Seven Noteworthy 505(b)(2) Submissions

By Charles O. Jaap, V, MBA, RAC, Jodi Hutchins, RAC, CQA and Mikel Alberdi, MPH, RAC

As drug and device consultants, the scientists and regulatory experts at PDG® spend a considerable amount of time working on 505(b)(2) NDA submissions. This paper highlights notable features of a cross section of recent 505(b)(2) approvals and provides a variety of everyday issues to consider as you contemplate your next drug development project.

Generic companies are turning to more complex dosage forms, 505(b)(2) development, and even biosimilars as a hedge against increasingly crowded traditional markets. PDG's® President spent the first 20 years of her career in the generic industry (including 505(b)(2) development) before founding PDG® in 1999. While 505(b)(2) development represents a significant share of our practice, we continue to help our clients with 505(j) submissions and other support services such as BA/BE study design, literature searches, scientific writing, etc. For others, we function as an extension of operations, addressing scientific and regulatory strategy, complex regulatory submissions, communications with FDA, quality/compliance, clinical, nonclinical and safety surveillance concerns. This includes sourcing and oversight of API suppliers, CROs, CMOs, laboratories, and other vendors.

According to the guidance, a 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."[1] In other words, the 505(b)(2) is the type of NDA that holds the potential of getting a new drug approved based on studies chronicled in the scientific literature.

For the purpose of illustration, we provide a brief analysis of seven different 505(b)(2) approvals,[2] including notable features and a tabular overview of each. We have also appended an excerpt from the current guidance[3] (Appendix 1) that describes examples of 505(b)(2) applications.

Bendeka™ (bendamustine hydrochloride)

The 505(b)(2) for Eagle Pharma's Bendeka™ was approved in December 2015 with the same indications as its predecessor/RLD Treanda®: treatment of patients with chronic lymphocytic leukemia (CLL) and patients with indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.[4]

Treanda® is a powder that requires reconstitution. The application for Bendeka™ presented a modified dosage form; comprised of a ready-to-dilute solution, providing for multiple doses and less infusion time. Relying upon previous clinical studies conducted on Treanda®, Eagle was permitted to demonstrate evidence of bioequivalence (BE) to Treanda® for the approval of Bendeka™. Of note, like Treanda®, Bendeka™ secured orphan designations for both of its indications. While no accelerated review programs were designated, the review was completed within the PDUFA goal of 10 months.[5]

Also notable, Bendeka's™ new dosing advantages proved to be a financial success. Launched by marketing partner Teva in January 2016, by of the end of the first quarter, the drug had captured 70% of the total market.[6, 7]

Table 1

505 (b)(2) Approved Drug	Bendeka™
RLD(s) & Original Approval Date(s)	Treanda®, 3/20/2008
505 (b)(2) Submission Date	2/13/2015
505 (b)(2) Approval Date	12/7/2015
What changed in 505 (b)(2)?	Modified dosage form
Basic Study Requirement	BE
Expedited Review? Y/N If yes, which?	N
Orphan Drug? Y/N	Y
Revenue stats	$29.6 Million Q1 2016

Zuplenz® (ondansetron)

Ondansetron prevents post-operative, chemotherapy and radiation-induced nausea and vomiting.[8] Originally developed by GSK in the 1980s, ondansetron was approved in the US as an oral dosage form (trade name Zofran) in 1992[9] and later as a disintegrating tablet.

By 2008, Monosol Rx (the developers of PharmFilm® technology) and Strativa (a division of Par) had entered into a licensing agreement granting Strativa the US commercialization rights to a thin film sublingual dosage form.[10]

Known as Zuplenz®, the 505(b)(2) referenced both the Zofran tablets (NDA 020103) and Zofran oral disintegrating tablets (NDA 020781). In 2010, Zuplenz® was approved based on demonstration of bioequivalence to the oral disintegrating tablet.[11]

The story does not end there. Since approval, the drug has been marketed by no less than four companies, including at least one discontinuation (and two launches): Strativa, Vestiq, Galena and, as of December 2015, Midatech Pharma. It is reported that Midatech acquired the franchise in a deal valued at up to $29.75 million, including a $3.75 million up-front cash payment.[12] Midatech re-launced Zuplenz® in July 2015.[13]

