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Regulatory Exclusivity for Novel Drugs and Biologics

5-YEAR NEW CHEMICAL ENTITY EXCLUSIVITY AND 12-YEAR REFERENCE PRODUCT EXCLUSIVITY

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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.

George 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.

Introduction

- Introduction to FDA Lifecycle Management webinar series
  - Monthly installments addressing issues affecting lifecycle of pharma and biotech products
- First four installments will cover four key types of regulatory exclusivity
  - New Chemical Entity and Reference Product Exclusivity
  - Orphan Drug Exclusivity (March 16, 2023)
  - Pediatric Exclusivity (April 13, 2023)
  - 3-Year “New Clinical Investigation” Exclusivity (May 11, 2023)

Today's Agenda

- 5-Year New Chemical Entity (NCE) Exclusivity
  - Background policy and evolution of FDA approach
  - General operation of NCE exclusivity
  - Strategic considerations
  - Eligibility for NCE exclusivity
    - Application to certain product categories
- 12-Year Reference Product Exclusivity
  - Basic operation of 12-year exclusivity
  - Eligibility of subsequent products for second period of exclusivity
  - Precedent and open issues

NEW CHEMICAL ENTITY EXCLUSIVITY

CURRENT ISSUES

New Drug Applications

- The Hatch-Waxman Act codified three types of new drug applications:
  - **505(b)(1) NDA** – ***full showing of safety and effectiveness***; all data owned by applicant (or right of reference)
  - **505(b)(2) NDA** – approval ***relies in part*** on findings of safety and effectiveness for previously approved NDA(s) and/or studies reported in literature; patent certification to "listed drug(s)"
  - **505(j) ANDA** – approval ***relies in full*** on prior findings of safety and effectiveness for a single previously approved NDA; patent certification to "reference listed drug" (RLD)
    - ANDA approval based on bioequivalence and sameness of active ingredient(s), strength, dosage form and route of administration
- In exchange for the ability to rely on other products for approval, the ***timing of final approval*** will depend on patent certifications, patent litigation and regulatory exclusivity.

New Chemical Entity (NCE) Exclusivity

- Eligibility: If an NDA is approved "***for a drug, no active moiety…of which has been approved*** in any other [NDA]"
  - Statutory language amended in 2021 to replace "active ingredient (including any salt or ester of the active ingredient)" with "active moiety," mirroring FDA's existing regulations

- Scope: Then "no application ***which refers to the drug . . . may be submitted*** [under this subsection] before the expiration of five years…"
  - Blocks the ***submission*** of 505(b)(2) NDAs and ANDAs for ***same active moiety*** for any use for 5 years from date of NDA approval
  - 505(b)(2) NDAs and ANDAs can be submitted after 4 years, on "NCE-1" date, if they contain Paragraph IV patent certification(s)

NCE Exclusivity – Some Background

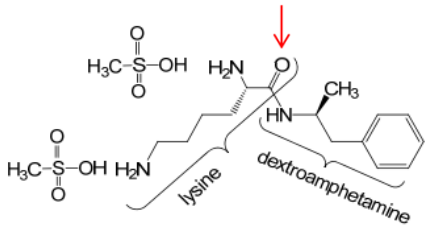
- The NCE exclusivity provision is designed to reward the development of a novel drug compound, a "new chemical entity"
  - In principle, this reflects the investment to develop the compound and the required non-clinical and clinical data
  - Evolution of policy into bright line rules
- Similar provisions throughout FDCA and elsewhere
  - New molecular entity (NME): An NDA classification for "an active ingredient that contains no active moiety that has been previously approved [in an NDA] or has been previously marketed as a drug in the United States."
  - Orphan Drug Act: "same drug" definition for small molecules
  - Priority Review Voucher eligibility
- Considering these provisions and NCE exclusivity together can be a valuable tool

Eligibility for NCE Exclusivity: What is the active moiety?

