Intellectual Property & Technology Law Journal

Edited by the Technology and Proprietary Rights Group of Weil, Gotshal & Manges LLP

VOLUME 36 • NUMBER 10 • NOVEMBER-DECEMBER 2024

Old Drugs, New Tricks: Repurposing Through 505(b)(2) Submissions

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FDA DRUG APPROVAL PATHWAYS

505(b)(1) New Drug Application

De novo drug development is costly and time consuming. Some studies estimate that research and development costs for a 505(b)(1)[1] New Drug Application (NDA) range from $314 million to $4.46 billion.[2] Additionally, the time between drug development and launch generally takes about twelve years.[3] Whereas an approved NDA is required to market that drug in the United States, granted U.S. patents are needed to protect that market from copycats, by preventing competitors from making, using, selling, offering to sell, or importing a patented drug in the United States for a limited period.[4] Thus, drug developers must separately apply for both drug approval from the Food and Drug Administration (FDA) and patent protection from the United States Patent and Trademark Office (USPTO)[5] to market and protect their new drugs.

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The 505(b)(1) pathway is the most expensive, but also provides the opportunity to earn the most extensive patent and non-patent marketing exclusivities. NDAs under 505(b)(1) require the sponsor to conduct de novo preclinical and clinical studies firmly establishing the safety and efficacy of their proposed new drugs.

Once an NDA is approved, subsequent or "follow on" 505(b)(2) and 505(j) applications have the option to designate that new drug as a "reference listed drug" (RLD) to rely on the extensive safety and efficacy data to support their own approvals, thus bypassing the high costs for conducting their own studies. Of course, the benefits of bypassing those costs also come with various obligations on the subsequent applicants that take advantage of piggy backing on the RLD. For example, the FDA's online database Approved Drug Products with Therapeutic Equivalence Evaluations, colloquially known as the "Orange Book," publishes a list of all approved drugs and lists every patent that covers each drug.[6] Any subsequent applicant who designates another drug as its RLD must certify to any patents covering that RLD, and will be subject to potential delays, from either litigation or marketing exclusivities before receiving approval of their own drugs.

505(j) Abbreviated New Drug Application

Drug developers seeking to introduce low-cost generic versions of branded drugs need only submit an Abbreviated-NDA (ANDA) referencing its branded counterpart as the RLD under 505(j). An ANDA is substantially less expensive than an NDA because it is a duplicate of an approved new drug.[7] As a "duplicate," the ANDA does not have to demonstrate independent safety and efficacy of the proposed generic drug, but rather simply has to show that it is "bioequivalent"[8] to the corresponding branded RLD.[9] But a generic under the ANDA pathway must meet the FDA's strict "sameness" requirement that the proposed generic must be identical to the RLD with respect to active ingredient, salt form, dosage strength, dosage form, route of administration, labeling, and intended use. Consequently, there is limited opportunity to design around a brand drug's patents or make product modifications.

To incentivize early generic competition, Congress provided for certain economic rewards for being the first company to file an ANDA that challenges one or more Orange Book listed patents, and seeks to enter the market prior to patent expiration. This challenge is known in the industry as a "Paragraph IV certification."[10] Successful challengers are awarded 180 days of generic market exclusivity.[11]

505(b)(2) "Paper" New Drug Application

Faced with high approval costs for an NDA and crippling competition in the generic market, drug companies are turning to the 505(b)(2) NDA or the "Paper NDA." The 505(b)(2) pathway is a hybrid between a de novo NDA and an ANDA, having some features of each. Like an ANDA, a Paper NDA is partially abbreviated and benefits from referencing and relying on the safety and effectiveness data of an existing, approved, branded RLD.[12] Consequently, the 505(b)(2) applicant can avoid some of the time and costs associated with extensive preclinical and clinical safety and efficacy testing.[13] But – unlike an ANDA – the drug proposed in a Paper NDA will differ materially, often substantially, from the underlying RLD. The 505(b)(2) pathway permits proposed product modifications that deviate from the RLD, including the salt form, dosage form, route of administration, strength, new combination product, modified active ingredient, new indications for previously approved drugs, or an over-the-counter switch.[14] For example, the Paper NDA may seek approval of a transdermal or injectable form of an RLD that exists only in oral form. These approved product modifications allow drug developers to design around existing Orange Book patents. Accordingly, a drug approved under the Paper NDA is often viewed as a "new" drug, rather than a generic.[15]

The 505(b)(2) pathway presents the opportunity for significant economic and financial benefits. A 505(b)(2) applicant can rely upon the RLD's safety and efficacy data, saving potentially hundreds of millions of dollars. But, as a new drug that has its own niche market, the drug approved under the 505(b)(2) pathway can enjoy prolonged market exclusivity, unlike a generic under the ANDA pathway. The tradeoff is that 505(b)(2) sponsors must conduct "bridging" studies to account for the differences from the RLD, which is significantly more expensive than an ANDA, but far less expensive than a de novo NDA. Accordingly, the lack of a "sameness" requirement permits 505(b)(2) applicants to minimize costly studies while maximizing profitability.