There are interesting similarities between Bendeka™ and Zuplenz®. Each changed a dosage form and relied upon BE data for approval. Neither faces direct generic competition. However, Bendeka earned $29.6 million and 70% of the total market in its first quarter (Q1 2016), while Zuplenz® has struggled to gain traction. Besides the protracted launch, the difference is that Zuplenz® faces generic disintegrating tablets. With patent protection for sublingual Zuplenz® until 2029,[14] Midatech is apparently banking on enough differentiated benefit to overcome that of the disintegrating tablet. We will be watching this with great interest.[15]

Table 2

505 (b)(2) Approved Drug	Zuplenz®
RLD(s) & Original Approval Date(s)	Zofran Tablets, 12/31/1992 & Zofran ODT, 1/27/1999
505 (b)(2) Submission Date	4/7/2009
505 (b)(2) Approval Date	7/2/2010
What changed in 505 (b)(2)?	New oral dosage form
Basic Study Requirement	BE
Expedited Review? Y/N If yes, which?	N
Orphan Drug? Y/N	N
Revenue stats	$1.71 million for 2015[16]

Avycaz® (ceftazidime-avibactam)

Avcyaz® is a fixed combination antibacterial indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms: complicated intra-abdominal infections, used in combination with metronidazole and complicated urinary tract infections, including pyelonephritis in patients who have limited or no alternative treatment options. Notably, the avibactam component was a new chemical entity, while the ceftazidime is a previously approved third-generation cephalosporin.[17]

FDA agreed that a 505(b)(2) relying in part on the previous finding of safety and efficacy of ceftazidime could be submitted and that additional data would include data from nonclinical, Phase 1, and two Phase 2 trials. Also included was safety data on avibactam from patients who received the combination. Because the components could not be studied as monotherapy, the contribution of the avibactam component was primarily assessed in in vitro studies and in animal models of infection, where the addition of avibactam restored the activity of ceftazidime against ceftazidime-non-susceptible bacteria.[18]

This 505(b)(2) is also notable for its use of the "Generating Antibiotics Incentives Now" (GAIN) Program. GAIN was introduced as part of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). GAIN provides that certain "antibacterial and antifungal drugs intended to treat serious or life-threatening infections, including serious or life-threatening infections caused by antibacterial- or antifungal-resistant pathogens (including new or emerging pathogens), and serious or life-threatening infections caused by qualifying pathogens" may be designated as "qualified infectious disease products" (QIDPs). Under GAIN, a QIDP product is eligible for both, Priority Review and Fast Track designation as well as an additional five years of exclusivity to be added to certain exclusivity periods already provided.[19] Avycaz® was only the fifth approved antibacterial drug product approved under the GAIN program.[20]

According to FiercePharma, Allergan forecast Peak sales of Avycaz® at $300 million "but when early sales last year came in higher than expected, there was a suggestion that figure might get elevated by analysts. The drug brought in $22.1 million in H1 of this year with $13.7 million of that coming in the second quarter." However, Allergan has been confronted with a shortage of the API for Avibactam portion, which they expect to resolve in 2017.[21]

Table 3

505 (b)(2) Approved Drug	Avycaz®
RLD(s) & Original Approval Date(s)	Fortaz (Ceftazidime), 7/19/1985
505 (b)(2) Submission Date	6/25/2014
505 (b)(2) Approval Date	2/25/2015
What changed in 505 (b)(2)?	New combination – Avycaz is a ceftazidime-avibactam combination. Avibactam is a new chemical entity.
Basic Study Requirement	Clinical trials to support safety and efficacy of the combination and Phase IV commitment
Expedited Review? Y/N If yes, which?	Y, priority review
Orphan Drug? Y/N	N
Revenue stats	$13.7 Million Q2 2016[22]

Omnitrope® (somatropin rDNA origin)

Omnitrope®, a human growth hormone, is a notable because it was one of the early follow-on biologics[23] approved via the 505(b)(2) pathway, before Congress/FDA put a biosimilar program in place.[24]

Made from living organisms, biologics are relatively large and complex molecules compared to conventional chemical drugs. Biologics tend to be made up of proteins (and/or constituent amino acids), carbohydrates (e.g. sugars), or nucleic acids (e.g. DNA). Because of their complexities, biosimilars are never the same as their reference products but are substantially similar. In April 2006, the European Medicines Agency (EMA) approved Omnitrope® as Europe's first ever biosimilar.

