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Hatch-Waxman 101

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Meet the Speakers

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Overview

Topics

- Hatch-Waxman Act Overview
- Approvals and Exclusivities
- Patent Challenges

Housekeeping

- CLE
- Questions
- Materials
- http://www.fr.com/webinars

Hatch-Waxman Act Concerns “Drugs”

- Typically, though not always, small molecule chemistry
  - Acetaminophen (TYLENOL), Ibuprofen (MOTRIN)
- Relatively easy to manufacture
- Governed by Federal Food and Drug Act and Hatch-Waxman Act
- Protected typically by small number of patents

- Distinct from biologics
  - Adalimumab (HUMIRA), Erythropoietin (EPOGEN)
- Much harder to make
- Governed by Biologics Price Competition and Investment Act (BPCIA)
- Frequently protected by a large number of patents

Hatch-Waxman vs BPCIA

Hatch-Waxman

Drugs

Bioequivalence

30-month stay

Generic Exclusivity

Orange Book

Only active and method of using active authorized in litigation

Patent Certification

Carve-outs

BPCIA

Biologics

Biosimilar/Interchangeable

No 30-month stay

Interchangeability Exclusivity Only

No Orange Book Equivalent

Any patent

Optional “Dance”

Carve-outs

Notice of Commercial Marketing

Drug Discovery & Development

Drug Discovery
Preclinical testing
IND Approved
Phase I
Phase II & III
FDA Accepts NDA
Review of NDA
NDA approved by FDA
Phase IV (postmarket)

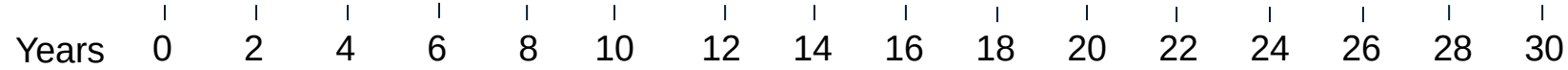
Patent Protection

US Patent Application Filed
US Patent Issued
Foreign Patent Applications Filed

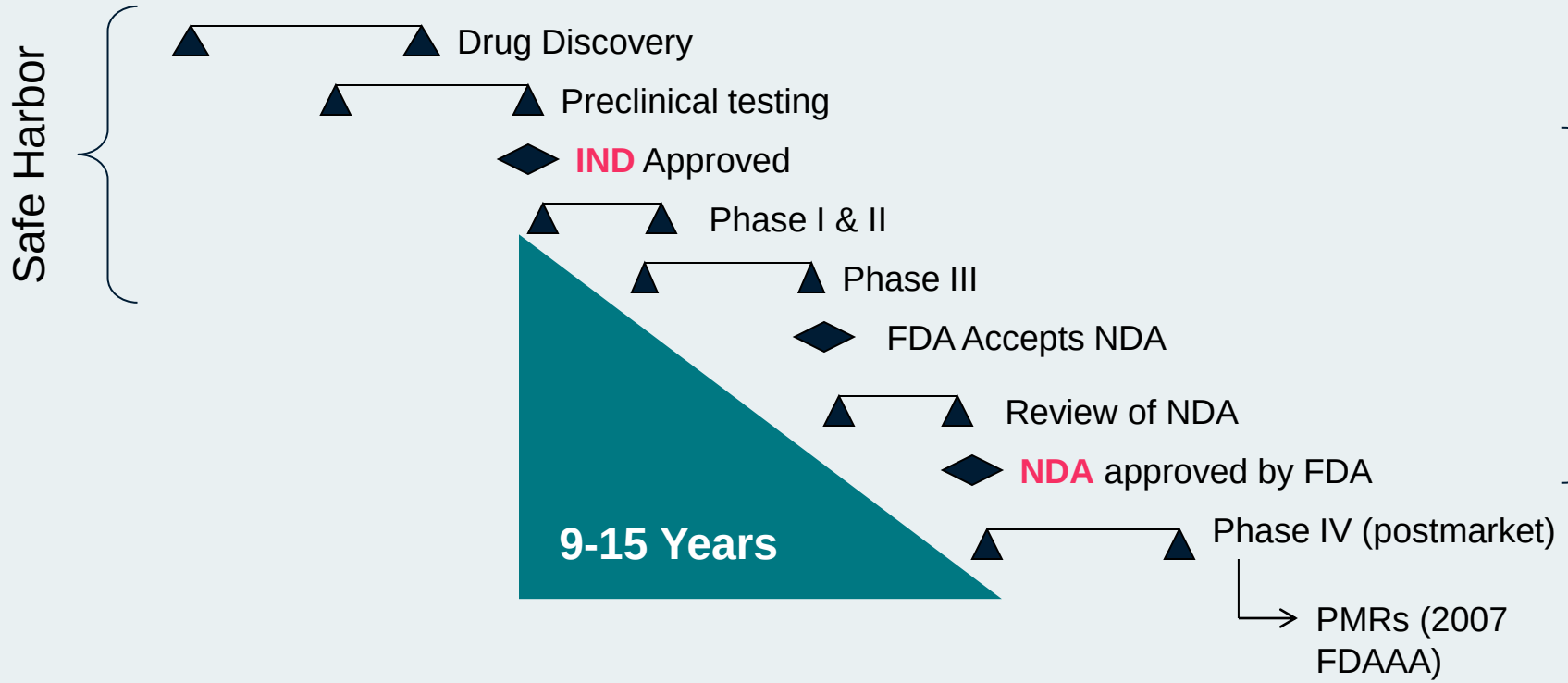
Hatch-Waxman Extensions
PTE & Ped.Ex.

