximeter, for example.

Q: It seems that a lot of products are sold that do not appear to have FDA clearance.

Robert Rose: You can go on Amazon, and you can buy remote patient monitoring devices from China and everywhere else that are not FDA-cleared. They get around it by calling it a wellness device.

I think our medical community is savvy enough to know the difference. But for end users, not so much. If something isn't clinical grade, it can mislead you.

The regulatory process is important. I know that when we were testing ECG, we found some things that needed to be cleared up in our ECG traces because of the FDA requirements; it was appropriate.

It's important to recognize where the value is. In the clearance process, you're going to get hit with stuff that doesn't have a whole lot of value.

One of the more difficult things to navigate with FDA, and I suspect it would be true with any government agency today, is the inconsistency of people. Often, you're dealing with one person leading the project this week, and then you come back in three months after you've done what that guy asked for, and there's somebody else who has no idea what you're talking about and asked for something else.

That's been challenging and it's getting worse now under the current administration with the cutbacks; you don't have as many people to work with. It's important to maintain continuity in who is doing the reviews.

Q: Can you talk a little bit about the guidelines that you have to meet. As with blood pressure, there's a certain range of accuracy that the FDA requires. Is the difference significant or is that acceptable range too great or too small?

Robert Rose: It's funny you should bring up blood pressure because it's kind of a black art. But, you know, some devices are – by definition – more accurate than others and can be tested for more variables.

I'll use the IR thermometer as an example. As we were going through the testing process, we had to look at the interactions between ambient air temperature, relative humidity, and the skin color; you do a whole design of experiments around that, but within a range.

The FDA or the IRB protocols allow for a range of, let's say, ambient of 60 degrees to 105. If you go outside of that you're away from the plus and minus guardrails. That's okay, so long as your results are based on working inside of that prescribed range.

You have to know what the limitations are to the device. With blood pressure, there's a lot of variation in the results based on different factors: white coat syndrome, whether your legs are crossed, is it your left arm or your right arm, and are you upset about something.

Blood pressure is a bit of a black art, but it's also interesting because right now we're going through clearance on an optical blood pressure system that uses the camera on a cell phone or tablet. It does not require calibration. This is pure optical blood pressure, and it works, and it is CE cleared now.

It's actually got CE2 clearance which helps as we're bringing it to the United States. This is my new company doing this, as part of our MD Remote Connect platform.

But it's an app, and we have been cycling with FDA on this, and there's no way that we can go back through the normal blood pressure guidelines to get this cleared; it has to go through the de novo process.

Q: That's interesting. So please talk a little bit about 510k versus de novo.

Robert Rose: 510k implies a precedent. Let's say that I've got a great blood pressure cuff and monitor and I want to get it cleared; you pick a predicate product. I go out and I find an iHealth or a Tenovi or whoever has a similar device that's been cleared, and the predicate has met certain standards and certain guidelines.

As long as you fall inside of those guidelines, and you can show that you can perform as well as and as safely as that device, you can obtain clearance.

But with de novo, you're establishing the guidelines for a new class of product. This leads to a more rigorous IRB review to start with.

In the case of our optical blood pressure, we're not touching the patient. Other factors now come into play with an optical blood pressure system that weren't there for a traditional cuff, such as ambient lighting. So now we have to test to other variables.

And these are without guardrails. We kind of make it up and then hope that they approve it.

What you're doing is you're establishing the predicate device when you take the de novo pathway. And the next guy who comes along will have to meet your predicate.

Obviously, it's more expensive to go to de novo route because you have to convince FDA that some theoretical aspects are tangible.

Q: So, de novo does offer kind of a defined path for innovation. While 510k is really doing it like we've done it before.

Coming back to the focus on innovation, what I'm hearing is that, to a large extent, regulation is a good thing because it provides guardrails, ultimately for the end user's benefit. But is it a drag on innovation?

Robert Rose: I'd say that it's a necessary obstacle. In its purest form, it's there to protect the public from, you know, medical devices.

We want to return accurate readings. We want to be able to give a clinician reliable information about life and death decisions for a patient

Q: And talking about data, it's also who's going to be the consumer of the data. For example, new parents often aren't equipped to understand the data from their baby monitors.

Robert Rose: Right. Even doctors have a tendency to look at blood pressure as an indicator and they can panic.

