Section V. The Abbreviated NDA (ANDA), 505(b)(2) Applications, and Patent and Exclusivity Issues

FDLI - Introduction to Drug Law and Regulation
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Overview of Section V

- Eligibility for ANDA Consideration
- Content and Organization of an ANDA
- Sameness, Bioequivalence, and Therapeutic Equivalence
- Office of Generic Drugs' Review Process
- 505(b)(2) Applications
- Patent Provisions
- Market Exclusivity
- Strategies Affecting Approval

ANDA History

- Before 1984, Safety and Efficacy of copies of approved drugs was assumed
  - ANDA Required Submission of Mfg. Process Info. & Labeling
  - “Paper” NDA Policy - Me-Too Drugs established Safety and Efficacy via Published Literature, Public Data

- The Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch Act)
  - Specifically permits “copying” of an already-approved drug
  - Revised ANDA to Modern Day Requirements, Adds Bioequivalence Studies
  - Patent Extensions & Market Exclusivity for NDA Drugs

Eligibility for ANDA Consideration

- FDA Must Preapprove (Office of Generic Drugs, OGD)
- Must Be Same As an Approved Drug (NDA)
- Bioequivalence Data comparing to RLD
- Labeling Must Be Identical
- Must File Patent Certification to RLD Orange Book listed patents
  - Wait to market until patent expires, or challenge validity of RLD patent(s)
- Automatic Substitution at Pharmacy (State Laws)
- Not eligible for patents or NDA exclusivities

Eligibility for ANDA Consideration – Key Terms

- *Reference Listed Drug (RLD)*
- The FDA-approved drug that the ANDA Applicant seeks to duplicate
- ANDA relies on the known safety & effectiveness of this approved drug
- Basis of Submission
- Must establish bioequivalence to this drug
- Selected by the Applicant
- In the pdf Orange Book as “+”

Eligibility for ANDA Consideration – Key Terms

- *Reference Standard (RS)*
- ANDA applicant uses samples of this drug to conduct the in vivo bioequivalence testing, if RLD is unavailable
  - Withdrawn, discontinued, old/no longer in market
- Selected by FDA
- Often RLD and RS are the same product
- If several approved generics (and no RLD), FDA will choose the market leader, based on commercial data
- In the pdf Orange Book as "!"
- Referencing Approved Drug Products in ANDA Submissions – Guidance for Industry (Final, 2020)

Eligibility for ANDA Consideration – Key Terms

- Orange Book – *Approved Drug Products with Therapeutic Equivalence Evaluations*
- 42nd edition, 2022 (pdf and electronic)
  https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
  Mobile app – Orange Book Express 2.0
- Extensive list of NDA and ANDA drugs, discontinued, patent listings, exclusivity listings, equivalence ratings
- RLD and RS designations
- Numerous search functions, e.g., active ingredient, dosage form, patents
- Safety-only and pre-1938 drugs are not included
- BPCIA: NDAs converted to BLAs in 2020 are not included

Eligibility for ANDA Consideration – Key Terms

- *Suitability Petitions*
- Used to Request a Change from the RLD
- Allowed Changes are to Strength, Dosage Form, or Formulation
- FDA Must Approve Before ANDA Is Filed With FDA
- Advantage – Niche Product, Unique
- Disadvantage – Public document, can be referenced by competitors, FDA answer time is long
- Effect of Pediatric Study Rule – Limits the use of S.P. since most changes trigger the need for pediatric data

Content & Organization of an ANDA

- Must refer to an approved “reference listed drug” (RLD)
- Conditions of use must be identical
- Identical active ingredient
- Identical route of administration, dosage form & strength
- Bioequivalent (BE) to the listed drug (unless eligible for waiver)
- Labeling must be the same as the RLD (but for minor differences due to different manufacturer)

