Trends in Biotechnology

CellPress

Science & Society

The liquidity paradox of the 505(b)(2) drug development pathway

Oded Ben-Joseph[1,*], and Stanislav Glezer[1]

Regulatory pathways strongly influence how drugs are developed, financed, and sold. This article compares the FDA's 505(b)(1) and 505(b)(2) routes, showing how the latter reduces both the development risk and the probability of postapproval transactions, and identifies strategies that can restore attractive, risk-adjusted investment returns.

Regulatory pathways as risk–return levers: 505(b)(1) versus 505(b)(2)

Pharmaceutical **R&D** (see Glossary) conducted under 505(b)(1) or 505(b)(2) pathways reflects distinct regulatory and economic profiles that map closely to risk–return trade-offs in drug development[i] (Table 1). The 505(b)(2) pathway was designed to avoid unnecessary duplication of studies for already-approved active ingredients. The sponsor needs to address only the changed elements, such as new formulation, dosage form, strength, route of administration, dosing regimen, or indication. This creates a dossier that combines newly generated data with prior evidence. 505(b)(2) programs usually require fewer and smaller trials, translate to shorter development timelines, and are less capital intensive than 505(b)(1) programs [1].

505(b)(1) programs are often the core value drivers in innovative biopharma portfolios and command higher upfront and milestone-heavy deal terms once Phase 2/3 data are positive. 505(b)(2) opportunities, while generally commanding lower pricing, may be attractive in business development as they provide faster integration, earlier cash flows, and more financing flexibility. Since the 505(b)(2) pathway allows sponsors to rely on previously generated data, early-stage development work is usually limited, rendering early-stage transactions largely irrelevant for 505(b)(2) assets. Given the limited risk in late-stage development, one would expect these assets to be involved in a large number of transactions, with pharma companies favoring Phase 3 or approved products. However, when we compared 505(b)(1) and 505(b)(2) regulatory pathways as levers shaping risk, cost, and exit premiums, we observed lower translatability and valuations of 505(b)(2) products as compared to the 505(b)(1) benchmarks, highlighting a **liquidity** paradox for 505(b)(2) assets. In this article, we discuss the **transactability** of 505(b)(2) assets and companies and strategies for improved value inflection.

Utilization and approval trends

Utilization of 505(b)(2) has expanded from a niche exception to a mainstream regulatory strategy, with approximately 40% of FDA approvals in 2024 obtained via 505(b)(2) and more than 40 such products receiving approvals annually in recent years (Box 1). This reflects a broader industry shift toward incremental innovation and lifecycle management, including new dosage forms, combinations, indications, and delivery technologies built on established pharmacology.

Expected valuation and exits

Historically, most biotech company or product acquisitions occurred after Phase 2 clinical trials, reflecting an optimal balance of acquisition cost, required capital, and residual risk [2]. By Phase 2 completion, **new chemical entities (NCEs)** typically have derisked safety, dosing regimen, and efficacy signal, leaving Phase 3 risks largely tied to confirming the magnitude of efficacy and detecting rarer adverse events. NCE Phase 3 and launch-related costs are high and often prohibitive for private companies. As a result, Phase 2 milestones have traditionally offered the best alignment of risk, valuation, and resource needs to drive transactions between biotech sellers and pharma acquirers.

In recent years, this conventional model has shifted. Some pharma companies now favor acquiring assets that are approved or have completed Phase 3 to accelerate revenue impact, even at a premium. Others have taken the opposite approach, licensing very early-stage assets—even prelead optimization—to place multiple lower-cost bets, gain development control, diversify risk, and manage deal costs through early termination decisions for weaker programs [3].

Observed 505(b)(2) transactions

Our analysis (Box 1) revealed that less than 10% of 505(b)(2) assets were subject to transactions following regulatory approval. We have identified only 16 relevant transactions, one being a full-company acquisition, two financing deals, and the remaining 13 structured as asset deals. Asset transactions typically range between $25 million and $50 million and occur within 1–4

Glossary

Composition of matter patent: a patent that protects new, nonobvious, and useful chemical combinations, mixtures, or compounds, covering the material itself rather than just its application or method of creation.
Liquidity: measure of how quickly and easily an asset (product or company) can be converted into cash without significantly affecting its market price.
M&A: the process of consolidation of companies or their assets through financial transactions, such as mergers, acquisitions, or tender offers.
New chemical entity (NCE): a drug substance containing an active molecule that has not been previously approved by the FDA in any application.
R&D: research and development, refers to activities undertaken to innovate, create new products or services, or improve existing ones.
Transactability: the capability of an asset to be easily bought, sold, traded, or transferred between parties.

