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The Orphan Drug Act

Developing Drugs and Biologics for Rare Diseases

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Today's Panelists

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George works with life sciences companies of all sizes to assist them in developing and marketing innovative products that are regulated by the US Food and Drug Administration, including drugs and biologics, medical devices, drug-device combination products, CBD and botanical products, medical foods and dietary supplements.

He has deep experience providing regulatory advice to pharmaceutical and biotech companies on lifecycle management issues, including regulatory exclusivities and FDA-facing patent issues. He is a leading expert on orphan drug matters, including orphan designation and exclusivity, and has successfully advocated on behalf of clients to FDA on matters related to prevalence, orphan subsets, and clinical superiority. George also regularly advises pharmaceutical and biotechnology companies on pediatric study and pediatric exclusivity issues arising under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

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Introduction

- Welcome to Mayer Brown's FDA Lifecycle Management webinar series
  - Monthly installments addressing issues affecting lifecycle of pharma and biotech products
- Next installments will cover additional types of regulatory exclusivity
  - Pediatric Exclusivity (April 13, 2023)
  - 3-Year "New Clinical Investigation" Exclusivity (May 11, 2023)

Today's Agenda

- Introduction to Orphan Drug Act
  - Designation
  - Exclusivity
- "Same Drug" Comparisons
- Clinical Superiority
- Scope of orphan exclusivity
  - Key precedents
  - The *Catalyst* case
- Identifying the appropriate disease
- Open issues

THE ORPHAN DRUG ACT

DESIGNATION AND EXCLUSIVITY

The Orphan Drug Act

- Goals: encourage the development of drugs for rare diseases where the market alone may not provide sufficient incentive
- Incentives:
  - Marketing exclusivity
  - Written recommendations/grants
  - Tax credits on certain clinical testing expenses
  - Exemption from required pediatric studies under Pediatric Research Equity Act (PREA)
  - Exemption from PDUFA application fees
  - Exemption from Prescription Drug Fees in ACA
  - 340B exemption
  - Inflation Reduction Act exemption (limited)

The Orphan Drug Act

- Key incentive is 7-year marketing exclusivity
  - Available for drugs and biologics
- **Broad**: Blocks 505(b)(1) NDAs, 505(b)(2) NDAs, ANDAs, "full" BLAs and biosimilar applications
- **Narrow**: Drug-specific and disease-specific
- Two-step process:

  Designation of the drug for a rare disease or condition prior to submission

  \+ ***Approval*** of the drug for an indication or use covered by the designation

  = ***Orphan Exclusivity*** (*with one important exception covered later*)

ORPHAN DRUG DESIGNATION

ELIGIBILITY AND PROCESS

Obtaining Orphan Designation

- Request for orphan designation contains 3-4 key elements (*see* 21 CFR 316.20)
  - ***Identification of the disease***: ordinarily must seek designation for entire rare disease or condition
  - ***Prevalence***: demonstration that disease affects < 200K persons in the US, ***at time the request is submitted***
    - Vaccines, diagnostics: used by < 200K persons in US in a given year
  - ***Scientific rationale***: provide evidence that drug will be effective in treating the disease
  - ***Clinical superiority*** showing, as needed
- Prevalence
  - Literature, registries, databases (SEER), prescribing data, expert epidemiologist
  - CAVEAT: Office of Orphan Products Development (OOPD) will use highest value in a range
  - Timing issues, if close to 200K threshold
- Scientific rationale
  - *In vitro*, *in vivo* animal studies, case reports, clinical studies relevant to drug and disease

Obtaining Orphan Designation

- Timing considerations: must be submitted prior to submission of marketing application
  - Implications for prevalence, type and amount of data, and use of tax credits
- Procedural requirements:
  - Submit *via* mail, e-mail, CDER NextGen portal
  - Joint EMA/FDA submissions possible
  - Form FDA 3045 (not required)
  - Self certification
- 90-day review by OOPD
  - OOPD often issues deficiency letter, allowing for subsequent amendments
- Orphan designations are public
  - Orphan drug records are not otherwise disclosable until after approval

