BLOCKING BREAKTHROUGHS: DELAYS AND DENIALS AT THE FDA

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TAXPAYERS PROTECTION ALLIANCE | TAXPAYERS PROTECTION ALLIANCE FOUNDATION

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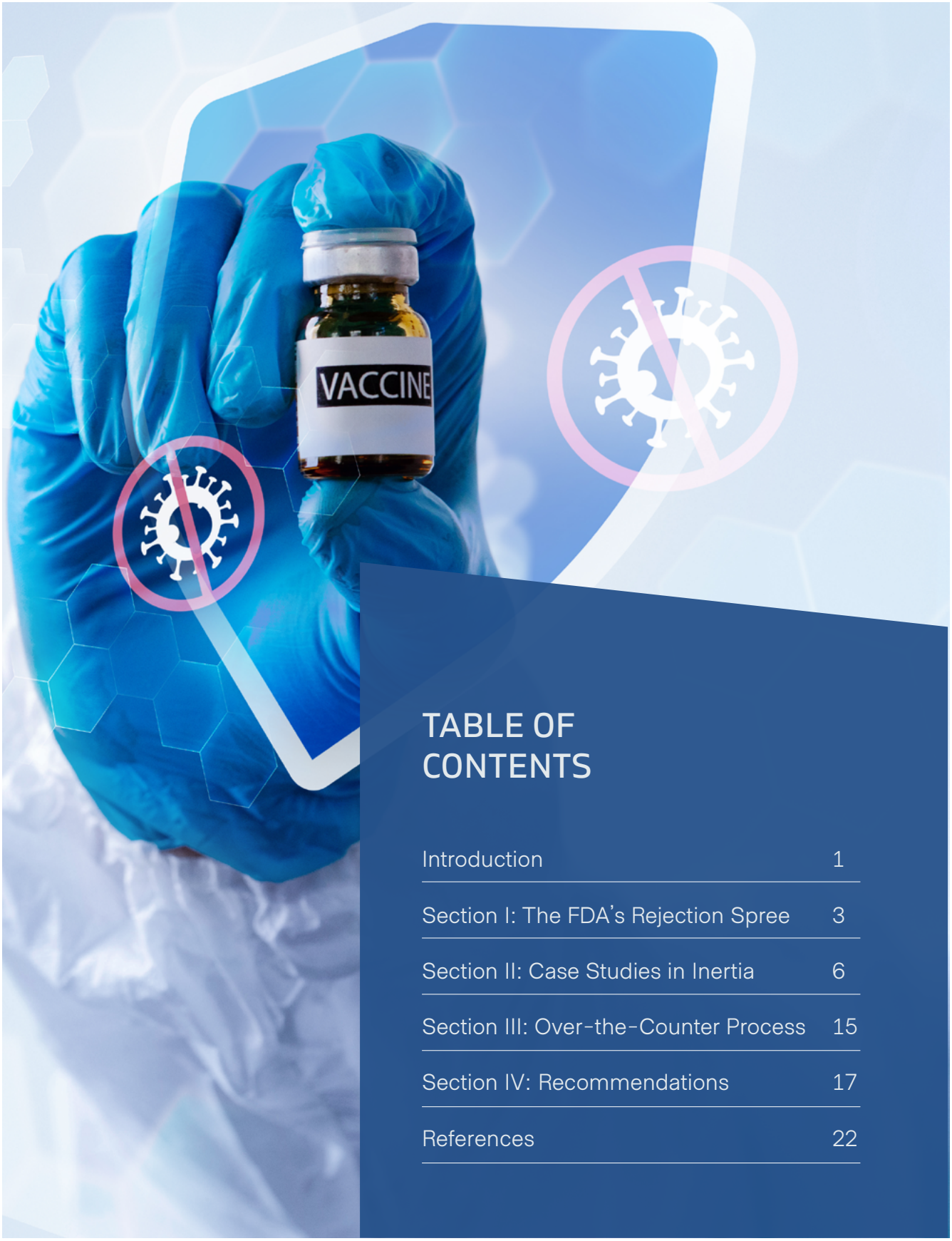

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Introduction

Few federal agencies are as important or have as much reach and impact in Americans' daily lives as the Food and Drug Administration (FDA). The agency, which spends about $7 billion per year,[1] regulates food, tobacco, and medical products that account for more than 20 cents out of every dollar that U.S. consumers spend.[2] The U.S. drug approval program, which focuses on both the safety and efficacy of medications as part of a multi-step pre-approval process, is considered the "gold standard" around the world with international regulators paying close attention to FDA policy.[3]

However, the FDA has received plenty of criticism over its near century in operation. One common critique is that the agency is far too permissive and fails to prevent ineffective or even dangerous products from coming to market. A November 2025 article appearing in the popular left-wing newspaper Jacobin claims, "The Food and Drug Administration, once a powerful regulatory agency, has been compromised by its cozy relationship with Big Pharma. Despite feigned concern for public health, the Trump administration is only worsening the agency's decline."[4] Studies produced and publicized over the years have claimed that companies are winning FDA approval for products based on insufficient evidence.[5] Even current Department of Health and Human Services (HHS) Secretary Robert F. Kennedy Jr. has repeatedly claimed that the FDA is compromised by undue influence from the pharmaceutical industry.[6]

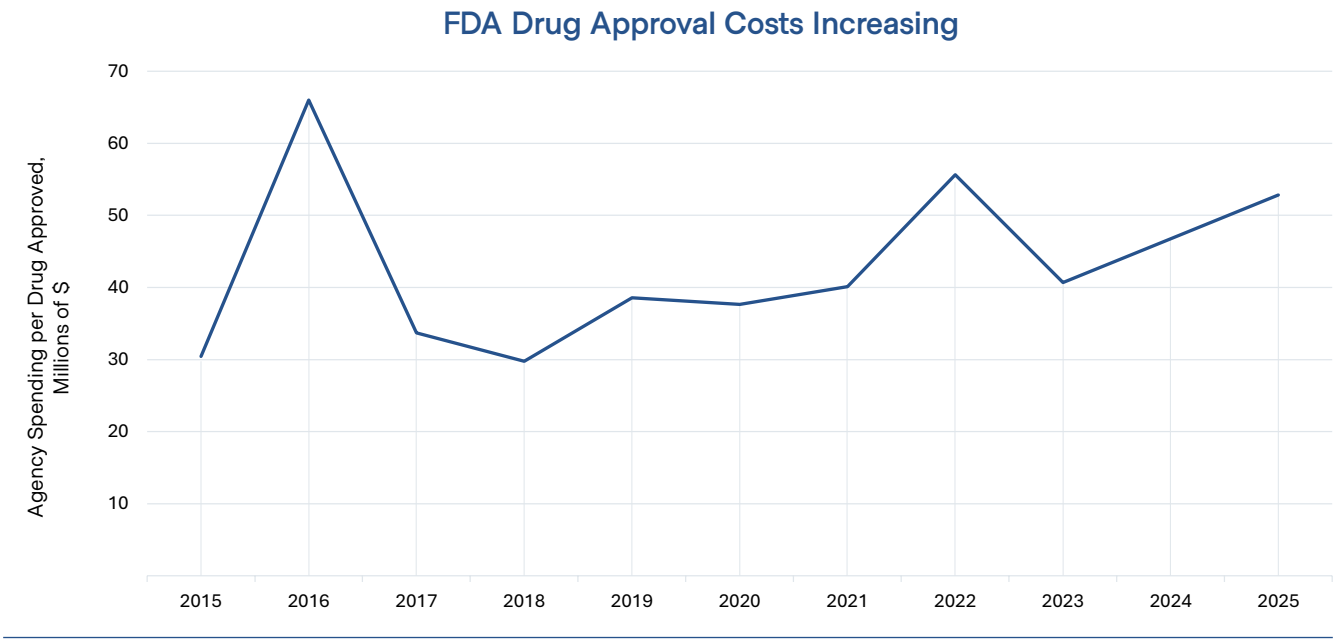
There have surely been drug approvals granted unwisely or prematurely. However, as the Taxpayers Protection Alliance (TPA) found in its 2023 "FDA Reform" report, controversial approval decisions—featuring disagreements between the agency and its scientific advisors—are far more likely to end in drug denial than approval. Furthermore, TPA used five approval decision case studies (Sintilimab, Surufatinib, I-Omburtamab, Bulevirtide, Lenacapavir) to gain greater insight into the FDA's approval philosophy.

