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FDA approval of benzgalantamine exposes flaws in the 505(b)(2) pathway for innovations on existing drugs

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When the US Food and Drug Administration (FDA) approved benzgalantamine (Zunveyl) in July 2024 for Alzheimer's disease, it was hailed by its manufacturer as a 'major breakthrough'.[1] In reality, benzgalantamine is a modified prodrug of an older, modestly effective drug, approved through an abbreviated regulatory process that required almost no new clinical evidence of benefit or safety. The decision illustrates how the FDA's 505(b)(2) pathway, originally intended to speed access to modified, similar versions of existing medicines, has the potential to become a shortcut to market access for products with uncertain clinical value.

The 505(b)(2) pathway to FDA approval

The 505(b)(2) pathway, created under the 1984 Hatch Waxman Act, was designed to streamline approvals for modifications of existing drugs by avoiding redundant trials.[2] Such modifications include new dosage forms, delivery routes and combinations.[2]

In 2004, the number of 505(b)(2) approvals exceeded that of new molecular entities approved through the traditional 505(b)(1) for the first time.[3] Since then, 505(b)(2) approvals have continued to increase and now annually exceed the number of new molecular entities approved, with >40 new approvals per year (figure 1).[3]

Benzgalantamine's path to approval

AlphaCognition, benzgalantamine's sponsor, argued that adding a benzyl moiety to galantamine did not create a new molecular entity, qualifying it for 505(b)(2) review.[4] This chemical addition potentially prevents intestinal metabolism, making the drug a prodrug that is converted hepatically to galantamine.

Galantamine itself, first approved in 2001, provides only a modest benefit in patients with Alzheimer's disease, improving cognition by a few points on rating scales without altering disease progression.[5] In a Cochrane review of >6000 participants, galantamine showed small improvements in cognition and global function but at the cost of frequent nausea, vomiting and dizziness.[5] The therapeutic effect is therefore limited, raising questions about whether its reformulation would meaningfully improve outcomes for patients.

For benzgalantamine's approval, the FDA relied on four open-label pharmacokinetic studies in about 35 healthy non-geriatric adults where bioequivalence to galantamine was intended to be demonstrated through plasma Cmax (peak plasma concentration) and area under the concentration-time curve (total drug exposure over time).[6] Importantly, bioequivalence studies were not completed in the drug's intended geriatric population.

Notably, benzgalantamine's Cmax was about 2% above the accepted equivalence range,

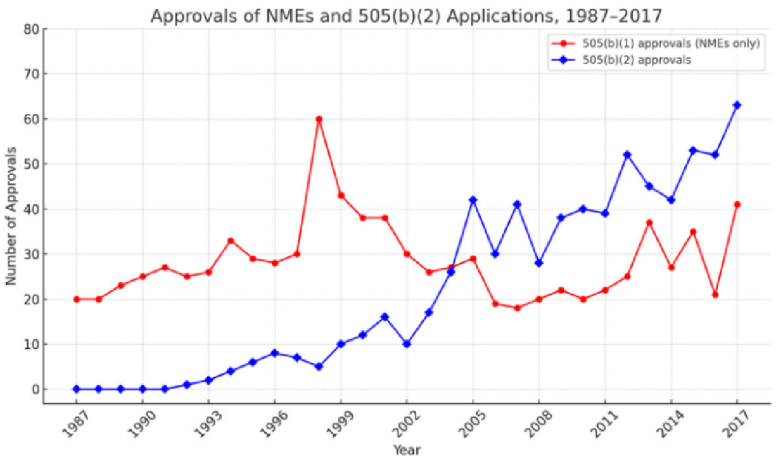

Figure 1 Comparison of approvals of new molecular entities (NMEs) via 505(b)(1) and prodrugs/reformulations via 505(b)(2), 1987–2017.

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technically failing to meet standard bioequivalence criteria. Still, FDA reviewers concluded the deviation 'was not expected to be clinically relevant'.[6]

This regulatory flexibility is striking given the target population: older adults with frailty, variable metabolisms, and high rates of polypharmacy. In this population, even small pharmacokinetic differences may amplify toxicity risk (bradycardia, syncope, gastrointestinal intolerance, drug-drug interactions).[7] Despite that, no geriatric safety data were required.

Misleading and potentially harmful marketing

Following approval, AlphaCognition made several misleading claims in its marketing materials. The company claimed that benzgalantamine 'represents a major breakthrough in Alzheimer's treatment'.[1] In fact, benzgalantamine is a prodrug of an older agent that itself delivers only modest clinical benefit, not a novel treatment. They then state that benzgalantamine 'offers the hope of better tolerability'.[1] As previously stated, it is unclear whether benzgalantamine is actually safer than its parent drug, given the lack of formal safety trials. Such claims risk misleading clinicians into assuming superior safety or effectiveness, particularly for a vulnerable older adult population.

