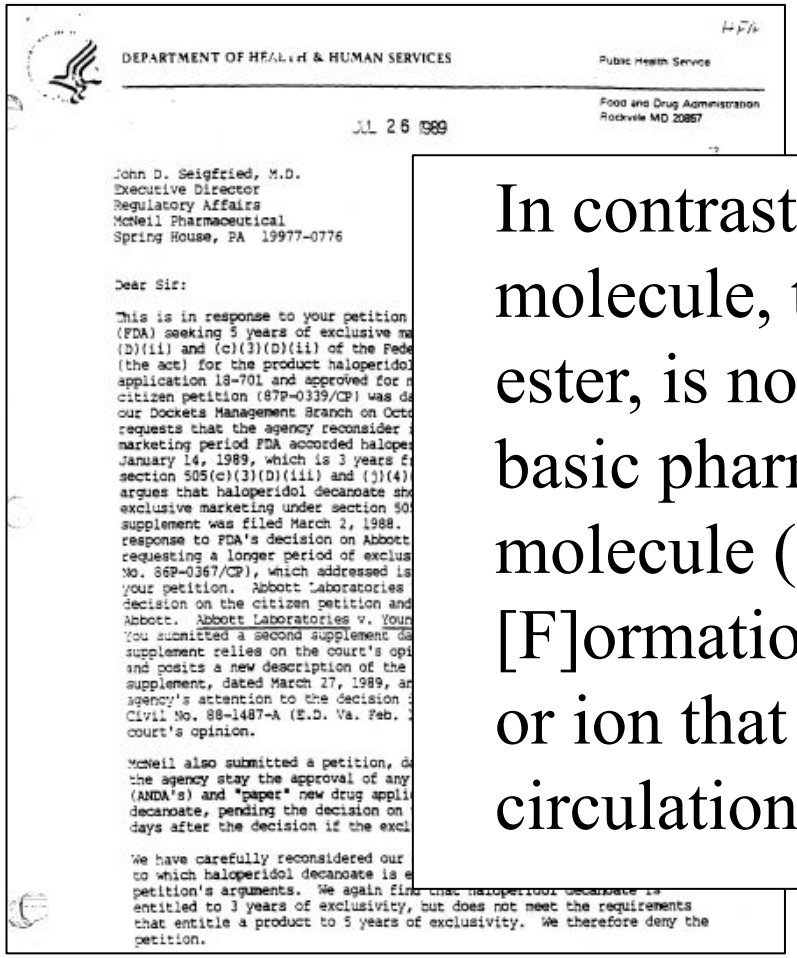
Hatch-Waxman Exclusivities

5-Year New Chemical Entity Exclusivity

5-Year New Chemical Entity (NCE) Exclusivity

- Eligibility:
  - "[A] drug, no **active moiety** (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) of which has been approved in any other application" under 505(b)"
  - **"Active moiety"** is "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an **ester, salt** (including a salt with hydrogen or coordination bonds), or **other noncovalent derivative** (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.3(b).
  - FDA focuses on the chemical structure of the "pre-ingestion drug molecule." *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010).

Rationale for the Active Moiety Approach



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 26 1989

John D. Seigfried, M.D.
Executive Director
Regulatory Affairs
McNeil Pharmaceutical
Spring House, PA 19977-0776

Dear Sir:

This is in response to your petition
(FDA) seeking 5 years of exclusive ma
(D)(ii) and (c)(3)(D)(ii) of the Fede
(the act) for the product haloperidol
application 18-701 and approved for n
citizen petition (87P-0339/CP) was da
our Dockets Management Branch on Octo
requests that the agency reconsider i
marketing period FDA accorded haloper
January 14, 1989, which is 3 years fr
section 505(c)(3)(D)(iii) and (j)(4)(
argues that haloperidol decanoate sho
exclusive marketing under section 50
supplement was filed March 2, 1988.
response to FDA's decision on Abbott
requesting a longer period of exclus
No. 86P-0367/CP), which addressed is
your petition. Abbott Laboratories
decision on the citizen petition and
Abbott. Abbott Laboratories v. Youn
You submitted a second supplement da
supplement relies on the court's opi
and posits a new description of the
supplement, dated March 27, 1989, ar
agency's attention to the decision i
Civil No. 88-1487-A (E.D. Va. Feb.
court's opinion.