The findings suggested that the FDA is far too rigid in evaluating drugs, spurning sponsors for—among other things—using historical data, relying on single-region studies, and having minor manufacturing issues.

This report provides an updated examination of FDA drug approval and drug classification processes, providing statistical analysis in addition to case studies. Section I uses aggregate data to demonstrate trends in approvals, including the taxpayer costs required to evaluate drugs. Section II examines recent FDA decisions on five medications (Ebvallo, ONS-5010, High-Dose Spinraza, Hetlioz, and Gefapixant) and describes agency rationales for rejecting these drugs. Section III provides an overview of the FDA's current approach to over-the-counter (OTC) medications. Section IV concludes and provides recommendations.

Section I: The FDA's Rejection Spree

To make sense of the FDA's regulatory processes and test various claims about the agency being too permissive (or not permissive enough), it is critical to examine trends related to drug approvals. The agency's Center for Drug Evaluation and Research (CDER), which evaluates novel medications as part of the Human Drugs Program, has kept annual drug approvals steady over the 2015-2025 period.[7] However, as seen in the below chart, the Human Drugs Program budget has significantly increased over the 2015-2025 period, resulting in a 77 percent nominal increase in approval costs per medication borne by taxpayers and sponsors through user fees.

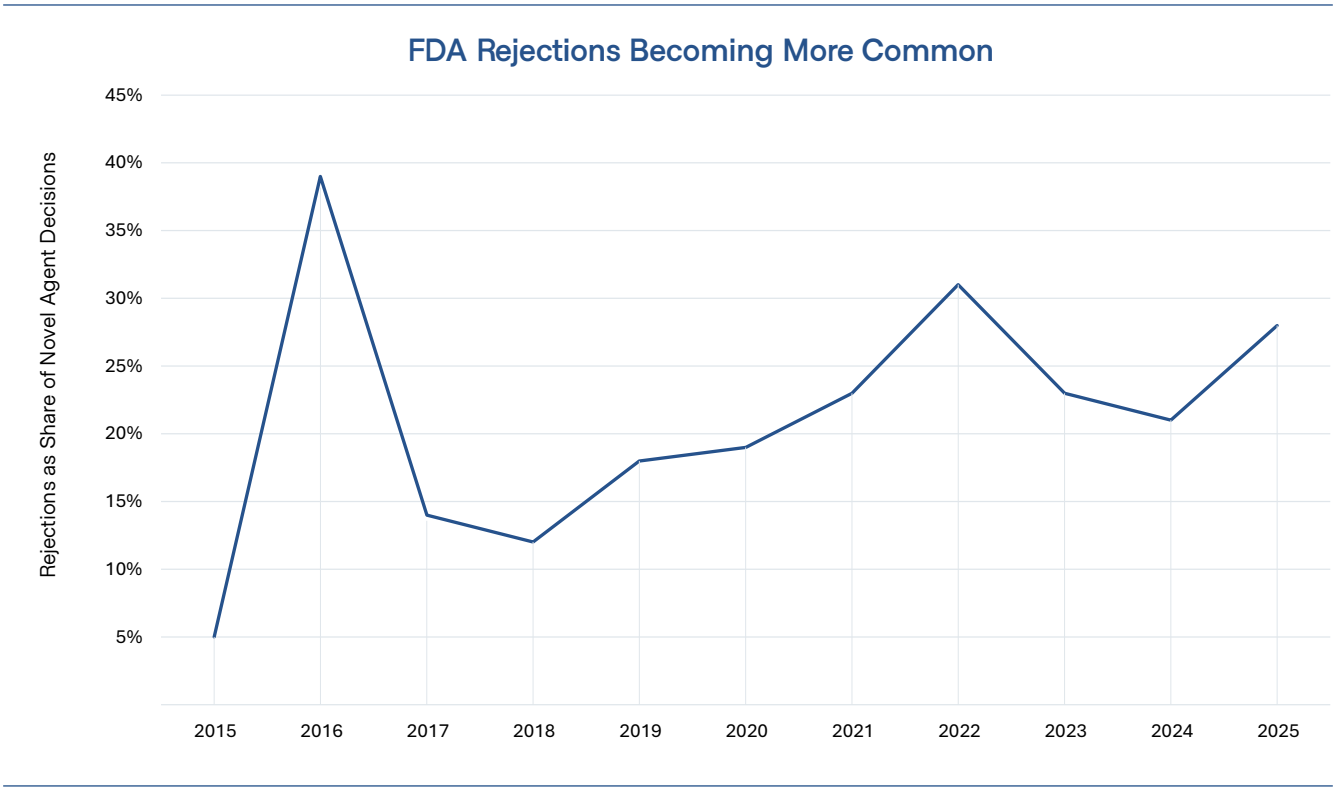


Sources: FDA Justification of Estimates for Appropriations Committees, FY 2017-2026; FDA CDER Novel Drug Approvals, 2015-2025.

Most—and an increasing percentage—of this approval cost is borne by drug companies applying to bring their medications to market. In 2025, taxpayers financed about 30 percent of the Human Drugs Program, with the remaining 70 percent being funded by user fees. Taxpayers used to be responsible for a greater proportion of costs. For example, in 2015,

taxpayers financed 35 percent of the Human Drugs Program.

