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Feds' Biotech Enforcement Efforts Are Too Heavy-Handed

By **Douglas Hallward-Driemeier, Laura Hoey and Alison Fethke** (May 13, 2024, 5:26 PM EDT)


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A recent federal government settlement involving California-based biotech Ultragenyx is the latest example of how the U.S. Department of Justice's heavy-handed approach to enforcement of the federal Anti-Kickback Statute can punish and deter conduct that benefits patients and poses little risk of fraud and abuse.

The December 2023 Ultragenyx False Claims Act settlement agreement resolved claims — initially brought by a whistleblower — concerning a genetic testing program sponsored by Ultragenyx.[1]

According to the government's allegations, Ultragenyx sponsored a testing program through an undisclosed testing laboratory to test for genes associated with a rare condition known as X-linked hypophosphatemia.

Ultragenyx allegedly covered the cost of the test for eligible patients and paid to receive certain testing data back from the lab, some of which it used to market its XLH-indicated product, Crysvita, to prescribers.[2]

After intervening in the case for the purposes of settling, the DOJ contended that this conduct ran afoul of the AKS and gave rise to False Claims Act violations.

The settlement comes amid increasing DOJ scrutiny of sponsored genetic testing programs. On Feb. 26, fellow biotech BioMarin Pharmaceutical Inc. announced that it had received a subpoena from the DOJ requesting certain documents related to the sponsored testing for two of its therapies, Vimizim and Naglazyme.

Also in late February, the acting U.S. attorney for the District of Massachusetts, Joshua Levy, indicated that his office was actively monitoring "kickback schemes involving genetic testing[.]"[3]

In this uncertain landscape, the settlement agreement has taken on outsize precedential importance among industry participants who lack clear guidance on program compliance and are largely left to guess at the government's primary concerns.

And the uptick in enforcement activity in this space is playing out against the backdrop of the U.S. Food and Drug Administration's continued efforts to incentivize pharmaceutical companies to deploy

innovative methods to discover and commercialize rare disease therapies.

The settlement agreement also illustrates a trend in AKS enforcement in which the government seeks to have it both ways by insisting that advisory opinions issued by the U.S. Department of Health and Human Services Office of Inspector General apply only to the parties and facts at issue, while later using that same advisory opinion as a cudgel to impose civil or even criminal liability if an industry participant is out of step with its limited, often ambiguous, guidance.

Rather than embarking on a campaign of regulation through enforcement actions and settlement agreements, the government — namely, the DOJ and HHS OIG — should educate industry participants on practical, reasonable steps they may take to ensure sponsored testing programs can be maintained in a form that continues to benefit patients, providers and sponsors while remaining compliant with fraud and abuse laws.

Emergence of Sponsored Testing Programs

With the growing trend toward personalized medicine in the provision of healthcare, sponsored genetic testing programs have increased in prevalence.[4]

In theory, sponsored genetic testing offers a win-win-win: Patients get access to a test that may lead them to a definitive diagnosis and a more effective treatment, resulting in better health outcomes; providers gain access to information highly relevant to their treatment decisions — information that they may not otherwise have had absent the testing program; and sponsors are able to better connect their therapies with the patients those therapies are approved to treat.

Moreover, the programs can bolster research efforts by providing the company valuable information about genetic variants implicating the disease state and can help recruit patients for clinical studies.

These several benefits also help to advance the FDA's goal of accelerating the discovery and development of novel cell and gene therapies indicated for rare diseases, an aim the agency has underscored as a critical priority in recent months and that Congress has encouraged through the grant of special exclusive marketing rights.

For example, the FDA formally solicited industry feedback regarding the challenges and opportunities in rare discovery[5] and, in recent comments by Peter Marks, director of the agency's Center for Biologics Evaluation and Research, indicated that accelerated approval for gene therapies aimed at rare diseases will be the norm because "[i]f we don't lean into accelerated approval, we're going to leave a lot of patients behind."[6]

Further, in September 2023, the FDA launched a pilot program to enhance communication between sponsors of rare disease products and agency staff, in the hopes of addressing clinical development issues.[7]

Another reason for sponsored testing programs' emergence in the U.S. has been most commercial and government payors' imposition of significant coverage hurdles for genetic testing for eligible rare disease patients.