In short, this pathway provides applicants an opportunity to use existing approved materials to hasten new products to market, so long as they establish a sufficient scientific "bridge" between the new product and the RLD.[16] The bridge must meaningfully underscore similarities between the new product and the RLD as well as highlight the ways in which the new drug product is genuinely new and different.[17] Depending on the extent and nature of deviation from the RLD, an approved product under the 505(b)(2) pathway can be designated either as a true generic that is AB-rated, a "branded" generic that is non-AB rated, or a stand-alone branded drug.[18] Ratings, also called "therapeutic equivalence evaluation codes," act as a measure of sameness. The FDA considers a drug product with an "A" code therapeutically equivalent to another product. Drug products with "A" code ratings are interchangeable by pharmacists. As a result, the FDA affords 505(b)(2) drug developers the option to choose whether to petition (in addition to the new drug application) to be substitutable with the RLD.

Table I. Comparison Among Different Application Pathways

		505(b)(1)	505(b)(2)	505(j) (ANDA)
Exclusivity	180-Day Exclusivity	–	–	✓
	NCE (5 years)	✓	Potentially	–
	New Clinical Investigation (3 years)	✓	✓	–
	Orphan Drug Exclusivity (7 years)	✓	✓	–
	Pediatric Exclusivity (6 months)	✓	✓	–
Litigation	Patent Certification	–	✓	✓
	30-Month Stay	–	✓	✓
	Section viii Carve-Out	–	✓	✓
	Must send Notice Letter	–	✓	✓
Safety & Efficacy		Full Analysis	Partial Analysis	No Analysis
Safety & Efficacy by Application		Full Analysis (No Previously Approved Drug)	Reduced Analysis (Only a Bridging Study is Required)	No Analysis (Duplicate of a Previous Approval)
Regulatory Review Period		~ 10–12 months	~ 10–12 months	~ 15–24 months
FDA Guidelines		PDUFA	PDUFA	GDUFA
U.S. Application Cost (2024 User Fee Rates) ⋆Excludes Program Fees		Clinical Data[20] $4,048,695 No Clinical Data[21] $2,024,348	Clinical Data[22] $4,048,695 No Clinical Data[23] $2,024,348	ANDA Fee[24] $252,453 + DMF Fee[25] $94,682
⋆The FDA assesses drug Program Fees annually. For new drug applications, the Program Fee rate[26] is $416,734. For ANDA applications, the Program Fee[27] is variable based on the number of ANDA applications filed.				

COMPARING PATHWAYS

As mentioned above, the 505(b)(1) NDA governs entirely new drug products, while the 505(j) ANDA provides for generic copies that are the "same" as an RLD. The 505(b)(2) application is a "hybrid" pathway, that has the same active drug moiety, but other new and different features.[19] As shown in Table I, each of the three pathways includes different terms of market exclusivity, safety and efficacy testing, and patent certification requirements. While each pathway is distinct, overlap exists.

Once approved, each drug pathway described above provides a certain period of exclusivity.

There are five types of regulatory (non-patent) exclusivities available for drug approval.[28]

- A new clinical investigation involves a new investigation other than bioavailability studies related to a new dosage form, new product, new patient population, or new combination. The product receives three years of exclusivity.[29]

- A new chemical entity may be approved for a never before approved active moiety. The product receives five years of exclusivity.[30]

- An orphan drug may receive approval for a rare disease where scientific data exists. The product receives seven years of exclusivity.[31]

- Pediatric exclusivity adds 6 months to all other exclusivities, including to the expiration date of any Orange Book patents, if sponsors conduct pediatric testing on drugs selected by the FDA.[32]

- A new antibiotic conforming to the requirements of the Generating Antibiotic Incentives Now Exclusivity (GAIN) Act may receive expedited

approval. The product receives additional exclusivity in addition to other forms of exclusivity.[33]

CASE STUDIES INVOLVING 505(b)(2) APPROVED PRODUCTS

This section explores the strengths, limitations, and usefulness of the 505(b)(2) pathway in comparison to the 505(b)(1) NDA and 505(j) ANDA pathways by examining five case studies. Through varying lenses, these case studies demonstrate how drug makers have leveraged the unique features of the 505(b)(2) pathway for multiple advantages, including optimize return on investments, circumvent a first ANDA filer's 180 day exclusivity, repurpose existing drugs into new products, and decrease market competition.