Because of the growing importance of user fees, one could claim—as HHS Secretary Kennedy does—that drug companies have taken over the Human Drugs Program by leveraging user fees to push the FDA toward granting more approvals. This theory is wholly inconsistent with the data. As seen in the graph below, the FDA has become significantly more restrictive over the past ten years and more likely to issue a Complete Response Letter (CRL)—or rejection. As discussed in footnote seven, the data from 2016 is an outlier given the unusually low volume of applications from that year.

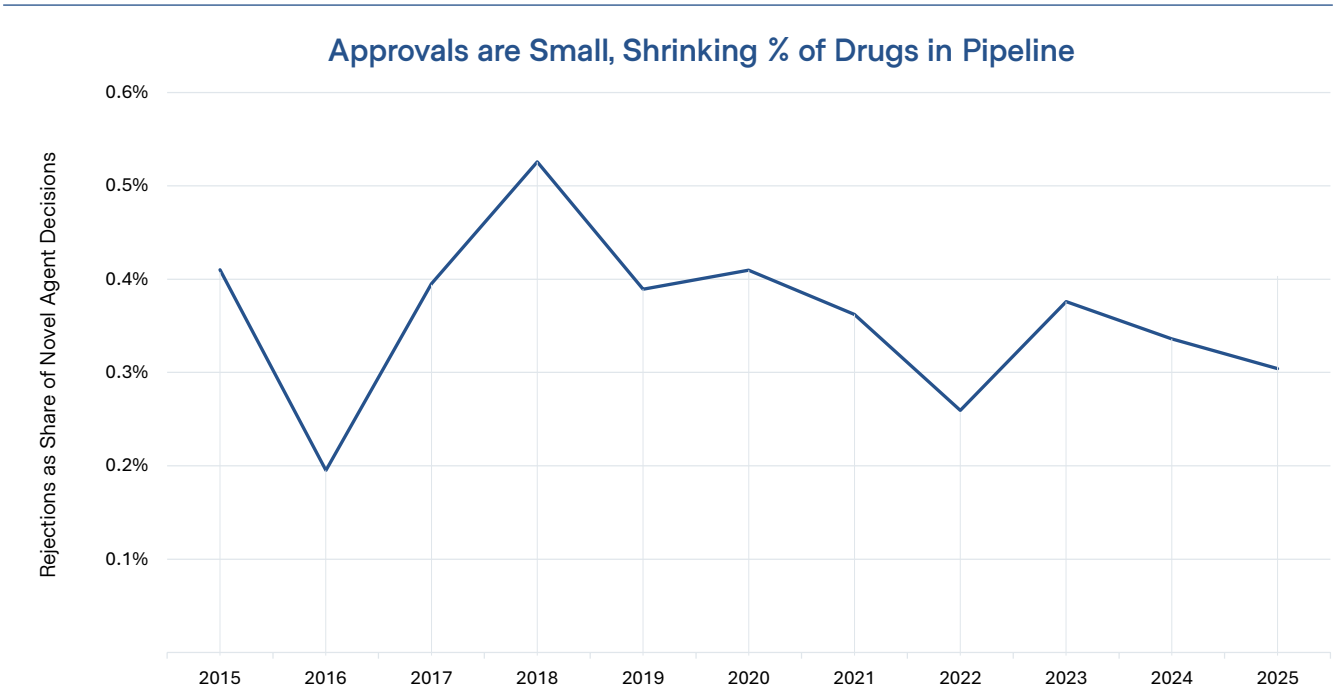


Sources: CDER and CBER approval data, 2015-2025; CRLs reported by various media and sponsor financials.

Not only have rejections increased as a share of agency approval decisions; there was a particularly sharp uptick from 2024 to 2025. Despite rhetoric from Food and Drugs Commissioner Marty Makary that the agency is "cutting red tape" and "accelerating cures,"[8] drug sponsors have expressed growing concern about surprise rejections even when medications seemed on track for approval.[9] The data validates this concern; 2025 rejection rates were near decade highs excluding 2016.

Another way of examining approvals data involves calculating drug approvals as a proportion of medications in the wider pipeline (i.e., drugs currently undergoing testing and

awaiting approval). Biotechnology data platform RxDataLab notes that the number of active "Investigational New Drugs"—which have not yet been approved but are undergoing trials—significantly increased from around 11,000 per year in the five years before the COVID-19 pandemic to more than 14,000 in recent years.[10] The pipeline of drugs awaiting approval has become more crowded even as the FDA is holding the aggregate number of annual drug approvals steady. As the below graph shows, this has resulted in a decline in the already-low percentage of "pipeline" medications being approved each year.



Sources: FDA CDER Novel Drug Approvals, 2015-2025; CDER Drug and Non-Biosimilar Biologic INDs with Activity Reports, 2015-2024.

**For 2025, TPA estimated the "INDs with Activity" count by extrapolating the previous-year growth rate forward.*

However, this data can only provide a high-level view and can shift in subtle but significant ways due to economic headwinds, fluctuating application numbers, and the absence of rigorous data on expanded indications—as opposed to novel drug approvals. It's critical to keep in mind that, beyond these graphs and bird's-eye statistics, FDA decisions impact millions of Americans who would greatly benefit from expanded access to specific drugs. In the following section, five medications (Ebvallo, ONS-5010, High-Dose Spinraza, Hetlioz, and Gefapixant) are analyzed in depth to determine how the FDA—and its international counterparts—reason through decisions.

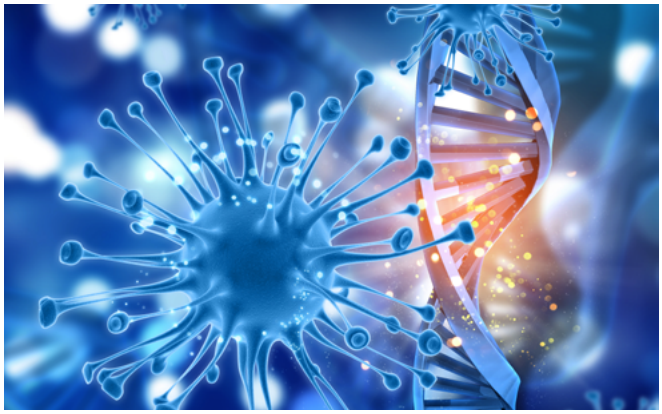
Section II: Case Studies in Inertia

In the following case studies, medications and the conditions they are designed to treat are described in detail. Additionally, the approval decisions and rationales of the FDA and international regulators are examined.

Ebvallo

Ebvallo (tabelecleucel, sometimes referred to as "tab-cel") is a T-cell immunotherapy designed to treat a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD). Unlike personalized cell therapies made from a patient's own cells, Ebvallo is manufactured from healthy donors and selected for a patient based on human leukocyte antigen (HLA) compatibility.[11] The basic idea is straightforward: EBV can drive malignant or pre-malignant lymphoid proliferation when the immune system is suppressed, so restoring targeted antiviral immune surveillance with EBV-specific T cells may control the disease without the broad toxicity of chemotherapy.

