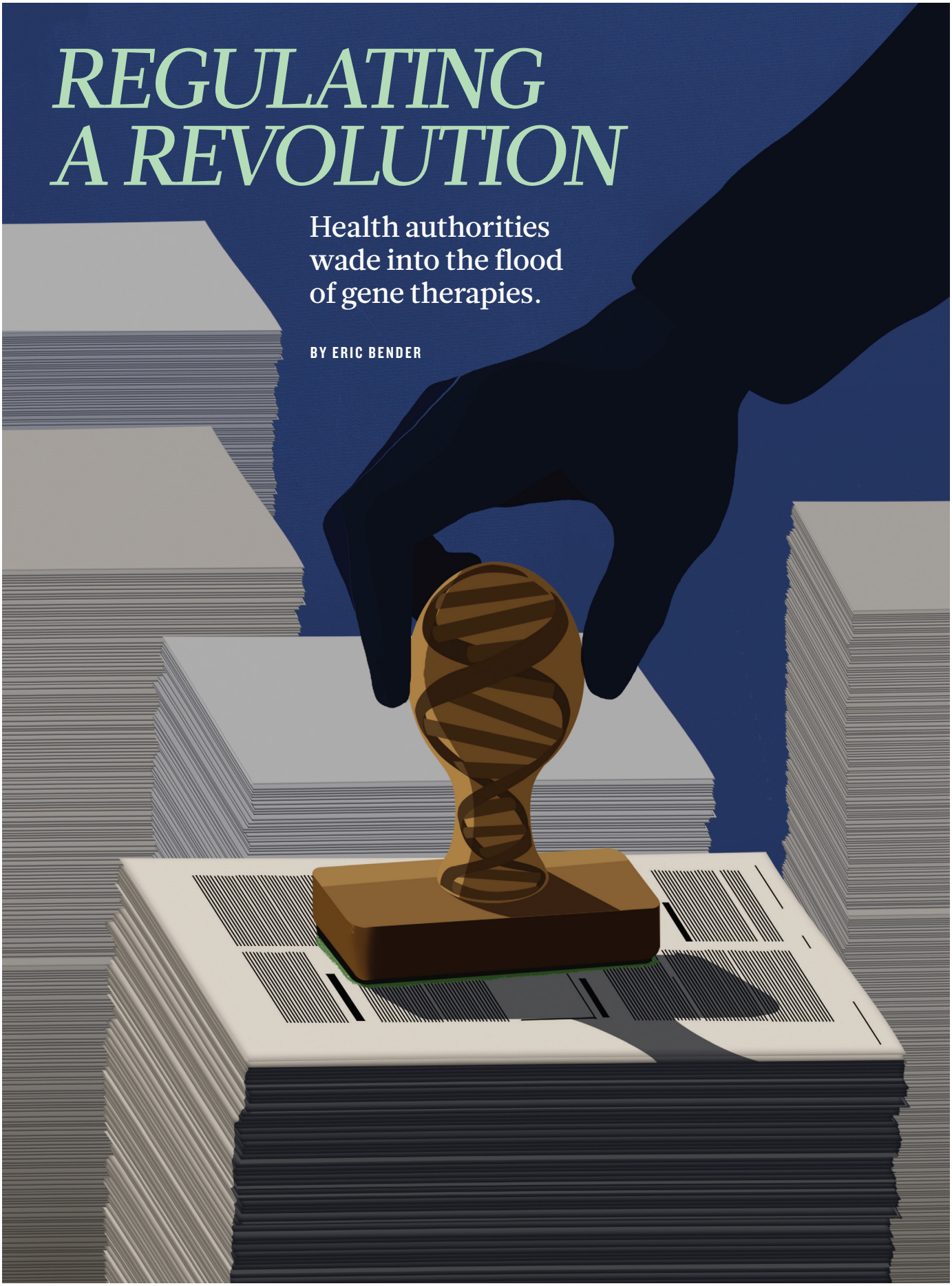
REGULATING A REVOLUTION

Health authorities wade into the flood of gene therapies.

BY ERIC BENDER



SAM FALCONER

For rare genetic diseases that affect the young, such as a neurodegenerative condition called spinal muscular atrophy, gene therapies bring much-needed hope — a chance for the child to live a relatively normal life. But they also raise serious fears about their efficacy and the potential risks that accompany irreversible one-off treatments.