If you have fairly normal blood pressure and you eat a high sodium meal such as a pepperoni pizza, your systolic blood pressure will spike to 180 or 190. Or you take your blood pressure after if you exercise a lot and it's 350 over 210, the immediate reaction is to panic and call an ambulance, right? But not really, because if you recover for a few minutes after the lift, you're going to be back to 120 over 80.

I participated on a panel a few years ago where everybody made the same statement; trend analysis is everything. But we tend to look at results from FDA-cleared remote patient monitoring devices as a point in time without applying context.

We have to apply common sense to what we're seeing from one of these devices. That means trend analysis, because you might be looking at an outlier. While you're trending in the right direction, why did this spike 30% today? Maybe it was an anomalous reading, so the clinician has to be very aware of what they're doing with the readings and not just reacting.

You also need predictive analytics, which leads to the cool thing about the recent advances in AI. Let's say you have a home blood pressure device, and even though there are outliers, when you look at the scatter plot you can put a linear trend line through it. With this, you can predict almost to the minute when a patient is going to cross a limit that is going to require further attention.

But without that, blood pressure is just a number. And all the clearance in the world doesn't change that.

All regulatory requirements are not bad, that's for sure. Sure, there may be some rocks to navigate in there, but, you know, for the most part, I would say I think we're better off with it than without it.

Q: And so, you know, you mentioned that you got CE clearance for your device. Does it help to have different standards with different countries?

Robert Rose: No, absolutely not. The FDA is robust. CE is fairly robust. I think that there are a lot of commonalities between the two. CE obviously covers the entire EU, except the UK, though it is still accepting CE right now.

So those two cover about 860 million people, which is a big portion of the global market. There are lots of places on earth that will look at FDA clearance and still require you to check all the other marks from an international commerce standpoint, and then they'll accept the FDA approval.

And then you have others that require you to go through the process again, while in some places there are no regulations at all, which in my opinion is just as bad.

Q: Yes, that's dangerous.

Robert Rose: So, it's still kind of the wild, wild west out there. I wish there was an international standard; it would make things a lot easier. But that's not the case currently, and I don't see any value in multiple regulatory authorities.

Q: Well, thank you so much for your time. I appreciate your perspective on these issues.

AI drives innovation

Nathan Buchbinder, Chief Strategy Officer and Co-Founder, Proscia

Q: Please start by sharing a bit about your background and how that relates to the topic of regulation.

Nathan Buchbinder: One of my other co-founders, David, and I were doing some research in a couple of cancer labs at Johns Hopkins.

We saw that pathology was woefully behind other areas of healthcare in terms of digitization, yet it had the biggest potential out of any medical field to take advantage of data-driven medicine and the shift towards a precision approach to drug development and drug delivery.

So that's where the concept of Proscia came to be. Proscia is a digital pathology and AI company. We are taking this very analog field of diagnostic medicine that has depended on 150-year-old technology: looking at a glass slide under the microscope and making an interpretation that influences 70% to 80% of downstream healthcare decision-making and spending.

We're taking that process and helping to transition it towards digital, towards the data-driven paradigm, where you can drive insights from digital images of these biopsy tissue specimens. You can then learn much more about the patient as well as develop new drugs that are targeted based on the patterns that are represented in histopathology.

Our platform, Concentriq, is a software solution that serves as an operating system for these image-based workflows and incorporates AI into all aspects of them, both in the diagnostic world as well as in the research domain. Today, we serve 16 of the top 20 pharma companies, the two biggest clinical research organizations (CROs). Something like 80% of global clinical trials are supported by our customers.

And on the diagnostic side, we're on track to support 8 million patient diagnoses in 2025, up 400% year-over-year.

Q: Is this similar to what has happened with other medical imaging such as x-ray, CT, and MRI, and how digital imaging can have AI do some analysis to support the human doctors?

Nathan Buchbinder: It is very similar. The shift to digitized radiology happened about 20 to 30 years before the shift to digital pathology started. And I would say that radiology was a little bit more natural of a shift because the devices themselves that captured these images fit so smoothly into the workflow.

Radiology went from a process that required physical image generation to one that required purely digital image generation. In pathology, it's a little bit more challenging because you're introducing a new step in the process.