Generic Competition

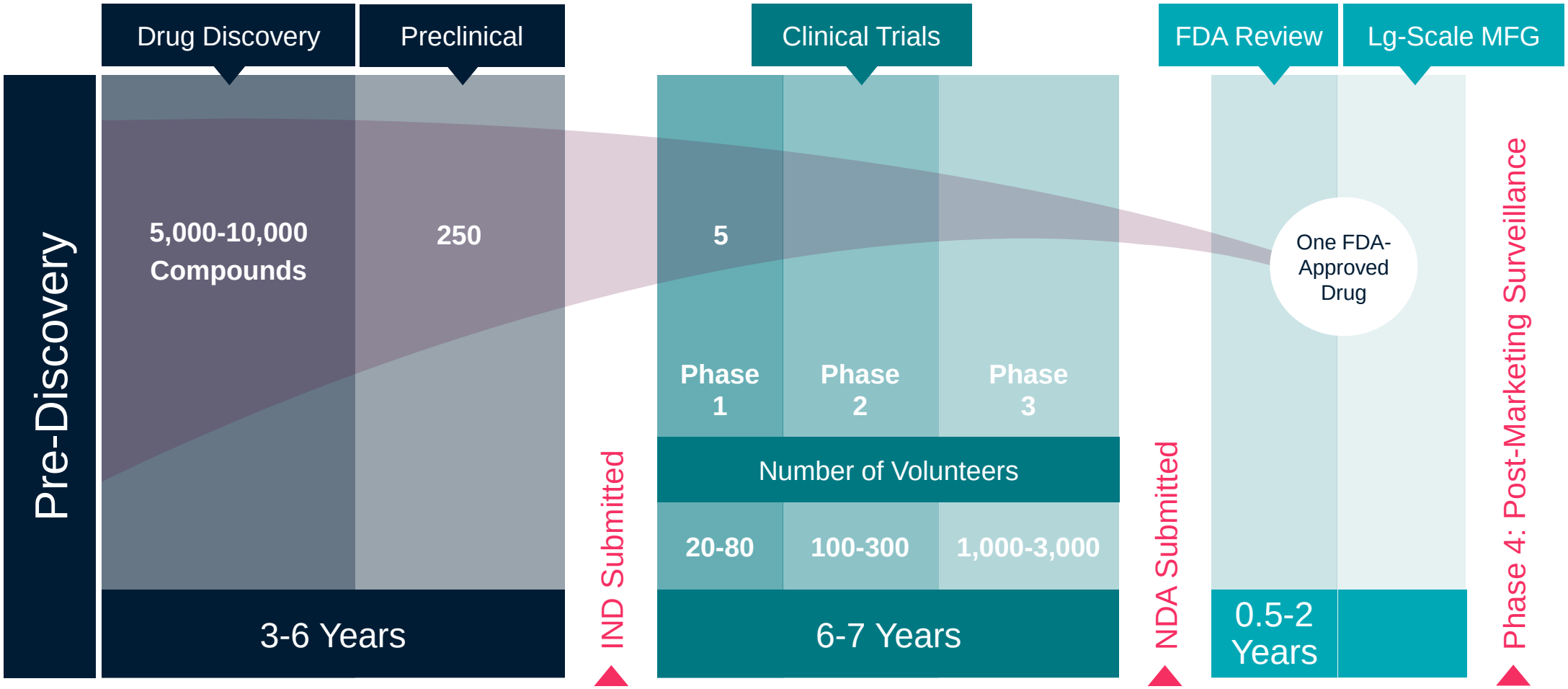
Generic Resource Commitment
Product Development & Bioequivalency Testing
ANDA Filed with FDA
ANDA Approved
Generic Marketed