McNeil also submitted a petition, d
the agency stay the approval of any
(ANDA's) and "paper" new drug appli
decanoate, pending the decision on
days after the decision if the excl

We have carefully reconsidered our
to which haloperidol decanoate is e
petition's arguments. We again find
entitled to 3 years of exclusivity, but does not meet the requirements
that entitle a product to 5 years of exclusivity. We therefore deny the
petition.

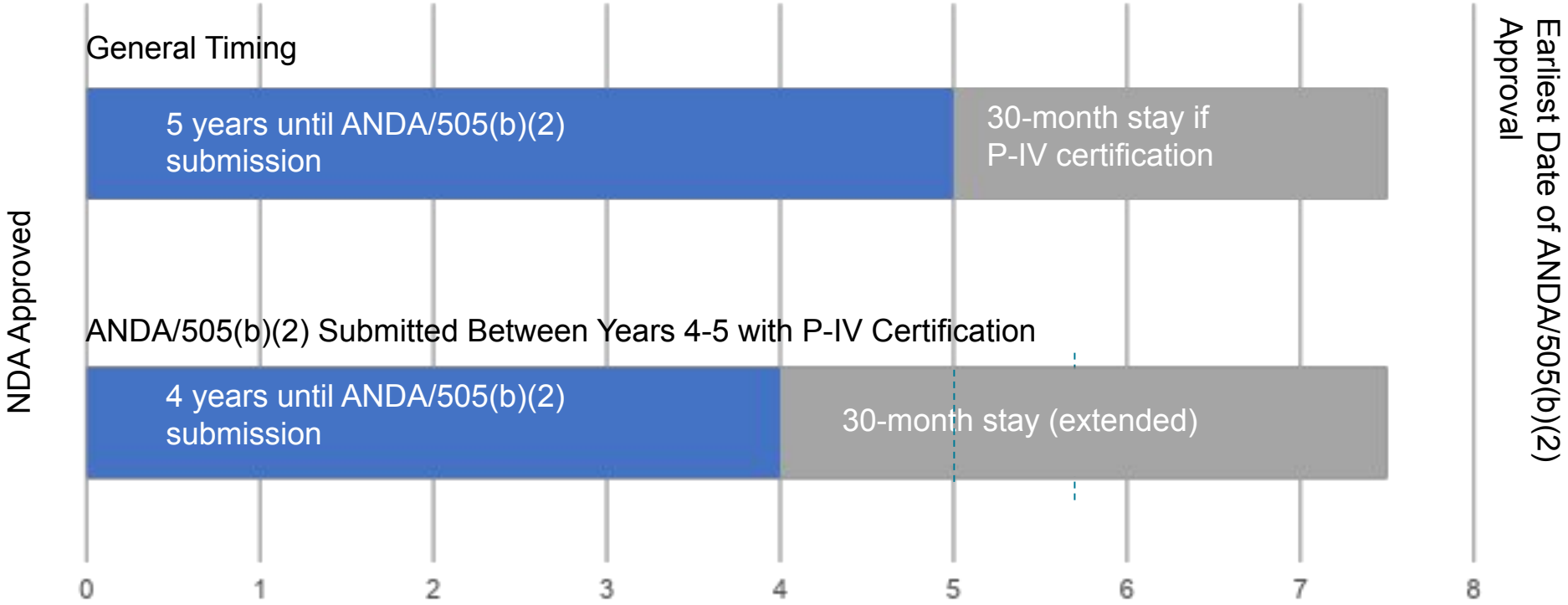
In contrast to most changes in the covalent structure of a molecule, the formation of a salt or a complex, or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule (except for possible local toxicity) . . . [F]ormation of salts and esters does not alter the molecule or ion that is actually absorbed into the systemic circulation and goes to the site of drug action.

