

Granting minors decision-making authority for vaccination also triggers reconsideration of the materials and associated communication needed to ensure that they can make informed decisions. Federal law requires that clinicians provide adult patients and children's parents or legal representatives with a Vaccine Information Sheet before vaccination. Since such materials are written at a 10th-grade reading level, they would most likely require revision if intended recipients were to include adolescents as young as 12 or 14 years of age.

Parental involvement in vaccination decisions remains important. Many vaccine-hesitant parents ultimately agree to vaccination. Yet adolescents need not be harmed by parental decisions that are based on misinforma-

tion or disinformation. Allowing adolescents to consent to vaccination despite persistent parental resistance facilitates access to a medically recommended and evidence-based treatment. It promotes the minor's health, poses minimal personal risk, and offers substantial prosocial benefits, including reinforcement of the norm of vaccination and enhancement of community protection against the spread of dangerous and costly yet preventable diseases. Given such benefits, we believe that states should enact laws that expand both access to vaccines and the rights of minors who are at least 12 to 14 years of age to consent to vaccination.

Disclosure forms provided by the authors are available at NEJM.org.

From the Richard M. Fairbanks School of Public Health and Robert H. McKinney School of

Law, Indiana University, Indianapolis (R.D.S.); the Department of Pediatrics, University of Washington School of Medicine, Seattle (D.J.O.); and the Rollins School of Public Health, Emory University, Atlanta (S.B.O.).

This article was published on June 5, 2019, at NEJM.org.

1. Ethan Lindenberger testifies on why he got vaccinated against his mother's will. C-SPAN. March 5, 2019 (<https://www.c-span.org/video/?c4784277/ethan-lindenberger-testifies-vaccinated-mothers>).
2. Katz AL, Webb SA. Informed consent in decision-making in pediatric practice. *Pediatrics* 2016;138(2):e20161485.
3. English A, Bass L, Boyle AD, Eshragh F. State minor consent laws: a summary. 3rd ed. Chapel Hill, NC: Center for Adolescent Health and the Law, 2010.
4. Centers for Disease Control and Prevention. General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP) (<https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/programs.html>).
5. Ford CA, Skiles MP, English A, et al. Minor consent and delivery of adolescent vaccines. *J Adolesc Health* 2014;54:183-9.

DOI: 10.1056/NEJMp1905814

Copyright © 2019 Massachusetts Medical Society.

Reforming the Orphan Drug Act for the 21st Century

Ameet Sarpatwari, J.D., Ph.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

Congress passed the Orphan Drug Act in 1983 to spur development of drugs to treat rare diseases. Among the law's incentives were exclusive marketing rights for 7 years for the rare-disease indication ("orphan drug exclusivity"), a 50% tax credit for costs associated with the clinical testing of such drugs (reduced to 25% in 2017), and grants for clinical trials. There has since been a marked increase in the number of drugs approved by the Food and Drug Administration (FDA) for rare diseases. Between 1983 and 2017, a total of 487 orphan-designated drugs entered the U.S. market.¹ In 2018, of the new drugs approved, 58% (34 of 59) were for a rare-disease indication.

At the same time, there has been growing concern that the Orphan Drug Act has been subject to gaming. The most recent controversy occurred in December 2018, when Catalyst Pharmaceuticals announced that it would price amifampridine (Firdapse), a treatment for the rare neuromuscular disease Lambert-Eaton myasthenic syndrome, at \$375,000 per year. Although the FDA had approved Catalyst's product as an orphan-designated drug in November 2018, amifampridine was not new. It had been marketed in the United Kingdom since 2010 at an annual price of less than £30,000 (about \$40,000) per patient and was available to U.S. patients with the syndrome for free under an expanded-access

program. In February 2019, Senator Bernie Sanders (I-VT) brought attention to this case and asked Catalyst to explain its pricing decision. The company responded in part by arguing that amifampridine's price is in line with that of other products used to treat rare, severe diseases.