FDA also approved Sandoz's Omnitrope® in 2006, but it followed an April 2006 court ruling that the agency must review the application. In doing so, FDA stated that the approval did not establish a pathway for approval of other follow-on biologics and that Congress would need to change the law in order for the agency to continue doing so.[25]

On March 23, 2010, the President signed the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) into law, which amended the Public Health Service Act (PHS Act) and created an abbreviated review pathway for biosimilars.[26] Meantime, the application for Omnitrope® had qualified as a 505(b)(2) "relying in part on previous findings of safety and effectiveness of Genotropin®"[27] as well as "extensive chemical analyses that the drug product is comparable, or substantially similar, to Genotropin®".[28]

While there were dissimilarities in the impurity profile, Sandoz was required to adequately characterize, control and establish acceptable product specifications.

The first approved indications were for the treatment of pediatric patients who have growth failure due to growth hormone deficiency and for replacement therapy in adults with either adult onset or childhood onset growth hormone deficiency (GHD).[29]

In 2010, Sandoz received approvals for three additional indications: treatment of children with growth failure due to Prader-Willi syndrome, children who are small for gestational age (SGA), and children with Idiopathic Short Stature (ISS). In 2011, Sandoz announced that the FDA approved Omnitrope® (somatropin [rDNA origin] for a sixth indication, the treatment of children with growth failure due to Turner syndrome.[30]

As with the initial approval, the supplemental applications relied upon literature and the previous FDA finding that this product is highly similar to the RLD; however the sponsor was required to conduct further studies to ensure safety.

Table 4

505 (b)(2) Approved Drug	Omnitrope®
RLD(s) & Original Approval Date(s)	Genotropin®, 8/24/1995
505 (b)(2) Submission Date	12/21/2001
505 (b)(2) Approval Date	5/30/2006
What changed in 505 (b)(2)?	Composition of active ingredient changed
Basic Study Requirement	BE (Chemically comparable; similar in rate and extent
Expedited Review? Y/N If yes, which?	N
Orphan Drug? Y/N	N
Revenue stats	$60 million in 2009[31]

Narcan® Intranasal (naloxone hydrochloride)

The 505(b)(2) for Narcan® was submitted by Adapt Pharma on July 20, 2015 and proposed a change to both dosage form and route of administration. Converting the drug product from injectable to intranasal, Adapt used injectable Narcan® (NDA 016636) as the RLD. The application relied upon a relative bioavailability study in healthy volunteers. However, because injectable Narcan® had been discontinued, Adapt used an injection as the comparator to bridge to FDA's previous findings for Narcan®.[32]

Indicated for emergency treatment of known or suspected opioid overdose, the application was granted priority review status as well as a rolling review, based on the product's importance to the public health.[33]

The application was approved four months after submission, on November 18, 2015 and was launched in early 2016: Primarily targeted were three markets 1) Current heroin addicts; 2) first responders who could administer naloxone in an emergency response situation; and 3) those who have opioid prescriptions. As a combination product with the drug being the primary mode of action, CDER reviewed and regulates Narcan®.[34]

Until Narcan® was approved; naloxone was only approved in injectable forms, most commonly delivered by syringe or auto-injector.[35] However, many first responders and primary caregivers, have reported that the nasal spray formulation is easier to deliver, and eliminates the risk of a contaminated needle stick.[36] Because the U.S. is currently experiencing what many consider to be an epidemic of opioid overdose the market for NARCAN® Nasal Spray may be in excess of $2 billion.[37]

In approving the application, FDA noted that "This application represents the first nasal naloxone spray to meet the criteria for novel naloxone products described by the Agency during the public meetings held in 2012 and in 2015[38, 39,40] Further, FDA recently announced that they plan to facilitate ways to encourage industry to submit an NDA for an Rx-to-OTC switch. The announcement directly addresses prescription naloxone, indicated for treatment of opioid overdose. This unusual step is consistent with FDA's opioid action plan and is aimed at making the drug more widely available.[41, 42]

As with the unfolding Zuplenz® saga, we will be watching naloxone developments with great interest.