Strategic Considerations

- Timing
  - Generally, earlier submission is better
  - Data-dependent
- Thorough and complete request for designation
  - Show your work on prevalence
  - Don’t rely on the fact that other sponsors have been designated for a specific disease
- Anticipate challenges
  - Clinical superiority
  - Creative advocacy

ORPHAN DRUG EXCLUSIVITY

ELIGIBILITY AND SCOPE

Orphan Exclusivity: Basic Application

- Blocks the ***approval*** of another sponsor's marketing application for the "***same drug*** for the ***same indication or use***" for ***seven years***
- To avoid a first drug's orphan exclusivity, a second drug can therefore be:
  - A "different drug" – structurally different or clinically superior – or
  - For a different indication or use

Exceptions:

- Withdrawal or revocation of designation
- Withdrawal of NDA/BLA
- Consent
- Failure to assure sufficient quantities

Scope of Orphan Exclusivity

- Under the statute, orphan drug exclusivity blocks approval of the "same drug" for the "same rare disease or condition"
  - By regulation, FDA has limited the scope of orphan drug exclusivity to the approved "indication or use" within the "rare disease or condition" for which designation was granted
- ***Same drug*** means:
  - Small molecule drug: "***same active moiety*** as a previously approved drug … for the same use … ***except*** that ***if*** the subsequent drug can be shown to be ***clinically superior*** to the first drug…"
  - Large molecules (macromolecules): "the ***same principal molecular structural features*** (but not necessarily all of the same structural features)" ***unless clinically superior***
    - The regulations provide additional criteria for proteins, polysaccharides, polynucleotides, and "closely related, complex partly definable drugs…"
    - Guidance documents for monoclonal antibodies and gene therapy products

Sameness of Drugs Composed of Small Molecules

- Active moiety test
  - "The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt … or other noncovalent derivative…." 21 CFR 316.3(b).
  - Same analysis as for 5-year NCE exclusivity
    - Structural analysis: *Actavis Elizabeth USA LLC* (the "Vyvanse" case)
- Application to certain product categories
  - Deuteration
    - Austedo (deutetrabenazine) is a different drug structurally than Xenazine (tetrabenazine)
  - Fixed-combination drugs
    - Considered a "different drug" for orphan purposes than the individual ingredients
    - Won't block approval of single ingredients for same disease, and *vice versa*
    - What about co-administration use?

Sameness of Drugs Composed of Large Molecules

- Macromolecule drugs – same principal molecular structural features
- 4 categories of products highlighted in regulations
  - Protein drugs
  - Polysaccharides: same if "identical saccharide repeating units," even if number of units varies and even if there were postpolymerization modifications
  - Polynucleotide drugs: same if "identical sequence of purine and pyrimidine bases…bound to an identical sugar backbone…."
  - "Closely related, complex partly definable drugs…"
- Agency did not want to diminish value of orphan exclusivity by permitting minor differences to render a second drug "different" for orphan purposes

Sameness of Drugs Composed of Large Molecules
Category 1: Protein products

- "[C]onsidered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior." 21 CFR 316.3(b)(14)(ii)(A).
  - In precedent, key differences appear to be ***pre-translational***
- Compare to 12-year Reference Product Exclusivity under BPCIA

Sameness of Drugs Composed of Large Molecules
Category 1: Protein products (continued)

- Coagulation Factors/Fusion Proteins
  - Idelvion (Coagulation Factor IX (Recombinant), Albumin Fusion Protein): "The genetic fusion of the cDNA of human albumin to the cDNA of human coagulation Factor IX, enables the gene product to be expressed as a single recombinant protein designated as rIX-FP."
  - Alprolix (Coagulation factor IX, Fc fusion protein): "One monomer of the dimer is manufactured fused to factor IX pretranslationally. The second monomer is then a post-translational modification. Therefore, the changes in structure to the factor IX protein do involve ***pre-translational modification***." (emphasis added)
- Monoclonal antibodies
  - Considered to be the "same drug" if amino acid sequences of the "complementarity-determining regions" (CDRs) are the same or if there are only minor amino acid differences between them.
  - By contrast, two antibody-drug conjugates would be considered the "same drug" if "both the CDR sequences of the antibody and the functional element of the conjugated molecule were the same."
- Pegylation = not sufficient to make a different drug

