Approval Is Not Exposure

A Category Error in Drug Safety and Informed Consent

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Abstract

FDA approval and accumulated human exposure are different forms of evidence. Approval establishes that a particular product satisfied an applicable benefit-risk and quality standard for a specified use, population, dose, route, and evidence package. Accumulated exposure establishes something else: the opportunity for common, rare, delayed, interaction-dependent, and population-specific effects to become visible over time. A newly approved treatment may possess strong evidence for its indicated use while retaining a larger horizon of unknown adverse effects than a familiar substance used by humans for generations. Conversely, a familiar substance may have extensive general safety experience while lacking adequate evidence for a new dose, duration, combination, or therapeutic purpose.

The category error occurs when approval status is treated as a complete comparative measure of safety. It is especially consequential when a novel, proprietary treatment is compared with a known, inexpensive, off-patent, or public-domain substance for which no economically viable sponsor has produced an indication-specific approval package. Nonapproval is then interpreted as the outcome of a failed safety evaluation even when no comparable evaluation occurred. This can impair informed consent by concealing differences in exposure history, residual uncertainty, evidence-production incentives, and the actual reason an alternative lacks approval.

Postmarket evidence demonstrates the practical importance of the distinction. In a cohort of 222 novel therapeutics approved by the FDA from 2001 through 2010, 71 (32.0%) were subsequently affected by a safety withdrawal, an incremental boxed warning, or an FDA safety communication. The median time to the first event was 4.2 years. Approval therefore cannot lawfully communicate that all material safety information is already known. This paper defines the category error, explains how it enters consent, identifies circumstances in which an approved novel treatment may carry greater residual unknown risk than an unapproved use of a historically familiar substance, and proposes a two-axis disclosure standard that preserves both indication-specific evidence and exposure-derived knowledge.

1. The Comparison Medicine Commonly Gets Wrong

Consider two treatment candidates.

The first is a novel substance approved for the condition being treated. It has undergone preclinical development and clinical trials. Its sponsor submitted an application, its manufacturing process was evaluated, and its label describes the evidence available at approval. Its benefit-risk profile has been assessed for an identified use.

The second is a substance that has been used by human beings for decades or centuries. It may be inexpensive, widely manufactured, off patent, naturally occurring, or otherwise difficult to control commercially. It has not been approved for the proposed therapeutic use. Its historical exposure

may reveal much about common tolerability and intrinsic toxicity, while providing little or no reliable evidence that it works for the condition now under consideration.

These candidates differ along at least two independent dimensions:

1. **Indication-specific evidence:** What is known about benefit and harm for the proposed use, formulation, dose, duration, population, and comparator?
2. **Accumulated human exposure:** How many different human beings have encountered the substance, under what conditions, for how long, and with how much opportunity for adverse effects to appear?

The first candidate may be stronger on the first dimension. The second may be stronger on the second.

The common shorthand collapses both dimensions into a single binary:

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FDA approved     = safer
not FDA approved = less safe
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That is the approval category error.

Approval is a regulatory and evidentiary status. Safety is a biological, clinical, temporal, and population-dependent condition. Approval contributes important information about safety, but it is not identical to safety and cannot rank every approved product above every nonapproved use of every known substance.

This distinction does not weaken standards of evidence. It makes the standards more exact.

2. What Novelty Preserves

No premarket program can reproduce centuries of human exposure before a new treatment enters the market. Clinical development observes a finite number of participants for a finite period under controlled eligibility criteria. It can identify frequent adverse effects, anticipated mechanism-related effects, and some serious risks. It is less capable of detecting:

- rare events requiring very large exposed populations;
- effects with long latency;
- effects emerging after prolonged or repeated use;
- interactions absent from the trials;
- harms concentrated in populations poorly represented during development;
- consequences of ordinary clinical use outside controlled trial conditions;
- effects that require years of changing health, age, diet, environment, or polypharmacy to become visible.