Content & Organization of an ANDA

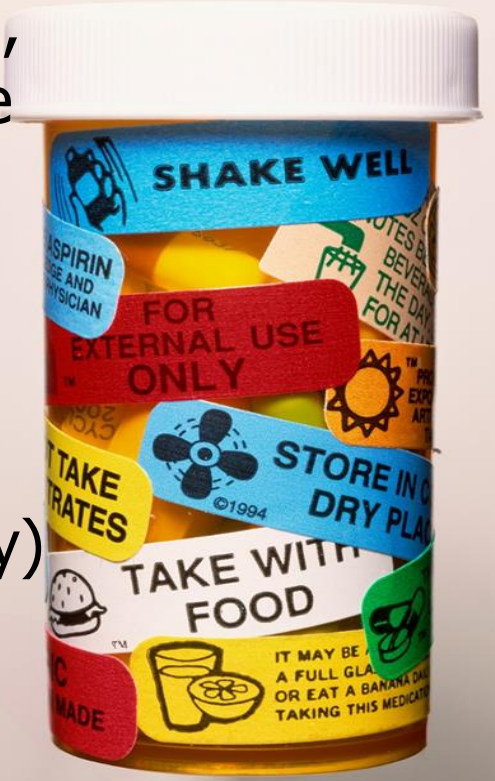
- Inactive Ingredients Need Not Be the Same as the RLD
  - Exceptions: Parenterals, Ophthalmics, Otics, Topicals (unless waiver is granted for pH adjuster)
- Chemistry, Manufacturing and Controls info
- CTD / eCTD Modules
- June 2019 Guidance on Content and Format
- Refuse-to-Receive Standards

NDA vs. ANDA Requirements

NDA Requirements	ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Sameness

- Active ingredient, Route of Administration, Dosage Form, Strength, Conditions of Use
- Pharmaceutically Equivalent
- E.g., both NDA and ANDA describe Naproxen Oral Tablets Delayed-Release, 500 mg
- Not a Pharmaceutical Alternative (naproxen and ibuprofen, tablet and spray)
- Draft Guidance – Sameness Evaluations in an ANDA – Active Ingredients (2022)



Bioequivalence

- Clinical Comparison of Generic and RLD (or RS)
- Testing Performed under patent “safe harbor”
  - 35 U.S.C. 271(e)(1) allows the use of patented inventions for “uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs”
- No Significant Difference in the Rate and Extent to which the Active Moiety Becomes Available (absorbed) at the Site of Drug Ingredient Action
- Plan for process to obtain drug samples of RLD, especially if specialty or restricted distribution

Bioequivalence (continued)

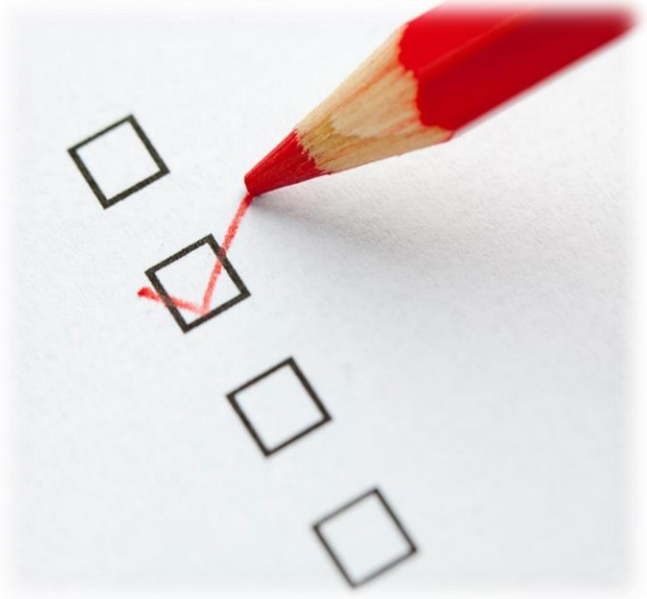
- May be self-evident, or demonstrated through in vivo studies (in human subjects) or in vitro studies (lab)
- Systemic Drugs - usually blood-level studies
- Topical Drugs – “scientifically valid” measurements, could be a Phase 3 clinical study
- Numerous FDA Guidances
  - Protecting Participants in Bioequivalence Studies for ANDAs During COVID-19 (Jan. 2021)
  - Extensive list of Product-Specific Guidances (PSG) – 2,038
    - Describe FDA’s current expectations for studies per RLD (e.g., number and type, fasting/fed, analyte to measure)

