Regulatory and Scientific Concepts Underlying 505(b)(2) and VAM Applications

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Agenda

- Historical Background
- Types of Regulatory Submissions
- Examples of 505(b)(2) Applications
- 505(b)(2) vs. VAM
- Fixed-Dose Combinations (FDC)

Background

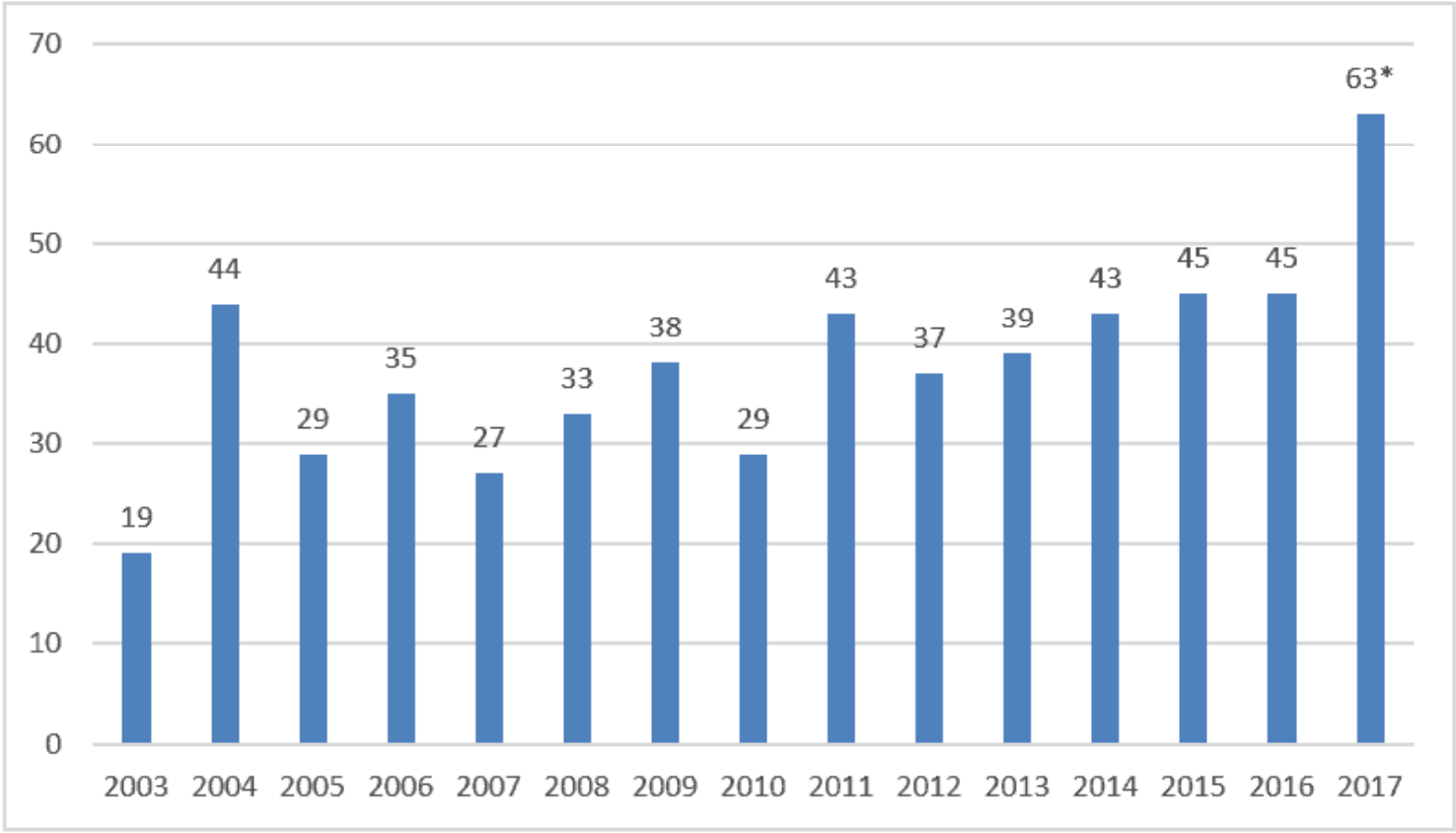
- FDA created the **paper NDA** policy in 1981 to permit approval of generic equivalents of post-1962 new drug products based on literature- and product-specific data.
- Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch) created Sections **505(b)(1)** and **505(b)(2)** of the Federal Food, Drug & Cosmetic Act.
- Intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: "*it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug*".