Table 1. Comparison of the FDA 505(b)(1) versus 505(b)(2) pathways

Category	505(b)(1)	505(b)(2)
Purpose	Full NDA for NCEs	NDA for modified versions of previously approved drugs
Data ownership	Applicant generates and submits all nonclinical and clinical data	Applicant combines efficacy and 'bridging' data with literature and/or references to prior FDA filings
Innovation	High: NCEs	Low to moderate: modified versions of approved drugs (new formulation, route, combination, strength, indication, etc.)
Nonclinical requirements	Full nonclinical program (e.g., toxicology and pharmacology)	Targeted nonclinical work to address differences from the reference product
Clinical development cost	High: extensive clinical development full Phase 1–3 program to establish safety, PK, dose, and efficacy	Lower: reduced clinical program focused on PK/bridging and efficacy studies tailored to the change (e.g., formulation and indication)
Development timelines	Longer: 7–12 years	Shorter: 3–7 years
Regulatory exclusivity	5 years plus extensions	3–7 years
IP protection of market exclusivity	Strongest: **composition of matter** plus use/formulation/manufacturing patents	Weak to moderate: typically, formulation, delivery, or method-of-use patents; easier for competitors to design around
Technical/regulatory risk	High: greater chance of late-stage failure	Moderate: safety largely derisked, focus on demonstrating efficacy and bridging
Competitive positioning	High: innovation, high-value assets, and large peak sales	Moderate in border indications; high in orphan indications
Commercial profile	High risk and high reward: potential for blockbuster impact	Medium risk–return: faster path to revenue and market validation
Sponsors	Innovative pharma and biotech	Specialty pharma, lifecycle management teams, and PE-backed platforms seeking derisked assets

years following market authorization. This market observation suggests that newly approved 505(b)(2) assets, especially from smaller private US sponsors, do not consistently trigger near-term strategic transactions, implying that transactable value is deferred until commercial performance is demonstrated. According to an IQVIA report, the mean transaction value for pharma licensing deals was close to US $400 million[ii], indicating that 505(b)(1) assets support higher valuations and multiples, especially when they are late stage or approved, while 505(b)(2) assets generally transact at lower values and often implicitly lower revenue multiples, reflecting more modest differentiation, smaller peak market potential, and shorter or narrower market exclusivity, but with significantly lower development cost and risk. As such, risk-adjusted returns may still be attractive.

Sponsor mix and transaction context

Sponsor composition helps explain muted deal activity: a substantial share of 505(b)(2) sponsors are public specialty or generic companies that tend to develop approved assets to augment inhouse portfolios, limiting sell-side supply and skewing transaction opportunities toward private sponsors. As a result, observable deal flow disproportionately depends on smaller private companies, where disclosures can be sparse and exits may be deliberately delayed to capture commercial proof points.

Orphan concentration and market size

A meaningful portion of 505(b)(2) approvals aligns with rare diseases and orphan designations, consistent with incentives and the feasibility of repurposing established actives for narrowly defined populations. Orphan drugs can receive 7 years of exclusivity for the designated use, strengthening the business case but often within constrained markets (<200 000 patients) that may be less attractive to large acquirers.

Exclusivity and Intellectual Properties (IP) considerations

Relative to composition of matter protection typical of NCEs, 505(b)(2) assets often rely on formulation, method of use, or dosing IP, which can be perceived as offering weaker protection of market exclusivity, and on regulatory exclusivities of 3 years (clinical investigations essential to approval), 5 years (NCE), or 7 years (orphan), with pediatric extensions adding 6 months where applicable[iii]. This protection profile, though meaningful, may be judged insufficient by acquirers to support precommercial valuations without clear barriers to substitution and durable payer positioning, dampening prelaunch **M&A** appetite and requiring the 505(b)(2) sponsor to launch the product on their own.

Shift in value inflection

Because 505(b)(2) reduces development and approvability risks by leveraging prior findings, a larger share of total project risk migrates to commercial execution. Consequently, meaningful value inflection may cluster around launch and early revenue ramp, delaying liquidity events until the establishment of the proof of commercial product viability through reimbursement and realized sales.

Box 1. How did we assess regulatory efficiency?

We assessed how the regulatory efficiencies of the 505(b)(2) pathway affect investor liquidity, time to value inflection, and key drivers of transactability in the current market. FDA New Drug Application (NDA) approval reports from the recent 5-year period (2020–2024) were downloaded from fda.gov[iv]. Following data tabulation, we identified 505(b)(2) approvals and categorized them by indication: rare/orphan, CNS, oncology, anti-infective, and other. We identified a sponsor for each of the approvals, compiled a list of sponsoring companies, and categorized them as specialty pharma, generic manufacturers, big pharma, or other. Approval data were crossreferenced with PitchBook and GlobalData©, commonly used and comprehensive transaction datasets, to identify related product or company transactions. Transaction information was tabulated based on the stage of product development or commercialization, time of the transactions relative to the time of approval, transaction type, and transaction value. Descriptive analysis was used for summarizing transaction activities within the sample (Table I). For transactability analysis, we focused on US and European companies, given incomplete visibility into foreign deals.