- ***Active moiety*** means 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 CFR 314.108(a).
  - ***New chemical entity*** means a drug that contains no active moiety that has been approved by FDA in any other NDA…. 21 CFR 314.108(a).
- FDA looks at the structure of the active ingredient as it exists in the finished dosage form ***before administration***
- FDA will look at ***structure only***, without consideration of in vivo pharmacological activity, including whether and how the appendage is cleaved off in the body
  - Hasn't always been the case historically

Eligibility for NCE Exclusivity: FDA's Structure-Based Approach

- Actavis Elizabeth LLC v. FDA (D.C. Cir. 2010), upheld FDA's 2009 exclusivity determination regarding Vyvanse (lisdexamfetamine dimesylate)
- Lisdexamfetamine consists of dextroamphetamine (a moiety that had previously been approved by FDA) bonded covalently to lysine through an amide bond
  - Prodrug of dextroamphetamine, which is responsible for drug's activity



- ***Structure is more important*** than pharmacologic activity
  - Ester prodrug ≠ new active moiety; non-ester covalent bond = new active moiety

Strategic Considerations

- Understand the chemistry
- Find the relevant precedent
- Create a record
  - Consistency across communications with FDA
  - Attention to nomenclature
  - Exclusivity request submitted with NDA
- Leverage related inflection points earlier in the process
  - NME classification
  - Orphan drug designation criteria
  - USAN
- Dispute resolution, citizen petitions and litigation

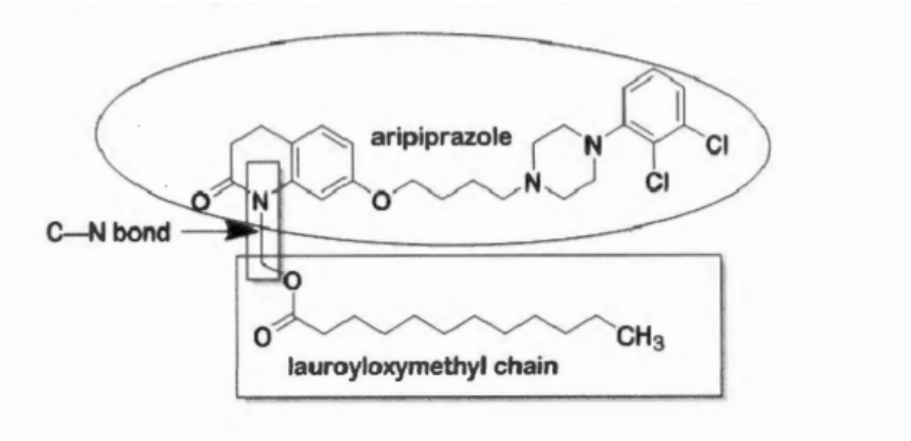
Eligibility for NCE Exclusivity: Post-*Actavis*

- FDA had to clean up or disavow some older examples:
  - Stable esters: the ester is responsible for pharmacological action
    - E.g., ISMO (isosorbide mononitrate) an ester of previously approved isosorbide dinitrate, had been awarded NCE exclusivity in 1991; isosorbide alone is inactive
  - Emend (fosaprepitant dimeglumine) for Injection
    - FDA reversed earlier decision denying NCE exclusivity; initially denied on the basis that fosaprepitant dimeglumine was merely a prodrug of, and quickly metabolized to, the same active moiety as in the previously approved Emend (aprepitant)
    - However, as a non-ester covalent derivative, fosaprepitant diemglumine, was ultimately awarded NCE exclusivity
- 2015: Aristada (aripiprazole lauroxil) = NCE, even though metabolizes to aripiprazole
- Esters don't have to be formed with a carbon center

Eligibility for NCE Exclusivity: Prodrugs Post-*Actavis*

- 2015: FDA awarded NCE exclusivity to Aristada (aripiprazole lauroxil), even though the linker appendage included an ester
  - Notwithstanding that Aristada was a 505(b)(2) NDA relying on FDA's prior approval of aripiprazole

"By virtue of the ester bond in its lauroyloxymethyl chain, aripiprazole lauroxil is an ester. Specifically, aripiprazole lauroxil is an ester of N-hydroxymethyl aripiprazole, not of aripiprazole."



Eligibility for NCE Exclusivity: Has the active moiety already been approved?