Case Study 1: Narcan – Obtaining a New Dosage Form and Route of Administration

Naloxone hydrochloride is used to treat opiate overdose. In 2015, Narcan Nasal Spray – an intranasal spray version of naloxone – was approved under 505(b)(2).[34] Naloxone,[35] the RLD, was initially approved by the FDA in 1971 as a solution to be administered via intravenous (IV), intramuscular (IM), or subcutaneous use (SU). In 2015, the FDA approved Narcan over the counter (OTC) for use via intranasal spray. Many patients find nasal administration less intimidating compared to an injection.

No New Safety Studies. During product development, the applicant, Adapt Pharma Inc., and the FDA concluded that designing an efficacy study to define an effective range of naloxone use in an overdose setting would be ethically unjustifiable because it would necessitate opioid administration to create an overdose. Consequently, the FDA permitted Adapt to rely upon an existing approved dosing regimen for naloxone and demonstrate that the new product matched or exceeded the pharmacokinetic parameters for a previously approved route. Thus, Adapt needed only demonstrate that the intranasal spray provided systemic naloxone similar to the IM injection.

The 505(b)(2) application relied on International Medicinal System's naloxone HCl injection USP pre-filled syringe[36] for the relative bioavailability study critical to construct the "bridge" to the FDA's previous Narcan findings. The 505(b)(2) pathway, thus, permitted Adapt to rely on the RLD's safety and efficacy information. This allowed for significant time and cost savings because the intranasal formulation required no new safety studies despite being a novel dosage form and route of administration.

Substantial Revenue. After acquiring Adapt, Emergent Biosolutions Inc. reported a 30% sales increase from $113.8 million, to $487.5 million of Narcan in 2023.[37] Emergent's commercial product sales also rose $50 million, or 31%, to $287 million in 2023, primarily driven by increased Narcan sales.[38]

Streamlined Approval of Two Products

Case Study 2: Lybalvi – Streamlined Approval for New Molecular Entity (NME) and Combination

In 2021, the FDA approved the combination drug Lybalvi (olanzapine; samidorphan L-malate) in NDA 213378 as both a new molecular entity combined with an old existing drug (olanzapine).[39] The NME approval for samidorphan L-malate (samidorphan) occurred under 505(b)(1). However, the FDA approved the new combination of samidorphan and olanzapine under a 505(b)(2) amendment to the new drug. Both approvals occurred on May 28, 2021.[40]

The applicant, Alkermes, Inc., performed clinical safety and efficacy studies on samidorphan alone and in combination with antipsychotic agents.[41] Instead of submitting separate datasets for samidorphan L-malate alone and in combination with antipsychotic agents, Alkermes was able to submit one set of data showing the safety and efficacy of its samidorphan and olanzapine combination.[42] Because the FDA had already reviewed olanzapine's safety profile in the RLD's approval, Alkermes was able to gain two approvals (paper and classic NDA) in one application without excessive research costs. By combining 505(b)(1) and 505(b)(2), Alkermes leveraged the benefits of both approval pathways by decreasing waste associated with duplicative research and FDA submissions.

New Indications

Case Study 3: Finasteride – Drug Repositioning via a New Dosage and Indication

In 1992, the FDA approved Merck & Co.'s finasteride (a synthetic 4-azasteroid compound) for

benign prostatic hyperplasia (BPH) in men with an enlarged prostate.[43] The approval covered a 5 mg film-coated tablet marketed under the brand name Proscar.[44] Five years later, in 1997, the FDA approved Merck's Propecia – a 1 mg finasteride oral tablet for male pattern hair loss (androgenetic alopecia), designating the prior Proscar product as the RLD.[45]

Leveraging Existing Materials. The 505(b)(2) pathway allowed Merck, like other 505(b)(2) applicants, to rely on its RLD's preclinical, phase I and phase II studies.[46] Merck conducted three phase III studies to provide evidence that a lower dosage of finasteride (Propecia 1 mg tablets compared to Proscar 5 mg tablets) is safe and effective for treating a new indication: male androgenetic alopecia. Further, Propecia received approval to directly extract and append portions of Proscar's initial labeling to its own to promote consistency between the products despite differing indications.