EBV-infected B cells (a type of white blood cell that produces antibodies) can proliferate uncontrollably, progressing from early lesions to aggressive lymphoma. Incidence varies widely by transplant type, intensity of immunosuppression, and EBV status (especially EBV mismatch between donor and recipient). There are about 150 new cases of the disease in the U.S. each year.[12]



The clinical stakes are high because outcomes are often poor once patients fail initial therapies. Standard management typically starts with reduction of immunosuppression and therapies such as rituximab (an anti-CD20 monoclonal antibody) with or without chemotherapy, depending on disease features and patient tolerance. However, as noted in a 2024 study in the scientific journal Bone Marrow Transplantation, "Patients who fail rituximab have poor outcomes with limited treatment options. Although results vary according

to protocol, up to 50% of patients with EBV+ PTLD post-HCT may experience failure to rituximab-containing treatment."[13] These failures and grim statistics have led to an "immune reconstitution" strategy like EBV-specific T cells attracting attention and research funding.

Approvals outside the U.S.

Drug regulators outside the United States have been more willing to accept the evidence and acknowledge the efficacy of using tab-cel to treat patients. The European Commission granted European Union (EU)-wide marketing authorization for Ebvallo on December 16, 2022, for adults and children aged 2 years and older with relapsed or refractory EBV+ PTLD after at least one prior therapy.[14]

Beyond the EU, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorization in May 2023,[15] and Swissmedic authorized Ebvallo in Switzerland on May 3, 2024, again for relapsed/refractory EBV+ PTLD in adults and children at least 2 years old.[16] These regulators have concluded that the therapy's benefit-risk profile justifies access, albeit with varying conditions and ongoing evidence expectations. However, the FDA has proven significantly more risk-averse in its assessment of the medication.

The FDA's reluctance and repeat rejections

The FDA first accepted the Biologics License Application (BLA) for Ebvallo in July 2024 and granted priority review. Despite hopes of rapid evaluation and approval in line with other countries, the FDA has repeatedly declined to approve the medication. This has resulted in significant frustration among patients, families, and advocates.

- **January 2025 CRL:** Ebvallo received its first CRL on January 15, 2025, with deficiencies identified during an inspection of a third-party manufacturing facility, rather than specific concerns about safety or efficacy.[17] Cokey Nguyen, PhD, president and chief executive of Atara Biotherapeutics, stated at the time, "Once the third-party manufacturer GMP compliance issues have been adequately addressed, we will file for a resubmission, which we would expect to be potentially approved within 6 months of resubmission."[18] This proved far too optimistic.

- **January 2026 CRL:** On January 9, 2026, Ebvallo received its second rejection. While previously-cited manufacturing issues were resolved, the FDA no longer considered data from the drug's Phase 3 ALLELE study adequate in demonstrating effectiveness for accelerated approval.[19] Even though the medication met its prespecified primary efficacy endpoint and demonstrated a generally tolerable safety profile, the FDA cited interpretability issues related to trial design, conduct, and analysis.[20] As Atara noted,

this was "a complete reversal of position" on a rigorous study that the FDA had already signed off on.[21] The goal posts for approval have now shifted, leaving patients in a precarious position.

ONS-5010

ONS-5010, which is commercially branded outside the U.S. as Lytenava, is intended to treat neovascular ("wet") age-related macular degeneration (wet AMD), a major cause of central vision loss in older adults. The "wet" form of AMD is characterized by abnormal blood vessels growing under the retina; these vessels can leak fluid and blood, causing swelling and damage. Wet AMD is commonly treated with periodic injections, and patients in the U.S. are already able to use a version of ONS-5010 to treat wet AMD. Critically, though, this version is only indicated for the treatment of various cancers and is not currently approved for the treatment of wet AMD.[22] Patients seeking to use Avastin (which is the oncology version of the drug) for treating wet AMD must make do with a repackaged product with a variety of accompanying risks.

> "As Szilárd Kiss, MD noted in a 2022 article for Modern Retina, "Although repackaged bevacizumab has helped millions of patients maintain and even improve vision for a variety of previously blinding retinal disorders, the approach may, nonetheless, unavoidably put patients at risk. This situation is largely due to the process of drawing up multiple syringes from a single vial, as well as to the fact that bevacizumab—developed and packaged for oncologic use—is not formulated to meet the FDA's specific standards for ophthalmic injectables. The agency's chemistry manufacturing and controls standards are an integral part of the FDA requirements for any drug approval, and the syringes that contain aliquoted bevacizumab have not undergone this rigorous review and vetting."[23]

The status-quo would be significantly improved for patients if the FDA approved a wet AMD-specific version of an already-widely-used drug. Regulators in other countries have already embraced this approach.

Approvals in other countries

The European Commission granted EU marketing authorization for ONS-5010 under the brand name Lytenava for adults with wet AMD in May 2024, based on promising safety and efficacy results from NORSE ONE, NORSE TWO and NORSE THREE clinical trials.[24]

In the United Kingdom, the MHRA granted marketing authorization for Lytenava for wet AMD in July 2024 based on the same clinical trial data that convinced EU regulators. Commenting on the UK approval, Professor Tim Jackson, PhD, FRCOphth, Consultant Ophthalmic Surgeon, King's College Hospital and Professor of Retinal Research, King's College London, stated, "We have waited a long time for a brand of bevacizumab that is authorized for eye use, and it is good news that [Lytenava] has now entered the market. … To date, many ophthalmologists have been hesitant to use an off-label bevacizumab, when licensed products are available. We value being able to utilize products that meet the standards required for marketing authorization."[25] However, continued FDA rejection forces U.S. patients to use off-label bevacizumab, exposing them to aforementioned repackaging risks.

FDA rejection

The FDA has broken ranks with its international counterparts by repeatedly denying approval of ONS-5010.

- **August 2023 CRL:** The FDA first rejected the medication in August 2023, citing Chemistry, Manufacturing, and Controls (CMC) issues, negative observations from manufacturing inspections, and a lack of substantial evidence. Producer Outlook Therapeutics called the CMC issues "addressable" and "manageable" and contracted with Fujifilm Diosynth Biotechnologies and Ajinomoto Biopharma Services to assist with reformation. While committing to remedying these issues, Outlook noted that continued FDA rejection would result in the continued use of off-label versions that "have known risks of contamination and inconsistent potency and availability."[26]

- **August 2025 CRL:** The FDA's second CRL, issued following approval in other countries, claimed a lack of substantial evidence of effectiveness based on the medications failure to achieve the primary efficacy endpoint in the phase 3 NORSE EIGHT trial. However, the FDA acknowledged that the previous NORSE TWO trial met its primary effectiveness endpoint and identified no other outstanding deficiencies in the resubmitted BLA. Outlook Therapeutics immediately requested another meeting with the FDA to chart a path forward on approval, while announcing its intention to expand to European markets with more flexible regulatory regimes.[27]

- **December 2025 CRL:** The FDA rejected yet another ONS-5010 BLA submission at the end of 2025. According to a report in Ophthalmology Times, "The FDA stated in the CRL that the additional mechanistic and natural history data included in the BLA resubmission did not change its prior review conclusion … Although the single adequate and well-controlled study demonstrated efficacy, the FDA again recommended that confirmatory evidence of efficacy be submitted to support the application, without indicating what type of confirmatory evidence would be acceptable."[28] This lack of insight as to what additional evidence would be needed will likely further delay an already excruciatingly slow approval process.