The responsibility for balancing these hopes and fears lies with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Their credentials as gatekeepers to the therapies will soon be tested by a flood of clinical trials. This year the FDA expects to receive about 250 applications to start clinical trials for novel cell and gene therapies, says FDA commissioner Scott Gottlieb.

Faced with rapid advances in biological understanding and therapeutic delivery technologies, the two regulatory agencies are establishing new guidelines for clinical trials and are preparing to make tough decisions about which drugs to approve for marketing. But drawing on their experience with hundreds of earlier studies, the agencies are confident that they can assess gene therapies as effectively as they do any other novel therapeutics.

STANDARDIZING SAFETY

Gene therapy has long been haunted by a very small number of deaths, originally in a 1999 US clinical trial and then in a European study a few years later. However, a series of successful clinical trials over the past decade has created sufficient confidence to move forward with these treatments.

One milestone, in December 2017, was the first FDA approval of an *in vivo* gene-therapy product, for Luxturna from Spark Therapeutics, based in Philadelphia, Pennsylvania. Luxturna treats a rare, inherited eye condition caused by mutations to a gene called *RPE65* that can cause blindness.

Another was the announcement in August 2018 that gene therapies no longer need to be reviewed before clinical studies can begin by a US National Institutes of Health (NIH) advisory committee on recombinant DNA that was created at the dawn of genetic medicine. "There is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable — or that the field still requires special oversight that falls outside our existing framework for ensuring safety," wrote Gottlieb and NIH director Francis Collins in a paper published earlier this year (F. S. Collins & S. Gottlieb *N. Engl. J. Med.* **379**, 1393–1395; 2018).

Even so, such a new class of medicines still poses serious risks. "It's not that people say: 'Oh, it's all safe, don't worry'," says Katherine High, a haematologist and president of Spark. "It's that now we really have some parameters inside which we can work."

She points out, for example, that previous trials have gathered plenty of evidence about therapies such as Luxturna that are delivered by adeno-associated viruses (AAV), especially for systemic administration or for commonly targeted tissues such as the eye. Such AAV therapies often create a short-term immune response in the liver, but this problem can generally be treated by using steroids. "For other target tissues, or for doses that are higher than people have used to date, you may need additional information," High says. "There actually are a wealth of approaches to overcome immune response, and it's a matter of doing the clinical investigations and finding answers."

Barry Byrne, director of the Powell Gene Therapy Center at the University of Florida in Gainesville, says it is far too soon to declare today's gene therapies safe. "There's very limited experience," he cautions, "and there's much more work to be done to understand how these might be used in a variety of conditions."

There are many unanswered questions, such as what happens if a patient who receives a gene therapy delivered by AAV has previously been exposed to some form of the virus, or if proteins created by gene therapies provoke a reaction because the immune system has not been trained to recognize them as 'self', Byrne adds. But he believes that strategies are emerging to avoid or control such immune problems.

> "YOU CANNOT HAVE TWO STANDARDS FOR SAFETY."

New forms of gene-therapy delivery and mechanisms of action sometimes do not perform as expected when they enter clinical studies. In September 2018, Sangamo Therapeutics, based in Richmond, California, reported the initial results of the first trial of gene editing inside the body, for a therapy to treat a rare metabolic disease called Hunter syndrome. The disease, which primarily affects males, causes a host of serious symptoms, and treatment currently requires weekly injections of enzymes. But the initial Sangamo trials failed to demonstrate clinical benefit, and they are now continuing with higher doses.

The regulatory agencies are seeking to provide more guidance on such emerging gene-editing therapies. The EMA and the FDA are working together "to avoid digressions between the two of us", says Hans-Georg Eichler, senior medical officer at the EMA. "In gene therapy in general, we like to believe that we know what the major risks are, but you can never know," Eichler says. "Tomorrow, something totally new could come out of the blue. But that doesn't say that gene therapy shouldn't be made available to patients."

BETTER BY DESIGN

Given the novelty and the potential risks and rewards of gene therapies, their sponsors tend to start working with regulatory agencies early in development — often, very early. "Ideally, you talk with the agencies when you are designing your preclinical development," says Anne-Virginie Eggimann, vice-president for regulation at biotech company Bluebird Bio in Cambridge, Massachusetts. "You can have a general discussion with them on designing that programme, as well as how you see your first-in-human clinical trial." In October, Bluebird Bio submitted a marketing application to the EMA for its LentiGlobin gene therapy, which is designed to treat a rare blood disease called transfusion-dependent β-thalassaemia.

