ANDA Policy and Regulatory Considerations Prior to Filing

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Overview

- Discuss common policy and regulatory challenges encountered prior to submitting ANDAs to FDA
  - Identifying the basis of submission
  - Submitting suitability petitions
  - Determining whether to submit a 505(j) or 505(b)(2) application
  - RLD Access Issues

Identifying the basis of submission

- Regulations require an ANDA to contain a “basis for ANDA submission”
- When an applicant submits an ANDA for a generic drug that is the same as its reference listed drug (RLD), the basis of submission is the RLD

Identifying the basis of submission (cont'd)

- RLD is the specific listed drug on which the ANDA applicant relies in seeking approval of its ANDA, i.e., the approved drug product the proposed generic drug seeks to duplicate
- A "reference standard" is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of an ANDA

Identifying the basis of submission (cont'd)

- Where the RLD *is marketed*, ordinarily it is also the drug product selected by FDA as the reference standard
- Where the RLD has been *discontinued from marketing* for other than safety or effectiveness reasons, FDA may select a different listed drug to serve as the reference standard

Identifying the basis of submission (cont'd)

- In instances in which FDA cannot select the RLD as the reference standard (RS), FDA generally selects as the RS a drug product that is therapeutically equivalent to the discontinued RLD and is the market leader based on units sold
- While the RS is not part of the basis of submission, it should be identified in the relevant sections of the ANDA that include information pertaining to bioequivalence

Submitting suitability petitions

- An applicant may submit a suitability petition requesting permission to file an ANDA for a generic drug that differs from an RLD because it has one different active ingredient in a fixed-combination drug product, or has a different route of administration, dosage form, or strength
- An ANDA citing a suitability petition that has not been approved will not be received for review

Submitting suitability petitions(cont'd)

- FDA will grant a suitability petition **unless**:
  - Safety and effectiveness of the proposed change cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA, or
  - The petition is for a drug product for which a pharmaceutical equivalent (PE) has been approved under 505(c), including, for example, a 505(b)(2) application that referenced the same listed drug

Submitting suitability petitions(cont'd)

- If the petition is for a drug product for which a pharmaceutical equivalent (PE) has been approved, the ANDA applicant should reference the approved PE designated by FDA as the RLD
- After approval of a drug product that is a PE to the drug described in the petition, the suitability petition and listed drug described therein may no longer be used as the basis for ANDA submission by applicants

Determining whether to submit a 505(j) or 505(b)(2) application

- Under the FD&C Act, there are four different routes for the two broad categories of drug applications (NDAs and ANDAs)
  - Stand-alone NDA (505(b)(1))
  - 505(b)(2) NDA
  - ANDA (505(j))
  - Petitioned ANDA (505(j)(2)(C))

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- ANDAs
  - Demonstrate sameness to the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions)
  - Include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- ANDAs
  - May contain certain types of differences from an approved drug product as long as clinical investigations are not necessary to establish the safety or effectiveness of the drug product

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- 505(b)(2) applications
  - Contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- 505(b)(2) applications
  - May rely on FDA's finding of safety and/or effectiveness to the extent that the proposed drug product shares characteristics with the listed drug
  - Must include sufficient data to establish safety and effectiveness to the extent the proposed drug product and the listed drug differ

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- Any application that can be submitted under 505(j) should be submitted as an ANDA under 505(j)

Determining whether to submit a 505(j) or 505(b)(2) application (cont'd)

- In general, an application may not be appropriate as an ANDA if, for example:
  - The proposed drug product requires any studies that go beyond the scope of limited confirmatory studies
  - The proposed drug product contains an active ingredient that cannot be demonstrated to be the "same" as an RLD using information and data that may be submitted in an ANDA
  - The proposed drug product contains differences that necessitate or result in a change to the route of administration, dosage form, or strength of the proposed product as compared to the RLD (in absence of an approved suitability petition)

RLD Access Issues

- Section 505-1(a)(1) of the FD&C Act authorizes FDA to require submission of risk evaluation and mitigation strategies (REMS) if FDA determines the REMS is necessary to ensure that the benefits of a drug outweigh its risk
- FDA may also require elements to assure safe use (ETASU) in certain circumstances
  - Providers who prescribe or administer the drug have particular training or certification
  - Patients who use the drug are monitored and/or enrolled in a registry
  - Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified

RLD Access Issues (cont'd)

- FDA is aware of instances in which an RLD holder has refused to sell drug product to a prospective ANDA applicant seeking to conduct the testing needed to obtain approval citing the REMS ETASU as justification
- FDA developed a process for Agency review of BE study protocols proposed by the prospective generic applicant to assess whether they provide safety protections comparable to those in the applicable REMS ETASU

RLD Access Issues (cont'd)

Process for requesting protocol review

1. Prospective applicant prepares and submits BE protocol(s) and informed consent that incorporate RLD labeling and ETASU necessary to conduct study safely to OGD
2. OGD's Office of Bioequivalence (OBE) reviews the protocols and informed consent documents
3. If the protocols contain adequate safety measures, including safety protections comparable to those in the applicable REMS with ETASU, OBE notifies the prospective applicant as such via letter

RLD Access Issues (cont'd)

Process for requesting letter to RLD holder

1. The prospective applicant submits a disclosure authorization to OGD, as instructed in the OBE letter
2. OGD issues a letter to the RLD holder stating that FDA will not consider it a violation of the REMS ETASU to provide the prospective applicant with supplies of the RLD to permit testing to support the prospective applicant's ANDA

References

- Draft guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*
- Draft guidance for industry on *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn*
- Guidance for industry on *How to Obtain A Letter from FDA Stating that Bioequivalence Protocols Contain Safety Protections Comparable to Applicable REMS for RLD*

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