Table 5

505 (b)(2) Approved Drug	Narcan® Nasal Spray
RLD(s) & Original Approval Date(s)	Narcan® injectable, 4/13/1971
505 (b)(2) Submission Date	7/17/2015
505 (b)(2) Approval Date	11/18/2015
What changed in 505 (b)(2)?	Change in dosage form and route of administration
Basic Study Requirement	Relative BA, Phase IV commitment
Expedited Review? Y/N If yes, which?	Y, priority review
Orphan Drug? Y/N	N
Revenue stats	$6.7 million Q1 2015, $10.3 million Q1 2016

Xuriden™ (uridine triacetate)

Developed by Wellstat for the treatment of the rare and potentially fatal disease, hereditary orotic aciduria (HOA),[43] Xuriden™ (uridine triacetate) demonstrates how a new chemical entity may be reviewed as a 505(b)(2).

HOA is an autosomal recessive inborn error of pyrimidine metabolism. Since 1959, only 20 patients with HOA have been reported in the medical literature. Uridine triacetate, the new chemical entity, is converted to uridine in the body, the active moiety in Xuriden™.

Because of the discontinuation of an expanded access IND for Xuriden™ (uridine) by another company in December 2012, there was no longer a commercial source. Moreover, only 4 patients were available for study. However, results of past uridine studies were available in the scientific literature. The application was submitted with a clinical trial of uridine triacetate compared to a review of the medical literature describing uridine treatment in HOA patients. Because the safety and effectiveness of Xuriden™ (uridine triacetate), including dose selection, relied upon uridine literature, the 505(b)(1) was amended to a 505(b)(2) application before being approved.[44]

Table 6

505 (b)(2) Approved Drug	Xuriden™
RLD(s) & Original Approval Date(s)	N/A
505 (b)(2) Submission Date	1/8/2015
505 (b)(2) Approval Date	9/4/2015
What changed in 505 (b)(2)?	New chemical identity
Basic Study Requirement	Small clinical trial = 4 patients; uridine medical literature review
Expedited Review? Y/N If yes, which?	Y, priority review
Orphan Drug? Y/N	Y
Revenue stats	Unavailable

Yosprala™ (aspirin-omeprazole)

We conclude with a 505(b)(2) that is noteworthy because of what it combines and what it yields: a prescription, fixed dose combination of two drugs that are 1 – old, 2 – available OTC as monotherapy, 3 – available in cardiac event prevention strengths, one of which may deliver pain relief (albeit not indicated for pain relief) and 4 – potentially make the drug safer.

Yosprala™ is a combination of two common generic drugs: aspirin, an anti-platelet agent, and omeprazole, a proton pump inhibitor (PPI). It is indicated for patients who require aspirin for secondary prevention of cardiovascular events and who are at risk of developing aspirin associated gastric ulcers.[45] Gastrointestinal symptoms are often cited as the main reason patients discontinue their daily aspirin therapy to prevent cardiac events.[46] It should be noted that Yosprala™ is a delayed release agent and thus should not be used when immediate release is desired.

While Aspirin and omeprozale have previously and commonly been prescribed together, there is not a therapeutic equivalent, nor can Yosprala™ be interchanged with the individual components of aspirin and omeprozale.[47] It is hoped that the new combination will facilitate greater compliance, with the convenience of a one dose pill and that omeprazole will mitigate gastric concerns associated with continuous aspirin therapy. Because of the wide availability of data in the scientific literature, FDA relied upon previous studies to approve the combination, but also required pre-approval safety studies as well as a post-market commitment for additional study of the safety of the combination.[48, 49]

Table 7

505 (b)(2) Approved Drug	Yosprala™
RLD(s) & Original Approval Date(s)	Review unavailable
505 (b)(2) Submission Date	3/25/2013 Original
505 (b)(2) Approval Date	9/14/2016
What changed in 505 (b)(2)?	New combination
Basic Study Requirement	PK/PD & 2 clinical studies of 524 patients due to combination
Expedited Review? Y/N If yes, which?	N
Orphan Drug? Y/N	N
Revenue stats	Unavailable

Charles Jaap is Vice-President of Operations and Business Development for PDG®, a global pharmaceutical and medical device consultant with extensive experience in the strategic development of drug products and medical devices.