High-Dose Spinraza

Spinal Muscular Atrophy (SMA) is a neuromuscular disorder marked by degeneration of lower motor neurons in the spinal cord, causing progressive muscle weakness, atrophy, and respiratory failure. It is estimated to impact anywhere from 10,000 and 25,000 children and adults in the U.S.[29] Spinraza (nusinersen), which is currently approved in the U.S., is a medication used to treat SMA in pediatric and adult patients by increasing production of Survival Motor Neuron (SMN) protein, crucial for motor neuron health, and is delivered via spinal injection. It works by targeting the SMN2 gene to bolster protein production and has shown benefits like improved motor function and reduced risk of mortality in infants with severe SMA. However, it is not a cure and requires ongoing treatment.

While the standard approved nusinersen regimen comes in a 12 mg/5 mL injection, emerging evidence suggests that a higher dose regimen—consisting of a faster loading phase with two 50-mg doses given 14 days apart, followed by a higher maintenance dose of 28 mg every 4 months—is safe and effective for patients.[30] According to results from the randomized, controlled, dose-escalating DEVOTE trial, patients receiving higher doses of the medication showed statistically significant improvement in motor function compared to an untreated control group. Additionally, the rate of adverse events in high-dose recipients was actually

lower than their counterparts given the lower, approved 12-mg dose.[31]

Regulatory scrutiny

Multiple regulatory authorities have responded to the success of the DEVOTE trial by approving high-dose Spinraza for SMA patients. Following approval in Japan in 2025, the European Commission followed suit in January 2026.[32] Commenting on the EU approval, Eugenio Mercuri, M.D., Ph.D., Professor of Pediatric Neurology at the Catholic University, Rome, Italy noted, "The DEVOTE results provide encouraging evidence that this new dosing option could deliver meaningful treatment outcomes with a safety profile generally consistent with the 12 mg dosing regimen. … The European Commission approval of the high dose regimen of SPINRAZA is an important step toward addressing those challenges and advancing how we care for people living with SMA."

However, the FDA was not convinced by the safety and efficacy data submitted by Biogen. On September 23, the company announced that the FDA issued a CRL for the supplemental New Drug Application (sNDA) for high-dose Spinraza. The letter failed to mention any deficiencies in the clinical data of the new regimen, instead requesting an update to the technical information be included in the CMC module of the sNDA.[33] It is unclear why this alleged deficiency in CMC information warranted a CRL as opposed to a stipulation that could have been completed post-approval. The FDA is currently undergoing another review of the resubmitted application, and a decision is expected in April.[34]

Hetlioz

The rise of affordable long-distance and international travel has transformed millions of lives for the better. However, jet lag disorder spurred by circadian misalignment can lead to significant short-term and even long-term health consequences. According to a 2024 analysis published in the journal Cureus, "disruptions to [circadian] rhythms, particularly due to trans-meridian travel and shift work, can lead to significant health issues, including jet lag, metabolic imbalances, and neuropsychiatric disorders."[35]

These issues can result in a long-run "negative-feedback loop between circadian disruption, diabetes, and obesity."[36] One 2021 analysis published in The Journal of Clinical Investigation finds that "circadian misalignment might induce hypertension and inflammation" and may lead to an increased risk of heart attacks, strokes, persistent weight gain, and metabolic disorders.[37]

While there is currently no FDA-approved therapy for jet lag, medications used to treat sleep

irregularities may prove helpful in alleviating the condition. Tasimelteon (Hetlioz) has shown promise in reregulating circadian rhythm by acting upon the MT1 and MT2 receptors and is approved by the FDA for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), as well as for nighttime sleep disturbances in Smith-Magenis Syndrome (SMS).[38] However, the FDA has been reluctant to approve the medication for treatment of jet lag despite ample safety and effectiveness data.

In 2018, sponsor Vanda Pharmaceuticals applied for approval to market the medication as a jet lag treatment. Vanda relied primarily on data from three clinical trials, which tracked primary endpoints such as the ease and duration of sleep and more indirect evidence such as patients' perceived alertness.[39] Despite statistically significant evidence that the medication helped travelers rest more easily and stay alert, the FDA issued a CRL in 2019 because it was "not clear how [the] primary endpoints assess the fundamental sleep disturbances associated with jet lag disorder."[40] Furthermore, the FDA claimed, "[o]ther important aspects of the disorder," beyond sleepiness, were not examined by the clinical trials. Vanda responded to the rejection by filing two formal dispute-resolution requests and arguing for a narrower indication (treatment of insomnia symptoms associated with jet lag), but the FDA spurned these requests and claimed that seeking a narrower indication fell outside the scope of said requests.[41]

Vanda persisted in attempting to persuade the FDA to reconsider its decision and twice requested an opportunity for a hearing in 2022. The agency denied these requests, claiming despite the abundance of sleep-related evidence submitted that there was "no genuine and substantial issue of fact justifying a hearing."[42]

Frustrated by the FDA's unyielding stance, Vanda petitioned the U.S. Court of Appeals for the District of Columbia Circuit claiming—among other things—that the FDA's decision denying Vanda a hearing was arbitrary and capricious. The court sided with Vanda, rejecting the FDA's argument that it properly denied Vanda a hearing "in light of the company's complete failure to establish that tasimelteon improved impairment in next-day functioning." As noted in the opinion, Vanda had in fact "offered pages of expert testimony describing that improvement on [subjective sleepiness scales] corresponded to improvement in next-day functioning. And here, FDA primarily dismissed Vanda's arguments as assumptions without adequately explaining any flaws in Vanda's evidence."[43]

Decided in August 2025, the case was remanded to the FDA for further proceedings. The FDA reevaluated the evidence and issued another rejection in January 2026, dubiously claiming that clinical trial protocols were not "sufficiently analogous to actual jet travel." As Vanda noted in response, though, "Phase advance models [used in the clinical trials] are widely accepted

in circadian rhythm research as valid and reliable surrogates for simulating the core circadian misalignment underlying eastward jet lag—the primary driver of the disorder's hallmark symptoms."[44] The saga continues for jet lag sufferers, who cannot catch a break—or sleep—despite judicial rebukes of the FDA.