By leveraging its existing drug, Proscar, and repurposing some of its development materials, Merck was able to expedite the production and approval of the same drug, finasteride, with a new dosage and indication in Propecia, saving time and money via the 505(b)(2) pathway. While Merck spent about $1 billion in marketing and research, such expenditures were dwarfed by the estimated over $4 billion in Propecia sales between 1998 and 2015.[47] The 505(b)(2) pathway allowed Merck to advantageously leverage its earlier Proscar studies and materials to accelerate the lucrative Propecia's development process.

Follow-On Products

Case Study 4a: Austedo – Follow-On Product Obtains New Chemical Entity (NCE) Exclusivity

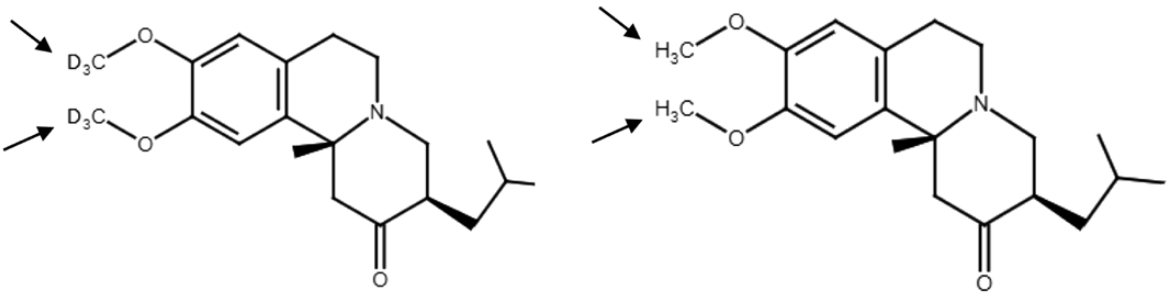
In April 2017, the FDA approved Teva Pharmaceuticals, Inc.'s Austedo (a deuterated form of tetrabenazine) via the 505(b)(2) drug approval pathway for the treatment of chorea associated with Huntington's disease and tardive dyskinesia.[48] The FDA's approval of Austedo via the 505(b)(2) pathway affirms that even slight structural differences, like deuteration, renders drugs sufficiently distinct. In deuterated drugs, deuterium – a heavier stable hydrogen isotope – replaces one or more hydrogen atoms.[49] Deuterated drugs provide an extended half-life due to decreased metabolic rate from the kinetic isotope effect. Thus, two groups of three hydrogen atoms replaced by deuteriums, essentially six neutrons in difference (see Figure 1), bestowed Austedo with NCE status over the RLD, Xenazine.[50]

Deuteration May Receive NCE Status with Prolonged Protection. Because the FDA classified Austedo as an NCE, it received 5-year market exclusivity, otherwise only available to NDA applicants.[51] For Austedo, the substitution of hydrogen atoms for deuteriums, involving non-ester covalent bonds, produced an acceptable structural difference as compared to Xenazine. Thus, Austedo procured 5 years of exclusivity by obtaining NCE status premised on the substitution of hydrogen atoms for deuteriums.

Case Study 4b: Austedo XR – New Dosage Form

In 2023, the FDA approved Austedo XR (extended-release) under the 505(b)(2) pathway.[52]

Figure 1.



Austedo **Xenazine**

Table II. 505(b)(2) U.S. Drug Products Revenue

505(b)(2) Drug	RLD	505(b)(2) Change	Revenue first full calendar year after approval (millions of US $)
Narcan Nasal Spray	naloxone HCl injection[60]	New Dosage Form[61]	242.6 ⋆ [62]
Lybalvi	olanzapine and samidorphan L-malate[63]	New Combination[64]	1,548.49 [65]
Propecia	Proscar[66]	New Dosage Form[67]	76 [68]
Austedo XR	Xenazine; Austedo[69]	New Formulation[70]	1,225 ⋆⋆ [71]
Epsolay	benzoyl peroxide[72]	New Formulation[73]	1.2⋆⋆⋆ [74]

Austedo XR is taken once daily compared to Austedo's twice daily instructions.[53] The applicant, Teva Pharmaceuticals, relied upon its prior Austedo clinical studies to support Austedo XR. With Austedo XR, Teva was *twice* able to take advantage of the 505(b)(2) pathway, first with Austedo (deuterated tetrabenazine) and then later with Austedo XR (an extended release version of deuterated tetrabenazine). Since the launch of Austedo XR, Teva's Austedo revenue has increased by 27% to $1.2 billion.[54]