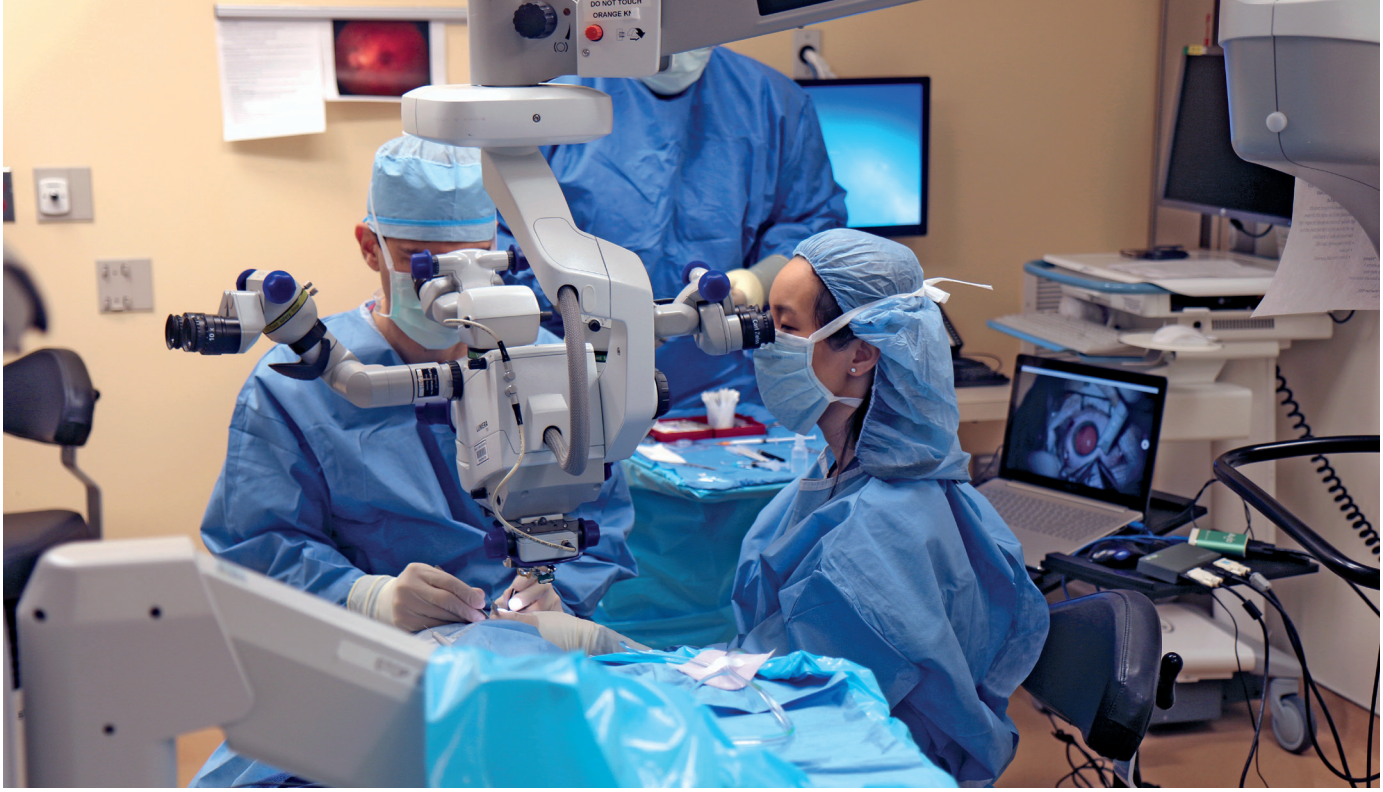
Like LentiGlobin, about 70% of the investigational new drug (IND) applications for gene therapy submitted to the FDA are for rare diseases. Most of these conditions first appear in childhood, and most of those have devastating results. But running a normal clinical trial, which includes large numbers of subjects and a control arm, is often impossible.

"We know that in these situations you have to exercise some flexibility, and that is exactly what we usually discuss with the companies when they come early," says Eichler. "We negotiate and see how can we get the best that is doable in the circumstances."

Given the devastating nature of many rare inherited diseases that strike children, parents often press for accelerated clinical tests. But developers emphasize that lowering safety standards is not an option. "I really understand the urgency of parents whose child has a serious illness," says High. "On the other hand, this is a field where you cannot have two standards for safety."