Sameness of Drugs Composed of Large Molecules
FDA Guidance: Monoclonal Antibodies

- Two Regions
  - Variable Region (light)
    - Antigen-binding site
  - Constant Region (dark)
    - Carries out Effector Function
- FDA considers the binding sites (CDRs) of the Variable Regions to be the "principle molecular structure"
  - Amino acid sequences of CDRs
  - Same analysis with a fragment

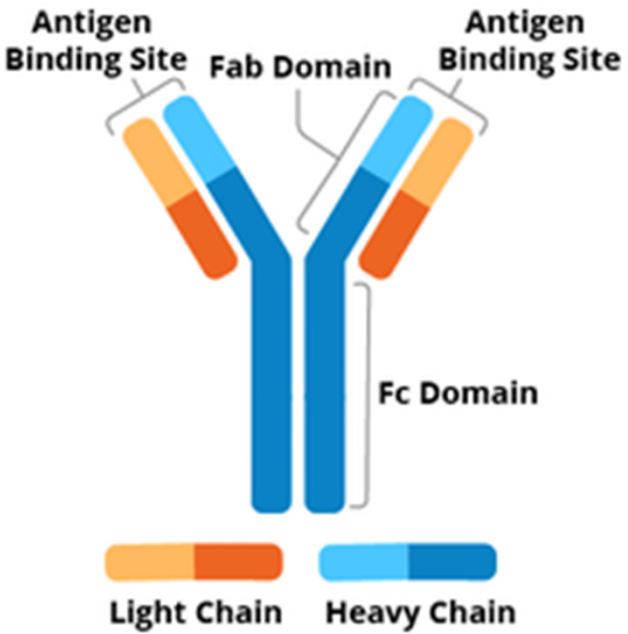

Image credit: addgene Blog

Sameness of Biologics and other Macromolecules
Category 4: Complex, Partly Definable Drugs

- "Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior." 21 CFR 316.3(b)(14)(ii)(D).
  - Lung surfactants
    - Complex mixtures of lipids and proteins derived from bovine or porcine lungs
    - Considered same drug for orphan purposes – but each was awarded NCE exclusivity
  - Liposomal and non-liposomal preparations of the same active moiety
    - Hasn't always been applied consistently
  - Human immunoglobulin products
  - Antivenom products

Sameness of Drugs Composed of Large Molecules
FDA Guidance: Cellular and Gene Therapies

- *Final Guidance, Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations* (September 2021)
  - FDA will consider certain key features such as transgenes and vectors used in gene therapy products to be "principal molecular structural features"
- For example, for two gene therapy products intended for the same use or indication:
  - Same vector + different transgene(s) (*e.g.*, transgenes that encode different enzymes for treatment of the same rare disease) = different drug
  - Different vector + same transgene(s) = different drug
    - FDA "generally intends to consider" vectors from a different viral group (*e.g.*, gammaretrovirus vs. adeno-associated virus (AAV)) to be different

Sameness of Drugs Composed of Large Molecules
CAR-T Products

- YESCARTA (axicabtagene ciloeucel): BLA approved 2017 for treatment of adult patients with diffuse large B-cell lymphoma (DLBCL)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - ***Retroviral*** transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to ***CD28 and CD3-zeta co-stimulatory domains***
- KYMRIAH (tisagenlecleucel-T): sBLA approved 2018 for same indication(s)
  - CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a ***lentiviral*** vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for ***4-1BB (CD137) and CD3 zeta***.
- OOPD and CBER/OTAT consulted and determined they were different drugs
  - Each received orphan drug exclusivity; didn't block the other
  - *See also* BREYANZI (lisocabtagene maraleucel)