Therapeutic Equivalence

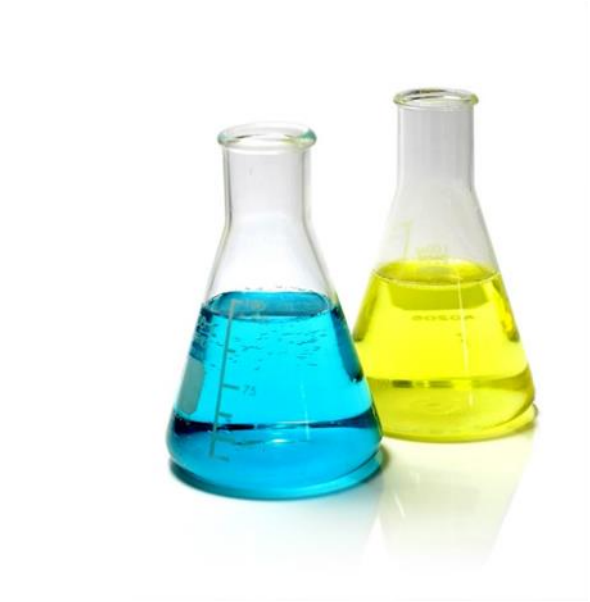
- Pharmaceutical Equivalence + Bioequivalence
- Generic is expected to have the same clinical effect and safety profile as the RLD, when administered under labeled conditions
- Supports automatic substitution at pharmacy
- Evaluation of Therapeutic Equivalence, Guidance for Industry (Draft, July 2022)

Polling Question

- True or False:
  An Abbreviated New Drug Application must always include an identification of the Reference Standard (RS) as the basis for submission.



Office of Generic Drugs' Review Process



Generic Drug User Fee Act I (2012 - 2017)

Program Goals

- Safety
  - Ensure that industry participants in the U.S. generic drug system are held to consistent, high-quality standards and are inspected biennially using a risk-based approach
- Access
  - Expedite the availability of low cost, high quality generic drugs by bringing greater predictability to the review times for ANDAs, amendments, and supplements (goal dates)
- Transparency
  - Require the identification of facilities involved in the manufacture of generic drugs and associated APIs

GDUFA II (FDA Reauthorization Act, 2017- 2022)

Program Goals

- Submission review performance goals
  - Review and act on original ANDAs, ANDA amendments, standard PASs, PAS amendments in certain timeframes
- ANDA review program enhancements – transparency and communication
- Pre-ANDA program and mid-review-cycle meetings *for complex products*
- DMF review program enhancements
- Facilities/GMPs - Enhanced communications regarding inspections and with foreign regulators

GDUFA II

Fee Types

- One-time ANDA filing fee: $225,712 per application
- Generic Drug Applicant Annual Program fee (FY2022)
  - Small (1-5 ANDAs), Medium (6-19), Large (20 and up)
  - $153,686 $614,742 $1,536,856
- Annual Facility fee
  - Domestic and Foreign API facility fee
  - Domestic and Foreign Finished Dosage Form facility fee
  - Domestic and Foreign Contract Manufacturing Organization facility fee
- Drug Master File fees

GDUFA III (FDA Reauthorization Act, 2023- 2027)

Program Goals – GDUFA III Commitment Letter

- Submission review performance goals - Review and act on ANDAs in certain timeframes, and controlled correspondence
- ANDA review program enhancements – Reduce the number of assessment cycles; issuance of product specific guidances
- More meetings - Enhancements to product development and pre-submission scientific meetings *for complex and PSG-impacted ANDAs*
- DMF review program enhancements, continued
- Facilities/GMPs - Enhanced communications, continued
- Suitability petition enhancements (FY2024)
- 5 – 10 Guidances published since Oct. 1, 2022

GDUFA III

Fee Types

- One-time ANDA filing fee: $240,582 per application
- Generic Drug Applicant Annual Program fee (FY2023)
  - Small (1-5 ANDAs), Medium (6-19), Large (20 and up)
  - $162,056 $648,222 $1,620,556
- Annual Facility fee
  - Domestic and Foreign API facility fee
  - Domestic and Foreign Finished Dosage Form facility fee
  - Domestic and Foreign Contract Manufacturing Organization facility fee
- Drug Master File fees

R&D Phase

- Pre-ANDA Meetings
  - Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Oct. 2022, Rev. 1)
  - Clarify regulatory expectations for prospective applicants early in product development
  - Product development meetings, pre-submission meetings, and mid-cycle review meetings
  - P.S. “Review” is changing to “Assessment”

R&D Phase (continued)