Citizen Petition Response re: Haloperidol Decanoate, at 12 (July 26, 1989)

5-Year New Chemical Entity (NCE) Exclusivity

- Bar on follow-on submission:
  - ANDA/505(b)(2) referring to that drug cannot be submitted for **5 years** after approval of drug product containing NCE
  - ANDA/505(b)(2) with a paragraph IV certification (i.e., asserting patent noninfringement, invalidity, or unenforceability) can be submitted after **4 years**

5-Year New Chemical Entity (NCE) Exclusivity



Hatch-Waxman Exclusivities

3-Year New Clinical Investigation Exclusivity

3-Year New Clinical Investigation Exclusivity

- Eligibility
  - Application contains **new clinical investigations** other than bioavailability studies (i.e., not previously relied upon by FDA to demonstrate effectiveness, or to establish safety for a new patient population)
  - **Essential to approval** (i.e., no other data available to support approval)
  - **Conducted or sponsored by the applicant** (i.e., applicant was identified as the sponsor on Form FDA-1571 or provided substantial support)

3-Year New Clinical Investigation Exclusivity

- Bar on approval of ANDA/505(b)(2) for three years after approval of the NDA or sNDA
  - Protection extends to approved change or conditions of approval
  - FDA interprets scope as **the innovation**; e.g., dosage form (e.g., extended-release), indication, or labeling information

Braeburn Analysis re: Scope of 3-Year Exclusivity

- **Step 1**
  - What unique question did the clinical studies answer for the first time about safety and/or efficacy of the active moiety?
- **Step 2**
  - Do clinically meaningful characteristics of the drug further define (i.e., narrow) the scope of the innovation?