- If an NDA is approved "for a drug, no active moiety…of which ***has been approved in any other application under subsection (b)***…"
  - FDA's exclusivity regulations at 21 CFR 314.108 define this more clearly as "an NDA submitted under section 505(b) and approved on or after October 10, 1962, or an application that was 'deemed approved' under section 107(c)(2) of Public Law 87-781," i.e., the 1962 amendments
- **Strategy**: The Orange Book and Drugs@FDA are not sufficient!
  - They do not include many pre-1962 NDAs
  - Search Federal Register notices and other FDA lists ("Ever Approved" list)
  - 2016: CDER Exclusivity Board decision regarding E-Z-HD (barium sulfate) for oral suspension (NDA 208036); approved on January 11, 2016, denied NCE based on NDA 006624 for Metabarin (barium sulfate), "made effective" in 1948 and withdrawn in 1970

Eligibility for NCE Exclusivity: The Aubagio case

- Sanofi-Aventis US LLC's Aubagio (teriflunomide) oral tablets (NDA 202992) was approved on September 12, 2012
  - FDA awarded NCE exclusivity until September 12, 2017, meaning an ANDA containing a Paragraph IV certification could not be filed until September 12, 2016 (the NCE-1 date)
- Sandoz sought to submit its ANDA in August 2016, on the basis that FDA should not have awarded NCE exclusivity to Aubagio, because teriflunomide was present in another Sanofi product, Arava (leflunomide), approved in 1998
  - Big potential impact for Sandoz who would have been the sole "first applicant" eligible for 180-day exclusivity; instead of sharing exclusivity with 20+ ANDAs identified as having been submitted on NCE-1 date
- FDA rejected this argument, concluding that terflunomide was an ***impurity*** in Arava (leflunomide), not an ***active ingredient or active moiety***; affirmed in Sandoz v. Becerra (DC Cir. 2023)

Effect of NCE Exclusivity

- Blocks the ***submission*** of ANDA or 505(b)(2) NDA containing the same active moiety for 5 years from date of NDA approval, for any use/indication
  - Shortened to 4 years if ANDA or 505(b)(2) NDA contains Paragraph IV patent certification
  - Typically results in multiple first applicants on "NCE-1" date
  - See 2020 FDA Petition Response regarding cocaine HCl products
- 30-month stay operates differently with NCE exclusivity
  - If ANDA or 505(b)(2) NDA is submitted between years 4 and 5 post-approval, regulatory stay extended to 7.5 years post-approval
- For drugs subject to DEA scheduling after approval, "date of approval" will be later of FDA approval letter and DEA scheduling order

Effect of NCE Exclusivity: Umbrella Exclusivity

- NCE exclusivity blocks all ANDAs and 505(b)(2) NDAs that contain the same active moiety, ***even if those applications refer to a different NDA containing the same active moiety***
- Derives from 1989 preamble interpretation of language in exclusivity statute
  - "no application may be submitted under this subsection which ***refers to the drug*** . . . before the expiration of five years . . ."
  - Otherwise, would discourage innovation during exclusivity period
- Example:
  - NDA 212526 for Piqray (alpelisib) approved on May 24, 2019
    - Awarded NCE exclusivity expiring May 24, 2024
  - NDA 215039 for Vijoice (alpelisib) approved on April 5, 2022
    - Listed with "umbrella" NCE exclusivity expiring May 24, 2024

Eligibility for NCE Exclusivity: Product Categories

- Fixed-dose combinations
- Deuterated drugs and other isotopes
- Enantiomers
- Metal-ion complexes
- Natural mixtures

Fixed-Dose Combinations: FDA's Historical Approach

- What happens when a novel active ingredient is combined with a previously approved active ingredient?
- For a long time, FDA took a harsh view and denied NCE exclusivity to numerous products, under the previous iteration of the statute
  - If an application is approved "***for a drug, no active ingredient*** (including any ester or salt of the active ingredient) ***of which has been approved*** in any other application" then "no application may be submitted under this subsection which refers to the drug . . . before the expiration of five years . . ." 21 USC 355
  - FDA looked at the term "drug" and read it as "drug product": does the entire "drug product" – including each of the active ingredients – contain no previously approved active moiety?
- Example: Kaletra (lopinavir; ritonavir) approved in 2000
  - Lopinavir was new, but ritonavir had previously been approved = No NCE