Addressing Generic Competition

Case Study 5: Decreased Market Competition – Epsolay

Sol-Gel Technologies Ltd. invented an encapsulated 5% cream of benzoyl peroxide for the treatment of inflammatory lesions of rosacea in adults.[55] During clinical trials, its microencapsulated formula of benzoyl peroxide proved to be more effective than other existing benzoyl peroxide treatments.[56] Although benzoyl peroxide treatments were available over the counter, Epsolay's reformulated product was approved under 505(b)(2) relying not on any particular product, but on published literature regarding benzoyl peroxide.[57] Epsolay retails as a prescription at over $600 for a 30-day supply, while over-the-counter benzoyl peroxide may retail for under $10 for the same amount of active ingredient.[58] Sol-Gel was able to rely on a well-known product to obtain approval and carve out a niche to avoid competing with that product.

Table II outlines revenue generated from certain drugs approved via the 505(b)(2) pathway. There are significant financial gains generated within the first market year of filing a 505(b)(2). Unlike NDA and ANDA applicants, Paper NDA applicants do not have direct market competitors due to their hybrid nature and carry more than 180 days of exclusivity.[59]

Litigation Impact: Two-Sided Litigation

As a consequence of the hybrid nature of 505(b)(2) applications, applicants must prepare for two fronts of patent litigation. On the one hand, because 505(b)(2) applicants have to certify to the brand RLD's patents, the brand drug owner will bring a suit for infringement. On the flip side, because 505(b)(2) drugs are often their own niche branded product – that provides for the opportunity to obtain their own patents – some generic developer will eventually seek to copy the drug and challenge the 505(b)(2) applicant. Examining the interplay between NDA protection, ANDA affordability, and the hybrid nature of Paper NDA applications, can inform intellectual property management decisions and determine strategies for maximizing profitability.

CONCLUSION

The 505(b)(2) drug approval pathway provides drug developers many options and benefits. In pursuit of best practice, drug developers should know the wide array of possibilities that 505(b)(2) offers as a route to approval. Drug developers can design strategies to extend a drug's period of market exclusivity, save time and costs associated with research and development, and capitalize on niche market needs to bring new drugs with subtle, yet

meaningful, differences to market. An important part of taking full advantage of the 505(b)(2) pathway is to design the proposed drug product such that a patent estate can be built around the modifications from the RLD, to fully maximize the pecuniary benefits of proceeding down the road of obtaining approval of a novel product under 505(b)(2).