In recent years, several manufacturers have earned hundreds of millions of dollars in annual revenue from rare-disease drugs. The cystic fibrosis treatment lumacaftor-ivacaftor (Orkambi), the idiopathic pulmonary fibrosis treatment pirfenidone (Esbriet), and the spinal muscular atrophy treatment nusinersen (Spinraza) each generated more than \$1 billion in sales in 2018. Such cases raise the question of whether the

Orphan Drug Act should be reformed to better align with patients' needs.

The law's history provides some insight into current controversies surrounding its implementation. Manufacturers could originally qualify for incentives under the law only by demonstrating that there was "no reasonable expectation" of their drug's generating a profit. However, after manufacturers appeared reluctant to open their financial books to the FDA to earn the orphan designation, Congress amended the law in 1984 to create an alternative standard based on disease prevalence: any product intended to treat a condition affecting fewer than 200,000 people in the United States could qualify as an orphan drug.

This threshold may initially have been an adequate surrogate for profitability. The pharmaceutical market has undergone radical changes, however, including dramatically increased prices for rare-disease drugs. In 2017, the 100 best-selling rare-disease drugs had an estimated mean annual cost of more than \$147,000 per patient, about \$116,000 higher than that of the 100 best-selling drugs for other diseases.² On May 24, 2019, Novartis announced that it would price one-time administration of its orphan-designated gene therapy for spinal muscular atrophy, onasemnogene abeparvovec-xioi (Zolgensma), at \$2.1 million per patient.

Orphan designation has also been given to drugs that gained a much broader market after approval. Among all drugs approved for treating rare diseases between 1983 and 2016, a total of 22% (98 of 449) also have a non-rare-disease indication. The rare-disease indication was obtained before or concurrently with the other indication for 45% (44) of these

drugs.³ Concurrent or subsequent approval for a non-rare-disease indication does not nullify incentives awarded under the Orphan Drug Act, which has led to questions about whether manufacturers have "sliced" indications to secure the statutory benefits.

Advances in precision medicine have contributed to this trend. Between 2009 and 2015, of 84 new orphan-designated drugs entering the U.S. market, 15% (13) were for biomarker-defined subsets of more common diseases.⁴ Given the similar pathophysiology of certain conditions — particularly cancers — it is not uncommon for such drugs to be used more widely off-label after approval or to be approved for multiple supplemental indications. For example, although the FDA initially approved the kinase inhibitor dabrafenib (Tafinlar) for treatment of BRAF V600E-mutated metastatic melanoma, a narrow indication, in 2013, the drug had global sales of \$1.2 billion in 2018 in part because of its subsequent supplementary approvals for treatment of other BRAF V600E-mutated cancers.

What are possible solutions? One option would be to revoke the 7-year exclusivity period for drugs that are already available in other markets (as in the amifampridine case) or to curtail it for rare-disease drugs that are used in larger populations of patients after approval or bring in substantial revenue. In the European Union, for example, the 10 years of exclusivity offered to rare-disease drugs designated on the basis of a likelihood of generating insufficient return on investment can be reduced to 6 years if it can be shown that a drug is "sufficiently profitable" after 5 years on the market.

Shortening the exclusivity pe-

riod alone will not affect generic competition for most rare-disease drugs, however. A review of orphan-designated drugs approved since 1984 showed that exclusivity granted under the law has increasingly been outlasted by product-related patents.⁵ Many rare-disease drugs also lack generic competitors because of their small markets or because they are complicated biologic products.

A complementary reform would be to require certain manufacturers to repay the tax credits and research grants they received for developing a rare-disease drug. Such a policy could reframe the incentives provided under the Orphan Drug Act as a minimum guarantee. Were revenue from a drug to exceed a certain level (e.g., \$500 million), its exclusivity would be terminated and the funds that manufacturers would be required to repay could be invested in rare-disease research through the National Institutes of Health. For this provision to be enforced effectively, manufacturers could be required to report annual revenues for orphan-designated drugs to the government.