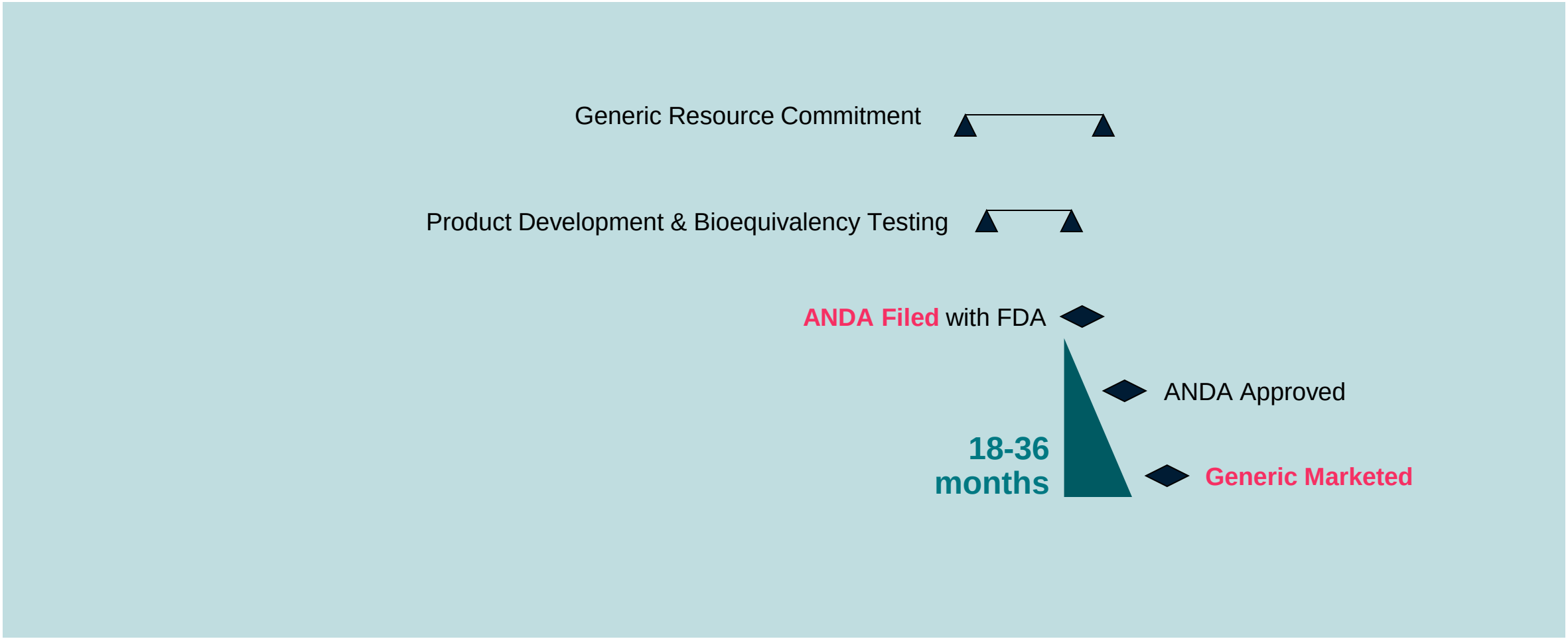
Drug Discovery & Development



Drug Discovery & Development – A Long Risky Road



Generic Competition



Hatch-Waxman Act is a Compromise

"[The Hatch-Waxman Act strikes] a balance between two potentially competing policy interests—inducing pioneering development of pharmaceutical formulations and methods and facilitating efficient transition to a market with low-cost, generic copies of those pioneering inventions at the close of a patent term."

Novo Nordisk A/S, et al. v. Caraco Pharmaceutical Laboratories, Ltd., et al., No. 2010- 1001 (Fed. Cir., April 14, 2010), at 2.

The Compromise

- Brand Industry (§ 505(j)(5)(F))
  - 5 year “filing” exclusivity (“data exclusivity”) for new chemical entities (NCE)
  - 3 year “marketing” exclusivity based on new clinical trials
  - Patent Term Extension for time patented product is under review by FDA

- Generic Industry
  - Use of Abbreviated New Drug Applications (ANDAs)
  - 180-Day Generic Drug Exclusivity for first Paragraph IV filer(s)
  - Ability to develop product free of worry of infringement suit (safe harbor)

- Both
  - Opportunity for Court to decide patent issues pre-launch

Hatch-Waxman Act – Key Concepts

- Hatch-Waxman Act amended the Patent Act and the FFDCA
- Routes of Approval
- Patent Term Extension
- Exclusivities
- Orange Book -- List of relevant patents
- Safe Harbor
- Generic certification and notice re: patents
- Patent Challenge
- Stay of Approval
- 180-Day Exclusivity
- Litigation/Settlement Considerations

Routes to Drug Approval (21 USC § 355)

- 505(b)(1) or New Drug Application (“NDA”)
  - Full clinical trials, patent declaration

- 505(b)(2) or “paper" NDA
  - New drugs – partial clinical trials, reliance on published safety and efficacy data, patent declaration
  - Generic drugs – partial clinical trials, reliance on published safety and efficacy data, patent certification