The FDA describes this boundary directly: complete safety information is impossible at approval, and the safety profile continues to evolve over the market life of a product.[1]

The size of the remaining uncertainty is not merely theoretical. Downing and colleagues examined all 222 novel therapeutics approved by the FDA from 2001 through 2010. During a median follow-up of 11.7 years, 71 treatments, or 32.0%, acquired at least one postmarket safety event: a withdrawal for safety, an incremental boxed warning, or a safety communication. The study identified 123

[1] U.S. Food and Drug Administration. "Step 5: FDA Post-Market Drug Safety Monitoring." Accessed July 2026. https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring

events in total, including 61 boxed warnings. The median time from approval to the first event was 4.2 years.[2]

The ten-year estimated proportion affected was 30.8%, with a 95% confidence interval from 25.1% to 37.5%. The proportion was 36.1% among biologics and 39.3% among treatments receiving accelerated approval, although subgroup estimates were less precise.[3] The accurate general statement is therefore that approximately one-third of the novel therapeutics in this major cohort developed a serious postmarket safety event. Some clinically important subgroups exceeded one-third.

Another study using an internal FDA database examined 219 newly approved small-molecule drugs. Eleven were withdrawn for safety and 30 received postmarket boxed warnings. Its authors concluded that many serious postmarketing events were not discernible from information available during premarket review.[4]

These findings do not show that approval makes a drug dangerous. They show that approval does not abolish the consequences of novelty. A novel treatment can be appropriately approved and still carry an unavoidable residual burden of undiscovered risk.

3. What Long Human Use Establishes

A substance used by humans for generations is not automatically safe. Historical use may be poorly documented. Products may vary in purity. Longstanding practices can preserve harm as easily as benefit. Rare events may remain unrecognized, and an old substance used in a new way can create new risks.

Even with those limitations, elapsed human exposure is evidence.

If a substance has been consumed or administered by large and diverse populations for a long period, then common, observable adverse effects compatible with those historical conditions have had repeated opportunities to appear. The inference is bounded:

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long exposure without an observed common effect
does not prove absence of all harm

but

long exposure creates more opportunity to reveal common effects
than brief exposure creates
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The relevant qualification is **compatible conditions**. Historical exposure at a low dose does not establish safety at a high dose. Food exposure does not establish intravenous safety. Short intermittent use does not establish the safety of continuous treatment. Use by healthy people does not resolve interactions in medically complex patients. Familiarity with the substance does not prove that it treats a disease.

[2]Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863. https://doi.org/10.1001/jama.2017.5150

[3]Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863. https://doi.org/10.1001/jama.2017.5150

[4]Schick A, Miller KL, Lanthier M, Dal Pan G, Nardinelli C. Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals. *Drug Safety*. 2017;40(6):497-503. https://doi.org/10.1007/s40264-017-0526-1

These are uncertainties introduced by the proposed regimen. They should be identified as such. They should not erase the separate information carried by the substance's human history.

A familiar substance can therefore possess:

- comparatively low uncertainty about common effects under historical use;
- substantial uncertainty about a new therapeutic regimen;
- inadequate evidence of efficacy for the proposed condition.

A novel approved treatment can simultaneously possess:

- stronger evidence of efficacy for the approved condition;
- better-defined manufacturing and dosing controls;
- comparatively high residual uncertainty about rare, delayed, and population-scale effects.

There is no contradiction. The contradiction appears only after different forms of evidence are forced into one approved-or-unapproved category.

4. Why Known Substances Often Lack Approval for New Uses

The public is commonly invited to imagine that plausible treatments enter a neutral comparative process, receive equivalent investigation, and emerge either approved or rejected. Under that model, nonapproval appears to mean that a candidate was examined and failed.

That is not how evidence is produced.

Approval requires an applicant or sponsor. The sponsor must organize development, fund or obtain the necessary studies, secure a sufficiently controlled product, prepare the regulatory submission, respond to review, and maintain the resulting obligations. A patent or period of market exclusivity can make these expenses recoverable.

A widely available public-domain or off-patent substance may offer no comparable ability to recover the cost. Any manufacturer may be able to sell the same substance after another party pays to establish the new use. The social value of the evidence may be large while the private return for producing it is small.