Types of Regulatory Submissions

- 505(b)(1); NME/NCE
- **505(b)(2)**
- 505(j); ANDA; Generic Application

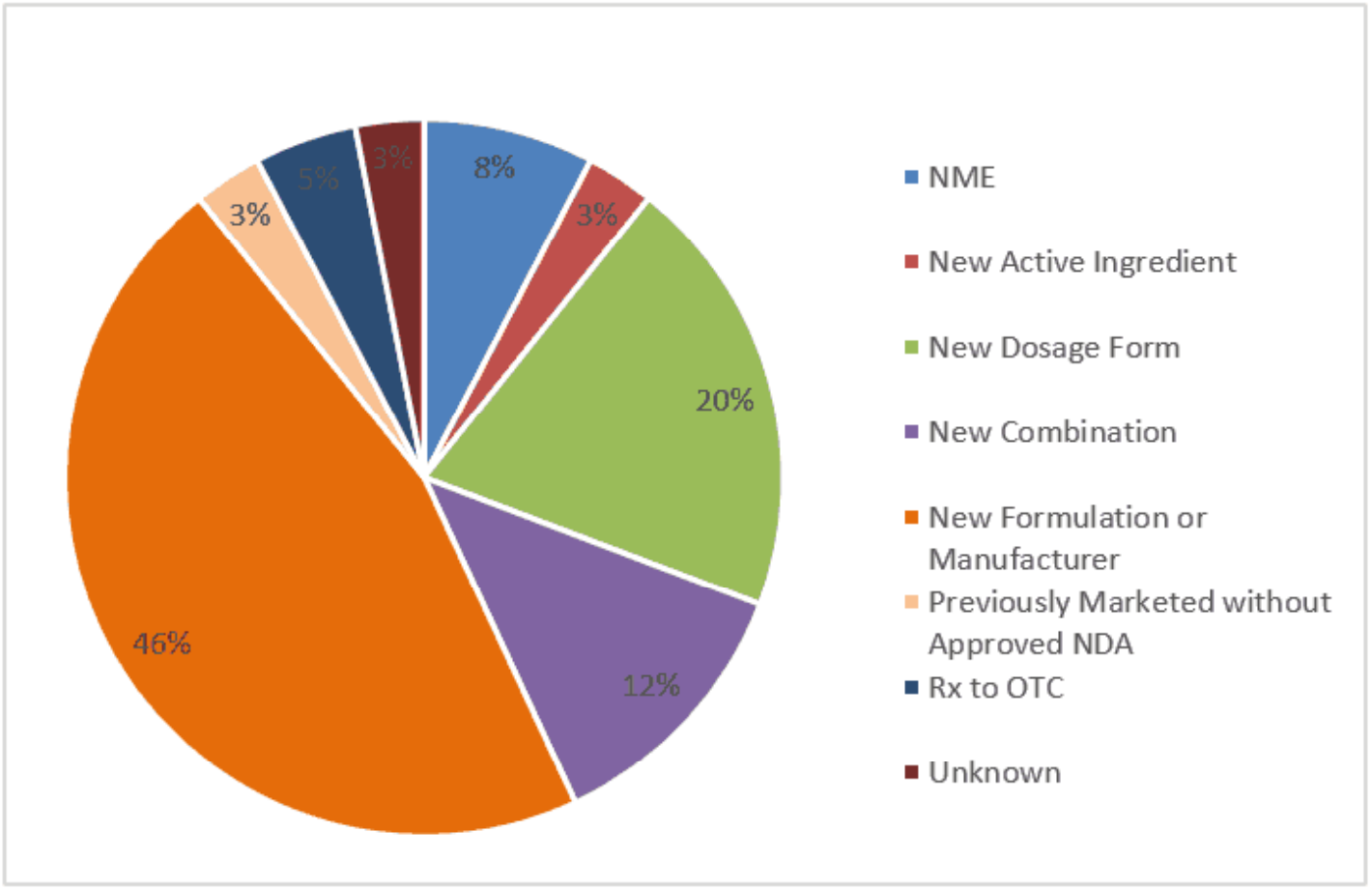
505(b)(2) NDA Approvals (2003-2017)

Figure 1 505(b)(2) NDA Approvals (2003-2017)



*** https://camargopharma.com**

505(b)(2) NDA Approvals (2017)



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Required Data by Type of Submission

505(b)(1)	505(b)(2)	505(j)
Preclinical	Preclinical	---
CMC	CMC	CMC
PK & BA	PK & Comp. BA	BE
Clinical	Clinical	---
Pediatric Use	Pediatric Use	---

Development Timeline

	DISCOVERY	NONCLINICAL RESEARCH	CLINICAL STUDIES
505(B)(1)	2-5 YEARS	1-5 YEARS	8-15 YEARS
505(B)(2)	<1-3 YEARS	< 1-2 YEARS	2-5 YEARS

*www.camargopharma.com

Types of Exclusivity

- NME – 5 years

- 505(b)(2) application – 3 years (if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant), 5 years (if either single active ingredient or component of FDC is NME)

- First filed ANDA – 180 days

- BLA Exclusivity – 12 years

- Orphan drug exclusivity – 7 years

- Pediatric exclusivity – additional 6 months

US FDA Guidance on 505(b)(2)

جامعة البترا

Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

For additional copies, contact:

Drug Information Branch
Division of Communications Management, HFD-210
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm.