Gefapixant

Chronic cough may seem trivial to outside observers, but for the people who live with it day in and day out, it can profoundly diminish quality of life. Defined clinically as a cough that persists for eight weeks or longer,[45] chronic cough can lead to sleep disturbance, urinary incontinence, rib fractures, dizziness, social embarrassment and isolation, anxiety, and depression. In adults with refractory chronic cough (RCC)—where cough persists despite appropriate treatment of underlying conditions such as asthma or reflux—or unexplained chronic cough (UCC) where the underlying cause cannot be identified despite a thorough evaluation, clinicians and patients currently have no FDA-approved therapies in the United States.[46] This unmet need has spurred drug development efforts, most prominently Merck's investigational compound gefapixant.[47]

Gefapixant represents a new class of cough treatment. It is an orally administered non-narcotic selective P2X3 receptor antagonist that targets receptors found predominately on sensory nerve fibers in the airway lining. These P2X3 receptors are involved in the nerve signaling pathways that trigger the cough reflex. By blocking these receptors, gefapixant aims to dampen the hypersensitive cough reflex that characterizes RCC and UCC, thereby reducing cough frequency and severity.[48]

The mechanism is conceptually different from traditional cough suppressants like codeine or dextromethorphan; gefapixant works at a receptor level rather than simply numbing the cough reflex or sedating the central nervous system.

> Early phase 3 clinical trials—labeled COUGH-1 and COUGH-2—suggested that patients taking the higher dose of gefapixant experienced statistically significant reductions in cough frequency compared with the placebo treatment.[49]

Despite these statistically significant findings and the clear unmet need, the FDA has twice rejected gefapixant's application for approval in the U.S. In its most recent CRL issued in December 2023, the agency concluded that the evidence submitted did not provide substantial evidence of effectiveness for treating refractory or unexplained chronic cough. No safety concerns were raised.[50]

FDA reviewers and an advisory committee (who had previously voted 12-1 against approving the drug without the participation of a specialist familiar with treating or diagnosing patients with chronic cough) raised concerns that the observed effects—though measurable—may not be clinically meaningful to patients in real-world settings. They questioned whether the ostensibly small reduction in objective cough frequency truly translated into noticeable benefits in daily life or improvements in patient-reported outcomes like quality of life.[51] The FDA's December 2023 rejection followed an earlier CRL issued in January 2022, which also raised efficacy concerns without flagging safety issues.[52]

Outside the U.S., regulatory agencies have taken a more balanced approach to the medication. Gefapixant is approved in Japan (since January 2022)[53] , in the European Union and United Kingdom (since September 2023)[54] under the brand name Lyfnua for adults with refractory or unexplained chronic cough. These regulators concluded that the observed efficacy, coupled with a manageable safety profile, was sufficient for authorization. Despite these international approvals and the clear unmet need for patients in the U.S. experiencing chronic cough, the FDA's repeated rejections reflect a reluctance to approve innovative new medications even when safety has been established.

Section III: Over-the-Counter Process

As shown in the previous sections, it is often exceptionally difficult for drug manufacturers to bring their products to market. However, the question of whether a product can be sold and marketed is only one part of the FDA approval process. The FDA and manufacturers must also agree on whether the product will be "behind-the-counter" (i.e., prescription-only) or "over-the-counter" (OTC or nonprescription).

This designation need not be permanent. In practice, though, switching can be an onerous process. The FDA explains, "To initiate a full switch, a sponsor submits an efficacy supplement to an approved NDA or a 505(b)(2) application. After a full switch, the drug is only available as a nonprescription drug. … To initiate a partial switch, a sponsor submits a new NDA. After a partial switch, the drug is available as a prescription drug for certain conditions of use and a nonprescription drug for other conditions of use."[55]

In recent years, policymakers have expressed concern that the switch process is too difficult, resulting in medications that would be perfectly safe for OTC use yet remain tethered to prescription status. Commissioner Makary recently echoed these concerns, asking, "Why do we make people sit in the ER to get a simple medication that should be available over-the-counter?"[56] President Trump has also endorsed expanded use of OTC status, claiming that a more permissive approach would "lower healthcare costs and increase consumer choice by strengthening price transparency, increasing competition, and reducing the need for costly and time-consuming doctor's visits."[57]

Healthcare experts have also advocated for this policy shift away from prescription status and toward OTC. In May 2025, healthcare and biotechnology writer Alex Kesin urged HHS Secretary Kennedy to reclassify statins—which lower blood cholesterol levels—as OTC medications.[58] He noted, "Say only one percent of the 130 million U.S. adults aged 40-75 grab an OTC statin. … you avert 14,000 heart attacks and strokes."

The risks of this strategy are minimal; "Serious muscle injury from statins occurs in <0.1% of users; hepatotoxicity is an order of magnitude rarer." Drug manufacturers such as Merck have long made these observations and tried to switch statins to OTC but have had little success. In 2005, an expert panel at the FDA "rejected a proposal to permit over-the-counter sales of Merck's statin lovastatin (Mevacor), arguing that the risk of the drug could outweigh its benefits in many potential users."[59]

Asthma patients could similarly benefit from reclassifying albuterol as an over-the-counter medication. Albuterol (a fast-acting bronchodilator) is widely used to treat asthma, and its safety profile supports over-the-counter availability. Its use is generally well-tolerated over long periods of time, and common side effects (e.g., nervousness, coughing, throat irritation) are very rarely emergency situations.[60] Lack of access to asthma medications is far more dangerous than ready access for the 25 million Americans who have asthma. According to a 2014 analysis in Allergy and Asthma Proceedings, "In 1095 adult ED [Emergency Department] patients with acute asthma, we found that 30 [percent] ran out of their inhaled asthma medications before the ED visit."[61] While critics raise concerns about overuse, missed diagnoses, or poor asthma management, these concerns are likely outweighed by the benefits of access in severe and deadly episodes.[62]

Cancer patients could also conceivably benefit from a shift to OTC. Ondansetron (brand name Zofran), a 5-HT3 receptor antagonist used to treat nausea and vomiting, has a strong safety record and high tolerability for even the most vulnerable patients. Originally approved in the U.S. in 1991 for chemotherapy-induced nausea, ondansetron is now widely prescribed off-label for pregnancy-related nausea, viral gastroenteritis, and post-operative nausea. Patients have noticed its ability to eliminate nausea in as little as thirty minutes.[63]

Like statins and albuterol, ondansetron is generally well-tolerated and side effects (e.g., headaches, fatigue, dry mouth, malaise, and constipation) are relatively mild. Numerous clinical studies confirm its minimal sedative effect.[64] The main argument for limiting OTC access appears to be the association between ondansetron and a rare but potentially fatal heart condition called QT prolongation. However, this arrhythmia onset is exceedingly uncommon after taking the medication, and there is not a link at all for certain age groups.[65]

Under the reauthorization of the Over-the-Counter Monograph User Fee Act (OMUFA II), FDA is required to develop guidance aimed at improving the process for switching NDA-approved products from prescription to nonprescription status. However, the timing for this remains unclear.

Section IV: Recommendations

Healthcare analysts and public officials have long claimed that the drug approval process is too deferential to pharmaceutical companies. As seen in high-level data and anecdotes presented in this report, the opposite problem of bureaucratic inertia is a far more pressing concern. Fortunately, a few reforms can improve the approval process and bring FDA decisions in line with its international counterparts. These reform suggestions are outlined below:

Enact regulatory reciprocity with other nations.