Formal routes for repurposed or off-patent medicines exist. Their existence does not ensure a viable path for every candidate. Reviews of drug repurposing identify persistent financial, regulatory, legal, organizational, and implementation barriers.[5][6] A 2025 lifecycle analysis reported that off-patent medicines often lack sufficient private incentives and that academic and nonprofit sponsors face additional regulatory limitations. The expert assessment in that study placed the likelihood of successful authorization below 30% under the conditions examined.[7]

The resulting asymmetry is straightforward:

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commercially recoverable evidence
-> sponsor
-> confirmatory trials
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[5] Garcia-Diaz M, Epstein D, Espin J. Overcoming barriers to off-patent drug repurposing: a lifecycle-based policy solutions. *Frontiers in Pharmacology.* 2025;16:1670845. https://doi.org/10.3389/fphar.2025.1670845

[6] Breckenridge A, Jacob R. Overcoming the legal and regulatory barriers to drug repurposing. *Nature Reviews Drug Discovery.* 2019;18(1):1-2. https://doi.org/10.1038/nrd.2018.92

[7] Garcia-Diaz M, Epstein D, Espin J. Overcoming barriers to off-patent drug repurposing: a lifecycle-based policy solutions. *Frontiers in Pharmacology.* 2025;16:1670845. https://doi.org/10.3389/fphar.2025.1670845

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-> regulatory application
-> possible indication approval

publicly valuable but privately unrecoverable evidence
-> weak sponsorship
-> incomplete confirmatory program
-> no application
-> no indication approval
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The second pathway does not establish that the substance works. It establishes that absence of approval has multiple possible causes.

A nonapproved use may lack approval because it is ineffective, unsafe, insufficiently studied, abandoned, commercially unattractive, impossible to standardize, unsupported by a sponsor, or never seriously investigated. Approval status alone cannot distinguish among these histories.

When nonapproval is communicated as though it were the result of an equal test, an economic and institutional outcome is misrepresented as a comparative biological finding.

5. How the Error Damages Informed Consent

Informed consent is not satisfied by providing a correct label for one treatment. It requires a decision maker to receive material information about the proposed intervention, its potential benefits, its risks, its uncertainties, and relevant alternatives.

The approval category error can damage that process in five ways.

5.1 It understates residual uncertainty in novel treatments

The word *approved* can be heard as *fully tested*. A patient may reasonably infer that rare and long-term risks have already been resolved. The postmarket safety record shows that this inference is not warranted.

5.2 It converts missing evidence into negative evidence

The absence of an approval package for a public-domain substance may result from missing sponsorship rather than a failed trial. When the absence is presented as evidence that the substance is more dangerous, an unknown state has been converted into a negative finding.

5.3 It conceals the difference between efficacy and intrinsic toxicity

A familiar substance may be ineffective for the proposed illness and still have fewer unknown common adverse effects than a novel treatment. Conversely, a novel treatment may be demonstrably effective while carrying more residual unknown toxicity. Consent requires both facts. The approval binary encourages one to replace the other.

5.4 It prevents meaningful comparison of alternatives

A statement that one option is approved and another is not may be accurate but materially incomplete. It does not tell the patient:

- which treatment has stronger evidence of benefit;

- which has deeper cumulative human exposure;
- which adverse effects are established;
- which risks remain unknown;
- whether the proposed use differs from historical exposure;
- whether the absence of evidence reflects negative results or absence of investigation.

5.5 It transfers the decision from the patient to the category

When approval is allowed to answer every question at once, the patient's role is reduced to accepting or rejecting an institutional conclusion. The person does not receive the information necessary to decide how efficacy, uncertainty, historical exposure, product quality, and personal risk tolerance should be weighed.

Public misunderstanding is documented. A nationally representative survey of 1,744 U.S. adults found substantial misperceptions about the scope and meaning of FDA prescription-drug oversight.[8] The category error is therefore not an abstract possibility. It enters a population already inclined to assign more meaning to approval than the designation contains.

6. When the Approved Treatment Can Present Greater Risk

No rule makes every approved treatment safer than every unapproved use. In some comparisons, the approved treatment can present greater risk.

This can occur when:

- the approved treatment is a novel molecular entity with limited cumulative exposure;
- the comparator is a substance with extensive and relevant human use;
- the approved treatment has serious known toxicity accepted because the treated disease is severe;
- the comparator's historical dose and route are close to the proposed use;
- the approved treatment's residual rare or delayed risks remain unresolved;
- the comparator's product identity and purity are adequately controlled;
- the comparison concerns toxicity or unknown adverse effects rather than proven therapeutic efficacy.

Approval is based on benefit relative to risk for an intended use. It is not a certification that the treatment has less intrinsic risk than all alternatives. A toxic oncology drug can be approved because its expected benefit justifies its danger. A familiar substance may be less toxic while having no demonstrated anticancer effect. Calling the approved treatment *safer* would be incorrect even if choosing it remains medically justified because it works.