You still create the glass slide, but now instead of looking under the microscope, you have to take it and put it in a scanner and create these big images.

But I would say that the potential benefits are so much greater in pathology than other medical imaging. In radiology, your average image is dozens to maybe hundreds of megabytes in size. But there are more than a billion pixels — a gigabyte of information — stored in each and every one of these histopathology images, This data represents the patterns that underpin diseases such as cancer, which could reveal the specifics of who to treat and how to treat them with the therapies that are going to work best.

Q: I've seen how the digitization of medical data has led somewhat to democratization of health access. Is there a roadmap that takes this out of the wizard's hands in the basement to bring it out to the field where you can shorten the loop on analysis and diagnosis?

Nathan Buchbinder: Yes, absolutely. There are operational benefits of going digital that allow you to decouple the physical location of the pathologist and the specimen from each other.

What that means in practice is that if you have an expert pathologist in a particular subspecialty, say renal cancer, but they're based somewhere else in

the world, you used to have to FedEx that glass slide for them to look at.

Q: And that's the one and only specimen, right?

Nathan Buchbinder: Exactly. Not only does shipping take days, there's a risk of the sample getting lost. You can't do anything meaningful while it's in transit, but with digital, you get instant access.

Once the image is generated, you can share it with that expert, and they can provide a review. The other thing that it does is it solves what I would say is an even bigger challenge in pathology, which is the shortage of pathologists.

The number of pathologists over the last 10 years has steadily declined by between 1% and 2% per year, while the number of cases that pathology is seeing has gone up by about 2% to 3% per year.

That imbalance means that an average pathologist today reads about 40% more cases than they had to 10 years ago to just keep pace.

That's not sustainable, and digitization allows you to address some of the geographic challenges that come up as a consequence. Sparsely populated regions often don't have a lot of healthcare resources. People all over need access to the best care, and digitization allows us to spread out that imbalance. You can give more immediate access in real time to the best experts around the world.

Q: This relies on a whole lot of novel technologies, which I think leads us directly into the government. What has your experience been with government regulation? Has it encouraged or has it inhibited new technologies such as yours?

Nathan Buchbinder: If you're using digitized images to support a patient's diagnosis, the technology that enables that process is considered a medical device and subject to regulation. In fact, each of the components in that workflow, whether it's the scanner, the viewing software, or the monitor, is classified as a medical device. The challenge is that this was a completely new domain.

Because there wasn't an existing predicate device in digital pathology, the 510(k) pathway was unavailable. Rather than default to the highest risk classification, requiring a PMA, the FDA worked with industry to create a brand-new product classification and special controls through the de novo application process. The FDA had a lot of questions, like: how do you treat each of the components in the process? Are the scanner that creates the image, the software you use to view it, the monitor you're looking at to make the diagnosis, and even the AI applications that come afterwards one device, or are they multiple devices? Can they be separated so you can mix and match?

At first, the FDA took a pretty conservative approach. They defined an end-to-end "pixel pipeline" that included the scanner, the digital pathology software, and the monitor. So when we went through our 510(k) clearance for our Concentriq platform, we had to prove performance using a specific scanner and monitor. Everything was locked in. If we wanted to swap in a new scanner, or a different monitor, or another platform, we'd have to do additional studies, sometimes even clinical studies, to show there was no difference in the diagnostic outcome.

AI has added another layer of complexity. And this isn't just true in pathology, it's happening across healthcare. To be candid, in the early days the FDA was often seen as a barrier to adoption. Before any clearances were granted, it could take years, and the process lacked clarity. But more recently, we've seen a real shift. The FDA has been engaging much more actively with industry and with the medical community. They have shown a willingness to adapt their approach to reflect what's happening in practice, which has opened the door for innovation to move faster and for deployment to be more flexible.

A great example of this is the introduction of predetermined change control plans, or PCCPs. These plans allow you to "future-proof" a regulatory submission by laying out in advance the criteria that need to be met to extend an approval. For Proscia, that means we can continue to evolve our software, adding new features and improvements, without having to start the clearance process from scratch every time.

Q: I think people are really, in all fields, but especially health and medical, are trying to wrap their head around just what AI is and how it applies to these kinds of products and services. For example, there's the whole question of what population you are using and data gathering procedures you are using for your training and testing data?

