

Abbreviated New Drug Applications

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Office of Generic Drugs

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ANDAs

- Generic drug program
- ANDA approval requirements
- Patents
- Hurdles to approval and tips for applicants
- Determining whether to submit an ANDA or 505(b)(2) application

ANDAs

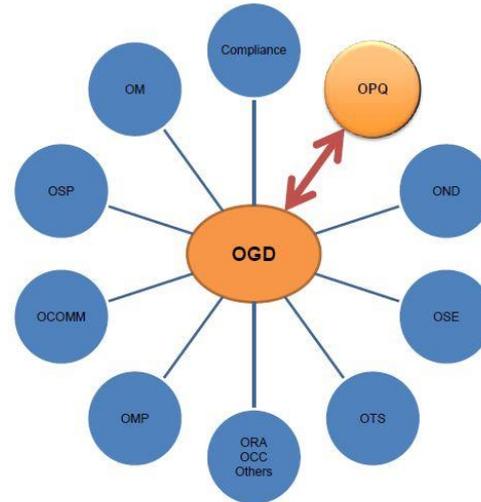
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Office of Generic Drugs



Office of Generic Drugs

Assesses
ANDAs in
coordination
with other
CDER and
Agency offices





Generic Drug User Fee Amendments (GDUFA)

- An agreement negotiated by industry and FDA, then authorized by Congress and the President
 - Results in a Commitment Letter
- GDUFA allows FDA to assess user fees from industry
- FDA commits to meeting specified performance goals for reviewing applications and to program enhancements
- Reauthorized every 5 years
 - GDUFA I: October 1, 2012 – September 30, 2017
 - GDUFA II: October 1, 2017 – September 30, 2022

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Foundations of Generic Drug Approval

- Approval of generic drug starts with a “listed drug” – generally an “innovator” drug approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
 - This is the reference listed drug (RLD)
- ANDA relies on FDA’s finding of safety and effectiveness for the RLD

Contents of an ANDA

- Identify RLD
- In general:
 - Same Conditions of Use
 - Same Active Ingredient
 - Same Route of Administration
 - Same Dosage Form
 - Same Strength
 - Same Labeling
 - Bioequivalence to the RLD
- Identify and characterize inactive ingredients and provide information demonstrating that they do not affect safety or efficacy
 - ANDA applicants for certain routes of administration also need to demonstrate that the proposed product uses the same inactive ingredients in the same concentration as the RLD

Contents of an ANDA (cont.)

- Patent Certifications, Exclusivity Statement
- Chemistry, Manufacturing, and Controls (CMC) Information – same standards as new drugs
 - Components and composition
 - Manufacturing and controls
 - Batch formulation and records
 - Description of facilities
 - Specifications and tests
 - Packaging
 - Stability

Current Good Manufacturing Practices

- ANDAs are held to same high standards for cGMPs as NDAs
- Purpose is to assure quality of marketed drug products
- Mechanisms:
 - Manufacturing/testing plant inspections
 - Product testing

Same Labeling

- ANDA product labeling generally must duplicate RLD's labeling
- Certain exceptions:
 - Changes required because of differences approved pursuant to a suitability petition
 - Differences because the generic and RLD are produced or distributed by different manufacturers

Bioequivalence

- A drug is considered to be bioequivalent to a listed drug if the rate and extent of availability of the proposed drug product's active ingredient or active moiety at the site of action do not differ significantly from that of the listed drug
- Bioequivalence (BE) may be demonstrated with in vivo or in vitro data, or both (21 CFR 320.24)
 - Measure concentration of active ingredient or active moiety in blood, plasma, etc. as function of time
 - Measure pharmacodynamic effect
 - Comparative BE studies with clinical endpoints
 - Dissolution and formulation data
 - Any other approach deemed appropriate by FDA

The Orange Book

- *“Approved Drug Products with Therapeutic Equivalence Evaluations”*
- Lists drugs approved on the basis of safety and effectiveness under FD&C Act
- Resource for information on drug marketing status, therapeutic equivalence evaluations, and patent and exclusivity information

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Patent Basics

- Granted by U.S. Patent and Trademark Office
 - Granted at any time in the “life” of a drug
 - Patent term can be as long as 20 years
- FDA assumes “ministerial” role with respect to patent listings
 - FDA does not review the scope or validity of patents
- Patents are listed in the Orange Book by the NDA holder
 - May be challenged by a third party
- Disputes involving patents are resolved in court - Agency does not act as intermediary/referee

Patent Information

For each patent listed for RLD in the Orange Book, applicant must make a certification:

- Patent information has not been filed (“paragraph I certification”)
 - *FDA can approve ANDA when ready**
- The patent has expired (“paragraph II certification”)
 - *FDA can approve ANDA when ready**
- The date the patent will expire (“paragraph III certification”)
 - *FDA can approve ANDA when patent expires and ANDA is ready**
- The patent is invalid or not infringed by the drug product proposed in the ANDA (“paragraph IV certification”)
 - *complex approval landscape*

(* Unless another patent or exclusivity bars approval)

Paragraph IV Certification

- After FDA notifies applicant that ANDA is sufficiently complete to review, applicant must notify NDA holder/patent owner of Paragraph IV certification
- NDA holder can sue for patent infringement when it receives notice
- If NDA holder sues within 45 days of notice, ANDA approval generally stayed for 30 months
- No lawsuit within 45 days = FDA can approve ANDA when ready



