

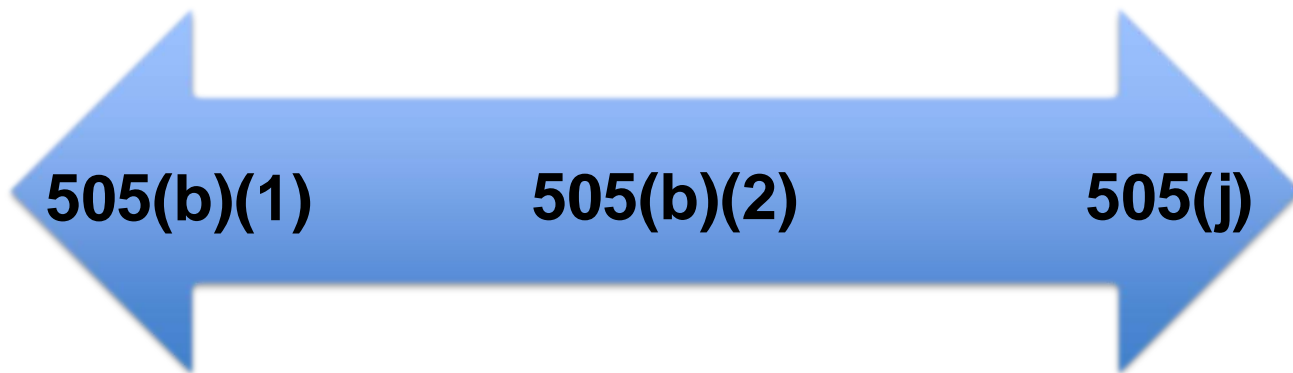
OVERVIEW OF THE 505(B)(2) REGULATORY PATHWAY FOR NEW DRUG APPLICATIONS

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Section 505 Applications



Section 505(b)(1) NDA

- ✓ **“Stand-alone” NDA**
- ✓ **Submitted under section 505(b)(1) and approved under section 505(c)**
- ✓ **Contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use**
 - ✓ **Non-clinical information (toxicology, carcinogenicity, etc.)**
 - ✓ **Clinical pharmacology**
 - ✓ **Clinical safety and effectiveness data**
 - ✓ **Chemistry, manufacturing, and controls**

Section 505(j) ANDA

- ✓ Submitted and approved under section 505(j)
- ✓ Generally duplicates previously approved drug and relies on the findings of safety and effectiveness of a reference listed drug (RLD)
 - ✓ In general, same as the RLD wrt active ingredient(s), dosage form, route of administration, strength, and labeling (with permissible differences)
 - ✓ Bioequivalent to the RLD
 - ✓ If studies are required to demonstrate the safety and effectiveness of the product, then cannot be submitted under this pathway

Section 505(b)(2) NDAs

- ✓ Submitted under section 505(b)(1) and approved under section 505(c)
- ✓ 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*
- ✓ Allows for flexibility in the characteristics of the proposed product without having to conduct studies on what is already known about the product

Examples of sources of reliance

- ✓ **FDA’s finding of safety and/or effectiveness of a listed drug**
 - ✓ Support for any differences between the proposed drug product and the relied-upon listed drug to demonstrate the safety and effectiveness of the proposed drug product
 - ✓ Cannot rely on a listed drug approved under section 505(j)
 - ✓ Establish a “bridge” to the relied-upon listed drug (e.g. comparative BA, nonclinical study)
- ✓ **Published literature**
 - ✓ Establish a “bridge” to each source necessary for approval (scientific relevance to the proposed product)
 - ✓ Published literature that describes a listed drug is considered to be reliance on the listed drug

Reliance on Previously Approved Drugs

- ✓ Reliance on older drugs may be difficult, in part, because the marketing of the drug may be discontinued or the NDA may be withdrawn
- ✓ If NDA is discontinued or withdrawn, sponsor may still be able to rely on it but will be contingent on the Agency's consideration of whether the drug was discontinued from marketing for reasons of safety and/or effectiveness
 - ✓ Sponsor may consider submitting a petition requesting the Agency's determination of whether the NDA was discontinued/withdrawn for reasons of safety and/or effectiveness
 - ✓ May use a generic drug that references the NDA for "bridging" studies

