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Beware of BIMO: Complete Response Letter, Warning Letter and Shareholder Lawsuit Follow FDA Data Integrity Findings

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Applied Therapeutics, a clinical-stage biopharmaceutical company, is under heightened scrutiny following the issuance of a November 2024 Warning Letter[1] from the US Food and Drug Administration (FDA) on the heels of a routine preapproval bioresearch monitoring (BIMO) inspection.[2] FDA's BIMO program is designed to ensure the integrity of data submitted to FDA, and to protect the rights, safety and welfare of research participants. The company also now finds itself the the subject of two shareholder lawsuits and recent leadership changes. This quick cascade of events stems from the BIMO inspection uncovering critical issues with the company's AT-007-1002 trial of its product candidate, govorestat, in children ages 2 – 17 for the treatment of galactosemia.

Brief history of events surrounding the govorestat NDA

In support of its New Drug Application (NDA) for govorestat for the treatment of galactosemia, Applied Therapeutics relied on data from its phase 3 ACTION-Galactosemia Kids trial in children ages 2 – 17 with galactosemia and its phase 1/2 ACTION-Galactosemia trial in adult patients with galactosemia, as well as preclinical studies.[3] On January 3, 2024, the company announced that its NDA was under priority review by FDA. In March 2024,[4] the company announced that FDA extended the review period to provide additional time to review supplemental analyses of data the company had previously submitted.

FDA proceeded to conduct a routine preapproval BIMO inspection that concluded in May 2024, and reviewed Applied Therapeutics' AT-007-1002 trial (NCT 04902781, the ACTION-Galactosemia Kids trial) for Good Clinical Practice (GCP) compliance. At the conclusion of its inspection, FDA issued an FDA Form 483, to which the company responded on May 9, 2024. As documented in the 483, FDA found during the inspection that a dosing error occurred during the dose escalation phase of the trial. On November 27, 2024, the company announced it had received a Complete Response Letter (CRL) from FDA for its NDA, and shortly thereafter it received a Warning Letter, which the company disclosed on December 2, 2024. As stated by the company, the CRL indicated that FDA had completed its review of the application and made the determination that it was unable to approve the NDA in its current form, citing deficiencies in the clinical application.[5] On December 17, 2024, shareholders brought suit against the company.

FDA Warning Letter expands scope of FDA Form 483

The Warning Letter to Applied Therapeutics identified critical issues, specifically regarding dosing error, data integrity and protocol adherence issues, including deficiencies tied to 21 CFR Part 11,[6] which governs electronic records, systems and signatures of FDA-regulated entities (see our recent alert on the updated Part 11 FDA guidance). As a brief refresher, FDA's updated Part 11 guidance, released in August 2024, emphasizes heightened standards for ensuring electronic data reliability, audit trails and controlled access. Key compliance areas, also noted in the Applied Therapeutics Warning Letter, include:

1. Preserving audit trails.
2. Maintaining data integrity.
3. Managing vendors to ensure they also comply with Part 11.

Highlights of the 2024 Warning Letter to Applied Therapeutics include:

- **Protocol deviations – dosing error**: During the dose-escalation phase of the AT-007-1002 trial, FDA noted that at least 19 patients at one inspected clinical site received doses lower than those specified in the trial protocol. Between March and June 2021, clinical sites administered the mislabeled product, which was a concentration approximately 80% lower than the dose stated in the protocol. The company reported the dose listed in the protocol as the administered dose and not the actual dose. As stated in the Warning Letter, the company failed to provide FDA with a description or analysis of the nature and extent of the dosing errors related to the mislabeled product, which is critical in evaluating the safety and effectiveness of govorestat. FDA noted in the Warning Letter that the company's failure to provide critical information raised "significant concerns about the validity, reliability, and integrity of the data."

  Interestingly, this finding was not included in the FDA Form 483 issued to Applied Therapeutics, and thus the Warning Letter expanded the scope of the BIMO inspection observations.[7]

- **Data deletion by third-party vendor**: A third-party vendor contracted by Applied Therapeutics deleted certain electronic records, including associated audit trails, for all 47 study participants enrolled in the AT-007-1002 trial at all clinical sites just two days after FDA preannounced its inspection of one of the clinical sites. The deleted data included certain electronic clinical outcome assessments performed for measuring primary and secondary efficacy endpoints. As a result, FDA could not access, copy and verify records and reports for certain electronic data collected and maintained in this system.[8] The FDA Form 483 was limited to 11 subjects at a particular clinical site, but the Warning Letter expanded this, noting this occurred for all 47 participants.