Notes

1. 21 U.S.C. § 355.
2. Sertkaya et al., Costs of Drug Development and Research and Development, JAMA (June 28, 2024), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820562.
3. Agrawal et al., Fast to First-in-Humans, McKinsey & Co. (Feb. 10, 2023), https://www.mckinsey.com/industries/life-sciences/our-insights/fast-to-first-in-human-getting-new-medicines-to-patients-more-quickly.
4. See 35 U.S.C. § 271.
5. While pursuing patent protection is critical for drug products, this paper focuses on providing drug developers with insight into the 505(b)(2) drug pathway.
6. Orange Book Preface, FDA (Jan. 25, 2024), https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.
7. 21 C.F.R. § 320.32(b).
8. "Bioequivalence" exists when two products that are equal in the rate and extent to which the active pharmaceutical ingredient becomes available at the drug action site(s). Bioequivalence, FDA (Jan. 24, 2024), https://www.fda.gov/animal-veterinary/abbreviated-new-animal-drug-applications/bioequivalence.
9. 21 C.F.R. § 320.32(b).
10. A "Paragraph IV certification" is a generic applicant's affirmation that an Orange-Book-listed patent is invalid, unenforceable, or will not be infringed by the generic product.
11. Market exclusivity means that the FDA will not approve an identical drug product for a limited, statutorily defined period.
12. 21 U.S.C. § 355(b)(2).
13. See id.
14. See 21 C.F.R. § 314.3(b).
15. Sameness Evaluations in an ANDA, FDA (Nov. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch.
16. See 21 U.S.C. § 355(b)(2); see also Determining Whether to Submit an ANDA or a 505(b)(2) Application, FDA (May 10, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/determining-whether-submit-anda-or-505b2-application (discussing the importance of a determining a sufficient scientific bridge between the RLD and the drug in the application).
17. Compare 21 C.F.R. § 314.54(a) (noting requirements for relying on previous information), with 21 C.F.R. § 314.54(b) (noting requirements for newness).
18. Drug Price Competition and Patent Term Restoration Act of 1984 – Public law 98-417.
19. An additional benefit includes the possibility patent term extension (PTE). Where due to regulatory delays during a regulatory review period the term of a patent may receive an extension. See 35 U.S.C. § 156.
20. Prescription Drug User Fee Amendments.
21. Id.
22. Id.
23. Id.
24. Generic Drug User Fee Amendments, FDA (Dec. 21, 2023), https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments.
25. Id.
26. Prescription Drug User Fee Amendments.
27. Generic Drug User Fee Amendments, supra note 24.
28. Frequently Asked Questions on Patents and Exclusivity, FDA (Feb. 5, 2020), https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongexclusivity.
29. 21 C.F.R. §§ 314.08(b)(4)-(5).
30. Id. § 314.08(b)(2).
31. Id. C.F.R. § 316.34.
32. 21 U.S.C. § 355a(c).
33. Id. § 355f(a).
34. FDA, Summary Review NDA 208411 (2015).
35. FDA, NDA 016636 (2023).
36. FDA, ANDA 072076 (2014).
37. Emergent Biosolutions Inc., Annual Report (Form 10-K) 69 (March 8, 2024).
38. Id. at 70.
39. Letter from Eric P. Bastings to Dr. Douris, FDA NDA 213378 Approval Letter (May 28, 2021).
40. Id.
41. FDA, NDA 213378 (2021). See generally U.S. Patent No. 10,716,785.
42. See NDA 213378, supra note 41.
43. FDA, NDA 20180 (1997).
44. Id.
45. NDA 20788.
46. FDA, NDA 20788 Medical Review (1997).
47. Merck & Co., Inc., Annual Report (Form 10-K) (1998-2015).
48. FDA, NDA 208082 (2015).

49. Rao et al., Deuterated Drugs, Pharm. Chem. J. (2022), https://doi.org/10.1007/s11094-022-02584-4.
50. FDA, Pharmacology Review for NDA 208082 (2017).
51. Letter from Sharon R. Hertz to Richard E. Lowenthal, FDA NDA 208082 Approval Letter (Nov. 18, 2015); see also 21 U.S.C. § 355(j)(5)(B)(iv)(I).
52. Teva Announces Austedo XR, Teva Pharm. Indus. Inc. (May 29, 2024), https://www.tevapharm.com/news-and-media/latest-news/teva-announces-austedo-xr-deutetrabenazine-extended-release-tablets-now-u.s.-fda-approved-as-a-one-pil/.
53. Austedo XR Label.
54. Teva Pharms., Inc., Annual Report (Form 10-K) 62 (2023).
55. See, e.g., U.S. Patent 11,877,997.
56. Sol-Gel, Report of Foreign Issuer (Form 6-K) (July 8, 2019).
57. FDA, Other Review NDA 214938 (2020).
58. Compare Epsolay, GoodRx, https://www.goodrx.com/epsolay (last visited July 1, 2024), with Benzoyl Peroxide, GoodRx, https://www.goodrx.com/benzoyl-peroxide?form=tube-of-gel&dosage=60g-of-5%25&quantity=1&label_override=benzoyl-peroxide (last visited July 1, 2024).
59. See CDER Small Business and Industry Assistance, FDA (Feb. 11, 2016), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity.
60. FDA, Summary Review NDA 208411 (2015).
61. Drugs@FDA: FDA-Approved Drugs, FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208411 (last visited July 8, 2024).
62. Emergent Biosolutions, Annual Report (Form 10-K) (Feb. 24, 2020).
63. FDA, Summary Review NDA 213378 (2021).
64. Drugs@FDA: FDA-Approved Drugs, FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208411 (last visited July 8, 2024).
65. Alkermes, Annual Report (Form 10-K) (Feb. 21, 2024).
66. FDA, Medical Review NDA 20788 (1997).
67. Drugs@FDA: FDA-Approved Drugs, FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208411 (last visited July 8, 2024).
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69. FDA, Other Review NDA 216345 (2024).
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71. Teva Pharmaceuticals, Annual Report (Form 10-K) (Feb. 12, 2024).
72. FDA, Other Review NDA 214510 (2021).
73. Drugs@FDA: FDA-Approved Drugs, FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208411 (last visited July 8, 2024).
74. Sol-Gel, Annual Report (Form 20-F) (Mar. 13, 2024).