The United States should adopt a formal system of regulatory reciprocity with trusted peer nations that maintain rigorous drug approval standards comparable to those of the FDA. Countries and regulatory systems such as the European Union, the United Kingdom, Canada, Japan, and Australia already evaluate medicines using scientific frameworks that closely mirror U.S. practices. Requiring manufacturers to duplicate lengthy and expensive approval processes for drugs that have already been deemed safe and effective abroad delays patient access, raises costs, and offers little additional public health benefit. Regulatory reciprocity would allow the FDA to rely on or fast-track approvals based on foreign regulatory determinations, reserving its resources for novel therapies and high-risk products.

Such a system would not eliminate FDA oversight but rather recalibrate it toward verification and post-market surveillance instead of redundant pre-market review. By recognizing approvals from trusted regulators, the U.S. could shorten timelines for patient access, encourage pharmaceutical competition, and reduce development costs that are ultimately borne by consumers. Importantly, reciprocity would also incentivize global regulatory cooperation and discourage protectionist barriers that slow innovation without meaningfully improving safety.

Implementing this reform would require significant changes to existing law and FDA practices and may raise concerns that reciprocity subordinates U.S. interests to that of foreign countries. However, reciprocity in practice would mean that the U.S. regulatory system is more, not less, responsive to consumer needs, competitive, and does not cede ground to geopolitical rivals such as China.

Require the FDA to reassess OTC/prescription status for commonly-used medications.

Many medications such as statins that remain prescription-only in the United States have long safety records, are routinely used by patients for chronic or low-risk conditions, and are already available over the counter in other developed countries. The FDA should be required to conduct periodic, mandatory reassessments of a drug's prescription status based on real-world safety data, international practice, and the degree of clinical supervision actually required for safe use. Without such reassessment, drugs can remain locked behind prescription requirements long after the original rationale has eroded.

Expanding over-the-counter access for appropriate medications would reduce unnecessary physician visits, lower costs for patients, and improve adherence for treatments that patients already manage independently. It would also ease strain on the healthcare system by allowing clinicians to focus on more complex cases. Clear labeling, pharmacist consultation requirements where appropriate, and post-market monitoring can ensure safety while still empowering consumers with greater access and choice.

Permit provisional approval of medications that meet safety but not efficacy thresholds, with prominent labeling.

For patients facing limited treatment options—particularly those with chronic, rare, or hard-to-treat conditions—the FDA should permit provisional approval of medications that have demonstrated acceptable safety but have not yet met full efficacy thresholds. Under this framework, drugs could be made available earlier with strict transparency requirements, including prominent labeling that clearly

discloses the limits of existing efficacy data. This approach would respect patient autonomy by allowing informed consumers and physicians to weigh potential benefits against known uncertainties.

Provisional approval would also create stronger incentives for continued data collection and real-world evidence generation, rather than forcing companies into an all-or-nothing regulatory gamble. By pairing early access with robust post-market surveillance and the possibility of withdrawal if efficacy is not ultimately demonstrated, the FDA can protect public health while accelerating innovation. This model recognizes that regulatory caution should not come at the expense of patients who are willing to accept uncertainty when no better alternatives exist.

Currently, the FDA provides accelerated pathways for earlier access, but the agency also requires at least some evidence of efficacy as a part of benefit/risk determinations. Under present practices, it is not sufficient to simply determine that the risk is low or very low, if benefits are not likewise defined to the agency's liking. That gives the FDA far too much discretion to shift goalposts regarding measured benefits to the detriment of patients.

Evaluate clinical trial data by the quality of empirics, not the country of origin.

A sufficiently large, randomized study can usually yield valuable insights about the safety and efficacy of a medication. These insights do not stop at the U.S. border. Data primarily pertaining to one ethnic or racial group should be contextualized in labeling and post-market surveillance, not dismissed outright. Many disease mechanisms are biologically conserved across populations, and well-designed trials conducted abroad can meaningfully inform regulatory decision-making in the United States.

Overemphasizing country of origin risks substituting geopolitical skepticism for scientific rigor. The proper question is not where a trial was conducted, but whether its design, endpoints, statistical power, and execution meet established evidentiary standards. The FDA already accepts foreign clinical data in principle;

in practice, however, skepticism toward non-U.S. trials can result in redundant studies that delay patient access without materially improving safety. A more disciplined focus on empirical quality—paired with transparent labeling where population-specific uncertainties exist—would better balance scientific integrity with timely access to care.

Embrace external controls.

Historical datasets may have shortcomings, but they also bring considerable value to the drug evaluation process. When possible, regulators should allow submitted data to be meaningfully benchmarked against well-curated external controls, ensuring that comparisons between treatment effects and real-world outcomes are properly contextualized. This approach is especially relevant in rare diseases, oncology, and conditions where placebo-controlled trials are impractical or ethically fraught.

Rigid insistence on contemporaneous randomized controls can, in some cases, elevate methodological purity over practical relevance. Advances in data harmonization, electronic health records, and longitudinal registries have substantially improved the reliability of external controls when used thoughtfully. While such datasets should never be accepted uncritically, neither should they be categorically discounted. Clear standards for validation, adjustment for confounders, and sensitivity analyses can allow external controls to supplement, rather than supplant, traditional trial designs, accelerating development without sacrificing analytical credibility.

Relegate manufacturing/logistics issues to post-approval monitoring.

Virtually every industry has experienced manufacturing and distribution disruptions, and the pharmaceutical sector is no exception. These issues are often resolved only through real-world scaling and iterative process improvements. Denying or delaying approval based on fixable manufacturing challenges can unnecessarily postpone patient access to otherwise effective

therapies, particularly when clinical benefit has already been convincingly demonstrated.

While genuine safety-related quality control failures do exist (even for well-established medications such as metformin), they are frequently distinguishable from routine scale-up or supply-chain problems. In many cases, such issues can be addressed within weeks or a few months through corrective action plans, enhanced inspections, or limited distribution strategies. A more pragmatic regulatory posture would pair conditional approval with heightened post-market oversight, rather than imposing blanket delays. This approach preserves patient safety while recognizing that manufacturing perfection is rarely achieved prior to real-world deployment—and that learning often occurs most efficiently after approval, not before it.

References

1 https://www.reuters.com/business/healthcare-pharmaceuticals/trump-proposing-68-bln-budget-us-fda-commissioner-says-2025-05-22/.

2 https://www.fda.gov/media/182749/download.

3 https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years.

4 https://jacobin.com/2025/11/fda-pharma-approval-corruption-maha.

5 https://www.usatoday.com/story/news/health/2023/02/13/fda-approval-drugs-missed-goals/11247727002/.

6 https://www.statnews.com/2024/11/20/rfk-kennedy-fda-corruption-medicines-vaccines-pharmaceuticals/.