In many instances, a patient suffering from a genetic condition will spend years searching for a correct diagnosis, and access to life-saving therapy is generally dependent on a confirmatory genetic test. That

has created a void in the U.S. healthcare system that sponsoring manufacturers have increasingly stepped in to fill.

Notwithstanding sponsored testing programs' potential to improve health outcomes for rare disease patients, the programs have drawn the attention of FCA whistleblowers and federal enforcement agencies, which have argued that they may lead to AKS and FCA violations.

HHS OIG Advisory Opinion 22-06 and the Ultragenyx Testing Program

Until the Ultragenyx settlement, however, the only specific guidance concerning sponsored testing programs was a favorable Advisory Opinion 22-06[8] issued in April 2022 by the OIG, the government watchdog that interprets and enforces the AKS and other healthcare fraud and abuse laws.

Advisory Opinion 22-06 cited three primary factors in determining whether the sponsored testing program under review posed a sufficiently high AKS risk to warrant prosecution:

- Whether features of the testing program make it likely to lead to "overutilization or inappropriate utilization" of the sponsor's treatment, including, most significantly, the nexus between the genetic test and a product order;[9]

- Whether the testing program is likely to "skew clinical decision making or raise concerns regarding patient care";[10] and

- The presence of safeguards in place to prevent the use of the testing program as a "marketing or sales tool to induce physicians to order additional items or services" or to target specific providers or patients.[11]

A close read of the Ultragenyx settlement agreement and government press release suggests that Advisory Opinion 22-06 and its factors provided a playbook for the DOJ's prosecution of the matter.[12]

But, as discussed more fully below, the concerns animating the factors in Advisory Opinion 22-06 do not apply across the board to all sponsored testing programs — particularly those programs which, like Ultragenyx's, involve testing for rare or ultra-rare diseases that have only one FDA-approved therapy, and thus operate in a noncompetitive market.

First, the risk of inappropriate utilization — a factor that Advisory Opinion 22-06 evaluated against the backdrop of the nexus between paying for the test and its result and the clinical treatment decision.

The government's thinking behind this factor appears to be that the closer the link between the genetic test result and a prescription resulting from diagnosis, the more likely the testing program could lead to unnecessary federal reimbursement. This point is reiterated in the Ultragenyx settlement agreement and press release.[13]

But this factor will often work in the opposite direction: In many cases, the closer the nexus between the test and a definitive diagnosis, the less the risk of overutilization, because a negative diagnosis would presumably eliminate the need for the therapy for the patient, and a positive diagnosis could provide strong, even potentially conclusive, evidence that the therapy is medically necessary for the patient. Neither Advisory Opinion 22-06 nor the settlement agreement address that dynamic.

Second, though the risk of skewing medical decisions may be a legitimate government concern for some testing programs, that worry is largely irrelevant in circumstances where there is only one FDA-approved therapy for a given disease and the test definitively identifies such disease.

The officials quoted in the DOJ's press release highlight this factor as a primary enforcement goal,[14] but neither the press release nor the settlement agreement explains why the particular testing program at issue in the Ultragenyx program posed any risk of skewing clinical judgment.

Nor do the press release or settlement agreement explain how the Ultragenyx program might undermine patient safety or quality of care. Indeed, it seems more likely that the program delivers a net benefit for patient safety and quality of care, by shortening time to diagnosis and decreasing the chance that inappropriate or ineffective treatments are selected.

Third, the DOJ has yet to explain how the presence of safeguards to prevent the use of the testing program as a marketing or sales tool or as a means to target ordering providers or patients relates to whether a crime has been committed under the AKS.

Perhaps the clearest takeaway from Advisory Opinion 22-06 and the settlement agreement is that HHS OIG and DOJ view a sponsoring company's sales team's use of a testing program or the data therefrom to target prescribers as off-limits under the AKS.

While the involvement of a company's sales force may well reflect the company's entirely legitimate interest in selling its product, that is not, of course, a crime. And it is unclear why involvement of the sales force in activities that are otherwise medically appropriate and socially desirable — such as helping ensure that doctors have the information that allows them to accurately diagnose and treat their patients' debilitating diseases — converts that activity into a crime.

