## Title

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# FDA Approval Based on Novel Surrogate Endpoints: Lessons From the Voluntary Withdrawal of Voxelotor in Sickle Cell Disease

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To the Editor,

On September 25, 2024, Pfizer Inc. announced the voluntary withdrawal of Oxbryta (voxelotor), a hemoglobin S polymerization inhibitor, in all markets where it is approved and the discontinuation of all active clinical trials worldwide [1]. Voxelotor received accelerated US Food and Drug Administration (FDA) approval in 2019 for patients 12 years of age and older with sickle cell disease. The approval was based on the HOPE trial (NCT03036813) [2]. HOPE showed the drug was capable of an increase in hemoglobin from baseline of more than 1.0 g/deciliter at week 24 (1.1 g/dL), which is the primary endpoint. The only clinically relevant endpoint of the study was vaso-occlusive crises, which was reported as a secondary outcome. The drug was developed by Global Blood Therapeutics, a biopharmaceutical company, which was acquired by Pfizer in 2022. In 2024, Pfizer's stated reason for withdrawal was due to an imbalance in vaso-occlusive crises and fatal events, where the overall benefit no longer outweighed the risk of the drug. Further information has not yet been provided.

A careful review of the regulatory history of voxelotor reveals concerns regarding the product, present since the initial submission. Specifically, how did a 1.0 g/dL rise in hemoglobin come to constitute a surrogate endpoint thought reasonably likely to predict benefit? The case of voxelotor raises lingering questions regarding the FDA's process for soliciting novel, surrogate endpoints from companies, and the timeliness of post-marketing studies to adjudicate benefit.

Over the last decade, the US FDA has encouraged the development of novel surrogate endpoints by sponsoring companies, and engages with sponsors to provide guidance regarding feasibility and acceptability. Novel biomarker endpoints are often developed for specific diseases—for instance, those lacking good treatment options or for agents with new mechanisms of action. One example is the recent approval of Xolremdi (mavorixafor) for WHIM syndrome, a rare genetic disease, that was based on improvement in absolute neutrophil count as a primary endpoint.

In the case of voxelotor, the FDA raised concern as early as the initial submission that a small rise in hemoglobin may not be considered a surrogate reasonably likely to predict clinical benefit [3]. The sponsor responded with data from 2 trials, STOP2 (NCT00006182) [4] and SIT (NCT00072761) [5], that studied prophylactic transfusions in preventing stroke and silent cerebral infarction, respectively. The sponsor's argument was that the rise in hemoglobin is a surrogate for the reduction in transcranial doppler (TCD) flow velocity, and TCD velocity is a predictor of stroke and silent infarct risk. The FDA requested further evidence for the chosen cut-off (1 g/dL) and study duration.

At the time of approval, the logic behind utilizing a 1 g/dL hemoglobin rise was dubious. The American Society of Hematology partnered with the FDA and engaged 7 panels of clinicians, investigators, and patients in 2019 to develop

a consensus recommendation for clinical trial endpoints in sickle cell disease trials [6]. The consensus document noted that there are limited data to suggest that TCD measurement changes after starting therapy predict stroke risk and advise caution in interpreting change in TCD measurements. In other words, it is undetermined whether normal TCD velocities after therapy are associated with lower incidence of stroke compared to persistent abnormal TCD velocities. There are also no data to suggest that decreasing TCD velocity from normal to slightly lower velocity adds benefit.

The FDA's acceptance of hemoglobin as an endpoint contains multiple weak links of association: Does a modest Hgb increase change TCD velocity? Does a modest change in TCD velocity change stroke risk? And, does a change in stroke risk in an unselected population, not enriched for high stroke risk as in STOP and SIT, translate into improvement in quantity and quality of life for the overall population? Using hemoglobin as a surrogate for TCD essentially meant linking an unproven surrogate to an uncertain one.

The threshold of 1.0 g/dL of hemoglobin improvement and the interval of 24 weeks were also problematic and arbitrary. Laboratory tests that are repeated tend to regress to the mean, even without effective intervention. In fact, 9% of patients in the placebo arm had a hemoglobin response at 24 weeks.

We see four lessons in the case of voxelotor. First, greater transparency and increased stakeholder involvement in the evidence behind the initial acceptance of a novel surrogate endpoint should be solicited by the agency. The process of reviewing and accepting a 1.0 g/dL hemoglobin rise remains opaque and did not appear to incorporate any input from the medical community and patients. No advisory committee was commissioned on the topic, and notably, no physician or patient was allowed to present the case against the endpoint.

Second, the post marketing commitment appears inadequate. The FDA's accelerated approval requirement to the sponsor only required completing a phase 3 randomized trial (HOPE Kids 2) in patients aged 2 to $<15$ with a change in TCD velocity at 24 weeks as the primary outcome. In the absence of a sizable safety signal, this endpoint could itself have concealed a lack of clinical benefit or even harm from the product.

Third, the voluntary withdrawal has lacked transparency. Does voxelotor increase death? Patients deserve to know. Voxelotor has been on the market with regulatory approval for 5 years with many patients exposed to the drug and potential side effects. The press release only alludes to "imbalance in vaso-occlusive crises and fatal events requiring further assessment." Pfizer and the FDA should share the new data that has come out since accelerated approval in 2019 leading to withdrawal.

Fourth, voxelotor should be considered a sentinel event for the FDA. The agency should commission an external review asking what processes may be improved in the future as they consider novel surrogates. How can the agency avoid the risk of exposing an at-risk and vulnerable population (children with sickle cell disease) to a product with no established clinical value, high cost, and potential to cause harm. Finally, it took 5 years to withdraw this product. Could this time span have been reduced?

The one-time acceptance of a novel surrogate marker that is later invalidated has longstanding and significant downstream effects. Response rate is now widely used for accelerated approval in hematology despite the lack of evidence as a surrogate marker. This has resulted in the withdrawal of drugs such as romidepsin in peripheral T-cell lymphoma and idelalisib in non-Hodgkin lymphoma.

The FDA publishes a list of surrogate endpoints and encourages early engagement of sponsors when designing trials with novel biomarker endpoints for drugs with novel mechanisms of action. Based on the withdrawal of voxelotor, the process of accepting novel surrogate endpoints for regulatory approval would benefit from greater transparency and increased stakeholder engagement that includes patients and clinicians. The responsibility of drug manufacturers does not end with the voluntary withdrawal of a drug. The newly generated data suggesting greater harm than benefit should be publicly shared. The FDA should institute a process of reviewing the operational problems leading to the use of novel surrogate endpoints that fail.

### Ethics Statement

In accordance with 45 CFR §46.102(f), this review was not human participants research and was not submitted to an institutional review board and did not require informed consent procedures.

### Conflicts of Interest

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, and Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube, and Substack. M.K. declares no conflicts of interest.

### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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