Nathan Buchbinder: Generally speaking, I see a lot more openness and a lot more effort being put into understanding where the technology is heading, and how to adapt regulations and standards and approaches towards that.

I'm not suggesting that any one person or group has the answer right now, but the mindset change has been noticeable. It's certainly encouraging that regulators can partner with industry and have solid awareness of where the industry and clinical practice of medicine are heading. The FDA seems open to adapting their approach to what the future looks like and to encourage that kind of innovation.

Q: Are you seeing a lot more de novo applications in recent years than traditionally?

Nathan Buchbinder: In our space, we're certainly seeing that same kind of thing, and we expect that to continue because, again, the use cases that technology is going to be able to address or that it can, in theory, address today are so different than what was possible even just two or three years ago.

You're going to start to tackle indications and use cases in clinical practice today that would have been unimaginable two or three years ago.

In these scenarios, there will not always be a predicate. There's going to need to be new thought that's given into what the riskiness of a certain device is in a certain scenario. What controls need to be put in place to ensure that you're safely delivering this in a way that benefits the patient and doesn't add new risks?

Q: From the outside, it seems to me that AI can handle complex factors such as comorbidities better than the individual healthcare professional working off their own experience.

Nathan Buchbinder: The promise of AI is enormous, but I want to be clear, there will always be a very critical role for the medical practitioner, for the pathologist, for the radiologist, for the oncologist, whoever it might be, to play in this process.

And it's not simply as a translator of AI results to the patient. AI is extremely adept at pattern recognition, it's able to catch subliminal hints of something that might be missed, it's a phenomenal second set of eyes. And it's an extremely rapid mechanism of interpretation. It will catch things sometimes that a pathologist or a radiologist might miss.

But there are always going to be those edge cases, situations where the human knows better or is aware of information that's not been pulled into the AI application. I think that AI allows pathologists and other diagnosticians and medical practitioners to practice at the top of their license.

It's allowing them to avoid spending their time on the extremely mundane, on the extremely time-consuming manual aspects of their work, on the tasks that don't have anything to do with their training as a medical doctor and have more to do with the paperwork and the logistics and the mechanics and the very basic aspects of diagnostic or clinical medicine. AI technology puts those into the bucket of automatable tasks, so that the healthcare professionals can spend their time focusing on the most challenging and complex cases, armed with new tools that allow them to derive new insight from those cases.

I think this is where healthcare is heading, and we're seeing the changes happen very rapidly. And again, we've seen regulators recognize that that's the situation.

We've seen CMS start to track some of this, to get a sense of where AI is making an impact, who's using these types of technologies, who wants to use these types of technologies, and who wants to modify their own behavior as a consequence.

And at the end of the day, the one who benefits the most is the patient. The patient is the one who gets a faster diagnosis, faster turnaround. The patient is the one who gets more insight into what's going

on with them and what treatment they should pursue.

The patient is the one who feels more confident. It's not quite the case in pathology today, but in radiology, for example, I don't need to tell you that it's not uncommon for a patient to receive their radiology results before their physician sees them.

Pathology is not that far away from that same type of patient experience. And again, the patient is the one who gets the better outcome.

Q: So, have you been engaged in international? We've got CE, we've got FDA, Korea's got their own clearance requirements. There seem to be all these different hoops to jump through.

Nathan Buchbinder: We've obtained many of these regulatory authorizations across the US, Canada, Europe, and beyond.

What's interesting is that historically, I would have said that Europe and other geographies were ahead of the U.S. on the innovation curve. Five years ago, Europe had a much easier mechanism of driving innovation.

But that's starting to shift. We are seeing much more nimbleness from the FDA, with a forward-looking approach that is more dynamic. This allows us and others in our space to make decisions with the confidence that there'll be an open-mindedness to the path that needs to be followed to get a novel, innovative solution to market.

Across the board, domestically in the U.S., as well as internationally in Europe, the Middle East, and Asia, we're seeing a big push towards the advancement of medicine and the incorporation of novel technologies to make that happen.

Q: That's encouraging. Finally, is there any point that you want to make sure that we cover?

Nathan Buchbinder: One thing that's been hinted at but which we haven't touched on explicitly is that this transition to a data-driven approach in diagnostic medicine is having a corresponding impact on drug discovery and drug development.