Fixed-Dose Combinations: FDA's New Position

- 2013: Three sponsors submitted citizen petitions to FDA requesting that FDA change its interpretation
- October 2014: FDA agreed and finalized a guidance document to announce the new interpretation
  - Now, "drug" is read as "drug substance" (i.e., active ingredient): Is there any active ingredient in the fixed-dose combination drug product that contains no previously approved active moiety?
  - FDA initially declined to apply the policy retroactively to products that were denied the exclusivity (and the subject of the petitions)
- September 2016: federal district court ruled that FDA's prior policy was unlawful (*Ferring v. Burwell*, (D.D.C. 2016)) and that NCE exclusivity should have been awarded to petitioners' products

Deuterated Drug Substances

- Deuterated compounds replace hydrogen atoms with heavy hydrogen or deuterium (2H)
  - May extend the half life of the drug substance and/or create metabolites
- FDA awarded NCE exclusivity to Austedo (deutetrabenazine) (NDA 208082) in 2017, notwithstanding prior approval of Xenazine (tetrabenazine)
  - Consistent with treatment of other isotopes, e.g., Urea, C-13 and Urea, C-14, both awarded NCE exclusivity in the 1990s
- **Strategy**: Indicia from orphan drug designation and FDA classification as a new molecular entity (NME)

Enantiomers and other isomers

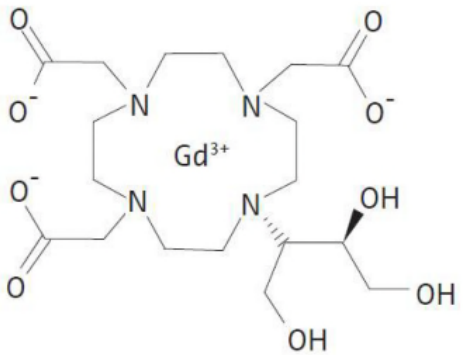
- Stereoisomers are molecules that are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms
  - "Enantiomers (mirror images), geometric (cis/trans) isomers, and diastereoisomers (isomers of drugs with more than one chiral center that are not mirror images of one another)." See FDA Guidance Document, Development of New Stereoisomeric Drugs (May 1992)
- Drugs were often developed as racemic mixtures of both enantiomers, but technological advances permit development of single enantiomers, which may be better candidates than racemic mixture
- FDA historically denied NCE exclusivity to a single enantiomer of a previously approved racemic mixture (or vice versa), on the basis that the two products contain the same molecule/active moiety

Section 505(u) Provides NCE Exclusivity for Certain Single Enantiomer Products

- 2007: As part of FDAAA, Congress added FDCA section 505(u), which provides NCE exclusivity to single enantiomer products even where the racemic mixture had previously been approved, IF:
  - the single enantiomer previously approved only in the racemic mixture;
  - the NDA for single enantiomer product includes full reports of new clinical investigations (other than bioavailability studies) —
    - Necessary for the approval of the NDA, and
    - Conducted or sponsored by the applicant;
  - the NDA for single enantiomer product does not rely on any clinical investigations that are part of the approved racemic mixture NDA; and
  - the single enantiomer product is for a use in a different "therapeutic category"
- Labeling disclaimer and therapeutic category restrictions

Metal-Ion Complexes

- Coordination complexes or chelates of a metal ion can create novel active moieties, if metal-ligand bond is covalent
  - Gadolinium-ion based imaging reagents
  - Other radiopharmaceutical products
- FDA's 2015 MAPP 5018.2 describes "weight-of-evidence" test to determine whether a metal-ligand bond is covalent:
  - Evaluation of energy level, inter-atomic distance, strength, geometry and stoichiometry
- FDA has not always been consistent
  - Nanoparticle parenteral iron products