- 505 (j) or Abbreviated New Drug Application (“ANDA”) – true generic
  - Clinical trials often not required, reliance on data for the approved branded drug, patent certification
  - Can petition FDA to change active ingredient (combination drug), route, dosage or strength
  - Inactive ingredient changes permitted in some cases

Exclusivities

- Scope: drugs, combinations regulated as drugs, new antibiotics (since 1997)

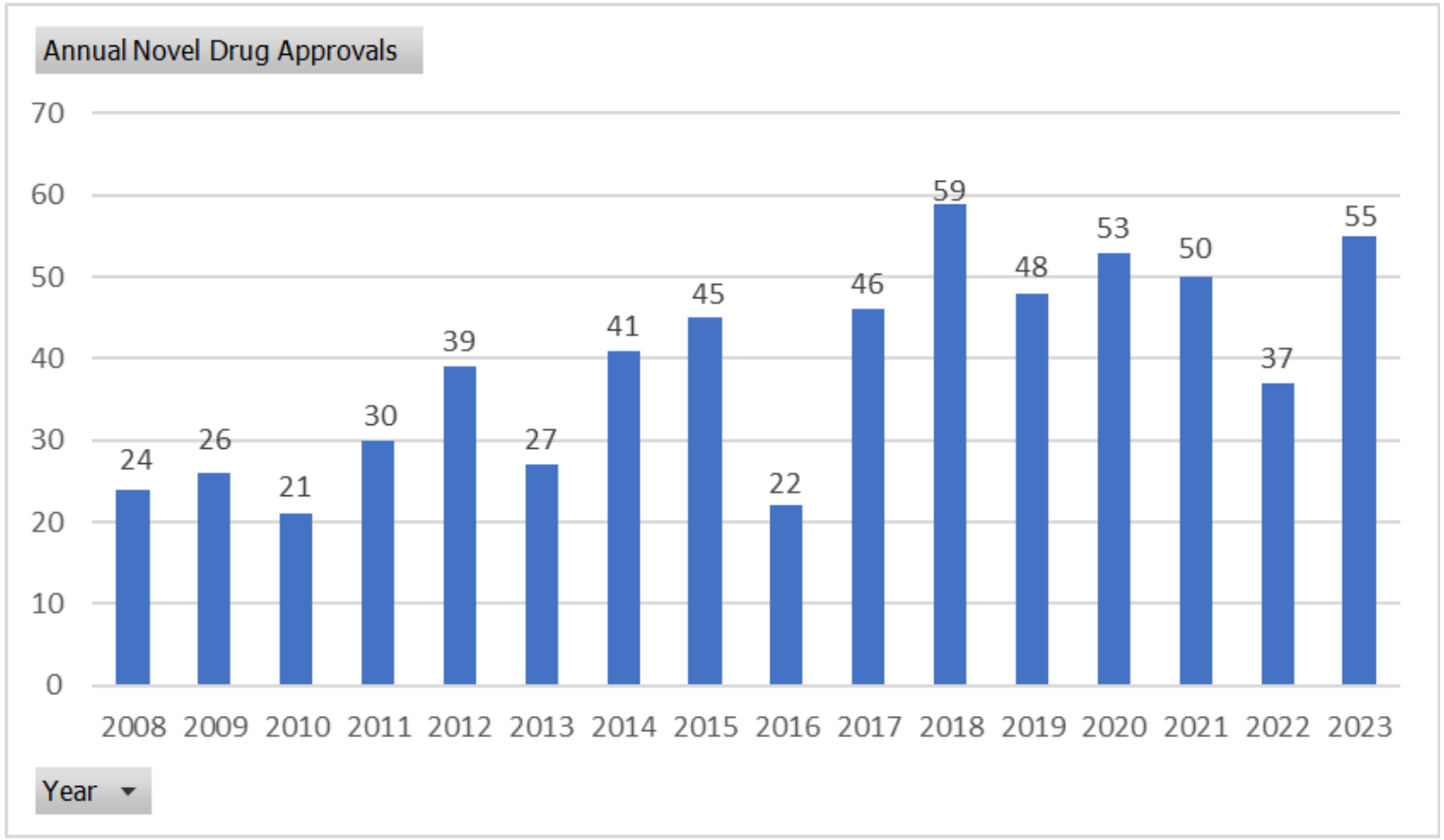
- Types of Exclusivities
  - 5-year “data” New Chemical Entity (“NCE”) Exclusivity
  - 180-day Generic Exclusivity
  - 3-year “Marketing” Label Exclusivity
  - Pediatric Exclusivity
  - Orphan Drug Exclusivity

Five-Year Data Exclusivity for NCE

- Prevents the submission of ANDAs and 505b2s for the same active moiety
- New active moieties only
- No generic or 505(b)(2) application can be ***filed*** for 5 years
- Four-year ***filing*** option if an Orange Book patent is challenged -- Paragraph IV certification.
- If brand timely files suit, FDA prevented from approving at earliest for 30 months from 5 year date

CDER's Annual Novel Drug Approvals: 2008 - 2023

In 2023, CDER approved 55 novel drugs. The 16-year graph (right) shows that from 2008 through 2023, CDER has averaged about 39 novel drug approvals per year.