Big news was made this past year when AstraZeneca brought out a new Phase 2 clinical study that they were conducting, with an image-based AI-powered companion diagnostic.

Essentially, a precision diagnostic that indicates — or that will indicate when it gets approval — whether an individual patient is or isn't a good fit for a targeted therapy that has a very high response rate for that subpopulation of respondents.

And we think that this is a sign of things to come. We think that this data-driven, data-rich transition that medicine has taken — and pathology in particular — is not just better for the clinician. but It's also opening up a whole new world of drug discovery and drug development. Pathology images represent a new data modality providing one of the most detailed and direct profiles of diseases like cancer. This data can also inform next generation therapies.

So it's a flywheel, and we think that it's starting to spin pretty rapidly.

Q: That's an exciting vision. Thank you for sharing your time and insights to support this project.

The value of outside advice

David Lennarz, Founder and President at Registrar Corp.

Q: Please tell me a bit about your company and your interaction with the FDA?

David Lennarz: Registrar Corp. is a 22-year-old business that helps companies regulated by the Food and Drug Administration comply with their various regulations. We work not just in the medical device sector, but also pharmaceuticals, cosmetics, and food and beverage as well. We focus on three main offerings: services, software, and training.

First, we have 30 to 40 different services that we provide to companies around the world. Most of our clients are foreign companies exporting products to

the US or are involved in the supply chain somewhere.

We also have software products that we commercialize. The third focus is on training; we have an online, 100% online training platform with asynchronous learning courses that individuals can take, covering medical device regulations.

In the area of medical devices, I could call it med tech, but we handle everything from eyeglasses which are regulated as a Class One device by FDA, right on through to an artificial heart, for example.

We have a partner who handles the more technical or scientific oriented submissions, such as 510ks for products that are not exempt from requiring clearance. These are higher risk products that actually require an FDA review and are based on a predicate device that is already on the market.

There is also a pre-market approval process for products, and pathways as for novel products as well.

Q: That's helpful. In your view, how does regulation help or hinder innovation?

David Lennarz: Our perspective is shaped by our prospects, which includes literally everywhere in the world, including the U.S. They often come to us with an assumption that there's a very easy pathway to getting their products to market in the U.S. This includes prospects who are creating products here in the U.S.

Q: It sounds as though you work with a lot of founders of startups.

David Lennarz: Actually, there are a couple of types of prospects. Certainly, a percentage of them are startups.

But there's also a large percentage that have products that are already commercialized in another market. They might be in the EU, or Thailand, Taiwan, China, or India, for example. And they're actually producing this product and they're selling it in their country and they're exporting it to other countries.

Typically, there is a sort of an initial surprise, even shock; they feel overwhelmed by what they need to do to be able to get their products onto the U.S. market.

These companies will come to us and say, "Here's my device. I've been commercialized this in Taiwan or wherever, and I've got a buyer in the U.S. that I'm going to export it to next month." We have to tell them to slow down, and we explain what the process is.

Obviously, if it's a Class One device it's exempt, and we do lots and lots of Class One devices. Still there is a registration requirement.

There's a product listing requirement. There's proper labeling. There are good manufacturing practices – GMPs – that have to be followed. But that's a fairly simple, quick process that takes of a matter of days to weeks to get through.

When it comes to products that are not exempt, know, step one is to determine how the product is classified. It takes a lot of time and money to obtain FDA clearance for a medical product. Once a company understands what the pathway is and the cost associated with that process, that can just close the door on their project.

All registered FDA products – whether they are exempt or not – pay an annual fee of about $11,000. This can be an expensive obstacle for something simple such as eyeglasses.

The fee is based on the actual costs of running the registration program at the FDA and can go up or down, but mostly it tends to go up.

Large companies can afford this fee with little difficulty, but it can be a significant obstacle for small companies and startups. I think these fees are one of the greatest reasons that we see the stifling of innovation.

And again, I'm not even talking about the fees to submit a 510k or a pre-market approval, which are even more.

Q: And then there's the testing required to prove that the product does what you say it does and is safe and effective.

David Lennarz: Yes, there is all that other stuff that a company has to do for FDA clearance. This money doesn't go to FDA; it goes to independent companies to do the testing.