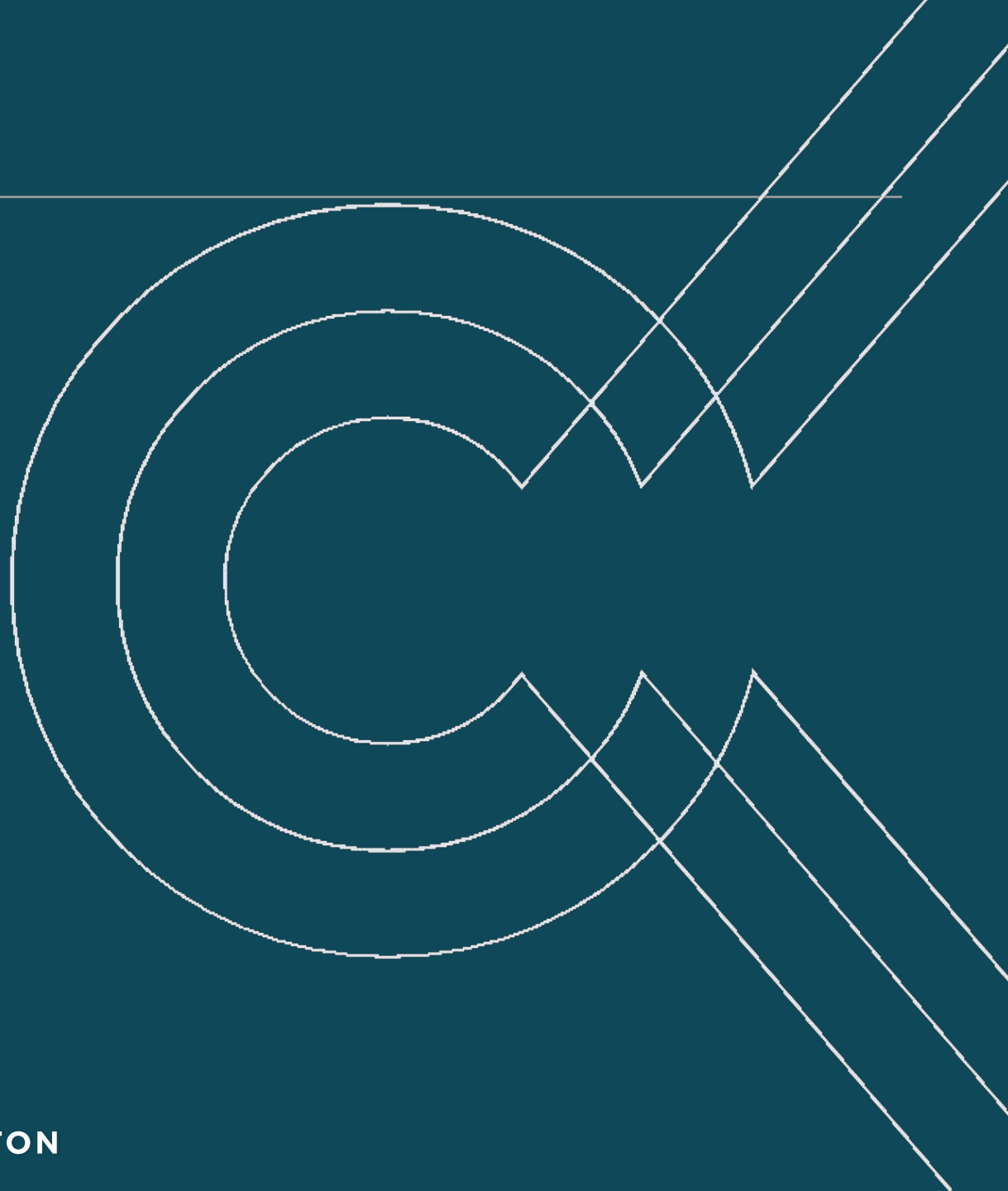
Labeling Carve-Outs

- Reference listed drug (RLD)
  - Indication A
  - Indication B (subject to 3-year exclusivity)
- FDA usually can approve a generic product solely for indication A.
- The RLD may be subject to automatic pharmacy-level substitution with the generic product, even if the generic product will be used for indication B.

Limitations on Labeling Carve-Outs

- The carve-out may not "render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7).
- Carve-out denied (i.e., generic not approvable) where, for example, patients taking the drug product for the non-protected condition of use previously took, or might in the future take, the drug product for the protected condition of use, and the information is necessary for them.
  - Rapamune: high-risk v. low-to-moderate risk (covered by 3-year exclusivity) populations
  - Colcrys: prophylaxis v. treatment (covered by 3-year exclusivity) indications
- Other examples: Lonsurf (renal impairment), Xyrem (drug-drug interaction)

GAIN Act Exclusivity



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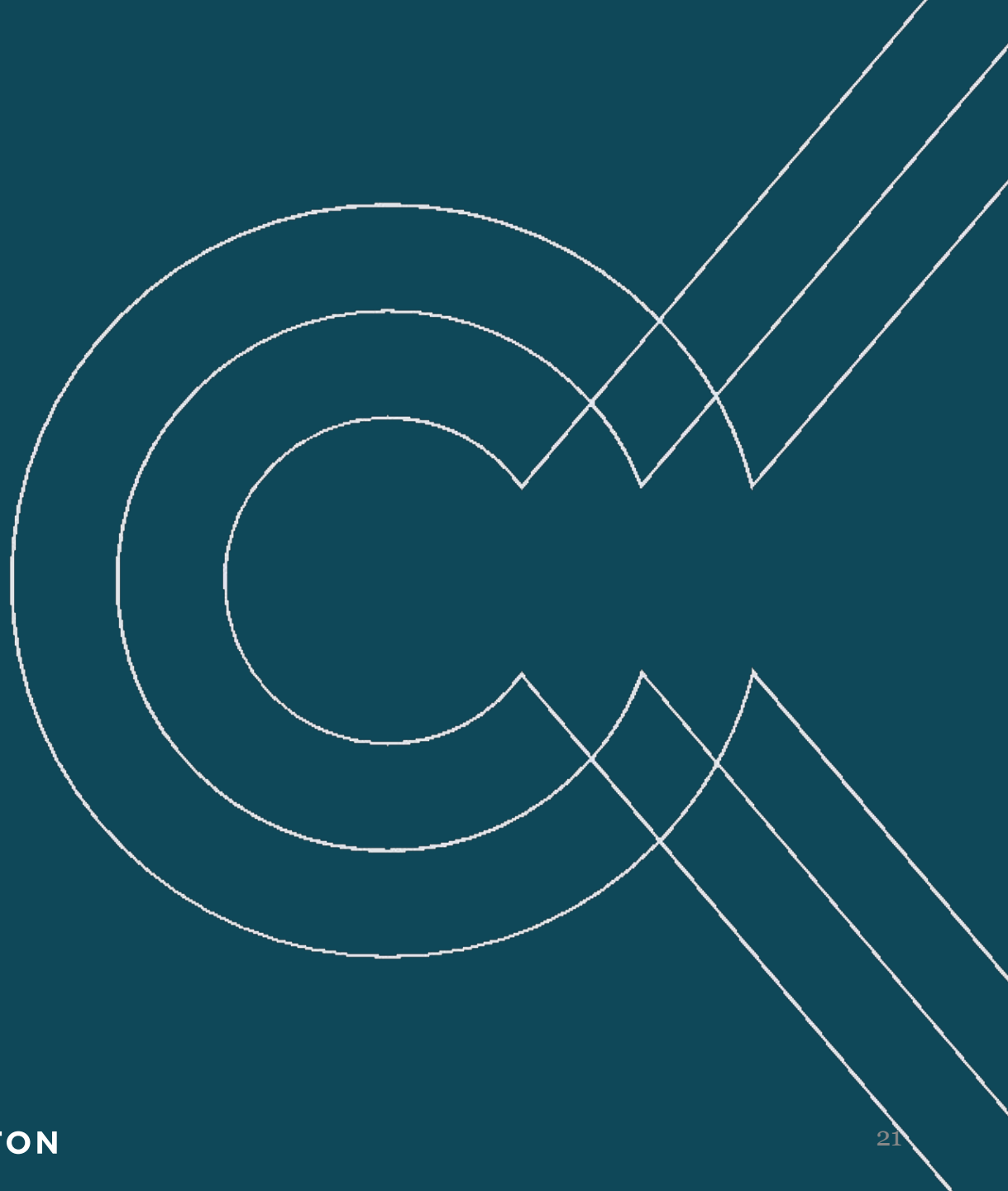
GAIN Exclusivity for Drugs