Mikel Alberdi, MPH, RAC is Director of Regulatory Affairs/New Product Development for PDG®. He has over 13 years of regulatory affairs experience, with expertise in facilitating FDA meetings and compiling NDA, 505(b)(2), and ANDA submissions.

Jodi Hutchins is an Independent Regulatory and Quality Consultant with over 15 years of global medical device registration experience, to include FDA 510(k) submissions. She held her most recent position for 9 years, as QA/RA Director for a worldwide distributor of medical devices.

The opinions and statements in this paper are solely those of Charles Jaap, Mikel Alberdi, and Jodi Hutchins and do not necessarily reflect those of PDG®.

PDG®
PHARMACEUTICAL DEVELOPMENT GROUP
13902 North Dale Mabry, Suite 230
Tampa, FL 33618
Ofc: (813) 963-3062 | Fax: (813) 963-0972
www.pharmdevgroup.com

Sources:

1. Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999.
2. Drugs@FDA: FDA Approved Drug Products.
3. Ibid@1.
4. Bendeka® Package Insert, December 2015.
5. Bendeka® (Bendamustine Hydrochloride Injection) Summary Review.
6. Teva Pharmaceuticals and Eagle Pharmaceuticals Announce FDA Approval of BENDEKA™ (bendamustine hydrochloride) Injection; Teva Press Release, December 8, 2015.
7. Eagle Pharmaceuticals, Inc. Reports First Quarter 2016 Results; Bendeka Achieves 71% Total Market Share, Eagle Press Release, May 9, 2016.
8. Ibid@2.
9. Zofran (ondansetron) Consumer Safety Fact as accessed at www.consumersafety.org on December 12, 2016.
10. PAR Pharmaceutical Form 10-Q for the quarterly period ended: September 30, 2010.
11. Zuplenz® (ondansetron) Summary Review, July 2, 2010.
12. Galena Biopharma to Sell Zuplenz® (ondansetron) Oral Soluble Film, Completing Divestiture of Commercial Operations; Galena Biopharma Press Rrelease, December 18, 2015.
13. Midatech agrees to acquire marketed oncology product, Zuplenz®, from Galena Biopharma, Inc., Midatech Pharma Press Release, December 18, 2015.
14. Ibid@13.
15. Ibid@13.
16. Midatech chief talks Zuplenz launch and 2015 sales beat, Proactive Investors Australia; Video Release April 13, 2016 as accessed at http://www.proactiveinvestors.com.au/ on January 6, 2017.
17. Avycaz (ceftazidime-avibactam) Summary Review, February 25, 2015.
18. Ibid@17
19. Working Together to Address the Challenges of Rare and Neglected Diseases: Statement of Jesse L. Goodman, M.D., M.P.H. Chief Scientist Food and Drug Administration, June 27, 2013.
20. FDA approves new antibacterial drug Avycaz; FDA News Release, February 25, 2015.
21. Allergan says manufacturing issue creates shortage of Avycaz; Eric Palmer, FiercePharma, August 15, 2016.
22. Ibid@21.
23. Public Workshop Regarding Scientific Considerations Related to Developing “Follow-on” Protein Products (69 FR 50386 Docket No. 2004N-0355), August 16, 2004. Comments of Pfizer Inc.
24. Omnitrope® (somatropin rDNA origin) Medical Review, May 30, 2006.
25. Biologics and Biosimilars: Background and Key Issues, Judith A. Johnson, Specialist in Biomedical Policy, September 7, 2016:; Congressional Research Service Report 7-5700 RL44620 Prepared for Members and Committees of Congress.