ORPHAN DRUG EXCLUSIVITY

CLINICAL SUPERIORITY

Clinical Superiority: Basic Overview

- A drug that is clinically superior is not the "same drug," even if structurally the same
- ***Clinically superior:*** "significant therapeutic advantage"
  - ***Greater effectiveness*** as assessed by effect on a clinically meaningful endpoint in adequate and well-controlled trials
  - ***Greater safety*** in a substantial portion of the target population
    - "Inherent" or cross-label comparison of adverse events
  - In unusual cases, a demonstration that the drug makes a ***major contribution to patient care***
    - "[C]onvenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration"
- Case-by-case and disease-specific determinations; approximately 30 determinations

Clinical Superiority: Precedent and Practical Considerations

- FDA now required to publish clinical superiority determinations on its website
  - None posted since 2020
- Greater efficacy is comparatively rare
  - 3-4 examples, all with head-to-head clinical trials
- Greater safety falls into two categories (approximately 15 examples)
  - Inherent: recombinant vs. human; properties based on change in route or dosage form
  - Cross-label comparison of adverse events
- MCtoPC: increasingly common (approximately 10 examples)
  - Improved dosing schedules and patient convenience; lower sodium; faster administration
  - Often based on change in route of administration or dosage form

Clinical Superiority: When is this showing required?

- To obtain designation, if there is a previously approved "same drug" for "same indication or use"
  - Lower bar: plausible hypothesis of clinical superiority
- To obtain approval, by "breaking" a competitor's ongoing orphan exclusivity
  - Expressly provided for in 1992 regulations
- To qualify for orphan exclusivity, where there is a previously approved "same drug" whose orphan exclusivity has expired or that never had orphan exclusivity
  - Not provided for in regulations until 2011
  - However, FDA imposed clinical superiority as a prerequisite for obtaining orphan exclusivity since at least the 1990s
  - Now provided for in statute (FDARA) following *Depomed* and *Eagle* litigation

Different standards at designation stage and approval stage

Designation

- If there is a previously approved version of the same drug for the same disease or condition, a sponsor must provide a "plausible hypothesis of clinical superiority" to that product
- Relatively low hurdle, to encourage development of innovative drugs

Approval

- Must affirmatively substantiate hypothesis of clinical superiority
  - Can demonstrate clinical superiority on a different basis than hypothesized in designation
- If there is an intervening approval – meaning designation did not require hypothesis of clinical superiority – must nevertheless demonstrate clinical superiority to that drug
- Higher hurdle, to protect value of orphan exclusivity
- Showing required against ***all*** previously approved "same drugs"

Clinical Superiority Evolution
Originally a creature of regulation…

1983 Statute

- Orphan exclusivity: Approval of designated drug blocks approval of another sponsor's application for "such drug" for "such disease or condition"

1992 Regulations

- Orphan exclusivity: Approval of designated drug blocks approval of another sponsor's "same drug" for "same disease or condition"
- "Same drug" means chemical sameness (same active moiety or principal molecular structural features)
- But a clinically superior drug is not the "same drug" and thereby avoids previous drug's orphan exclusivity

2013 Regulations

- Added clinical superiority as prerequisite for obtaining exclusivity

Clinical Superiority as Prerequisite for Exclusivity
The *Depomed* and *Eagle* cases

- Depomed's drug Gralise (gabapentin HCl) was granted designation for post-herpetic neuralgia (PHN) on the basis of a plausible hypothesis of clinical superiority (greater safety) to Pfizer's Neurontin (gabapentin HCl) which had already been approved, but had never obtained orphan designation or exclusivity
- Previous version of the statute and regulations contained no mention of clinical superiority as prerequisite for exclusivity
  - Designation + Approval = Exclusivity
- At the time of approval in 2011, FDA denied orphan exclusivity on the basis that Depomed had not substantiated its hypothesis of clinical superiority
- Depomed challenged in court under Administrative Procedures Act

Clinical Superiority as Prerequisite for Exclusivity
The *Depomed* and *Eagle* cases