While there are some legitimate fraud and abuse concerns around this third factor in conjunction with the first two factors — overutilization or skewing prescriber decisions — that concern is, again, heavily mitigated in a program operating in a market where there is only one FDA-approved product and the manufacturer does not market or promote its product for patients who have not obtained a definitive diagnosis.

In a noncompetitive market — which a significant proportion of currently available sponsored testing programs are in — the so-called marketing activity about which the government professes concern is necessarily focused on provider education and connecting providers to the most knowledgeable sources of information about a rare disease, not trying to convince the provider to treat the patient's condition with Therapy A instead of Therapy B or C or D.

The Ultragenyx settlement agreement appears to take a sledgehammer to these important nuances, ostensibly mandating that a sponsor company must blind its sales and marketing team to the identity of the ordering provider to ensure compliance, regardless of the type of testing program or market.

Such a bright-line rule seems overly rigid. And it opens the door to more questions around whether and how sponsors may receive and use testing data and remain in compliance.

For example, if Ultragenyx's medical personnel had access to the data and had called on the ordering providers instead of its sales representatives, would the DOJ have had the same concerns?

Difficult to say. But this is one of the many questions industry participants will likely need to wrestle with to ensure compliance.

DOJ AKS Enforcement May in Some Cases Harm Patient Quality of Care

What has emerged in the wake of Advisory Opinion 22-06 and the Ultragenyx settlement is a regulatory landscape that may erode the quality of care for rare disease patients, all while doing no favors to providers and payors.

Due to rapidly advancing discoveries and clinical achievements in the rare disease space, providers may not know much about the rare condition potentially at issue or have the tools to make a definitive diagnosis.

Provider education facilitated by sponsored testing programs can help narrow that information gap. Eliminating or hollowing out sponsored testing programs would mean less education for providers, not more — and that ultimately harms patients.

In the long term, sponsored testing programs can also benefit commercial and government payors by getting patients on the most effective treatment earlier. Currently, it takes a rare disease patient an average of 4.8 years to arrive at the correct diagnosis.[15]

Bringing that average down and offering providers education on the only, or one of the few, available treatment options will ease the financial burden on payors by reducing their spending on treatments that do not work or do not work as well, and on treatments for uncontrolled symptoms and other related health issues that can be caused by delayed diagnosis or treatment.

Sponsored testing programs are not the only initiatives designed to help rare disease patients that have been swept up by the government's overly broad interpretation of the AKS.

Under the DOJ's approach in recent cases, it doesn't matter whether the drug manufacturer had a corrupt or even reckless intent in offering a type of patient support. And it apparently didn't matter in the Ultragenyx case; nothing in the settlement agreement suggests that Ultragenyx developed the testing program to gain an improper advantage for its treatment at the expense of other treatments, or that it intended or suspected the program would result in medically unnecessary federal reimbursements.

This expansive interpretation untethers the AKS from its legislative purpose — to root out healthcare fraud and abuse — and deters industry actors from undertaking any initiative to provide assistance to patients unless the government has explicitly blessed that initiative through an advisory opinion.

This stifles innovation, hamstrings the FDA's mission for advancements in rare disease and ultimately undermines patient care. Moreover, given the current barriers to accessing coverage for genetic testing at most payors, the government's approach restricts testing access to only those who can afford to pay for the tests out of pocket.

Opportunity for Thoughtful Government Engagement on Testing Programs

Sponsored testing programs remain an important diagnostic tool in a world where one in 10 people, around 50% of whom are children, suffer from a rare disease, and where 95% of rare diseases still lack

an FDA-approved treatment.[16]

Instead of engaging in enforcement activity that could risk regulating the testing programs out of existence, and potentially stifle development of precision therapies, there is an opportunity for thoughtful government engagement with industry participants.

The government could solicit feedback from providers and patients on the programs' administration and their practical impact on clinical decision making and patient health. And it could issue informal guidance providing a framework for industry participants to maintain these programs in a form that is compliant with fraud and abuse laws but also capable of delivering meaningful benefits to the key stakeholders.

Two areas in need of further clarification by the HHS OIG or by courts reviewing HHS OIG advisory opinions include:

- Whether and how compliance considerations might change for testing programs operating in a competitive market versus a noncompetitive market; and

- The types of data that sponsor companies can receive from sponsored testing programs, and how such data can be utilized and shared within the company.