There is a Small Business Determination program where a company can qualify for a reduced FDA user fee, or have it waived entirely.

Q: But do you see this impacting the attitudes of the investors who might be more hesitant?

David Lennarz: If I were an investor in a med tech startup, I'd want to be darn sure that the inventor and small business owner who's doing this has clearly done their homework around their strategic pathway for being able to market this legally in the U.S. The last thing I'd want is to find out that, they need an additional $200,000 to get this through an approval process.

It's another thing for companies that have a product that is already being commercialized elsewhere in the world. And then they and then they say, hey, our strategy for next year is to enter the US and then they, you know, find out that, oh, my gosh, you know, this is this is going to be a couple hundred thousand dollars, and it's probably going to take six to 12 months or more.

Q: So, so one of the recurring themes I hear – and inferring it from what you're saying – is that you need a team of outside experts to handle all the different aspects of the clearance process. People don't know that they don't know. Right?

David Lennarz: Obviously I'm in this business, so yes, of course. But I look at it from the two perspectives of founders and of an existing company with an existing product.

Founders typically know their product. They know how to produce that product, but they don't understand the regulatory landscape unless they've done this before, which isn't generally the case.

I think their path of least resistance and path to most likely success is to have an outsider who has the expertise and knowledge who can ultimately save them time and money.

The other perspective is from a foreign manufacturer of a product that's already being commercialized in a foreign market, and they want to export it here.

Typically, we see that if they have a regulatory person, depending on the size of the company, often that regulatory person is an expert in their home market, and they may have a cursory understanding of the U.S. requirements. But because of language barriers and other factors, they may lack understanding of what all the requirements are.

In the case of foreign firms, there's a lot of value to have an outside third party who can really walk them through the system for the same reasons as for startups: time and money. Being faster to market means being quicker to get revenue coming in.

Q: Do you see any progress, any hope for harmonization between the requirements of the different countries' regulatory agencies?

David Lennarz: No, I really don't. Everyone thinks that their way is the best. There are some similarities, some crossovers conceptually, and some recognized certifications or schemes, but generally, everyone is pretty different.

In food, it's interesting because there are some countries in Africa that have copied the FDA's food safety regulations.

But for the vast majority of FDA-regulated products, countries have their own processes and own requirements, and they can differ pretty dramatically, this can present a challenge if you're trying to commercialize something on a global basis.

Q: This has been great. We have covered a lot of ground, and your perspective is valuable. Thank you for your time.

Get help with regulatory strategies

Michael Kisch, Head of Global Healthcare Incubation, LG NOVA

Q: Clearly, you've had a lot of experience with products that get involved in FDA clearance or regulation. Can you share a bit of background about that?

Michael Kisch: I've been the Founder/CEO or just CEO for three different healthtech businesses, all of which required a regulatory strategy.

I've gone through the FDA process at least four times; three of those were for 510k, one for de novo.

In addition, the companies that I've led have also secured regulatory approvals in Europe, Canada, and Australia. I wouldn't consider myself an expert, but I have a good perspective.

Q: Can you contrast your experience with 510k and de novo routes to clearance?

Michael Kisch: 510k is the most common path for Class II medical devices. I would say that 95% of submissions to the FDA are for the 510k pathway where you're just trying to demonstrate substantial equivalence to an existing product that has already been cleared.

That can include both the accuracy of the product as well as its intended use; who will be allowed to use it? What benefits you might claim from its use?

The 510k path is not without its complexity, but you kind of have a North Star when you go through the process because you only need to be as good as the existing product.

Then we have the de novo path, which is taken by maybe 5% to 10% of submissions. It's a very underutilized pathway.

The primary reason for that is by its very name, you are the first. This means that you must define not only what is a "good enough" accuracy or the performance characteristics of the product, you also have to define who it's for and what claims can be made about its use.

This requires a lot more work because you're the first and there's a lot more ambiguity and room for interpretation. This creates increased risk which ultimately leads to a lot more time and money required to get to your product approved. This is a challenge even for large companies, but especially for small startups.

But the more innovative products have to go with de novo because they are the first of their kind and a predicate device or substantial equivalent does not exist.

So, it is always ironic to me when people "We were super innovative, and we went down the 510k path" By its nature, that's not innovation. That's effectively imitation.

Q: What about a breakthrough designation? Does that have any impact on the process?

Michael Kisch: I think that breakthrough designation is a valuable program.

Through the lens of a startup, a breakthrough device designation builds credibility amongst investors and partners and customers in advance of a formal regulatory approval.

Breakthrough device designation also gives you more attention and focus from the FDA, which has always been difficult to get and will be given the recent cutbacks at the FDA. That extra help is very important.

And on the back end of breakthrough device designation, there can be an expedited pathway to reimbursement. The CMS can play a role as part of as one of the partners within the program, which brings a lot of value as well.

I do think that oftentimes it's quite hard to qualify for breakthrough device, however.

I think that some companies will alter their product to increase the likelihood that of getting a breakthrough device designation, but by doing that, they create other potential risks or limitations on what the product can do, and its potential commercial of focus.

As with all these things, there are advantages and disadvantages. There is no perfect pathway. You need to be knowledgeable about the pros and cons, then choose the one that is appropriate for you.

If you're a big company, you can take more risk because you have more resources. But if you're a smaller company, the determination of the FDA could be a life-or-death decision for your company. You must be very pragmatic about how you engage in a regulatory process.

You're not going to get everything you want the first time through. You need to start and then you need to have a strategy, a roadmap over time for successively going back to the agencies for improvements, such as expanding the intended patient population or the product claims.

A great example of this are the CGMs, continuous glucose monitors. They started out very focused on Type One diabetics who were using insulin and required daily calibration.

Today, these devices are now being used by pre-diabetics and non-diabetics. They're available over the counter direct to the consumer. And you may only have to calibrate once every two weeks, or possibly you don't have to calibrate at all, depending upon its intended use.

Companies such as Dexcom and Abbott have been in that business for the last 20 years, and they are good examples of a slow, steady incremental process that you have to go through if you want to find that balance of managing risk.

Q: You also mentioned all the countries that you've been involved with, with products. Is it a patchwork of regulations and different requirements and different processes and procedures you have to go through?

Michael Kisch: It certainly can be a challenge, but I think if you are thoughtful about how you're submitting in one region or country versus another, you may be able to look for some commonality. You build your application once, then use it twice. I think you can make your life a little bit easier, but there are distinctions.

For instance, the U.S. FDA likes to see that if you're presenting clinical data, that it's run on a representative population of people within the U.S. But if you're going for CE mark through a notified body in Europe, they may not care as much about where the clinical trial was run.

You need to have a top-down overall regulatory strategy and be thinking about different regions, different regulators, in a broader context. What's the sequencing? What are the shared resources or assets or components that you'll be able to leverage multiple times with multiple regulatory bodies?

Q: Do you think there's any movement towards harmonization between the different regulatory bodies, or are they going to remain pretty provincial in their views?

Michael Kisch: I think that they look at each other and they do pay attention. I think they do leverage some of the same criteria and resources.

For instance, in areas like blood pressure monitoring, there's an ISO standard for blood pressure measurement that's relied upon by everyone. It doesn't matter if it's U.S., or if it's Europe, or if it's Japan, or the China FDA. But then they all have their unique process.

I don't think that you're going to see them move towards some type of global standard on how they evaluate new devices or new software, however. The best example of harmonization is obviously Europe, where you do have a single framework for the 27 EU nations, which is very, very powerful because navigating that once gives you the ability to sell into all the other member countries. That does make things simpler.

And what's even more powerful about that is that CE mark is recognized by a lot of other countries outside of Europe. It gives you an expedited pathway into Australia, New Zealand, South Africa, Brazil, and Canada: up to another 17 countries all over the world. They may do some additional review of your submission, but ultimately, it's an accelerated pathway because you got the CE mark.

Q: Working with LG NOVA, you must have contact with lots of startups. Are most founders equipped to deal with the registration process on a global basis? How important is it for them to get outside expertise as a consultant or some other sort of support in the med tech space?

Michael Kisch: If you don't have experience dealing with a regulatory body, you need to go find that experience. And if you are not in a place in your

company's lifecycle where you can afford to hire a good person full time, then you need to find an advisor, of which there are many.

And you need to follow their direction, because they've been through this journey numerous times, and they'll help you kind of figure out the expedited, lowest risk path to getting your submission.

But to go in uninformed and ignorant to a regulatory process is just a massive red flag of poor decision-making as a CEO-founder; you're just taking on a really substantial risk. And if you're out trying to raise money, a regulatory denial or a poorly articulated regulatory strategy is one of the surefire ways to not get funding.

Q: My understanding is some accelerators provide access to that sort of expertise.

Michael Kisch: You should get this help wherever you can; you just want access to somebody that has the relevant experience.

Different types of products require different expertise. A new drug is different from surgical robot, which is different from an over-the-counter consumer device.

You want to find somebody that has taken products that are similar to yours successfully through the process. And if you have something that's truly novel, one of a kind, then you want to find a regulatory expert that's taken something truly novel through the process and has demonstrated a level of creativity in how they were able to get that done.

Q: I'd think that these consultants are very valuable and thus very expensive resources.

Michael Kisch: Many of them are already locked into later stage startups and very large companies. It's not like you can throw a stone and hit two of them. And the difference between someone who's okay at regulatory versus a superstar is significant. A founder who doesn't really understand regulatory well can struggle to distinguish between the two.

Q: Can investors be a source of regulatory consultants?

Michael Kisch: If you're dealing with a venture firm that invests exclusively in medical devices, you might find that they have a roster of regulatory experts.

But a lot of investment in healthtech comes from non-traditional, non-healthcare investors. These groups have less sensitivity to regulatory requirements, and they have less of an activated network. As a result, they might be less inclined to pursue an investment because it's an unknown for them. And if they do invest without fully quantifying the risks, they often can be disappointed later.

Q: Is there anything that we didn't touch on that you think would be important either to founders or med tech projects in general?

Michael Kisch: The advice I give to most founders is that regulatory is one of those areas where you always want a second opinion. That's not to say that the first advisor you engage with isn't awesome; it's just they can't know everything.

This is such a great area of risk that you don't want to take unnecessary chances. And there is a level of creativity required, which most people don't think about when they think of regulatory. There's quite a lot of creativity and strategy that goes into this.

So, this is one of those areas that you want to get a couple of people's opinions. At almost all of my businesses, we had multiple regulatory experts that consulted with us. We always had a primary; they led the overall project and managed the submission and the interaction with the agency. But we always had a couple of other regulatory people who were reviewing and brainstorming with us about what our approach could be.

Now that carries more expense, but once again, I view regulatory for a lot of healthtech companies as an existential threat, and you cannot over-resource an existential threat.

If you really don't understand regulatory, if you haven't been in it before, then treat it like getting a diagnosis of a disease. You might trust your physician, but you want to verify that the diagnosis and prognosis are supported by others. Regulatory is a great area to exercise that same type of approach.

Q: That's great advice. Thank you so much for being so generous with your time and your insights.

Conclusion

As with many complex systems, there is room for differing opinions. Taken in aggregate, however, these interviews present a composite picture of what it's like to be in the trenches of the approval process, albeit from the perspective of different roles.

The main take-away is that we must be vigilant about recognizing that often we don't know what we don't know. The insightful founder or executive will find resources that help fill in these blind spots, to mitigate risks and increase chances of success. There are many paths to success, but there are even more paths to failure.

The other take-away is that government regulation of healthtech products exists to protect patients, and ultimately the companies that produce the products that patients rely on for their health. Yes, it can be a messy, inefficient, and inconsistent process at times, but the system exists for the greater good. We can find it helpful to keep in mind that those involved have the best of intentions.

By being informed and strategic about the regulatory process, we can all play a role in fostering innovation in healthcare. We can make healthcare more broadly available, with lower costs and better outcomes.

Author (In order of contribution)

Alfred Poor, **PhD, Keynote Speaker, The HealthTech Futurist**
Alfred Poor, the HealthTech Futurist, is a dynamic speaker and author with an international reputation in technology fields. He was the Editor of "HealthTech Insider," a website that covered wearable and mobile devices for health and medical applications. A graduate of Harvard College, he is the author or co-author of 15 books and is widely quoted in major media outlets. He brings energy and humor to his presentations and tailors his programs to match the technical levels and interests of his audience.

For more information about the Coalition for Innovation,
including how you can get involved, please visit coalitionforinnovation.com.

View the Next Chapter