Table I. Financing, M&A, or asset transactions made within 5 years of 505(b)(2) approval

505(b)(2) approvals and transactions							
	2024	2023	2022	2021	2020	Mean	Cumulative
Total 505(b)(2) approvals	38	39	59	48	62	49	246
Sponsor type							
Big pharma	13%	5%	5%	2%	6%	6%	15
Generics	26%	33%	29%	29%	27%	29%	71
Specialty pharma	37%	33%	47%	58%	63%	48%	122
Other	24%	28%	19%	10%	3%	17%	38
Indication							
Rare/orphan	39%	23%	22%	21%	26%	26%	63
CNS	21%	21%	22%	25%	10%	20%	47
Oncology	3%	8%	8%	4%	5%	6%	14
Anti-infective	16%	18%	8%	8%	11%	12%	29
Other	21%	31%	39%	42%	48%	36%	93
Approvals for public companies	28	24	27	26	30	27	135
Approvals for private companies	10	15	32	22	32	22.2	111
Postapproval no deals/no data	37	36	55	43	59	93%	230
Postapproval financing	0	1	0	0	1	1%	2
Postapproval M&A/asset transaction	1	2	4	5	2	6%	14
Total postapproval deals	1	3	4	5	3	7%	16
Years from approval to transaction						1.76	

Financing implications

If exits are less probable before commercialization, financing plans should be sized to span both development and launch, possibly combined in the same round. With transactability and valuation being predominantly driven by launch success and given reduced clinical development costs for 505(b)(2) entities, the use of proceeds might need to be disproportionately skewed toward growth capital.

Role of private equity

Once a product has demonstrated real market demand, private equity firms may step in to acquire revenue-producing and profitable drugs approved under the 505(b)(2) pathway—especially when insurance coverage is in place and there is still time left on the product's market exclusivity to earn strong returns. However, companies built around a single product with only a short period of exclusivity remaining tend to be valued less highly. As a result, private equity investors usually prefer to acquire companies with multiple products or platforms, which offer more stable and diversified sources of revenue.

Platform and roll-up strategy

While a portfolio strategy that aggregates multiple 505(b)(2) products at staggered lifecycle stages may introduce incremental operational complexity and execution risks, it can mitigate cliff risk, exploit channel synergies, and sustain revenue despite finite exclusivity on individual assets. Such platforms may also transact earlier—prelaunch or preapproval—by underwriting commercialization across a pipeline of similar products, aligning sellers' needs for earlier liquidity with buyers' confidence in repeatable go-to-market execution.

Portfolio strategy as a path to liquidity

Companies should view 505(b)(2) products as strategic beachheads rather than terminal objectives—an entry point that builds presence and credibility in a target market while laying the groundwork for NCE-based drug development to drive up overall company valuation. Positioned effectively, a 505(b)(2) asset can accelerate market entry, drive early revenue, validate the commercial thesis, and confirm target prescriber and patient segments, laying the groundwork for NCE assets in the same segment or indication. The cash flow from the 505(b)(2) product commercialization can fund early development stages for the NCE assets, allowing the company to avoid equity dilution traditionally associated with corresponding financing needs. In fact, it is the higher valuation

and transactability of the follow-on NCE product that can become the key factor in selling the company, increasing potential returns for the investors in the initial 505(b)(2) asset.

Concluding remarks

The 505(b)(2) pathway, while highly efficient from a development and regulatory standpoint, does not reliably translate into early or robust liquidity for investors, pushing value inflection to the commercialization phase. The observed deals tend to be modest in value and sporadic in timing, reflecting the interplay of sponsor mix (with many approvals residing in public specialty and generic companies that favor product retention), perceived limitations of IP and exclusivity, orphan-driven niche market sizes, and acquirers' preference to wait for commercial proof points before underwriting meaningful premiums.

Sponsors who design their 505(b)(2) programs, capital plans, and business development strategies around this 'liquidity paradox' can still realize attractive risk-adjusted returns, but only by explicitly funding through commercialization, building credible go-to-market capabilities, and positioning assets within broader platforms that mitigate loss-of-exclusivity risks for individual assets due to diversification and enhance strategic relevance for both strategic and financial buyers.

Declaration of interests

The authors declare no competing interests.

Resources

[i]www.fda.gov/drugs/development-approval-process-drugs

[ii]https://www.iqvia.com/-/media/iqvia/pdfs/library/articles/iqvia-pharmadeals-review-2024-ungated.pdf

[iii]www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistancefrequently-asked-questions-new-drug-product-exclusivity

[iv]www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals

[1]Outcome Capital LLC, Boston, MA, USA

*Correspondence:
oben-joseph@outcomecapital.com (O. Ben-Joseph).

https://doi.org/10.1016/j.tibtech.2026.03.001

References

1. Freije, I. *et al.* (2020) Review of drugs approved via the 505 (b)(2) pathway: uncovering drug development trends and regulatory requirements. *Ther. Innov. Regul. Sci.* 54, 128–138
2. de Bloeme, C.M. *et al.* (2021) Stepping to the exit. *Nat. Biotechnol.* 39, 1048–1054
3. Dao, H. and Ledley, F.D. (2025) Sustaining pharmaceutical innovation after the Inflation Reduction Act: trends in R&D spending, equity investment, and business development. *Drug Discov. Today* 30, 104394