Trial sponsors and regulatory agencies also worry about how candidate products are manufactured, and how the products might be affected by changes in the manufacturing process over time. Making gene therapies is a highly complex process using biological materials, and extremely high quality must be assured at every step. Most academic labs and biotech startups lack the expertise and the equipment to pull off this feat well enough to produce commercial-grade therapies at a commercial scale. Few biomanufacturing facilities currently provide such services, and these operations are overloaded by the number of therapies now heading towards clinical trials. The difficulties are compounded by the need, as trials progress, to improve the manufacturing processes while keeping the product consistent enough to keep regulators happy.

"Manufacturing is something we will have to think about differently, so we can get it right the first time," says Peter Marks, director of the FDA's Center for Biologics Evaluation and



ED SHIPMAN/MASSACHUSETTS EYE AND EAR

Surgeons use Luxturna, the first *in vivo* gene therapy to be approved by the US Food and Drug Administration, to treat a boy with a genetic eye condition.

Research in Silver Spring, Maryland, which oversees gene therapies.

"Quite often people develop things on the lab bench at a very small scale, and they need to scale up and scale out their thinking," says Jacqueline Barry, chief clinical officer for the Cell and Gene Therapy Catapult, a UK government commercial incubator. "We try to work with them very early on about moving to a good manufacturing process and gathering data that will support the evolution of the product between clinical-trial phases without having to go back and redo studies."

Gene therapies also require follow-up for patients that extends for years after product approval because the long-term effects of these one-time treatments are simply not known. "Clinicians must come to grips with that idea," says Eichler. "As we treat, we must ascertain that the patient experience — good or bad — must somehow be fed back to decision-makers and contribute to long-term knowledge generation."

SEEKING APPROVAL

Europe and the United States have very different legal and regulatory regimes for approving gene therapies. The main difference is that the FDA oversees clinical trials, whereas the EMA does not. To run a clinical trial in any of the 28 members of the European Union, "you have to get approval from a competent authority and from the ethics committee in that member state," says Barry. You also have to get approval for using a genetically modified organism (GMO). However, "the clinical-trial directive and the GMO directive are translated slightly differently in each country," she points out.

Moreover, participation in decisions is structured differently in Europe and the United States, says Eggimann. At the EMA, committee members from various states meet to make decisions about marketing approval. At the FDA, reviewers within the appropriate division follow the drug candidate throughout its entire life cycle.

But the two agencies take similar data-driven approaches to assessing drug safety and efficacy, often actively working together in the process. Several times a year, for example, they hold teleconferences on gene therapies. "We all know there are so many uncertainties in this field, and so many new developments that we want to keep each other abreast of," says Eichler.

> "I DON'T SEE THE AGENCIES AS A BARRIER AT ALL."

Both agencies released major updates to their gene-therapy guidelines in 2018. The FDA, for example, offered its first draft recommendations by class of illness, starting with haemophilia, retinal disorders and rare diseases. It also added draft frameworks for certain manufacturing processes and requirements for long-term patient follow-up. The EMA also completely overhauled its frameworks for gene therapies. For instance, it reworked its guidance on the design, manufacture, characterization and testing of delivery mechanisms.

"As the field gains more and more experience, the broad outlines of what needs to be submitted to initiate clinical studies have come more clearly into focus," says High. "You find that reflected in the guidance documents that the FDA and the EMA provide."

Gene-therapy developers worry that the agencies lack enough experts to deal with the incoming wave of trials for cell and gene therapies, which the FDA estimates will reach 1,000 a year by 2021. "They don't have enough people to handle that kind of workload," says High.

"For the FDA, the issue is always around the budget, and being able to have the appropriate technology and people to deliver on their commitments," says Peter Saltonstall, president of the National Organization for Rare Disorders based in Danbury, Connecticut.

It is still early days for gene therapies, but so far, developers generally give both agencies high marks as partners. "I don't see the agencies as a barrier at all," says Byrne. "They have so many mechanisms for interacting with sponsors now, and they've always approached sponsors as collaborators in bringing these agents forward."

Eggimann agrees. "The regulators have been very supportive of innovation and gene therapy in general, and they are very eager to learn," she says. "Our challenge comes from the novelty of the science, not so much from the regulatory aspects."

Meanwhile, the therapies keep moving forward. Among them is AVXS-101, a gene therapy from AveXis based in Bannockburn, Illinois. AVXS-101 has raised high hopes in early clinical trials for the treatment of spinal muscular atrophy, that devastating neurodegenerative condition that affects children. In October 2018, AveXis applied to both the FDA and the EMA for marketing approval — yet another bridge that gene therapy is crossing on its journey from the lab to the clinic. ■

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