- Controlled Correspondence – Process for submitting specific product development questions to OGD. Answers help companies develop ANDAs that have a strong ability to obtain approval.
- Pandemic: Development of ANDAs During the COVID-19 Pandemic – Questions and Answers, Guidance for Industry (April 2021, Sept. update)
- New Guidance: Good ANDA Submission Practices (Jan. 2022)

R&D Phase (continued)

- Inactive Ingredient Database (IID): Provides details on which inactive ingredients are present in FDA-approved drug dosage forms
- Levels per dosage form:
  - Maximum potency
  - Maximum daily exposure (MDE), also called maximum daily intake (MDI) for oral drug products

- Self-identification: Required reporting to OGD by API and FDF manufacturing facilities; Primary packagers & labelers; Sites identified in a generic drug submission that perform BE or bioavailability testing; Sites that test one or more attributes of the FDF or API for GMP requirements

Expedited Programs: Priority ANDAs

- Priority review = 8 months (vs. 10 months)
  - Must pre-submit facility information, 60 days before ANDA
- An ***original*** ANDA or ANDA amendment will be eligible for priority review if it meets one of the following factors:
  - Submissions for which there are not more than three (3) approved drug products
  - Applications containing a paragraph IV certification
  - Submissions for which final approval is dependent on the expiration of a patent or NDA exclusivity
  - Submissions related to drug shortages or public health emergencies
  - Submissions that are subject to special review programs or other legal requirements
  - Submissions related to certain government purchasing programs
  - Submissions for which a priority review is requested
  - Submissions for "sole source" drug products
- FDA only evaluates whether priority review may be granted if:
  - The applicant requests it at the time of submission, OR
  - FDA itself determines the submission relates to a drug shortage or public health emergency

Expedited Programs: Competitive Generic Therapies

- FDA may designate a drug as a competitive generic therapy (CGT) after determining that there is inadequate generic competition for that drug.
- At the applicant's request, FDA may expedite the development and review of an ANDA for a CGT-designated drug.
- In granting such requests, FDA considers:
  - The complexity of developing an application for that drug
  - The potential public health impact of the product, including the severity of the condition treated and the size of the patient population
  - The impact on FDA resources
- Actions FDA may take to expedite development:
  - Product development meetings
  - Pre-submission meetings
  - Mid-review-cycle meetings
  - Cross-disciplinary review of CGT ANDA

Responses to OGD Adverse Decisions

- Refuse to Receive (RTR): In the first 60 days, FDA evaluates the ANDA to determine if it is "substantially complete" and can be received. Major deficiency or more than 9 minors.
  - Withdraw ANDA, Correct Deficiencies and Resubmit
  - If Information Request (IR), response due in 7 calendar days
- Complete Response Letter (CRL): Once review is complete, FDA letter describing deficiencies in an ANDA that must be addressed before the ANDA can be approved
  - Request a clarification meeting within 10 days
  - If no Co. response within 1 year = Request to Withdraw ANDA

Responses to OGD Adverse Decisions

- Request for Reconsideration: Applicant must try to resolve the issue through the RfR process. Explain the nature of the matter within 7 calendar days from the date of the regulatory action by FDA.
- Formal Dispute Resolution: Appeal escalation; based on the same information as was used to make the original decision; can include Advisory Committee.

Polling Question

- Which of the following is NOT included in GDUFA III?

A. Enhancements to the Inactive Ingredient Database
B. Standard and Priority Review goal dates
C. Pre-IND meetings
D. Controlled Correspondence
E. DMF fees

505(b)(2) NDA – 21 USC § 355(b)(2)

- Used for an approved chemical entity that has known therapeutic effects, but makes a change from the original approved drug
  - New dosage form -- Different strength
  - Expanded indication / subpopulation
- Can reference scientific data from published literature and/or known safety and efficacy of approved Listed Drugs (LD)
- Statute: Relies on data not conducted by or for the applicant, and for which it has no right of reference
- Data required will be based on unanswered questions raised by the product change (Animal Tox - Clinical Data)

505(b)(2) New Drug Application

- Usually a shorter, less expensive R&D phase
- Pre-clinical data (not frequently)
- Clinical studies
  - Phase I (not likely)
  - Phase II (probably)
  - Phase III (possibly)
- Bioequivalence “Bridging” Study comparing proposed drug to Listed Drug

