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505(j) or 505(b)? Helping to Choose the Proper Pathway

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On May 9, 2019, the United States Food and Drug Administration (FDA) released a final guidance entitled *Determining Whether to Submit an ANDA or 505(b)(2) Application* to guide an applicant's decision on which abbreviated approval pathway to pursue for their application to market a drug product with the FDA. This guidance highlights the criteria required under both the ANDA and 505(b)(2) pathways and advises on how to obtain assistance from FDA when choosing the appropriate pathway.

ANDAs (Abbreviated New Drug Applications)

The guidance reminds that an ANDA must demonstrate that:

- the proposed drug product and the applicable RLD (reference listed drug or the NDA product) are the same with respect to their
  - active ingredient(s),
  - dosage form,
  - route of administration,
  - strength,
  - conditions of use, and
  - labeling (with certain exceptions).[1]
- the proposed product is bioequivalent to the RLD [2]
- the proposed product's identity, strength, quality, and purity are ensured.

Certain types of differences from an RLD (*e.g.*, approved suitability petition changes, inactive ingredients, labeling, container closures) are also permitted if clinical investigations are not necessary to establish the proposed drug product's safety and efficacy.

505(b)(2) applications

The guidance reminds that 505(b)(2) applications must contain full safety and efficacy investigation reports for the proposed drug product but that some of the information can come from non-applicant studies[3] (*e.g.*, from published literature or in the FDA's finding of safety and/or efficacy for a listed drug).

An applicant can rely on the FDA's finding for a listed drug so long as the proposed drug product shares characteristics with the relied-upon listed drug such as active ingredient, dosage form, route of administration, strength, indication or other condition of use. To rely on data for a listed drug product, the applicant will need to establish a bridge-demonstrating that reliance is scientifically justified, using, for example, comparative bioavailability data—between the proposed drug product and each listed drug upon which the applicant relies.

To the extent there are differences between the listed drug and the proposed drug product, such as different dosage forms or the proposed drug product is more bioavailable than the listed drug, the 505(b)(2) application must include sufficient data to support those differences.[4] A scientific bridge

1 *See* section 505(j)(2)(A) and 505(j)(4) of the Federal Food, Drug and Cosmetics Act and 21 CFR 314.94 and 314.127.

2 *See* section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the Federal Food, Drug and Cosmetics Act and 21 CFR 320.21(b).

3 *See* 21 CFR 314.3(b).

4 *See* 21 CFR 314.54(a).

may not be necessary but a pharmaceutically equivalent listed drug product must be identified in the 505(b)(2) application if FDA had approved an NDA for a pharmaceutically equivalent listed drug before the date of submission of the original 505(b)(2) application.[5]

Regulatory considerations for submitting ANDAs and 505(b)(2) applications

1. *Duplicates:*

FDA will not accept for filing a 505(b)(2) application for a drug that is a duplicate of a listed drug—such duplicate drug products would only be approvable under the ANDA pathway.

2. *Petitioned ANDAs:*

ANDAs referencing an approved suitability petition can seek approval for a proposed drug product that "differs from an RLD in its route of administration, dosage form, or strength or that has one active ingredient in a fixed combination drug product."[6]

FDA will approve a suitability petition for a proposed ANDA product unless, for example, (1) it determines that the safety and effectiveness of the proposed difference from the RLD cannot be established without investigations that exceed those required for ANDAs[7] or (2) the petition is for a drug product that has already been approved as an NDA or 505(b)(2) application.[8] For (2), the petitioner should submit an ANDA referencing the approved NDA or 505(b)(2) product instead of referencing the suitability petition.

3. *Bundling:*

An applicant seeking approval for multiple drug products containing the same active ingredient may submit a single 505(b)(2) application if seeking approval for some products qualifying for an ANDA and some qualifying for a 505(b)(2) application (*e.g.*, for products with multiple strengths).

Scientific considerations for ANDAs and 505(b)(2) applications

1. *Types of studies, data, and information submitted in ANDAs:*

Data from clinical investigations other than a bioavailability study should not be submitted with an ANDA unless appropriateness is discussed in advance with FDA.

2. *Active Ingredient Sameness Evaluation:*

A proposed ANDA product's active ingredient must be demonstrated to be the same as that of the RLD using information and data that may be submitted with an ANDA. The guidance advises that a prospective ANDA applicant with questions about active ingredient sameness should contact The Office of Generic Drugs (OGD).