180-Day Generic Exclusivity

- Protects first generic to challenge listed patent
  - No other application can be approved until the expiration of 180-days of marketing by the First to file applicant
- Can be shared (same day first to file)
- Immensely valuable to generic because of states' mandatory substitution laws
  - All states require substitution of therapeutically equivalent generic product for a branded product
- Post 2003 MMA –exclusivity forfeitures to prevent "parking"
  - Failing to obtain tentative approval in 30 months
  - Failing to market within specified time after approval
  - Expiration of all patents with which exclusivity is associated
  - Withdrawal of the ANDA or all of the Paragraph IV certifications
  - Enters into agreement that is a violation of the antitrust laws

Three-Year Label Exclusivity

- Three-year Marketing
  - Prevents ANDAs and 505(b)(2)s from being ***approved*** for same "conditions of approval" for same active moiety.
  - Protects drug label information based on clinical studies (other than BA studies) essential to approval for which the sponsor has the right of reference.
  - But not all clinical label information is necessarily protected; must be "essential to approval."
  - Further, use exclusivities can be carved out of label by ANDA applicants without impacting AB-rating (automatic substitution by pharmacies).
  - So, what does three-year exclusivity really protect?
    - Labeling/marketing of a generic drug for the "conditions of approval."
    - Subsequent 505(b)(2) approvals for same active moiety for the same "conditions of approval" (Veloxis/Envarsus XR and Otsuka/Aristada cases).