Metal-Ion Complexes: The Velphoro case

- Velphoro (sucroferric oxyhydroxide) was approved in 2013 ***without*** NCE exclusivity (instead, 3-year exclusivity)
  - "Structurally, Velphoro is comprised of particles in which a hydrated, poorly soluble 'polynuclear' ferric oxyhydroxide 'core' is surrounded by an immediate layer of sucrose molecules that are loosely associated with this core, along with molecules of starch (specifically, potato and pregelatinized starch)."
  - FDA denied NCE exclusivity on the basis that polynuclear ferric oxyhydroxide core (FeO(OH)) had previously been approved in several products
- Sponsor submitted petition in 2016 requesting NCE exclusivity
  - FDA denied on the basis that sugars and starches not covalently bonded; and fall short of covalent on weight-of-evidence test. Citizen Petition Response, FDA-2016-P-1163 (May 26, 2021)

Natural Mixtures

- A naturally-derived product that consists of a mixture of constituent components, where ***the entire mixture*** is responsible for the action of the product:
  - Conjugated estrogens
  - Fish oil products
  - Pancrelipase products (now BLAs)
  - Lung surfactants (most now BLAs)
  - Botanicals (Fulyzaq and Veregen)
  - Cannabis-derived products
- When FDA approves these products, it typically does so by considering the mixture to be the active ingredient. In doing so, is it approving ***one active moiety*** or is it approving ***multiple active moieties***?
  - Which components are present and active?

Natural Mixtures: FDA's Historical Approach

- FDA's historical approach has been to consider the entire natural mixture as a single active ingredient for purposes of NCE exclusivity
  - With a single active moiety, although not well-explained by agency
- Presumption of NCE exclusivity in some cases
  - Hyaluronidase decisions in 2004: "NCE status depends on whether a product contains a previously approved active moiety. Until the proteins are fully characterized, the Agency will generally presume (in the absence of persuasive evidence to the contrary) that each new naturally sourced (non-recombinant) protein product does not necessarily contain any of the same active moieties as a previously approved naturally sourced protein product."
  - Pancrelipase policy in 2005: similar outcome

Natural Mixtures: The *Vascepa* case

- 2012: Approval of Amarin's Vascepa (icosapent ethyl) capsules (NDA 202057), which is a product derived from purified fish oil
  - Icosapent ethyl is the ethyl ester of eicosapentaenoic acid (EPA), an omega-3 fatty acid; EPA is the active moiety of Vascepa
  - FDA had previously approved Lovaza (omega-3-acid ethyl esters) capsules (NDA 021654), which contains a mixture of seven distinct omega-3 fatty acid ethyl esters obtained from fish oil (approximately 85% of mixture is ethyl esters of EPA and docosahexaenoic acid (DHA))
- 2014: FDA initially denied NCE exclusivity on the basis that EPA had been approved as an active moiety in Lovaza
  - A new "one-to-many" framework, where a single active ingredient could have multiple active moieties
  - And a new test for determining the active moiety/ies in natural mixtures
    - (1) Characterization, (2) Consistent Presence, and (3) Activity

Natural Mixtures: The *Vascepa* case

- 2015: Federal district court disagrees with FDA and remands
  - Court focused on (now amended) statutory language "a drug, no active ingredient (including any salt or ester of the active ingredient)…"
  - Concluded that the active ingredient in Vascepa – icosapent ethyl – had not previously been approved
  - Regulatory definitions of "new chemical entity," "active moiety" weren't applicable, per the court
- 2016: FDA awarded NCE exclusivity on remand
  - Acknowledged inconsistent precedent, with little record in some cases
  - Other fish oil mixtures also awarded NCE exclusivity
- 2021: Statute amended to replace "active ingredient (including any ester or salt of the active ingredient)" with "active moiety"