505(b)(2) New Drug Application

- Viewed as a “hybrid” between NDA and ANDA
- Reviewed by Office of New Drugs, not OGD
- Meetings, Review Timelines, Goal Dates and User Fees governed by PDUFA (not GDUFA)
- Clinical Studies Plus Bioequivalence Study
- Like a generic: Must file patent certification to Listed Drug’s patents; subject to Hatch-Waxman rules (e.g., 30 month stay)
- Like a brand: Eligible for Market Protections: Patent listings, Patent Extension, and Exclusivity for Clinical or Pediatric Studies (Less often for Orphan Drug or NCE)

Patent Provisions Applicable to NDAs and ANDAs

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FDA

Innovator Applicant's Duty – Patent Listing

- File Information With FDA On Any Patent That:
  - Claims The Drug in the NDA
  - Claims a Method For Using the Drug
  - Where a Claim of Patent Infringement Could Reasonably Be Asserted
- File Within 30 Days of NDA Approval or Patent Issuance
- Types of Patents: Drug Substance, Composition, Formulation, Product-by-Process, Method of Use Patents (on-label)
- But Not: Process, Metabolites, Intermediates, Packaging
- Delisting: Must Notify FDA within 14 days after invalidation by a court, USPTO, or the Patent Trial and Appeal Board of a listed patent, and request that such patent be withdrawn from O.B.

Generic Applicant's Duty
ANDA Patent Certifications

No Orange Book Patent

- Paragraph 1 – Patent information not submitted to FDA
- Paragraph 2 – Patent has expired
- No Relevant Patents Statement – No Patents exist

Yes Orange Book Patent

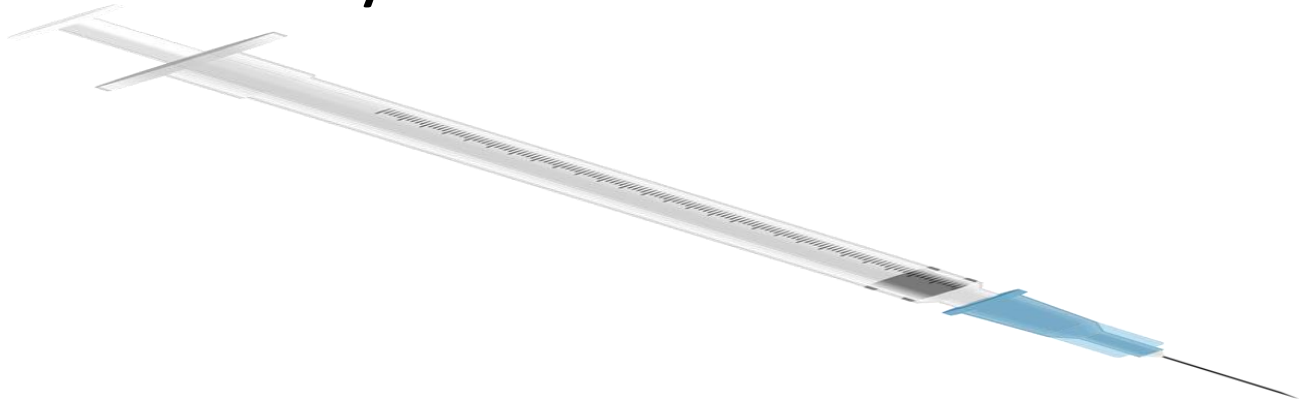
- Paragraph 3 – Will not market until patent expires
- **Paragraph 4** – Challenging the patent as invalid or not infringed
- Little viii Statement – Patent not infringed because not seeking approval for that use; use will not be on label (Method of Use Carve-Out)

PIV Challenges to Orange Book Patent Listings

- Notice of Paragraph IV Certification Sent to NDA Sponsor and Patent Holder within 20 days after FDA's ANDA Acknowledgement letter
- NDA Sponsor Has 45 Days to Sue, Starting Day After Notice is Received
- **Suit Triggers 30-month Stay Against FDA's Approval of the ANDA** (or until favorable court decision or settlement)
- Numerous detailed administrative requirements, 21 CFR 314.94 and 314.95
- One 30-month Stay per ANDA or 505(b)(2) NDA
- Orange Book Modernization Act of 2021: codifies existing FDA listing practices, as described in 21 C.F.R. 314.53