  As sponsors should be aware, even if they contract any services out to a third-party vendor – such as a clinical research organization – the sponsor is ultimately responsible for the conduct of the clinical trial and, therefore, the actions of third-party vendors. This magnifies the importance of sponsors continuously monitoring their third-party vendors for regulatory compliance and ensuring that appropriate access controls are in place.

Shareholder class-action lawsuit

Shortly after the issuance of the FDA Warning Letter, shareholders brought suit[9] against Applied Therapeutics on December 17, 2024, in a New York federal court. A second shareholder suit was brought in the Southern District of New York on December 27, 2024.[10]

The class-action lawsuits allege that the company ultimately failed to disclose the risks related to govorestat's approval and misled investors into believing that govorestat had a stronger chance at receiving FDA approval than it actually did. Specifically, the lawsuits allege that the company did not publicly disclose the dosing error or vendor data deletion issue and continued to issue positive press releases related to govorestat – including highlighting the drug's effectiveness in another indication and discussing its commercial plans for the drug.

The lawsuits, which seek to represent investors who purchased or acquired Applied Therapeutics' securities between January 3, 2024, and December 2, 2024, claim that the stock price dropped significantly once FDA's findings became public, causing investor losses.

Leadership change

Amid these challenges, Applied Therapeutics announced on December 20, 2024, the resignation of its founder and CEO, Dr. Shoshana Shendelman.

Key takeaways for sponsors of clinical trials

These events underscore FDA's continued focus on data integrity issues, its increasing focus on clinical trial conduct and the importance of publicly disclosing material events that could impact a product's ability to receive regulatory approval.

In light of these recent events, sponsors should consider the following lessons learned from the Applied Therapeutics Warning Letter, CRL and lawsuit:

- **Proactively disclose risks**: Companies should sufficiently disclose in their Securities and Exchange Commission filings, press releases and investor communications the risks associated with running clinical trials – including material deviations from protocols, data integrity concerns, vendor compliance issues and other issues that could impact the safety, efficacy and ultimate approval of a drug candidate. Such disclosures should be truthful, accurate and not misleading.
- **Provide timely updates on material developments**: Companies should provide timely updates when material developments occur – especially those that might be unexpected. Delayed disclosures, insufficient disclosures or omission of such disclosures can lead to shareholder litigation and loss of investor trust.
- **Establish robust internal controls and oversight over third-party vendors**: Companies should establish robust internal systems to monitor compliance with clinical trial protocols, vendor oversight and adherence to FDA regulations, including 21 CFR Part 11.
- **Cooperate with regulators during inspections**: Companies should be prepared to permit regulatory authorities on site and ensure that they have access to records and reports with the ability to copy and verify such records and reports relating to the conduct of a clinical investigation.[11] Companies should conduct mock inspections to prepare for these regulatory authority interactions, particularly in the lead up to NDA or other marketing approval application submissions.

For assistance with clinical trial compliance and managing such regulatory risks, please reach out to a member of the Cooley team.

Notes

1. See **FDA Warning Letter**, November 27, 2024, Applied Therapeutics.
2. The BIMO inspection resulted in the issuance of an FDA Form 483.
3. **Applied Therapeutics press release**, January 3, 2024.
4. **Applied Therapeutics press release**, March 28, 2024.
5. **Applied Therapeutics press release**, November 27, 2024.
6. **21 CFR Part 11**.
7. See supra note 1. The Warning Letter noted that this finding was not included on the 483 it received.
8. See 21 CFR 312.58.
9. ***Alexandru v. Applied Therapeutics, Inc.***, No. 24-cv-09715 (SDNY, filed December 17, 2024).
10. ***Ikram v. Applied Therapeutics, Inc.***, No. 24-9973 (SDNY, filed December 27, 2024).
11. 21 CFR 312.58.

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