To ensure that rare-disease drugs are affordable, receipt of incentives could also be conditioned on the manufacturer's setting a value-based price. This price could be determined using a higher quality-adjusted life-year threshold than is traditionally used for non-rare-disease drugs, a strategy used by the Institute for Clinical and Economic Review in the United States and the National Institute for Health and Care Excellence in England, which would help promote more equitable investment in treatments for various diseases. Challenges associated with implementing such a policy would include determining the scope of value for drugs (e.g.,

assessing clinical versus nonclinical costs and benefits) and accounting for the often-greater uncertainty regarding the long-term safety and effectiveness of rare-disease drugs as compared with non-rare-disease drugs at the time of FDA approval. Navigating these challenges is feasible, however, and setting value-based prices would probably improve payer coverage of orphan-designated drugs — a major concern for patients with rare diseases — while motivating manufacturers to preferentially bring transformative products to market.

The status quo increasingly threatens public health, as rising drug prices present growing ac-

cess challenges for patients and indication slicing hampers collection of critical preapproval information on the safety and efficacy of drugs when used in ways that will reflect their most common use in the market. We believe it is time to tackle these problems through sensible, patient-centered reform of the Orphan Drug Act.

Disclosure forms provided by the authors are available at NEJM.org.

From the Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.

1. Orphan drugs in the United States: growth trends in rare disease treatments.

Parsippany, NJ: IQVIA Institute for Human Data Science, October 2018 (<https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf>).

2. EvaluatePharma. Orphan drug report 2018. May 2018 (<https://info.evaluategroup.com/OD2018-SOC.html>).

3. Organisation for Economic Co-operation and Development. Pharmaceutical innovation and access to medicines. November 29, 2018 (<http://www.oecd.org/health/pharmaceutical-innovation-and-access-to-medicines-9789264307391-en.htm>).

4. Kesselheim AS, Treasure CL, Joffe S. Biomarker-defined subsets of common diseases: policy and economic implications of Orphan Drug Act coverage. *PLoS Med* 2017; 14(1):e1002190.

5. Sarpatwari A, Beall RF, Abdurrob A, He M, Kesselheim AS. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. *Health Aff (Millwood)* 2018;37:732-7.

DOI: 10.1056/NEJMp1902943

Copyright © 2019 Massachusetts Medical Society.

Sister First, Doctor Second

Saadia Sediqzadah, M.D.

“I think your brother has schizophrenia,” she said.

I was entering my third year of medical school when I received a phone call from my brother's friend. She shared enough detail to suggest that he had a brewing psychotic illness, whose signs were so insidious that we hadn't initially noticed them. In retrospect, his was a textbook case of schizophrenia: a 21-year-old man in his first year of university, slightly paranoid but holding it together enough to get by — until he couldn't anymore. He believed that he was being followed on campus and called his friend terrified, and then his friend called me. I decided I needed to do something; I had to save my brother. I packed my suitcase and headed home. The plan was to get him a psychiatry referral and start him on medications. Easy, right?

But it wasn't. What followed was a 2-year dance between my

brother and me. I would step in to help, and he would step back, insisting he didn't need it. For our family, the most challenging symptom of my brother's schizophrenia — and the most significant barrier to appropriate medical care — has been his lack of insight. The delusions and voices are real for him — why would he seek help when he doesn't think there's a problem?

A narrow window opened one day when he mentioned that he would consider undergoing an assessment. Knowing that the window might quickly slam shut again, we took him to a mental health emergency department to expedite the process. A psychiatry resident referred him to an outpatient adolescent psychosis program. When my brother hadn't heard back from that program after a week, he (astonishingly) called the clinic to follow up.

He was informed that the resi-

dent had made a mistake: the referral form had to be filled out by his family doctor, not a psychiatry resident. By that point, my brother's paranoia had made him wary of our family doctor, and he decided not to pursue the assessment further. The referral and my brother's case thus slipped through the cracks; an institutional barrier had cost him the treatment he was seeking of his own volition. At times, I kick myself for not taking matters into my own hands at that point, but as a medical student I didn't yet understand how the system works. If I'd known then what I know now, I could have gotten my brother through the door. I would call the clinic to explain his lack of insight. I would express my sense that we had a narrow window of opportunity to engage him in treatment and would request leeway in his case. I would ask his family doctor for her billing