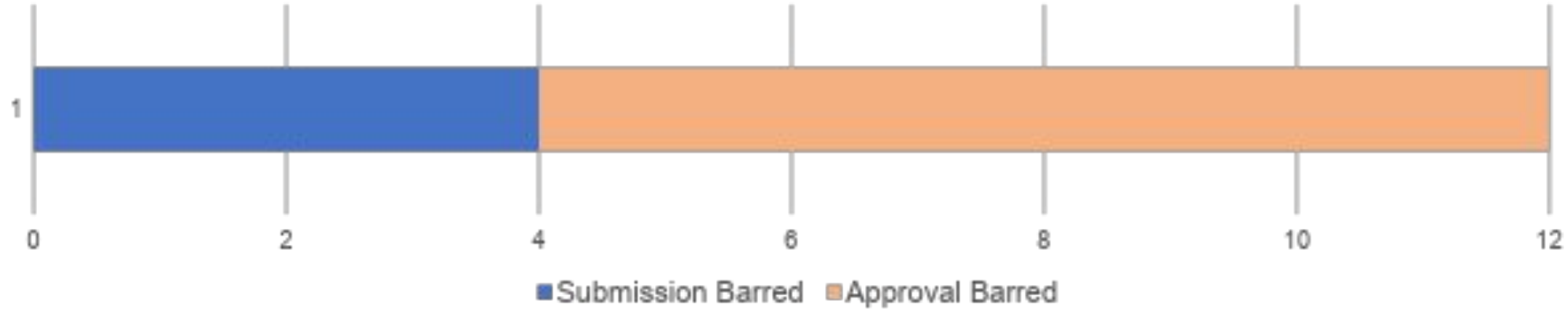
- 5-year extension of NCE exclusivity, new clinical investigation exclusivity, and orphan-drug exclusivity.
- For a drug that has been designated as a qualified infectious disease product (QIDP) and is approved for the designated use(subject to limitations)
- QIDP definition
  - [A]n antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by—
    - (1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens; or
    - (2) qualifying pathogens listed by the Secretary under [section 505E(f) of the FDCA].
- FDCA § 505E.