- DDC (Judge K. Jackson) held that Orphan Drug Act unambiguously prohibited FDA from imposing additional requirements for exclusivity beyond designation and approval
  - If FDA approves a designated drug for the rare disease or condition, "the Secretary may not approve another [NDA, ANDA or BLA] for such drug for such disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of [the application.]" 21 USC 360cc (2011).
- FDA announced that it would not apply the *Depomed* holding. Policy on Orphan-Drug Exclusivity; Clarification, 79 FR 76888 (Dec. 23, 2014)
  - FDA withdrew its appeal of the *Depomed* decision
  - But continued to deny exclusivity to several drugs on this basis, including…

Clinical Superiority as Prerequisite for Exclusivity
The *Depomed* and *Eagle* cases

- Eagle's Bendeka (bendamustine HCl) for CLL/iNHL; Cephalon's Treanda had expired orphan exclusivity for same drug for same indications
  - As in *Depomed*, Bendeka was designated on hypothesis of clinical superiority (major contribution to patient care), but FDA concluded at time of approval that Eagle hadn't substantiated clinical superiority and therefore denied orphan exclusivity
- **2018**: DDC overturned FDA's decision; *Chevron* Step 1, as in *Depomed*
  - **2020**: DC Circuit affirmed, *Eagle Pharms., Inc. v. Azar*, (DC Cir. 2020)
- FDARA (2017) codified a legislative fix while *Eagle* was pending at DDC
  - ***"…the Secretary shall require such sponsor, as a condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already approved or licensed drug that is the same drug"***

DESIGNATION AND EXCLUSIVITY

ISSUES RELATED TO THE DISEASE

Defining the Disease for Orphan Purposes

- Generally, must seek designation for entire rare disease or condition
  - *E.g.*, cancers of different organs are typically distinct diseases
  - FDA exercises judgment, and its thinking evolves over time
    - *E.g.*, tissue-agnostic therapies and genetic markers
    - Pediatrics no longer considered a distinct "disease" (July 2018 guidance)
    - Prevention distinct from treatment
  - Review OOPD's SOPP and orphan designation website/database for precedent
- Is it a "***rare*** disease or condition"?
  - Prevalence: affects < 200K persons in US ***at the time the request is submitted***
  - Cost recovery: affects > 200K, but no reasonable expectation of cost recovery from sales in US
  - Vaccines, diagnostics: used by < 200K persons in US in a given year

Orphan Subsets

- When can a subset of a larger (non-orphan) disease qualify as an orphan disease or condition?
  - Sponsor must show that use of the drug outside of that subset would be inappropriate because of some inherent property of the drug
    - Toxicity
    - Mechanism of action, *e.g.*, mAb and specific antigens
    - Lack of efficacy, *e.g.*, if no significant activity vs. high grade tumors, low-grade could be a subset
- FDA wary of artificial subsets, so-called "salami slicing"
  - Factors not relevant: price; study population; intended approval; disease stage (without more)
- Implications for personalized medicine/genetically targeted therapies?

Disease and the Scope of Exclusivity

- By regulation, FDA has interpreted the Orphan Drug Act's exclusivity provisions to limit the scope of exclusivity to the approved indication, which is often narrower than the designation
  - Designation: Treatment of multiple myeloma
  - Approval: Treatment of adult multiple myeloma patients who have received at least two prior therapies
- FDA's "indication-specific" approach has several important implications
  - A competitor can obtain designation of the "same drug" without a hypothesis of clinical superiority in the portion of the designation that is outside the scope of approval (e.g., first-line multiple myeloma or multiple myeloma in pediatric patients)
  - A competitor will not be blocked from approval for "same drug" if seeking approval for indication outside scope of first drug's approval
  - Orphan exclusivity can be obtained without clinical superiority showing