Market Exclusivity

- For Innovator Products
- Separate from Patent Terms
- Run concurrently with Patent Terms



5-Year Exclusivity

- Available To NDAs
- Awarded For A New Chemical Entity (NCE)
- Never Before Approved by FDA
- Controversy over Active Moiety vs. Active Ingredient
  - 505(u) subset for Enantiomers with Different Indication
  - Exceptions for Ingredient Mixtures, Two Actives
- Affect On ANDAs: May Not Be Filed With FDA Until Exclusivity Expires
- Exception For Paragraph IV ANDAs: May Be Filed With FDA After 4 Of The 5 Years Have Expired

3-Year Exclusivity

- Available To NDAs And NDA Supplements
- Awarded For “New” Clinical Studies (not BioE studies), “Essential” To The Approval Of The NDA, And “Conducted Or Sponsored By” The Applicant
- Attaches To The New Or Changed Item (Dosage Form, Indication, Strength, Etc.)
- Affect On ANDAs
  - May Be Filed With FDA, And Reviewed, But Will Not Be Approved Until Exclusivity Expires
  - Results In A Tentative Approval Letter
  - May Be Approved With “Carved Out” Labeling

Pediatric Exclusivity – 6 months

- Available To NDAs and NDA Supplements
- Awarded For Clinical Data In Children (Positive or Negative, On-label or Ex-label)
- Eligible Drugs – Those that May Produce Health Benefits in Children (Interpreted Broadly)
- Adds on to the end of existing patent terms and exclusivity, but for All of NDA Holder's Drugs/Dosage Forms With That Same Active Moiety
- Affect on ANDAs: Yes file, TA, Yes carve-out, Interrupts and Delays 180-Day Exclusivity

Orphan Drug Exclusivity – 7 Years

- Available to NDAs and NDA Supplements
- Awarded to Drugs for Rare Diseases and Disorders
  - Fewer than 200,000 People in U.S. or
    No Expectation of Cost Recoupment
- Indication-Specific
- Affect On ANDAs:
  - May Be Filed With FDA, And Reviewed, But Will Not Be Approved Until Exclusivity Expires
  - Results In A Tentative Approval Letter
  - May Be Approved With “Carved Out” Labeling

Antibiotic (GAIN) Exclusivity

- Generating Antibiotic Incentives Now
- Addresses the public health threat of antibacterial drug resistance
- For designations of Qualified Infectious Disease Products
- 5 years
- Added on to other existing exclusivities
- DALVANCE (dalbavancin HCl) Lyophilized Powder for Injection, 500 mg: Approved 2014, NCE to 2019, GAIN to 2024

Polling Question

- Can a 505(b)(2) NDA receive 3-year exclusivity if it includes a Paragraph III patent certification?

  Yes or No?

Market Exclusivity

- For Generic Products

180-Day Patent-Challenge Exclusivity

- Available To First ANDA(s) That Contain A Paragraph IV Patent Certification
- Awarded For Challenging A Patent (Regardless Of Success)
- Begins on First-to-File's First Commercial Marketing of the Generic
- Complex Forfeiture Rules
- Affect On Later-Filed ANDAs:
  - Affects Only Subsequently-Filed ANDAs with Paragraph IV Patent Certifications
  - May Be Filed With FDA, And Reviewed, But Will Not Be Approved Until Exclusivity Expires
  - Results In A Tentative Approval Letter
  - May Stop/Restart Due to Pediatric Exclusivity

180-Day Competitive Generic Therapy Exclusivity

- For the first-approved CGT ANDA(s), if there were no unexpired patents or exclusivities listed in the Orange Book for the relevant RLD at the time of ANDA submission
- Required to commercially market the generic within 75 calendar days after approval
- Where there is no 180-day patent-challenge exclusivity
- Triggered on the day of first commercial marketing
- Blocks later-filed ANDAs for 180 days, unless approved during 75-day launch window

Strategies Affecting Approval

Challenges to Eligibility for Approval

- Citizen Petition: RLD Sponsor (or anyone) May Challenge the Generic Drug's Eligibility for FDA Approval
- Post-filing Labeling Changes
- Life-cycle Management (product modifications/ sameness/indication carve-outs)
- Patent Litigation Settlements agreeing to delay generic launch (pay-for-delay)
- Authorized Generics
- REMS – product sample requests; shared systems

Questions?

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