US FDA Guidance on Whether to Submit 505(b)(2) or ANDA Application

Determining Whether to Submit an ANDA or a 505(b)(2) Application

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2017
Generics

505(b)(2) Application: Regulatory Definition

Food, Drug & Cosmetic Act: 505(b)

- *"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" (21 U.S.C. 355(b)(2)).*

Applicant Can Rely on…

- Published literature
- The *Agency's finding* of safety and effectiveness for an approved listed drug

Examples of 505(b)(2) Applications

- Change in active ingredient* (e.g., Pexeva; paroxetine mesylate, Nexium; esomeprazole)
- Change in strength (e.g., Antara; micronized fenofibrate Caps)
- Change in formulation (e.g., Doxil liposomal injection; doxorubicin)
- Change in dosage form (e.g., Tramadol orally-disintegrating Tabs, Ondansetron thin film sublingual dosage form)
- Change in dosing regimen (e.g., BID to QD)
- Change in route of administration (e.g., Duraclin; epidural clonidine, Protonix I.V.)

*i.e., Different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

Examples of 505(b)(2) Applications

- Change in indication (e.g., Cenestin; conjugated estrogen, sildenafil)
- Rx/OTC Switch (e.g., loratadine, omeprazole)
- Combination of two approved products. (e.g., Lotrel, Tekturna HCT, Janumet)
- Intentional bio-inequivalence (e.g., MR vs IR)
- Combo. of individually approved products (e.g., Naprapac; naproxen + lansoprazole)
- OTC monograph: drug product differs from monograph such as non-monograph indication or new dosage form
- Naturally derived or recombinant active ingredient (e.g., Omnitrope; rhGH)

505(b)(2) Applications Can Also be…

- NME (e.g., Thalidomide, quinine sulfate)
- A duplicate of a listed drug that is not ANDA-able (e.g., Abraxane; cremaphor-free paclitaxel).

What Can't be Submitted As a 505(b)(2) Application?

- The drug product is eligible for submission under Section 505(j)
  - 21 CFR 314.101(d)(9)
- The extent of absorption is less than the listed drug.
  - 21 CFR 314.54(b)(1)
- The rate of absorption is *unintentionally* less than the listed drug.
  - 21 CFR 314.54(b)(2)

Contrasting 505(b)(2) to VAM

- If any element of the key data is from literature (or from another source to which the applicant does not have a right of reference), Section 505(b)(2) applies rather than Section 505(b)(1). No such comparable distinction considered by EMA.

- Prodrugs may be approvable by the FDA under 505(b)(2) by relying on prior demonstration of safety and efficacy of the active moiety as simple drug. EMA considers such new prodrugs as different molecular entities and will require full MAAs according to Article 8(3) (e.g., Telzir; prodrug of amprenavir).