Examples of referenced studies

- ✓ **API**
- ✓ **Nonclinical**
 - ✓ Toxicology
 - ✓ Reproductive toxicology
 - ✓ Carcinogenicity
 - ✓ Dermal toxicology
- ✓ **Clinical pharmacology**
 - ✓ Mechanism of action
 - ✓ PK/PD
 - ✓ Special populations
- ✓ **Clinical studies**
 - ✓ Clinical safety and/or efficacy information

General content comparison of applications

505(b)(1) NDA	505(b)(2) NDA	ANDA
Preclinical	Preclinical	
Clinical	Clinical	
Pediatric Use	Pediatric Use	
Chemistry, Manufacturing, Controls (CMC)	CMC	CMC
Pharmacokinetics (PK) & Bioavailability	PK, Bioavailability, Comparative Bioavailability	Bioequivalence
Labeling	Labeling	Labeling
Patent Information	Patent Information	
	Patent Certification (if applicable)	Patent Certification
Exclusivity Request	Exclusivity Request	
	Exclusivity Statement	Exclusivity Statement

Examples of 505(b)(2) NDAs

- ✓ **New chemical entities/new molecular entities**
- ✓ **Changes compared to previously approved drugs**
 - ✓ **Indication**
 - ✓ **Active ingredient**
 - ✓ **Fixed-combination**
 - ✓ **Dosage form**
 - ✓ **Route of administration**
 - ✓ **Dosing regimen**
 - ✓ **Strength**
 - ✓ **Formulation (not approvable under section 505(j))**

Spectrum of 505(b)(2) NDAs

505(b)(2) NDAs can be New Chemical Entities (NCEs) OR 'almost' generics, for example:

Emflaza (deflazacort) NDA 208684 <-----VS----->
 (AP 2/9/17), an NME for Rx of
 Duchenne Muscular Dystrophy
 Granted NCE + Orphan Drug exclusivity

Tigecycline NDA 205645
 (AP 12/1/16)
 a new formulation injectable
*(not eligible for approval as
 ANDA, AP rated to innovator)*

If an application can be a generic, it *should* be a generic and FDA will Refuse to File the application

21 CFR § 314.101(d)(9)

Patents

- ✓ **Pre-approval**
 - ✓ **Must certify to patent(s) listed in the Orange Book for each relied-upon listed drug**
 - ✓ **Must also certify to one listed drug that is a pharmaceutical equivalent if one is approved**

- ✓ **Post-approval**
 - ✓ **Can list patents in the Orange Book upon approval**

Exclusivity

- ✓ **Pre-approval**
 - ✓ **Exclusivity for approved drug(s) may block the submission or approval of a 505(b)(2) NDA, or limit approved labeled uses**

- ✓ **Post-approval**
 - ✓ **May qualify for exclusivity**
 - ✓ **5-year exclusivity for new chemical entities**
 - ✓ **3-year exclusivity for new clinical investigations**
 - ✓ **7-year exclusivity for orphan drugs**
 - ✓ **6-month exclusivity extension for pediatrics**
 - ✓ **5-year exclusivity extension under GAIN**

References

FDA Regulations

- 21 CFR 314.3 (Definitions)
- 21 CFR 314.50 (Content and format of an NDA)
- 21 CFR 314.52 (Notice of certification invalidity, unenforceability, or noninfringement of a patent)
- 21 CFR 314.53 (Submission of patent information)
- 21 CFR 314.54 (Procedure for submitting 505(b)(2) application requiring investigations for approval ...)

CDER Guidance Documents

- Applications Covered by Section 505(b)(2) (draft) (Dec. 1999)
- Determining Whether to Submit an ANDA or a 505(b)(2) Application (May 2019)



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