Reference Product Exclusivity



Reference Product Exclusivity (RPE)

- **Biosimilar applications may not be:**
  - Submitted until 4 years after “first licensure” of the reference product
  - Approved until 12 years after “first licensure” of the reference product



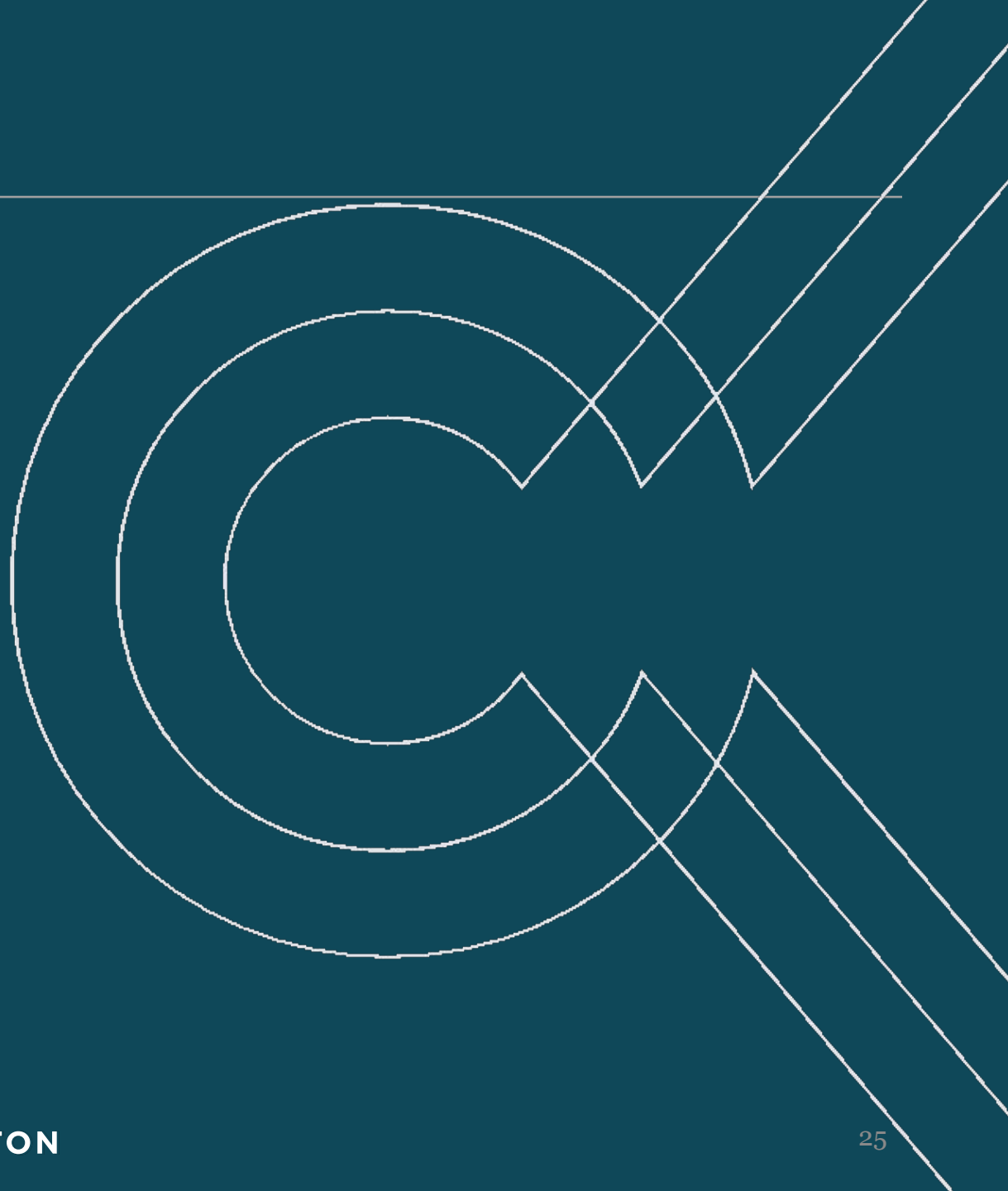
"First Licensure"

- "In most instances, the date of first licensure will be the initial date the particular product at issue was licensed in the United States."
- "Not every licensure of a biological product under 351(a) is considered a 'first licensure' that gives rise to its own exclusivity period."
  - FDA, Draft Guidance, *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (Aug. 2014).