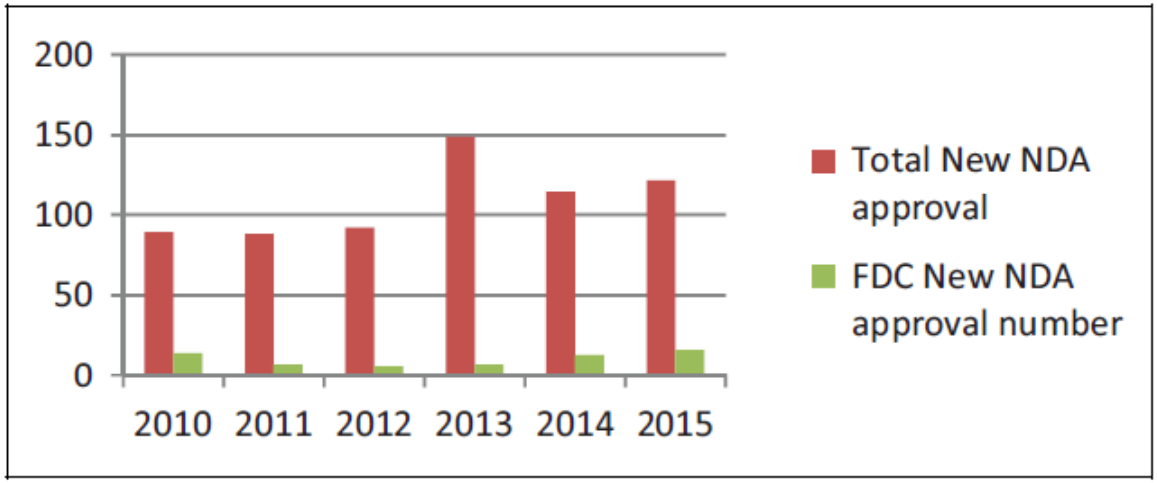
Contrasting 505(b)(2) to VAM

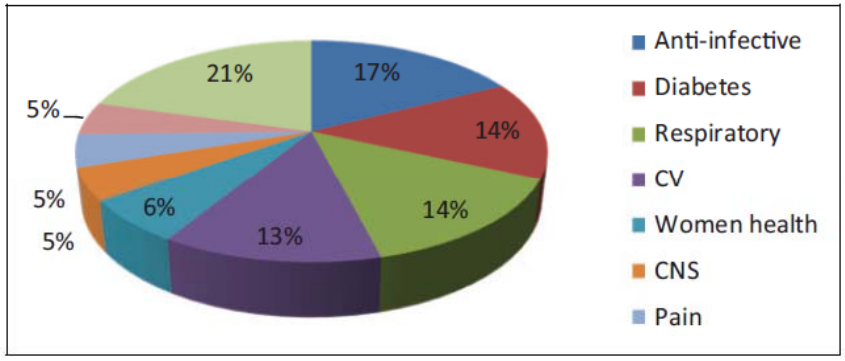
- 505(b)(2) applications may be filed for products with a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety. EMA accepts such changes for ‘‘regular’’ generic applications according to Article 10(1) and (2).

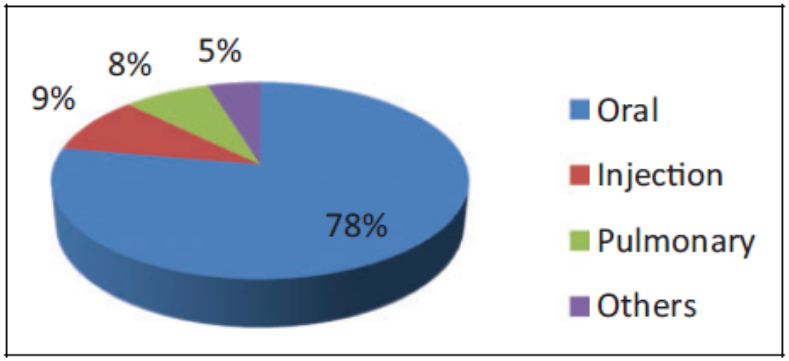
Contrasting 505(b)(2) to VAM

- ANDA route may, upon permission from the FDA, be used for drugs with a similar active ingredient or whose route of administration, dosage form, or strength differs from that of the RLD. Such changes have to be minor (e.g., the change from an immediate release tablet to a capsule or the addition of an intermediary strength). Such changes will usually have to be submitted as a hybrid application to EMA.

US FDA FDC Approvals (2010-2015)







*Kwon et al, 2017

Rationale for Fixed-Dose Combinations (FDC)

- **Improved patient compliance:** Simplified disease management for chronic diseases (e.g. HIV, asthma, diabetes, lipid regulation, hypertension, etc.)
- **Enhanced efficacy/safety:** Synergistic mechanisms, improved ADME & drug resistance
- **Simplified/cost effective handling & distribution:** especially for HIV drugs
- **Effective LCM strategy:** New products from proven molecules; patent/market exclusivity, may also combine formulation patent exclusivity

Data Package for FDC 505(j) ANDA

- To support ANDA (505(j)) applications, US FDA requires a fasted single-dose Bioequivalence study comparing the individual components in the test FDC to the reference FDC.

- A single-dose fed BE study in human subjects for each potential FDC is typically additionally required unless any of the following scenarios applies:
  - RLD's FDA-approved Package Insert does not mention food effects on drug absorption or administration
  - Package Insert stipulates the drug must be given on an empty stomach
  - BCS Class I

Clinical Data Package for FDC 505(b)(2) NDA

- Relative bioavailability study demonstrating comparable systemic exposure between FDC and individual components
- Satisfy combination rule (21CFR 300.50): Demonstrate the independent contribution of the individual components
  - In a factorial study comparing A+B to A and to B at their highest-approved doses, demonstrate that each component contributes to the clinical outcome, which shows that there is not complete overlap of the mechanisms by which the drugs exert their effects.
- Single, double-blind, and randomized Phase 3 trial
- Sponsor may rely on Agency's findings of safety and efficacy as well as published literature, as appropriate

List of References

- US FDA Guidance on 505(b)(2) applications
- http://www.fda.gov/cder
- www.cov.com (Covington & Burling)
- www.morganlewis.com
- www.alston.com
- http://www.ehcca.com
- www.pharmadevgroup.com
- www.pharmacircle.com
- Andreas Vogel, *Drug Information Journal*, 2012

Questions?