The distinction matters:

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more appropriate treatment != intrinsically safer substance
stronger evidence of benefit != fewer unknown adverse effects
approval for a use != comparative testing against every alternative
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Informed consent fails when these unequal statements are treated as synonyms.

[8] Sullivan HW, O'Donoghue AC, Aikin KJ. Consumer understanding of the scope of FDA's prescription drug regulatory oversight: A nationally representative survey. *Pharmacoepidemiology and Drug Safety.* 2020;29(2):134-140. https://doi.org/10.1002/pds.4914

7. A Two-Axis Disclosure Standard

The category error can be corrected without changing the legal status of any treatment and without lowering the threshold for therapeutic claims.

Every material treatment comparison should disclose two evidence axes separately.

Axis A: Evidence for the proposed therapeutic use

- approval status and exact approved indication;
- trial population and comparator;
- evidence of benefit;
- observed adverse effects;
- dose, duration, route, and formulation;
- product-quality controls;
- uncertainty specific to the proposed regimen.

Axis B: Accumulated human-exposure evidence

- length and extent of human use;
- similarity of historical exposure to the proposed regimen;
- diversity of exposed populations;
- known common and serious effects;
- latency available for delayed effects to appear;
- quality and completeness of historical records;
- remaining unknown intrinsic and interaction-dependent risks.

The reason evidence is missing should be disclosed separately:

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negative trial
safety failure
insufficient data
no sponsor
commercial abandonment
unresolved manufacturing problem
no investigation for the proposed use
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These are not equivalent states.

The disclosure should conclude with a calibrated statement rather than a binary:

> This treatment has stronger evidence for benefit in the proposed use. It is newer and retains greater uncertainty about rare or long-term effects.

or:

> This substance has extensive prior human exposure, reducing uncertainty about common effects under historical conditions. Its effectiveness and safety at the proposed therapeutic regimen have not been established.

Either statement can support a rational decision. Neither requires the patient to mistake regulatory status for a complete safety ranking.

8. Implications for Medicine and Pharmaceutical Development

For clinicians, the practical obligation is to avoid using approval as a substitute for describing material differences. A concise conversation can still distinguish evidence of benefit, known toxicity, historical exposure, and residual uncertainty.

For pharmacists, formulary committees, and health systems, the implication is that approval status should remain a required operational field without becoming the only field through which alternatives are interpreted.

For pharmaceutical developers, the distinction protects rather than devalues successful development. A completed approval program is strong evidence for a defined use. Its value does not require claiming knowledge that only time and larger exposure can provide.

For public funders, the analysis identifies a neglected evidence-production problem. When a plausible public-domain candidate lacks private appropriability, the absence of a sponsor can prevent society from learning whether the candidate is useful. Public investment is warranted where the expected value of resolving the question exceeds the cost of doing so, regardless of whether the answer is positive or negative.

For regulators and policy designers, the immediate need is not a universal approval pathway for every familiar substance. It is a means of distinguishing failure from noninvestigation and of making accumulated human exposure visible without allowing familiarity to substitute for indication-specific evidence.

9. Boundaries of the Claim

This analysis does not establish that any particular unapproved treatment is effective. It does not treat anecdote as a clinical trial, historical use as proof of safety, or familiarity as proof of manufacturing quality. It does not recommend replacing established care with an unevaluated therapy.

It establishes that:

1. regulatory approval and cumulative human exposure are different evidence categories;
2. novelty necessarily limits the amount and duration of human exposure available at approval;
3. serious adverse effects are frequently identified only after approval;
4. known public-domain substances can lack indication-specific evidence because the evidence has no reliable private sponsor;
5. nonapproval does not reveal which causal history produced the missing approval;
6. informed consent is impaired when approval is presented as a complete comparative safety judgment.

Approximately one-third of novel therapeutics in a major FDA cohort acquired a serious postmarket safety event. That observation should permanently end the assumption that approval closes the safety inquiry. It begins a period of larger human observation.

Approval is evidence. Exposure is evidence. Neither is everything, and neither can safely stand in for the other.

References

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Ikeda J, Kaneko M, Narukawa M. Post-marketing safety-related regulatory actions on first-in-class drugs: A double-cohort study. *Journal of Clinical Pharmacy and Therapeutics*. 2020;45(3):496-502. https://doi.org/10.1111/jcpt.13096