Reference Product Exclusivity (RPE)

- **The provisions describing RPE "shall not apply to":**
  - A supplement [sBLA] for the reference product, or
  - A subsequent application filed by same sponsor or "a licensor, predecessor in interest, or other related entity" for:
    - A nonstructural change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    - A structural modification that does not result in a change in safety, purity, or potency

Orphan-Drug Exclusivity



Orphan Drug Exclusivity: Overview

- 7-year market exclusivity
- ODE bars FDA from approving another sponsor's application for same drug for "same [rare] disease or condition" including:
  - Full application (NDA, BLA)
  - Biosimilar application
  - ANDA
  - Section 505(b)(2) NDA
- Statutory exceptions:
  - ODE holder cannot assure availability of sufficient quantities of drug to meet needs of orphan-designated disease or condition
  - ODE holder consents
- De facto exemption for clinically superior products
- Limited to rare disease or condition (potential for carve-outs)

What is an Orphan Drug?

- Drug or biologic intended for a “rare disease or condition”
- The Orphan Drug Act defines “rare disease or condition” to mean:
  - Any disease or condition affecting fewer than 200,000 persons in the U.S.; OR
  - Any disease or condition affecting more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the costs of developing and making the drug available in the U.S. will be recovered from U.S. sales of the drug

Orphan-Drug Designation (ODD)

- A sponsor must request ODD from FDA
  - The request must be made prior to the submission of the marketing application for the drug
  - The request may be for a new drug or for a new use of an already marketed drug
- FDA must designate a drug if FDA finds that the drug is being or will be investigated for a rare disease or condition and approval would be for that rare disease or condition
- Designation decisions "shall be made on the basis of the facts and circumstances as of the date the request for [ODD] is made"
- Need for plausible hypothesis of clinical superiority if FDA has previously approved the "same drug" for the same disease or condition

Scope of ODE: Structural Sameness

- "Same drug" for small molecules: a drug that contains the same active moiety as a previously approved drug
- "Same drug" for macromolecules: a drug that contains the same principal molecular structural features
- Specific examples in regulation
  - Proteins are the "same" if the only differences are due to post-translation events or infidelity of translation or transcription or minor differences in amino acid sequence; different glycosylation patterns or tertiary structures would not cause drugs to be considered different
- Guidance on sameness of monoclonal antibodies and gene therapy products

Catalyst Litigation re: Scope of ODE

Scope under FDA's regulations: approved indication

- ODD: treatment of LEMS
  - Indication: LEMS in adults
  - Indication: LEMS in patients aged 6 to <17