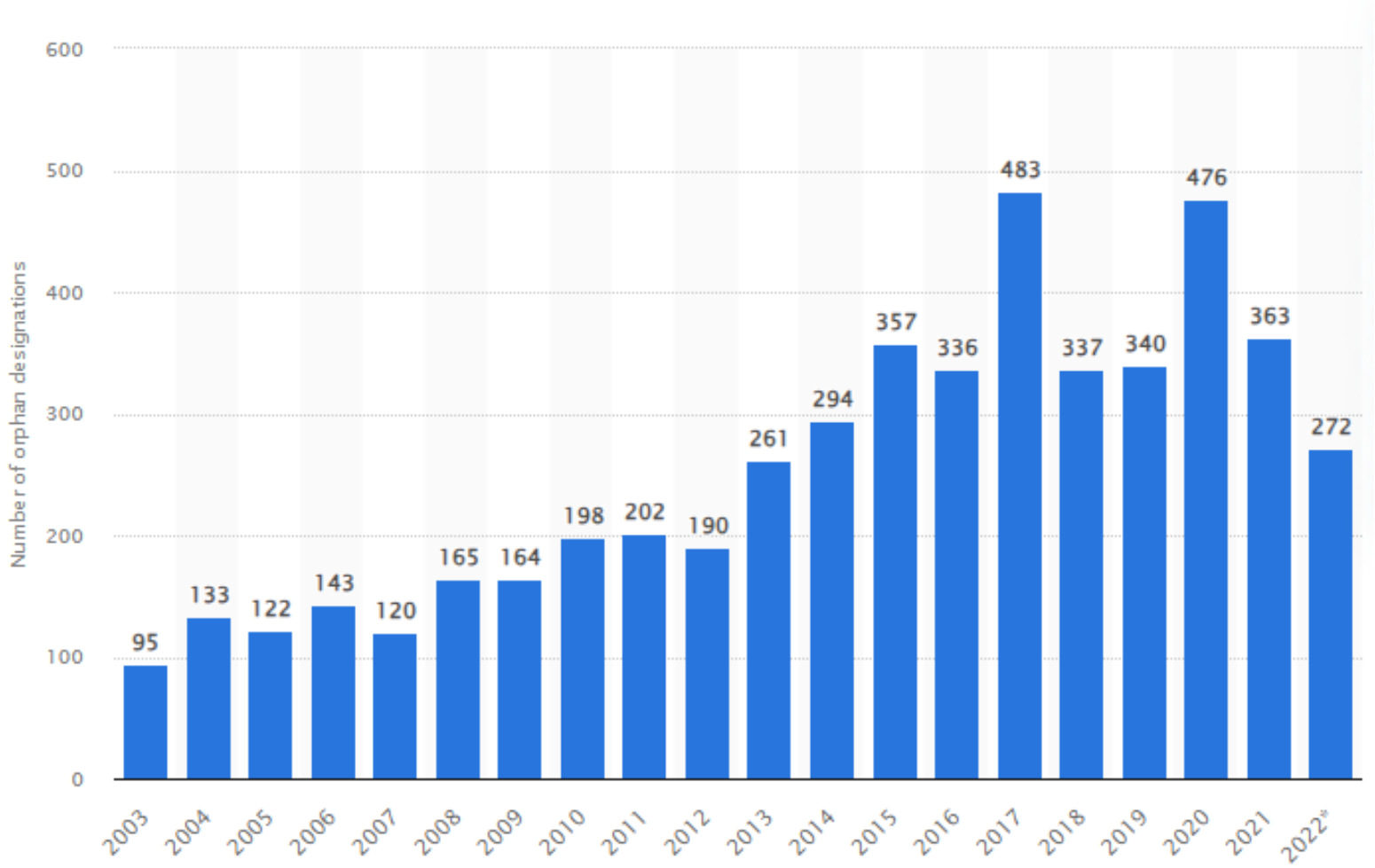
Six-Month Pediatric Exclusivity

- Scope: clinical studies in pediatric populations
  - Requires a “written request” from FDA for studies in a pediatric population/sub-population.
  - Requires studies to be conducted and submitted in accordance with WR; does not require positive results or labeling approval.
- Drugs and biologics (2009 ACA)
- Protects active moiety; all indications, dosages, strengths
- Adds 6 months protection to end of all other exclusivities
- Listed patents also get 6 months of protection

Seven-Year Orphan Drug Exclusivity

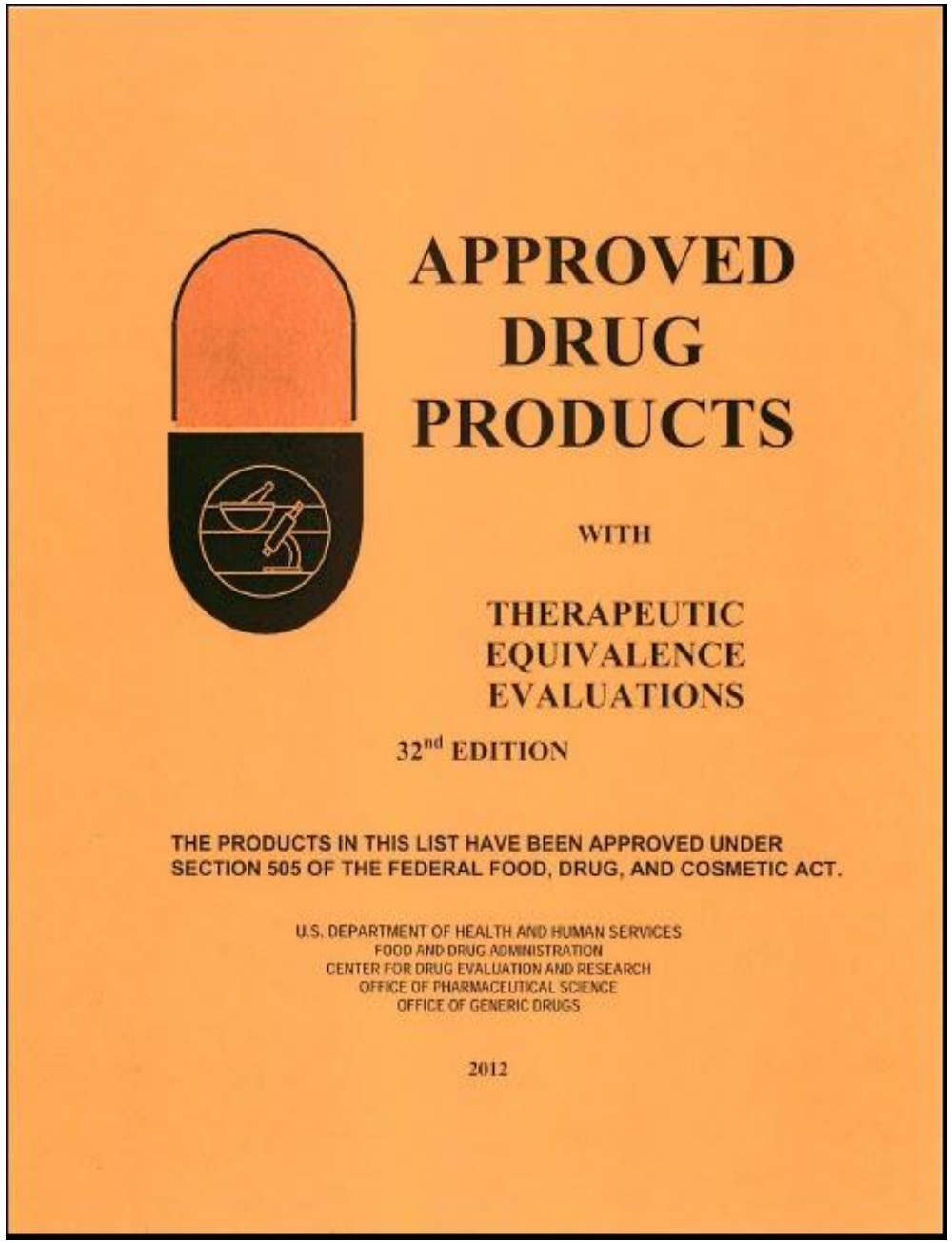
- Seven-Year Orphan – protects against approval of any drug with the same active moiety for the same approved "rare disease or condition."
  - Rare disease or condition means one that affects less than 200,000 persons in the US; or affects more than 200K and for which there is no reasonable expectation of cost recovery.
  - "Disease or condition" can be sub-divided into medically distinct patient populations; e.g. some biologics have received as many as 7 OD approvals for a single macro-molecule.
- Protection against NDAs as well as ANDA and 505(b)(2)s.
  - No FDA approval for same product for same indication unless clinically superior
    - Means safer or more effective than the approved use; flexible standard (dosage change from injectable to oral found superior in one drug; whereas change from oral to injectable found superior in another); or
    - Means "major contribution to patient care" – for severe or life-threatening diseases MC2PC can involve convenient treatment location; duration of treatment; patient comfort; improvements in drug efficiency; advances in the ease and comfort of drug administration; longer periods between doses; and potential for self-administration.