7 CDER approved 50 novel drugs in 2024 and 46 in 2025, similar to 2015's total of 45 drugs approved and 2017's total of 46. CDER regulators only approved 22 medications in 2016, owing to an unusually low number of drug applications. See https://www.fiercebiotech.com/special-report/new-drug-approvals-took-a-nosedive-2016-here-are-22-made-grade.

8 https://x.com/DrMakaryFDA/status/2002019893655302299.

9 https://www.statnews.com/2025/10/16/fda-chaos-hurts-innovation-two-examples-replimune-capricor/.

10 https://rxdatalab.com/blog/investigational-new-drug-receipts/.

11 https://icer.org/wp-content/uploads/2024/09/ICER_EBV-PTLD_Draft-Report_For-Publication_091224.pdf.

12 https://pmc.ncbi.nlm.nih.gov/articles/PMC10781634/.

13 https://www.nature.com/articles/s41409-023-02127-9#:.

14 https://investors.atarabio.com/news-events/press-releases/detail/301/atara-biotherapeutics-ebvallo-tabelecleucel; https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo.

15 https://investors.atarabio.com/sec-filings/all-sec-filings/content/0000950170-24-037644/atra-20231231.htm#:~:text=In%20October%202022%2C%20we%20filed,used%20product%20to%20be%20shown.

16 https://www.swissmedic.ch/swissmedic/en/home/about-us/publications/public-summary-swiss-par/public-summary-swiss-par-ebvallo.html#:~:text=Summary%20report%20on%20authorisation,positive%20post%2Dtransplant%20lymphoproliferative%20disorder.

17 https://www.targetedonc.com/view/fda-issues-complete-response-letter-for-tab-cel-in-ebv-ptld.

18 Ibid.

19 https://www.benzinga.com/Opinion/26/01/49916695/atara-outlook-as-ebvallo-hits-second-fda-crl.

20 Ibid.

21 https://www.fiercepharma.com/pharma/atara-pierre-fabre-allege-fda-about-face-agency-hands-down-2nd-ebvallo-snub.

22 https://www.ajmc.com/view/fda-issues-crl-for-bevacizumab-used-for-wet-amd.

23 https://www.modernretina.com/view/perspectives-on-intravenous-bevacizumab-repackaged-for-intravitreal-use#:~:text=FDA%2Dapproved%20manufacturing%20matters&text=The%20FDA%20demands%20that%20manufacturers,repackaged%20bevacizumab%20from%20compounding%20pharmacies..

24 https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeuticsr-receives-european-

commission-marketing.

25 https://ir.oncobiologics.com/news-releases/news-release-details/outlook-therapeuticsr-announces-uk-mhra-marketing-authorization.

26 https://www.fiercepharma.com/pharma/fda-turns-down-outlooks-avastin-reformulation-its-first-bid-get-eye-disease-nod.

27 https://www.hcplive.com/view/fda-issues-crl-outlook-therapeutics-ons-5010-for-treatment-wet-amd.

28 https://www.ophthalmologytimes.com/view/outlook-therapeutics-receives-crl-for-resubmitted-ons-5010-bla.

29 https://www.americanbrainfoundation.org/diseases/spinal-muscular-atrophy/.

30 https://www.neurologylive.com/view/fda-gives-complete-response-letter-higher-dose-sma-therapy-nusinersen.

31 Ibid.

32 https://investors.biogen.com/news-releases/news-release-details/biogen-receives-european-commission-approval-high-dose-regimen.

33 https://www.globenewswire.com/news-release/2025/09/23/3155096/0/en/Biogen-Provides-Regulatory-Update-on-High-Dose-Regimen-of-Nusinersen.html.

34 https://investors.biogen.com/news-releases/news-release-details/biogen-receives-european-commission-approval-high-dose-regimen.

35 https://pmc.ncbi.nlm.nih.gov/articles/PMC11554432/.

36 https://pmc.ncbi.nlm.nih.gov/articles/PMC8483747/.

37 Ibid.

38 https://pmc.ncbi.nlm.nih.gov/articles/PMC9521676/.

39 https://media.cadc.uscourts.gov/opinions/docs/2025/08/24-1049-2130249.pdf.

40 Ibid.

41 Ibid.

42 Ibid.

43 Ibid.

44 https://www.fiercepharma.com/pharma/vandas-shares-down-11-after-2nd-fda-rejection-hetlioz-jet-lag-disorder.

45 https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chronic-cough#.

46 https://www.prnewswire.com/news-releases/chronic-refractory-cough-market-still-unexplored-with-pharma-companies-eyeing-first-mover-advantage-in-the-us--delveinsight-302309439.html#:~:text=The%20total%20diagnosed%20prevalent%20cases,cough%20symptoms%20associated%20with%20reflux..

47 Merck is known as MSD outside of the US and Canada.

48 https://www.merck.com/news/u-s-fda-accepts-mercks-gefapixant-new-drug-application-for-review/.

49 https://pubmed.ncbi.nlm.nih.gov/35248186/.

50 https://www.fiercebiotech.com/biotech/merck-gsk-its-rearview-suffers-second-fda-rejection-cough-drug-gefapixant.

51 https://www.healio.com/news/pulmonology/20231117/fda-panel-votes-against-gefapixant-for-unexplained-chronic-cough.

52 https://www.hcplive.com/view/merck-receives-fda-complete-response-letter-chronic-cough-drug-candidate-gefapixant.

53 https://www.merck.com/news/merck-provides-u-s-and-japan-regulatory-update-for-gefapixant/.

54 https://www.ema.europa.eu/en/medicines/human/EPAR/lyfnua.

55 https://www.fda.gov/drugs/drug-application-process-nonprescription-drugs/prescription-nonprescription-rx-otc-switches.

56 https://x.com/DrMakaryFDA/status/2012627914219540855.

57 https://www.whitehouse.gov/fact-sheets/2026/01/fact-sheet-president-donald-j-trump-calls-on-congress-to-enact-the-great-healthcare-plan/.

58 https://www.alexkesin.com/p/mr-secretary-reclassify-the-statin?utm_source=post-email-title&publication_id=104087&post_id=163639638&utm_campaign=email-post-title&isFreemail=true&r=3o9&triedRedirect=true&utm_medium=email.

59 https://pmc.ncbi.nlm.nih.gov/articles/PMC545018/.

60 https://www.poison.org/articles/albuterol-use-and-safety-considerations.

61 https://www.ingentaconnect.com/content/ocean/aap/2014/00000035/00000003/art00002;jsessionid=16rlotiq27ar1.x-ic-live-01.

62 https://gaapp.org/diseases/asthma/severe-asthma/can-you-die-from-asthma.

63 https://www.goodrx.com/zofran/how-long-take-zofran-work.

64 https://pubmed.ncbi.nlm.nih.gov/9184738/.

65 https://pmc.ncbi.nlm.nih.gov/articles/PMC10317942/.

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