Pharmaceutical marketing has been shown to influence prescribing behaviour, including increased use of branded and higher cost drugs.[8] Nursing homes, where polypharmacy is common and residents are particularly vulnerable to adverse drug effects, represent a setting in which optimistic safety claims about new therapies may have outsized influence.[9] AlphaCognition's corporate materials for benzgalantamine indicate that the company has specifically targeted nursing homes.[4] Internal materials cite adverse effects of existing dementia drugs as a leading cause of drug discontinuation in this setting and explicitly claim that benzgalantamine is designed to avoid these effects, despite the absence of clinical trial evidence demonstrating improved safety.[4]

Zunveyl has entered the US market at about US$749 per month, >10 times the cost of generic galantamine.[10] AlphaCognition has projected over US$200 million in annual revenue.[4] While not enormous by pharmaceutical industry standards, these are costs to Medicare Part D without clear added benefit. In aggregate, such 'me too' approvals undermine efforts to contain drug spending.

Reforms to the 505(b)(2) pathway

Manufacturers are exploiting a regulatory loophole that allows approval of high-priced, minimally modified drugs based on limited data. This does not imply bad faith; benzgalantamine might indeed prove more tolerable than its predecessor. However, without adequate testing, this remains speculative at best. As 505(b)(2) use expands, the risk of approving reformulations that may lead to harm or waste will grow.

The FDA and the Centers for Medicare and Medicaid Services could strengthen oversight through three targeted reforms:

1. Require comparative safety trials in the target population whenever sponsors claim improved tolerability.
2. Coordinate FDA and Federal Trade Commission enforcement to curb unsubstantiated 'breakthrough' or 'safer' advertising.
3. Require Medicare Part D plans to cover only 505(b)(2) drugs that demonstrate proven clinical benefit.

Balancing innovation and safety

This tension between promoting innovation and protecting patients lies at the heart of the FDA's mission. In today's deregulatory climate, maintaining that balance is increasingly difficult.[11] Benzgalantamine is a small but telling example of how commercial incentives can outpace evidence. In turn, to safeguard public trust, regulators should ensure that evidentiary standards evolve alongside industry innovation and subject commercial claims to rigorous scrutiny. Only through such vigilance can healthcare advances continue to serve the public good.

Contributors NKR drafted the article and is the guarantor and corresponding author. He is a neurologist at the University of California, San Francisco (UCSF) and the San Francisco VA through the National Clinician Scholars Program. MAS and EW, geriatricians at UCSF and the San Francisco VA, contributed insights into how regulatory decisions such as the approval of benzgalantamine affect real-world patient care, particularly among older adults. JR and RR, researchers in regulatory policy and drug approval at Yale, provided policy and Food and Drug Administration (FDA) process analysis. NZ and RS, based at Public Citizen in Washington, District of Columbia, contributed expertise on pharmaceutical regulation. All authors critically revised the manuscript and approved the final version. Sources included FDA drug approval documents, corporate filings and peer-reviewed literature on the 505(b)(2) pathway and Alzheimer's pharmacotherapy.

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References

1 **Meglio M**. FDA approves new-generation acetylcholinesterase inhibitor alpha-1062 for mild-to-moderate alzheimer disease. Neurology Live; 2024. Available: www.neurologylive.com/view/fda-approves-new-generation-acetylcholinesterase-inhibitor-alpha-1062-mild-moderate-alzheimers
2 **Mossinghoff GJ**. Overview of the Hatch-Waxman Act and its impact on the drug development process. *Food Drug Law J* 1999;54:187–94.
3 **Darrow J**, *et al*. The 505(b)(2) Drug Approval Pathway. *Food Drug Law J* 2021;74.
4 Alpha cognition corporate presentation. 2025. Available: www.alphacognition.com/_resources/presentations/corporate-presentation.pdf
5 **Lim AWY**, Schneider L, Loy C. Galantamine for dementia due to Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev* 2024;11:CD001747.
6 Drug approval package: zunveyl. 2025. Available: www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218549Orig1s000TOC.cfm
7 **Mangoni AA**, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6–14.
8 **Datta A**, Dave D. Effects of Physician-directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. *Health Econ* 2017;26:450–68.
9 **Morin L**, Laroche M-L, Texier G, *et al*. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. *J Am Med Dir Assoc* 2016;17:862.
10 Benzgalantamine: drug information: uptodate. n.d. Available: https://www.uptodate.com/contents/table-of-contents/drug-information/patient-drug-information
11 Unleashing prosperity through deregulation. The White House, The United States Government; 2025. Available: www.whitehouse.gov/presidentialactions/2025/01/unleashing-prosperity-through-deregulation