The *Catalyst* Case

- **January 2022**: The Eleventh Circuit struck down FDA's "indication-specific" view of the scope of orphan drug exclusivity in *Catalyst Pharms., Inc. v. Becerra* (11th Cir. 2021)
- For several years, both Catalyst and Jacobus had been developing amifampridine for the treatment of Lambert-Eaton myasthenic syndrome (LEMS), a rare autoimmune disorder; both had orphan designation
  - **November 2018**: Catalyst's Firdapse (amifampridine phosphate) approved for treatment of LEMS "in adults"
    - Two pivotal trials that enrolled a total of 64 adults (aged 21 to 88 years)
  - **May 2019**: Jacobus's Ruzurgi (amifampridine) was approved for treatment of LEMS in pediatric patients 6 to less than 17 years of age
    - Tentative approval in adults, due to Catalyst's orphan exclusivity; no pediatric efficacy data
- **2019-2021**: Catalyst sues FDA; Jacobus intervenes
  - S.D. Fla.: Held that FDA's regulatory interpretation was permissible construction of the statute
  - 11th Circuit: Overturned and remanded back to FDA; statute unambiguous

The *Catalyst* Case (cont'd)

- Compare the statute to the regulation:
  - **Statute**: If FDA approves an application "for a drug designated under [section 360bb of this title] for ***a rare disease or condition***, the Secretary may not approve another application [...] ***for the same drug for the same disease or condition*** ... until the expiration of seven years from the date of the approval of the approved application ...." 21 USC 360cc(a) (emphasis added).
  - **Regulation**: "FDA may approve a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which the drug was designated, or for ***select indication(s) or use(s) within the rare disease or condition for which the drug was designated***. Unless FDA previously approved the same drug for the same use or indication, FDA will not approve another sponsor's marketing application ***for the same drug for the same use or indication*** before the expiration of 7 years...." 21 CFR 316.31(a) (emphasis added).
- The Eleventh Circuit held that the statutory language was unambiguous
  - On remand, FDA acquiesced and converted Rizurgi final approval to tentative approval in pediatric patients

Catalyst Aftermath

- **January 2021**: FDA begins deferring orphan exclusivity determinations and certain product approvals
- **July 2022**: Catalyst settles patent litigation with Jacobus and acquires rights to Rizurgi in the US
  - **September 2022**: FDA approves sNDA for Firdapse for treatment of LEMS in pediatric patients
- **July 2022**: User fee reauthorization bills include legislative fix with retroactive application
- **September 2022**: "Clean" reauthorization passes without legislative fix
  - **December 2022**: FDORA passes without legislative fix
- **January 2023**: FDA Federal Register Notice: "at this time, while complying with the court's order in Catalyst, FDA intends to continue to apply its regulations tying the scope of orphan-drug exclusivity to the uses or indications for which a drug is approved to matters beyond the scope of that order" 88 FR 4086 (Jan. 24, 2023)
  - Remember *Depomed*?

OPEN ISSUES

Open Issues

- Potential future litigation
  - A follow-on to the *Catalyst* case is likely
- A third round of litigation may be on the horizon regarding orphan exclusivity
  - *Depomed/Eagle*: eligibility for exclusivity; is clinical superiority required if previously approved orphan drug?
  - *Catalyst*: scope of exclusivity; "disease-specific" or "indication-specific"?
  - Scope of orphan exclusivity; does second drug's orphan exclusivity block approval of follow-on versions of older orphan drugs?

Open Issues

- A second drug can obtain orphan exclusivity after a first drug's orphan exclusivity expires
  - (1) If second drug is clinically superior to first drug
  - (2) in pre-FDARA cases, like Depomed and Eagle, where second drug didn't need to show clinical superiority to first drug to obtain orphan exclusivity
- Historically, OOPD has taken the position that a second drug's orphan exclusivity would not block approval of an abbreviated new drug application (ANDA) relying on the first drug's approval
  - Articulated in letters and court filings but not in the regulations
  - Remember: orphan exclusivity blocks approval of the "same drug" for same indication or use
    - Same drug means "same active moiety" unless clinically superior
  - Is a generic to the first orphan drug the "same drug" as the second orphan drug
  - What about a 505(b)(2) NDA that relies on the first drug?

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