Number of Approved Orphan Products by Year



Data Source: FDA Orange Book
Source: FDA Law Blog

Listings of Patents – The Orange Book



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Orange Book Listing

- Eligibility
  - Patent must claim a drug or method of using a drug for which a claim of patent infringement could reasonably be asserted
  - **2003 Orange Book Reforms – no packaging patents, metabolites or intermediates**
- FDA Form 3542 – Patent Information
  - Use patents must be identified on label
  - Patent “use code” provided for each method patent
  - Signed under “penalty of perjury”
- Timing
  - NDA Sponsor must submit within 30 days of approval of NDA or supplement and patent issuance
  - If submitted after 30 days, pending ANDAs do NOT have to certify
  - New patents (after NDA approved) must be filed within 30 days to perfect issue date in OB

Sections 505(b)(1)(G); (c)(2); 21 CFR 314.53

Act of Infringement

"35 USC 271(e)(2) makes the filing of ANDA or 505(b)(2) an act of infringement "if the purpose is to obtain approval … to engage in the commercial manufacture, use or sale of a drug … before the expiration of such patent."

Patent Certification

For each patent listed in the Orange Book, Generics must certify one of the following:

- **Paragraph I –** patent information has not been filed
  - FDA can approve ANDA whenever ready to
- **Paragraph II –** patent has expired
  - FDA can approve ANDA whenever ready to
- **Paragraph III –** date patent will expire
  - FDA can approve ANDA when patent expires and ANDA is ready to be approved
- **Paragraph IV –** such patent is invalid or will not be infringed by the manufacture use or sale of the drug for which the application is submitted
  - Much more complicated approval window

Paragraph IV Certification

- Generic applicant must state:
  - That an application that contains data from a bioequivalence or bioavailability study has been accepted for filing;
  - Seeking approval to engage in the commercial manufacture, use, or sale of the listed drug before the expiration of the listed patent(s); and
  - The factual and legal basis that the ANDA applicant believes that the patent is invalid or will not be infringed

- Generic must send notice letter within 20 days from ANDA "receipt" acknowledgement letter from FDA
  - No jumping the gun: if just "submitted" and not received for filing, paragraph IV is premature (Allergan v. Actavis, et al, 2:14-cv-00638-JRG (E.D.Tx. 2014)

- FDA does not police the sufficiency of the notice letter

Patent Challenge

- Filing of ANDA is an “artificial act” of infringement
- NDA sponsor can sue when it receives paragraph IV notice
- Infringement suit will thus usually begin before ANDA approval
  - In the case, infringement judged as if product were on the market
- If suit brought within 45 days of notice, ANDA approval is stayed for 30 months, provided patent tied to stay remains in case
  - Computation of 45-day time clock. (1) The 45-day clock described in paragraph (b)(3) of this section begins on the day after the date of receipt of the applicant's notice of certification by the patent owner or its representative, and by the approved application holder. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.107
- If no suit within 45 days, FDA can approve ANDA at its discretion
- If patent tied to stay dismissed, FDA can approve ANDA