3. Intentional differences between the proposed drug product and the RLD:

a. *Formulation differences*

A proposed ANDA product can be different from the RLD with respect to the specific formulation and inactive ingredients, so long as the ANDA contains information regarding the identity and quantity of the active and inactive ingredients, the characterization of the permitted differences, and a justification demonstrating no adverse effect of the differences on the safety and efficacy of the proposed drug product.[9]

The guidance explains that certain product types have certain restrictions with regard to formulation differences:

5 *See* 21 CFR 314.50(i)(1)(i)(c), 314.54(a)(1)(iii) and (vi), and 314.125(b)(19). *See also* 81 FR 69580 at 69620-21 (October 16, 2016).

6 *See* section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

7 *See* section 505(j)(2)(A) and 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93(e)(1)(i).

8 21 CFR 314.93(e)(1)(vi). *See also* 21 CFR 314.93(b).

9 21 CFR 314.94(a)(9)(ii). *See also* 21 CFR 314.94(a)(5) and (6).

- Parenteral products generally must contain the same inactive ingredients in the same concentrations, except for *exception excipients* such as preservatives, buffers or antioxidants.[10] All other inactive ingredients must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD.
- Ophthalmic products generally must contain the same inactive ingredients in the same concentrations, except for with *exception excipients* such as preservatives, buffers, substances to adjust tonicity, or thickening agents.[11] All other inactive ingredients must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD. FDA may also require an additional *in vivo* bioequivalence study (*e.g.*, bioequivalence study with pharmacokinetic endpoints and with clinical endpoints, as appropriate).[12]
- Otic products generally must contain the same inactive ingredients in the same concentrations, except for with *exception excipients* such as preservatives, buffers, substances to adjust tonicity, or thickening agents.[13]

The guidance advises that applicants considering submitting an application for a proposed drug product with impermissible differences should first contact OGD to discuss questions about permissible formulation differences and to determine whether a 505(b)(2) application should be filed instead.

b. *Differences in bioequivalence and/or bioavailability:*

An ANDA product must be bioequivalent to the RLD in terms of rate and extent of the absorption. If the rate and extent of absorption of the proposed drug product exceeds that of the RLD, approval could be sought by way of a 505(b)(2) application, but additional studies to show efficacy and safety may be required.[14] The guidance explains that if the rate and extent of absorption of the proposed drug product is less than that of the RLD, the 505(b)(2) pathway is not available.[15] Again, prospective ANDA applicants could contact OGD with questions.

c. *Differences in conditions of use:*

If the proposed labeling of the drug product does not reflect the labeling of the RLD with respect to conditions of use (*e.g.*, a new indication for the proposed drug product has been proposed), the FDA will not approve the application as an ANDA.[16] The guidance reminds, however, that "carve outs" of indications/conditions of use because of patents or exclusivity are permitted. Again, questions about changes to the conditions of use can be directed to the OGD before submission.

4. *Other differences*

A prospective applicant with any questions about other differences from the RLD should contact OGD before submitting an application.

a. *Device constituents*

The guidance advises that applicants considering developing a drug delivery device that differs from the RLD device should review the draft guidance for industry titled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017).

b. *Labeling*

While the guidance recognizes that certain labeling differences are permissible, it advises that if the differences in labeling are such that clinical investigations to establish safety and efficacy would be required, the applicant should seek approval as a 505(b)(2) application instead of as an ANDA.

10 21 CFR 314.94(a)(9)(iii).
11 *See* 21 CFR 314.94(a)(9)(iv).
12 *See* 21 CFR 320.21 and 320.22(b)(1).
13 *See* 21 CFR 314.94(a)(9)(iv).
14 *See* 80 FR 6802 at 6855-56 (Feb. 6, 2015).
15 21 CFR 314.54(b)(1) and (2).
16 21 CFR 314.94(a)(4)(i).

With respect to carve outs, the FDA will review the labeling with an eye toward whether the omitted information renders the proposed drug product less safe and effective as compared to the RLD, for its remaining non-protected conditions of use.

Requesting assistance from FDA

As discussed above, the OGD welcomes any prospective applicants' questions before submission of an application via submission of a controlled correspondence for specific or targeted inquiries about the drug development process or via submission of a request to GenericDrugs@fda.hhs.gov for a pre-ANDA meeting, if a dialogue with OGD would be more appropriate or desired.

For questions about a proposed 505(b)(2) product, the applicant is directed to contact the appropriate Office of New Drugs review division.

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The IP Pharmaceutical & Biotechnology team at Locke Lord LLP has extensive experience dealing with the FDA and advising clients on these issues. Should a prospective ANDA or 505(b)(2) applicant have any questions or concerns about any of the above issues and differences or about the controlled correspondence procedure, please contact the authors.

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