CAPITOL STREET

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ALERT: FDA Plausible Mechanism Guidance Forthcoming

CDER & CBER Directors at JPMorgan Assert FDA Legal Authority Over CNPV, Biopharma CEOs Want Non-Animal Models, Manufacturing Requirements Relaxed for Bespoke Pathway

Relevant Companies: BIOPHARMACEUTICALS

Our Take & Next Up

FDA Center leaders announced that the Plausible Mechanism guidance is coming very soon, and emphasized CNPV regulatory authority, as FDA is "on the hunt" for new medicines at venues like ASH, and other medical meetings. The Center for Biologics (CBER) leader, Vinay Prasad, MD, as well as the Center for Drugs (CDER) director, Tracy Beth Hoeg, MD, addressed the 44th Annual JPMorgan Conference today. The panel was at 7:30 am PST today, moderated by Houman David Hemmati MD, PhD, a co-founder and CMO of start-up OptigoBio.

Key Points

The duo – Tracey Beth Hoeg (CDER) and Vinay Prasad (CBER) – highlighted the Plausible Mechanism, or Bespoke pathway ("n of 1"), announcing guidance rollout in the near future, which we believe could be a matter of weeks. Baby KJ is the model. As a reminder, the pathway is intended for therapeutics that treat diseases for which the biologic cause is known, including genetic conditions with a clear connection between alternation and disease. See announcement in a NEJM editorial here, which identified a urea acid cycle metabolism issue. Researchers at the U Penn. and Berkeley, according to Dr. Prasad, engineered a treatment via liquid nanoparticle (LNP) that corrects the genetic mutation. The patient was treated within 7 days, with an accompanying single patient IND.

The pathway could apply to therapeutics *outside* of rare and ultra-rare space. The FDA will prioritize rare diseases, particularly those that are fatal or associated with severe disability in childhood.

- However, Dr. Hoeg noted that these flexibilities could apply to any disease with a defined mechanism and a treatment to address the mechanism (ex. Type 2 diabetes).
- Antisense oligonucleotides (ASOs) were noted as a therapeutic category where this may work well in the future and Spinraza (BIIB) was highlighted as what would have been an appropriate candidate.

Manufacturing flexibility from FDA: 3 CMC batches are not needed. We believe guidance will include significant procedural flexibility on CMC requirements. Manufacturing is an overwhelming burden to industry, particularly if you have a product and the patient population worldwide is limited (say 100). Given that manufacturers are providing a public service, Dr. Prasad noted that the agency would not hold biopharma companies to onerous standards anymore.

The Commissioner's voucher pilot program -- CNPV -- is on firm legal ground, per Prasad: This is the idea that approvals can be 1-2 months versus 12 months. In the past, FDA staff have stated that it takes 60 days to see if all info is included in the initial submission. It also takes one month to negotiate a drug label. FDA thinks that processes can be done faster, and the Commissioner has ultimate authority to approve and deny a drug, so the legal authority should not be called into question, according to the panelists at JPM today.

When FDA leadership went on the road in 2025 to meet biotech and pharma CEOs in a handful of markets, they heard from CEOs that animal testing should not be the norm. Animal testing can be burdensome, unnecessary and there is a desire to waive or reduce testing for toxicology. Dr. Hoeg noted that the initiative came from President Trump, and she stated that she has been working on this from March 2025 onward. Guidance was released on Dec. 2-- our take here -- for monoclonal antibodies.

Nonanimal testing for toxicity could be expanded beyond monoclonal antibodies. Hoeg stated that she is excited by the potential for predictive toxicology and CDER internally was working on a type of standardized list of toxicology requirements that will simplify the preclinical process.

Dr. Martin Makary, FDA Commissioner, will address the JPMorgan 44th annual conference in San Francisco today at 3:30 pm ET (here). We expect the Commissioner to hit on the aforementioned topics as well as 2026 outlook, a report card on Drug & Device approvals, as well as the slew of other initiatives not discussed at the smaller panel this morning: ultra rare pathway, reduced clinical trial requirements, advisory committee reform, AI in drug approvals, as well as agency-wide agenda items, like Most Favored Nation (MFN), which is weaved into the Commissioner's Voucher program (CNPV), despite drug pricing not being a part of the FDA's legal statute. FDA is tasked with determining whether a therapy is safe & effective; CMS is to determine for Medicare & Medicaid whether a medicine is reasonable & necessary.

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