12-YEAR REFERENCE PRODUCT EXCLUSIVITY

CURRENT ISSUES

The BPCIA Establishes Biosimilar Pathway

- In 2010, the Biologics Price Competition and Innovation Act (BPCIA) established approval pathway for biosimilar applications submitted under new Section 351(k) of the Public Health Service Act (PHSA)
  - Section 351(a): "Full" BLAs; original application relying exclusively on a sponsor's own data
  - Section 351(k): biosimilar applications; relies for approval on "reference product" approved in full BLA
- Biosimilar application must be shown to be "highly similar" to reference product, based on analytical studies, animal studies and a clinical study or studies
  - Same strength, dosage form, and route of administration as the reference product; and the conditions of use sought by the biosimilar must have been approved for the reference product. 42 USC 262(k)(2).
- No BLA equivalent to a 505(b)(2) NDA

Reference Product Exclusivity: Basic Operation

- Reference product exclusivity under the BPCIA operates quite differently from FDCA exclusivity provisions for drugs
  - Reference product exclusivity blocks ***approval*** of a ***biosimilar*** application until 12 years "after the date on which the reference product was first licensed" under section 351(a) of the PHSA. 42 UC 262(k)(7)(A).
  - Reference product exclusivity blocks the ***submission*** of a ***biosimilar*** application for 4 years from the same date. 42 UC 262(k)(7)(B).
  - Runs from "date of first licensure"; ***only blocks biosimilars***
- No equivalent to Hatch-Waxman's 3-year exclusivity for NDAs
- Orphan exclusivity and pediatric exclusivity remain available for BLAs, as was the case prior to BPCIA
  - Pediatric exclusivity can extend 12- and 4-year periods by 6 months

Reference Product Exclusivity: Subsequently Approved BLAs

- Not every product licensed under a 351(a) BLA is eligible for its own period of 12-year exclusivity
- 12-year exclusivity (including the 4-year bar on submission) is ***NOT*** available for:
  - a supplement to the reference product BLA (e.g., to make changes to the original conditions of use) or
  - a subsequent application (full BLA) submitted by the same sponsor (or licensor, predecessor in interest, or other related entity) for:
    - a change (not including a structural modification) 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.
    - 42 USC 262(k)(7)

Reference Product Exclusivity: Subsequently Approved BLAs

- Put affirmatively, the first biological product approval from a sponsor will likely be awarded reference product exclusivity
- A new period of exclusivity is available for a second "full" BLA from the same sponsor (or related entity), **ONLY IF**:
  - (1) The second BLA contains ***a modification to the structure of the biological product*** that
  - (2) Results in a ***change in safety, purity or potency.***
- If this standard is met, the second BLA will get its own "date of first licensure" and a new 12-year period of exclusivity

Reference Product Exclusivity: Practical Challenges

- FDA does not routinely make exclusivity determinations for newly approved BLAs
  - In the past, FDA said that it makes exclusivity determinations at the request of the sponsor or "for reasons of regulatory necessity," i.e., pending biosimilar application
  - 2020 law requires FDA to specify exclusivity in the Purple Book following an agency determination
- In practice, almost no exclusivity determinations have been made
  - The Purple Book identifies a "date of first licensure" for only 17 products, and it's not clear if these all represent final exclusivity determinations

Reference Product Exclusivity: Umbrella Exclusivity?

- As noted above, in NCE context, FDA recognized that umbrella exclusivity is important; otherwise, sponsors would be disincentivized to develop incremental improvements of their products
- Whether FDA will apply its umbrella exclusivity policy has been an open question since the passage of the BPCIA.
  - The agency itself has not made a definitive statement
  - Given the lack of exclusivity determinations, hard to tell
- For BLAs, longer exclusivity period makes issue more important
  - Particularly if supplemental BLA or subsequent "full" BLA does not earn its own exclusivity

Reference Product Exclusivity: FDA's Draft Guidance

- *Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (August 2014)
- Provides interpretations of key criteria:
  - "Same Sponsor (or Licensor, Predecessor in Interest, or Other Related Entity)"
  - "Modification to the Structure of the Biological Product"
  - "Results in a Change in Safety, Purity or Potency"
- Roadmap for the information that FDA would like to see in an Exclusivity Request submitted with BLA
  - Identify structurally-related products
  - Describe the differences
  - Evidence of change in safety, purity or potency

Reference Product Exclusivity: FDA's Draft Guidance

- "Same Sponsor (or Licensor, