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# Putting The Patient First: The Challenges And Opportunities To Improve Rare-Disease Therapy Development

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**ADVANCES IN IDENTIFYING** the genetic causes of diseases, and particularly cancers, coupled with regulatory incentives to encourage the development of therapeutic approaches to once poorly managed orphan diseases have fueled a surge in exciting new medicines. However, developing such drugs requires new approaches designed to tackle some of the challenges associated with rare diseases. To address some of these issues and explore potential solutions, Simbec-Orion in collaboration with Informa Pharma Intelligence convened a round table of experts attending the BIO International Convention. A consistent recommendation from the panel, which had representatives from organizations associated with different stakeholders in orphan drug development, was better and sustained engagement with patients.

## MODERATED BY:

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## PANELISTS:

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**Martin Babler,** *CEO,* Principia Biopharma

**Tim Considine,** *Senior VP, Strategic Development,* Recursion Pharmaceuticals

**Patrick Doyle,** *CEO,* Stelexis Therapeutics

**Gary Fortin,** *VP and Franchise Lead,* Severe Genetic Diseases, bluebird bio

**Seth Fritts,** *Corporate Engagement,* Global Genes

**Ralph Kern,** *Chief Operating Officer,* BrainStorm Cell Therapeutics

**Joanne Mason,** *VP, Biomarker Discovery,* Cambridge Epigenetix

**Dr. Kimberly Noonan,** *Founder and Chief Scientific Officer,*
WindMIL Therapeutics

**Ronald Openshaw,** *CEO,* Simbec-Orion

**Dr. Eleanor Perfetto,** *Executive VP, Strategic Initiatives,*
US National Health Council

**Aaron Sato,** *Chief Scientific Officer, Biopharma,* Twist Bioscience

**Alain Thibault,** *Chairman of Simbec-Orion's Oncology Advisory Board*

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# Putting The Patient First:
## The Challenges And Opportunities To Improve Rare-Disease Therapy Development

Pharmaceutical companies routinely talk about patient engagement. For rare-disease therapies, a close and mutually productive relationship with patients really is paramount. This is a category in which patient populations are fundamentally small and low-profile.

Further engagement challenges include disease complexity, difficulty recruiting trial participants, or overcoming skepticism about treatment costs and sustainable business models. Yet the cumulative potential of rare diseases is considerable. It includes 7,000 conditions affecting over 400 million people worldwide: equivalent to the world's third most populous country, Scientific advances such as genomics, attractive regulatory incentives and limited market competition have encouraged a surge in rare-disease development activity.

Thinking about patient-oriented value as an end goal, and from the earliest possible stages, can help companies avoid some familiar pitfalls of rare-disease development. Those might entail designing viable clinical trials, or convincing investors that a limited revenue base or novel drug target is commercially appealing.

"For me, there's a parallel path between developing your drug and developing the environment

your drug ends up in. That path starts preclinically," commented Martin Babler, CEO of Principia Biopharma.

The challenges begin with raising funds for development. As Oved Amitay, Chief Business Officer of Centogene, pointed out, many venture capitalists and even larger companies are "disinterested if the population is too small; they don't view it as a viable commercial opportunity."

Niche populations also complicate clinical-trial designs. "Typically, there's quite a wide range of clinical expression," Amitay noted. "If you take a small population that is heterogenous, how do you really develop a clinical program that can address this spectrum of clinical manifestation?"

**"If you show the pros and cons you've thought through, the agencies know they have a partner to talk with, and that accelerates things." – Alain Thibault, Chairman of Simbec-Orion's Oncology Advisory Board**

Moreover, many rare diseases "are just poorly understood," added Tim Considine, Senior VP, Strategic Development at Recursion Pharmaceuticals. "Clinical endpoints aren't well defined. It involves a whole lot of debate and discussion with authorities and agencies."

Patient enrollment is demanding too, especially for fledgling companies in a hurry, Considine noted. "If you're privately held and VC-backed, there's a time horizon. If it's going to take three years to enroll a 50-patient study, that will generate a horizon for funders trying to get into this space."

Clinical-development plans also need to "make sense for the population," stressed Gary Fortin, VP and Franchise Lead, Severe Genetic Diseases, at bluebird bio. "In a population with 1 in 100,000 births per year, looking for a randomized control trial and a classic approach with endpoints over three years just doesn't make any sense."

## SMOOTHING THE PATHWAY

Insights gleaned from patients and incorporated into development programs can smooth the regulatory pathway for therapies that may present as many hurdles for drug agencies as developers. Dr. Eleanor Perfetto, Executive VP, Strategic Initiatives at the US National Health Council, cited coming FDA guidance documents that address patient engagement and drug development.

"One key piece is helping to define the natural history of the disease and what endpoints are important," Dr. Perfetto told the roundtable. "Talk to patients early. Having that data in your back pocket when you get to that conversation with the agency is really changing the conversation."

As Alain Thibault, Chairman of Simbec-Orion's Oncology Advisory Board noted, part of a regulator's job is to "keep everybody thoughtful." Then, when a company comes to the agency with a rare-disease development proposition, "if you show the pros and cons you've thought through, the agencies know they have a partner to talk with, and that accelerates things," Thibault added.

Industry consortia can help to move the needle. "A lot of organizations are moving this forward with all the regulatory bodies as partners on how different models of clinical research will come together," said Robert Zambon, Senior Director, R&D Data Science Strategy & Innovation, Janssen Research & Development, LLC. "One company saying, 'We want to do X' is interesting. Twenty companies saying they want to do X encourages regulatory agencies to take a position."

## REALISTIC EXPECTATIONS

Patients themselves need to be realistic about how clinical trials operate and what rare-disease therapies can do for them. "The hardest thing to do is to manage expectations," commented Ralph Kern, Chief Operating Officer of BrainStorm Cell Therapeutics.

"Patients all want access, and you can't do a successful clinical trial without some type of clinical-trial enrichment," Kern added. "There have to be inclusion/exclusion criteria. I imagine that's even harder for the very rare monogenetic diseases. Because we want the [patient] support, but we can't have everyone in the trial if it is to be scientifically valid in terms of outcomes."

That also conflicts with varying priorities and agendas along the development chain. Payers are looking for "a very broad representation, so clinical-trial enrichment is really anathema to them," Kern noted. "The agencies want traditional placebo-controlled trials for everything, very large patient samples; they want it overpowered so there's very little risk of type 1 error, they want endpoints that may not be relevant to patients. Investigators love science, and the hardest thing for investigators is to say no: in other words, you can't measure everything."

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**– Ralph Kern, Chief Operating Officer, BrainStorm Cell Therapeutics**

It does not help either if patients are looking for miracles. "Very few patients actually are cured," said Dr. Kimberly Noonan, Founder and Chief Scientific Officer of WindMIL Therapeutics. "If you have high-risk myeloma and your overall survival rate is in the ballpark of 24 months, with a progression freeze of 14 months, what can we hope to do?" Yet there is still considerable value in controlling a disease and in "someone living a life that is unexpected," Dr. Noonan emphasized.

Dr. Perfetto agreed. "If you say to patients, 'We're not near a cure yet; however, you've told me the thing that impacts your life on a day-to-day basis is X, and we can help you with X,' they are usually perfectly happy with that." The key, added Steve Worsley, Chief Business Officer, Sutro Biopharma, is "setting expectations at the outset. You really have to help them understand what you

can deliver short of the cure, and why this makes a difference for them."

## THREADING THROUGH

As was clear from discussions at the round-table, patient engagement should really thread through the entire development process. It also needs to be much more than window dressing, as Seth Fritts, Corporate Engagement at Global Genes, underlined.

"What we find is that organizations say they are patient-focused, yet when you scratch the surface, there's usually no patient engagement at all, or very little," Fritts said. "I can't tell you how many calls I'm on each week where companies are entering a Phase III trial and say, 'Now we're going to engage the community.' And it's really five steps too late. Try to engage early and often, make it a meaningful engagement. Don't go in with, 'Here's what we want to do.' It's, 'How can we work with you to create meaningful change?'"

To avoid regulators falling back on established pathways that may cramp innovation, developers must show that they fully understand not just the science but what really matters to patients, in terms of meaningful, measurable endpoints and outcomes, biomarkers, side effects or quality of life. That will also help convince payers that rare-disease therapies can deliver cost-benefit gains at high-ticket prices.