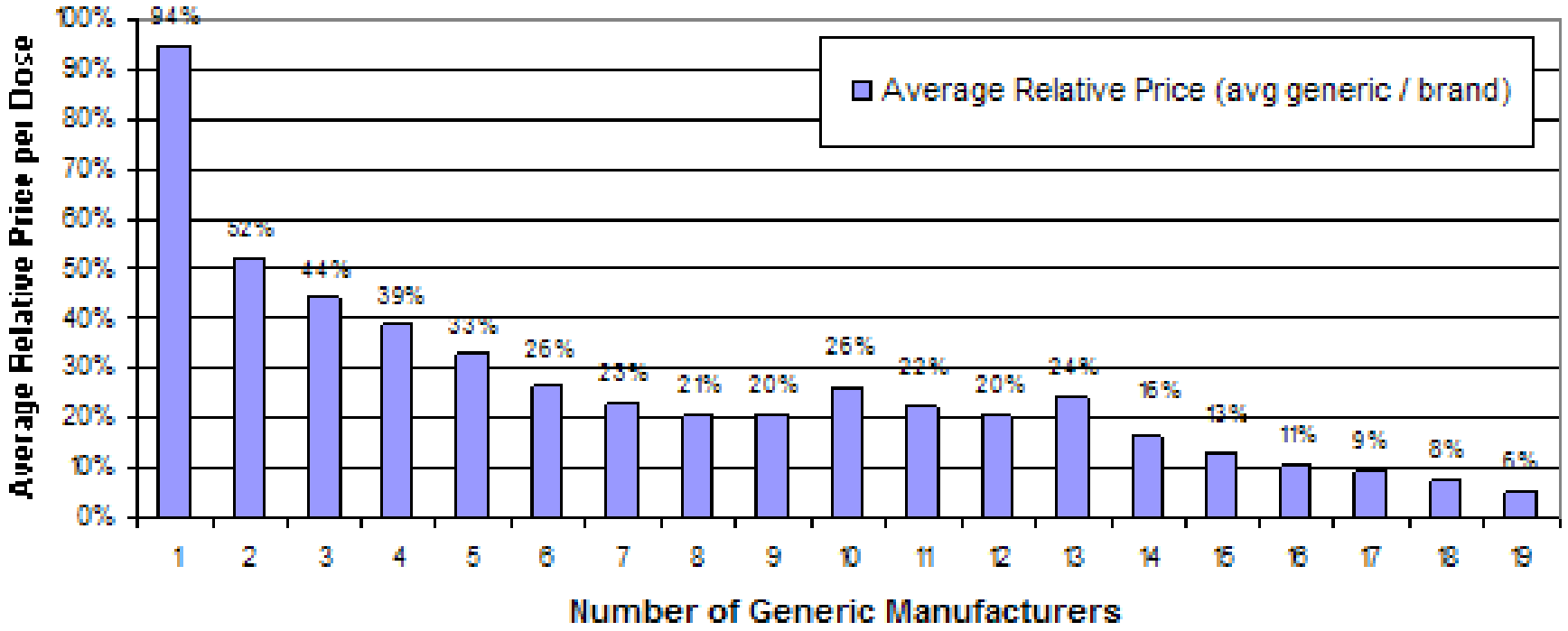
Stay of Approval

- Approval stayed pending outcome of suit (up to 30 months)
  - Can be shortened or extended by Court
  - Only get one 30-month stay
    - Later listed patents require certification but do not impact first to file status or 30-month stay.

- Tentative Approval
  - ANDA ready for approval but blocked by patent, exclusivity or stay
  - Only eligible for “tentative” approval

- Full approval not automatic
  - Must be requested
  - Will not be given until “block” is cleared
    - Expiration of 30-month stay
    - Generic wins
    - Settlement of Case

Drug Prices Based on # of Generics in Market



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective ™, 1999-2004, extracted February 2005

Orange Book Listing – Method of Use Patents Use Code

- When a Brand submits a method of use patent for listing, it must propose a “use code”
- Tool for FDA – identifies language on label protected by method patents
- Based on reasonable claim construction
- Identification of claim #s that read on label and label location(s) on which the patent claims read
- 240 character max
- Limited to “Approved” Method of Treatment -- but FDA approves the entire drug label. Is a patent claim that implicates any part of the label fair game?

Generic Can Challenge Use Codes – Caraco v Novo Nordisk (2012)

- Novo's Prandin approved for three indications
  - Repaglinide in combination with metformin (patented)
  - Repaglinide as monotherapy (non-patented)
  - Repaglinide in combination with TZDs (non-patented)
- Caraco sought approval for latter two indications only, which had corresponding use codes
- FDA changed indication for Prandin to "adjunct to diet and excercise to improve glycemic control"
- Novo changed use code to "method for improving glycemic control in adults with Type-2 diabetes"
  - FDA rejected carve-out based on the use code
- Held – Caraco could seek amendment of Novo's use code to be more narrowly tailored to the patented indication

“Section viii” Carve Out – 505(j)(2)(A)(viii)

- Permits a generic to “carve out” of label approved uses that it is not seeking approval for
  - Generic product must still be safe and effective for remaining approved uses
  - Impact: ANDA with carved out label can be approved even if there is a PIV on the carve out patent (i.e. no First to File blocking approval)

- Exception to Section viii Carve Out
  - Use code can be carved out only if the generic drug is as safe and efficacious as the brand for all remaining non-protected conditions of use.
  - Foreseeability of use is not relevant.
  - Minor language changes allowed in carved out label for clarity.

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