180-day Exclusivity

- The FD&C Act provides an incentive to ANDA applicants that expose themselves to the risk of patent litigation
- Grants a 180-day period of exclusivity vis-à-vis certain other ANDA applicants to the applicant(s) that files a substantially complete ANDA that contains a paragraph IV certification to a listed patent for the RLD on the first day such an ANDA is filed and that lawfully maintains the paragraph IV certification, and that does not forfeit exclusivity

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Select Variables Impacting ANDA Approval

- Innovator related
 - Unexpired patents and exclusivities
 - Changes to RLD product
- ANDA related
 - Failure to meet the requirements for approval
 - See, e.g., FDA's draft guidance for industry, *Good ANDA Submission Practices* (Jan. 2018)
 - 180-day exclusivity



Tips for Potential Applicants

- Refer to FDA's guidances for industry on generic drug products, including product-specific guidance
- Submit controlled correspondence for specific questions related to generic drug development
- Request pre-ANDA meetings as appropriate for complex products

Product-specific guidance (PSGs)

- Describe FDA's current thinking and recommendations on how to develop generic drug products, including methodology and evidence needed to support approval of an ANDA for a specific drug
- PSGs are available at:
<https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>

Contains Nonbinding Recommendations

Draft Guidance on Albuterol Sulfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Albuterol sulfate
Dosage Form; Route:	Aerosol, metered; inhalation
Strength:	EQ 0.09 mg Base/Inh
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) metered dose inhalers (MDIs) containing albuterol sulfate.

In Vitro Studies

FDA recommends that prospective applicants conduct the following in vitro studies using at least three batches each of T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

Controlled Correspondence (CCs)

- Generic drug manufacturers and related industry or their representatives can submit CCs requesting information on a specific element of generic drug development
- In general, FDA will respond to CCs within 60 calendar days (standard CCs) or 120 calendar days (complex CCs)
- Refer to FDA's guidance for industry, *Controlled Correspondence Related to Generic Drug Development* (Dec. 2020)



Pre-ANDA Meetings for Complex Products

- An enhanced pathway for discussions between FDA and a prospective applicant of a complex product
- Complex product:
 - Products with complex active ingredients; complex formulations; complex routes of delivery; or complex dosage forms
 - Complex drug-device combination products
 - Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement



Pre-ANDA Meetings for Complex Products, cont'd

- Product development meetings
 - Discuss specific scientific issues or questions regarding an ongoing ANDA development program (e.g., a proposed study design)
- Pre-submission meetings
 - Discuss the format and content of the ANDA to be submitted (e.g., types of data that will be contained in the ANDA)

Pre-ANDA Meetings for Complex Products, cont'd

- Mid-review-cycle meetings
 - Held during the first review cycle with applicants that have participated in a prior product development or pre-submission meeting
 - FDA may convey significant issues or concerns identified during ANDA review, ask the applicant clarifying questions, and outline next steps
- Refer to FDA's guidance for industry, *Formal Meetings Between FDA and Applicants of Complex Products Under GDUFA* (Nov. 2020)

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ANDA

- Application for a duplicate of a previously approved drug product (i.e., the RLD)
- Demonstrates sameness to the RLD:

Active ingredient(s)	Dosage form
Route of administration	Strength
Previously approved conditions of use	Labeling (with certain exceptions)

- Includes sufficient information to demonstrate BE and to ensure the product's identity, strength, quality, and purity
- May contain certain differences from an RLD *as long as* investigations are not necessary to establish safety and effectiveness

Petitioned ANDA

An ANDA applicant may submit an ANDA for a generic drug that is not the *same* as its RLD because:

- It has one different active ingredient (in a fixed combination drug product), or
- It has a different route of administration, dosage form, or strength than that of the RLD

The applicant must first obtain permission from FDA through the citizen petition process (such petitions are referred to as suitability petitions).

505(b)(2) Application

- Contains full reports of investigations of safety and effectiveness
- At least some of the information comes from:
 - Studies not conducted by or for the applicant
 - Studies for which the applicant has not obtained a right of reference
- Includes a “bridge” between the proposed drug product and each source of information that the applicant seeks to rely upon to demonstrate such reliance is scientifically justified

Highlighted Regulatory Considerations

- FDA may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the FD&C Act (21 CFR 314.101(d)(9))
- An applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration as an ANDA pursuant to a suitability petition

Requesting Assistance



If an applicant is developing a drug product:	And has questions on:	Contact:
<ul style="list-style-type: none">- Intended to have the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain differences) labeling as an RLD, and- Is <u>not</u> proposing clinical investigations to establish S&E	Submission through the ANDA pathway	Office of Generic Drugs
<ul style="list-style-type: none">- Has a different active ingredient, condition of use, route of administration, dosage form, strength, or labeling than a listed drug, and- Is proposing clinical investigations to establish S&E	Submission through the 505(b)(2) pathway	Office of New Drugs

Refer to FDA's guidance for industry, *Determining Whether to Submit an ANDA or 505(b)(2) Application* (May 2019)



Summary

- ANDA pathway generally requires demonstration of “sameness” of a number of characteristics to the RLD and additional information to permit reliance on FDA's finding of safety and effectiveness for the RLD
- Refer to PSGs and submit CCs and pre-ANDA meeting requests for questions about your development program
- If the product is eligible for approval under 505(j), use the ANDA pathway for approval



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