As Fritts pointed out, early patient engagement reaps benefits all the way down the line. "If you're getting a patient involved, even preclinical, each stage helps with your recruitment, your retention downstream and when you're actually heading in front of the FDA. Then when you're in front of payers, trying to convince them of the value proposition, it's an important message to say, 'We talked to the parents. What was significant to them was: my child can walk.' Now the payers are saying, 'OK, we don't have to send an ambulance every day to take that patient to school.'"

## LOBBYING SUPPORT

Patients can also provide useful support when rare-disease therapies come up against regulatory skepticism or payer restraints. "Think about using your patients to lobby regulators and payers," suggested Joanne Mason, VP, Biomarker Discovery at Cambridge Epigenetix. "Because that's when the message becomes really strong and helps you get through with something quite novel in terms of clinical-trial design. That's the way you really get people to change stuff."

Proactive patient engagement also saves on unnecessary development costs, Perfetto observed. "If you start early, it's less expensive than trying to retrofit something later where the expense really comes in. It's more expensive to find a new endpoint when you know you've got the wrong one."

Defining the exact population and indication for a rare-disease compound, so that it offers a credible prospect both of commercial payback and a workable development program, is another reason to get close to patients from day one. "For me it's about having a study that you can actually execute," commented Ronald Openshaw, CEO of Simbec-Orion.

"We had a client recently who was looking at a subpopulation of hemophilia. And they defined the indication so tightly that they were looking for unicorn patients and then for unicorn physicians," Openshaw explained. "Because actually you need to get that patient definition right, you need to get the physician definition right."

Consequently, the client was "spending so long trying to get those unicorn patients into the study that they actually ran out of money," Openshaw continued. "Then they had to go back to their VCs and say, we really believe this technology works and we actually can dose these subjects. But if you come back to that, you don't have a treatable market."

## DIAGNOSTICS AND TOOLS

Accelerating diagnostic capability is another important part of that effort. "I know a lot of companies think about it after they get something on the market," Zambon commented. "If you start diagnosis development before launch, it actually gets you in the door to talk with patients earlier. You can use social media to find new people with a rare disease who may not otherwise be diagnosed for two or three years, for example."

The wide range of tools now available to gather and analyze patient data and experiences, from qualitative research to electronic health records, wearables and social networks, can help to keep development programs patient-focused while lowering regulatory and practical hurdles.

"Looping in some of the digital technologies, the real-world data that are increasingly available," Zambon elaborated. "More and more wearables are being built or customized specifically for this type of use. That allows you to execute studies better, faster, cheaper. It makes it much easier to recruit a patient who might otherwise say, 'I don't want to be in a research study'."

## CHANGE OF MIND-SET

Patient engagement also requires a fundamental change of mind-set. "Molecule pushers" may believe passionately in expanding the boundaries of science. That needs to be tempered, though, by a medical sensibility that can take in the whole equation.

"I've been in several biotechs, and I can clearly see the difference between molecule pushers, where they're concentrating on the platform and can't see the endpoint, compared with a medical mind-set that's pulling through a very clever technology but translating that to a clinical endpoint," commented Patrick Doyle, CEO of Stelexis Therapeutics.

As Thibault pointed out, clinical-trial proposals may be missing a clearly defined vision of the product benefit. "For this I ask myself what will be the magnitude of that clinical effect? What does the pre-clinical model really tell me? Does it change the disease for the better? How am I going to know whether patients really benefit? What will it look like?"

It helps if companies can put the disease and its needs up front, rather than privileging scientific ingenuity. "For me, as an antibody guy, it took a while to think that antibodies aren't the solution to everything," admitted Aaron Sato, Chief Scientific Officer, Biopharma for Twist Bioscience. "So, really think about the disease and the best way to treat it. And then make sure the patients and everybody in the community understands that what you bring to the table is actually differentiating for that particular disease."

The same goes for convincing venture-capital investors. "We've done our net present value projections for getting funding, and everybody knows what's that like, where you tell yourself what answer you want to receive by adjusting the outcomes," Doyle said. "That's not the right way round, obviously. I think you need an absolutely patient-centric understanding of how you're going to have a differentiated product vis-à-vis the current therapy gold standard."

## PATIENTS AS PARTNERS

It also means addressing patients as genuine partners, as well as learning the associated culture and

language. "Don't just treat your patient population as future customers," Zambon stressed. "Treat them as people and part of the team you're working with. As numerous companies have shown, people who are invested in and feel connected to a company are more likely to have a positive outlook and work with them in the future."