Scope under *Catalyst* appellate decision: designation

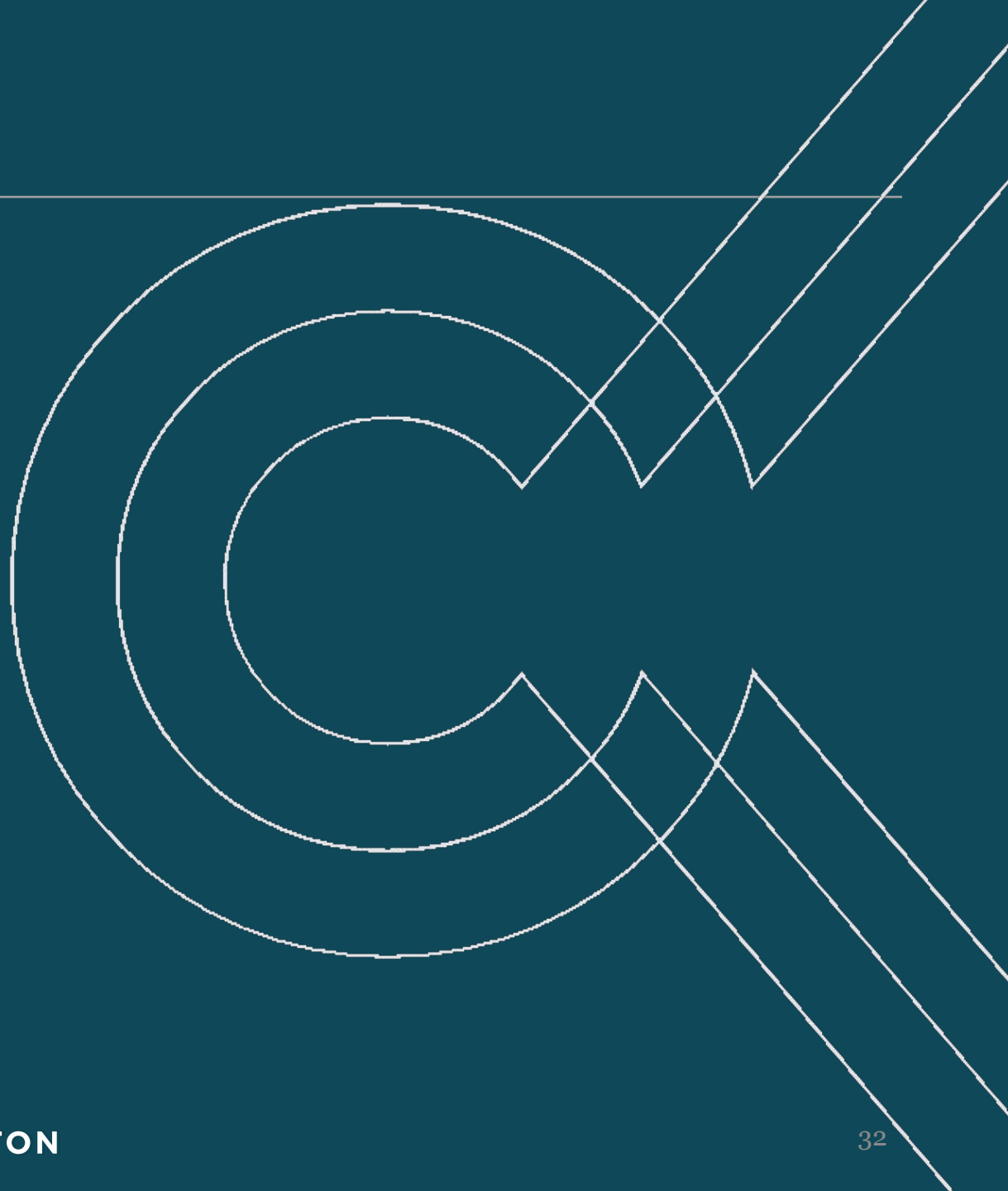
- ODD: treatment of LEMS
  - Indication: LEMS in adults
  - Indication: LEMS in patients aged 6 to <17

Federal Register notice (Jan. 24, 2023): "[A]t this time, the Agency intends to continue to apply its longstanding regulations tying the scope of orphan-drug exclusivity to the uses or indications for which the orphan drug was approved."

Clinical Superiority (21 C.F.R. § 316.3(b)(3))

- The subsequent drug "is shown to provide a significant therapeutic advantage over and above" that provided by the first drug
- (1) **Greater Effectiveness**
  - In "most" cases, direct comparative clinical trials are required
- (2) **Greater Safety**
  - In "some" cases, direct comparative clinical trials are necessary
- (3) **Makes a Major Contribution to Patient Care**
  - In "unusual cases"
  - Example: development of oral dosage form where first drug was available only in parenteral dosage form

Pediatric Exclusivity



Pediatric Exclusivity

- 6-month exclusivity extension for completing pediatric studies in response to a written request from FDA
- Attaches to:
  - All regulatory exclusivity in place at the time of the extension
    - Drugs: NCE, 3-year, orphan-drug, patent-based exclusivity
    - Biologics: 4- and 12-year reference product exclusivity, orphan-drug
  - For drugs, period of time during which FDA cannot approve a generic drug due to a listed patent
    - If patent has been challenged in paragraph IV certification, court must have found patent valid and infringed
- For drugs: applies to all of applicant's formulations, dosage forms, and indications for products that contain the same active moiety
- Generally unavailable for products with no remaining exclusivity

Written Request (FDCA § 505A)

- FDA may issue a written request (WR) for pediatric studies if it determines that information related to the use of a drug or biologic in the pediatric population may produce health benefits
  - WR may be issued for new drug or approved drug
  - WR may include both approved and unapproved uses
  - Response to WR is voluntary
  - WR include timelines
- FDA approach: WR includes all studies needed to provide meaningful information about active moiety for all pediatric populations in which drug is likely to be used
- An applicant may request a WR by submitting a Proposed Pediatric Study Request

Timeline for Pediatric Exclusivity