Sources:

26. FDA Regulation of Follow-On Biologics, Judith A. Johnson Specialist in Biomedical Policy, April 26, 2010: Congressional Research Service Report 7-5700 RL34045 Prepared for Members and Committees of Congress.
27. Ibid@24.
28. Ibid@24.
29. Ibid@24.
30. Sandoz expands Omnitrope® offering with FDA approval for a sixth indication; Sandoz Press Release August 31, 2011.
31. Sandoz' biosimilar sales top US$100mn in 2009; Generics Bulletin, February 2010.
32. Narcan (naloxone hydrochloride) Summary Review, November 18, 2015.
33. Ibid@31.
34. Ibid@31.
35. Ibid@2.
36. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose; FDA News Release, November 18, 2015.
37. OPNT: [Opiant Pharmaceuticals] Licenses Heroin Vaccine From NIDA; NARCAN Nasal Spray Approved by Health Canada, David Bautz, Ph.D. November 1, 2016, Zack's SCR Digest.
38. Ibid@32.
39. Exploring Naloxone Uptake and Use – A Public Meeting as accessed at www.fda.gov News & Events on December 12, 2016 (page last updated October 27, 2015).
40. Role of Naloxone in Opioid Overdose Fatality Prevention; Request for Comments; Public Workshop as accessed at www.fda.gov News & Events on December 12, 2016 (page last updated December 15, 2014).
41. FDA Supports Greater Access to Naloxone to Help Reduce Opioid Overdose Deaths; Karen Mahoney, M.D. August 10, 2016, FDA Voice.
42. Ibid@41.
43. Xuriden Package Insert, September 2015.
44. Xuriden (uridine triacetate) Summary Review, September 4, 2015.
45. Yosprala Package Insert, September 2016.
46. Aralez finally scores FDA approval for Yosprala, but the combo med could be a hard sell; Angus Liu, Fierce Pharma, September 27, 2016.
47. Yosprala (aspirin and omeprazole). Aralez Pharmaceuticals Portfolio Website accessed on December 13, 2016.
48. Yosprala Approval Letter (NDA 205103), September 14, 2016.
49. Yosprala Labeling (NDA 205103), September 14, 2016.

APPENDIX 1

"WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS?"

excerpted from:

Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted. Please note that in particular cases, changes of the type described immediately below may not require review of information other than BA or BE studies or data from limited confirmatory testing. In those particular cases, approval of the drug may also be sought in a 505(j) application based on an approved suitability petition as described in section 505(j)(2)(C) of the Act. The descriptions below address the situation in which the application should be filed as a 505(b)(2) application because approval of the application will require review of studies beyond those that can be considered under section 505(j). Some or all of the additional information could be provided by literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based upon studies conducted by or for the applicant or to which it has obtained a right of reference.

- **Dosage form:** An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.
- **Strength:** An application for a change to a lower or higher strength.
- **Route of administration:** An application for a change in the route of administration, such as a change from an intravenous to intrathecal route.
- **Substitution of an active ingredient in a combination product:** An application for a change in one of the active ingredients of an approved combination product for another active ingredient that has or has not been previously approved.

Following are additional examples of applications that may be accepted pursuant to section 505(b)(2) of the Act. Some or all of the additional information could be provided by the literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based on studies conducted by or for the applicant or to which it has obtained a right of reference.

- **Formulation:** An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.
- **Dosing regimen:** An application for a new dosing regimen, such as a change from twice daily to once daily.
- **Active ingredient:** An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- **New molecular entity:** In some cases a new molecular entity may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- **Combination product:** An application for a new combination product in which the active ingredients have been previously approved individually.

- **Indication:** An application for a not previously approved indication for a listed drug.

- **Rx/OTC switch:** An application to change a prescription (Rx) indication to an over-the-counter (OTC) indication.

- **OTC monograph:** An application for a drug product that differs from a product described in an OTC monograph (21 CFR 330.11), such as a non-monograph indication or a new dosage form.

- **Naturally derived or recombinant active ingredient:** An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- **Bioinequivalence:** Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically better than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9)).

For example, a 505(b)(2) application would be appropriate for a controlled release product that is bio-inequivalent to a reference listed drug where:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product.