Talking to patients is not the same as talking to regulators, doctors or scientists. Drug developers must learn to listen. "One thing we've done that has been tremendously impactful is, once we've essentially identified a lead, we've invited patients and members of the advocacy group to address the entire company," Considine said. "We can still be abstracted and ivory tower-based, we can define patient populations as severe or not severe. But all these words are entirely meaningless when faced with the reality of patients actually coming and talking to you directly."

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**– Ronald Openshaw, CEO, Simbec-Orion**

Companies should bear in mind that, even if rare-disease patients are desperate for new options, they may well have other, related concerns and needs, such as effective and early diagnosis, treatment economics or the impact on family, friends and work. Patient organizations are a valuable conduit here. They are experts in their field, although some patient groups have more influence than others.

"Don't assume that everybody is at the same level," Considine advised. "This is a real opportunity for collaboration and for a rising tide to float all boats. There are folks like the Cystic Fibrosis Foundation and Cure SMA who are super-sophisticated and really on top of it, to the extent that we can bring other groups along."

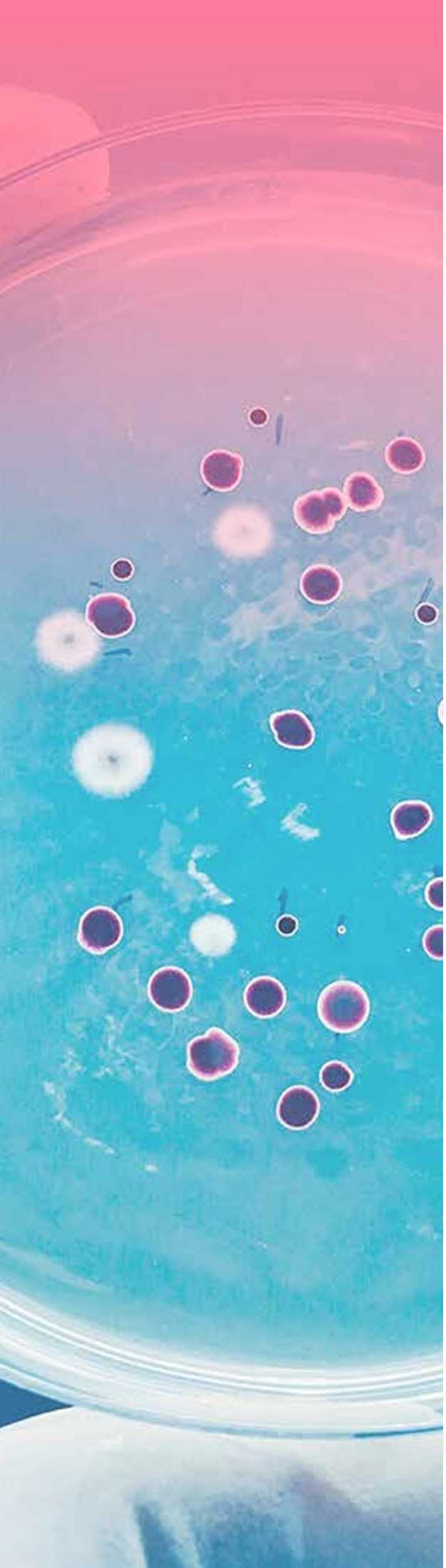
## THE RIGHT INVESTIGATORS

Another important factor in building an ecosystem for rare-disease development is identifying the right principal investigators to run clinical trials and take the innovation message forward. "Young and hungry" may be better than depending on higher-profile PIs, reluctant to step out of their comfort zone until there is more evidence of efficacy and safety.

"Often the biggest influencers are a little more conservative and not necessarily the most willing to be the early adopters," Amitay noted. "What we've been looking for is some profiling: those who are just on the cusp of being a thought leader, and can make their name by being the first one to treat the patient and get that next step."

With the right partners on board and a genuinely patient-centric view of the R&D process from the outset, developers can better negotiate development pitfalls and market-access barriers for rare-disease therapies. They can also generate truly differentiated therapies with tangible benefits for regulators, patients and health care systems.

"When developing a therapy for patients, you really have to go forward with the end in mind," Babler commented. "Go to the end and work backwards." Or, as Fritts put it, "It's really not just about the patient voice; it's about weaving the patient into the DNA of the organization."



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