Sponsored testing programs may well deliver a benefit to the sponsor company. But that alone, without some hint of corrupt intent on the part of the sponsor, should not be a justification for limiting access to genetic tests to only those patients who can afford to pay for them out-of-pocket.

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[1] Settlement Agreement in United States ex rel. Ruggiero v. Ultragenyx Pharmaceutical Inc., Civil Action No. 1:21-cv-11176-ADB (dated Dec. 19, 2023), available at: https://www.justice.gov/d9/2023-12/usa_v._ultragenyx_-_settlement_agreement.pdf ("Settlement Agreement").

[2] Japanese pharmaceutical company Kyowa Kirin assumed control of the rights to the Crysvita brand in April 2023. Press Release, "Kyowa Kirin North America Assumes Commercial Leadership Role for CRYSVITA® (burosumab-twza) Injection in North America," Kyowa Kirin (April 27, 2023), available at: https://www.prnewswire.com/news-releases/kyowa-kirin-north-america-assumes-commercial-leadership-role-for-crysvita-burosumab-twza-injection-in-north-america-301809690.html. The

Settlement Agreement's Covered Conduct recital says that the settlement covers the period from February 1, 2019 through May 30, 2022.

[3] Ben Penn, "Once-Renowned US Health Fraud Unit in Boston Gets an Inside Edge," Bloomberg Law (Feb. 27, 2024), available at: https://www.bloomberglaw.com/product/blaw/bloomberglawnews/bloomberg-law-news/BNA%200000018d-b278-d555-abbf-b3fa71430001.

[4] As of the date of this article, there were over 30 different genetic testing programs advertised on diagnostic laboratories Invitae's and PreventionGenetics' websites. The programs are offered through partnerships with over 20 different sponsors, including manufacturers and non-profit organizations.

[5] "Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; Request for Information," FDA (Sept. 21, 2023), available at: https://www.federalregister.gov/documents/2023/09/21/2023-20452/scientific-challenges-and-opportunities-to-advance-the-development-of-individualized-cellular-and.

[6] Zachary Brennan, "Accelerated approval will be 'the norm' for gene therapies, FDA's Peter Marks says," Endpoints News (Feb. 27, 2024), available at: https://endpts.com/accelerated-approval-will-be-the-norm-for-gene-therapies-fdas-peter-marks-says/.

[7] Press Release, "FDA Launches Pilot Program to Help Further Accelerate Development of Rare Disease Therapies," FDA (Sept. 29, 2023), available at: https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies.

[8] OIG Advisory Opinion No. 22-06, HHS-OIG (April 6, 2022) ("AO 22-06"), available at: https://oig.hhs.gov/documents/advisory-opinions/1028/AO-22-06.pdf.

[9] AO 22-06, at 7-8.

[10] Id. at 8-9.

[11] Id. at 9.

[12] See, e.g., Recital D of the Settlement Agreement, which specifically references AO 22-06.

[13] See e.g., Recital G of the Settlement Agreement ("Ultragenyx understood that, in some cases, a positive genetic test for a genetic mutation consistent with XLH would be required for an insurer (including Medicare or Medicaid) to reimburse Crysvita prescribed to a patient, or for a healthcare provider ("HCP") to make a definitive diagnosis of XLH and prescribe Crysvita.").

[14] Press Release, "Pharmaceutical Company Ultragenyx Agrees to Pay $6 Million for Allegedly Paying Kickbacks to Induce Claims for its Drug Crysvita," DOJ (Dec. 21, 2023), available at: https://www.justice.gov/usao-ma/pr/pharmaceutical-company-ultragenyx-agrees-pay-6-million-allegedly-paying-kickbacks-induce ("Kickbacks, in whatever form, have no business in our federal healthcare system. We are always on the lookout for financial kickbacks that can improperly influence medical decisions, undermine patient care, and cause waste to federal healthcare programs" and "A primary focus of this effort is the pursuit of kickback schemes that can allow third parties, such as

pharmaceutical manufactures, to insert themselves into the doctor-patient relationship and potentially undermine the objectivity of treatment decisions by physicians and patients.").

[15] RARE Disease Facts, Global Genes, available at https://globalgenes.org/rare-disease-facts/.

[16] RARE Disease Facts, Global Genes, available at https://globalgenes.org/rare-disease-facts/.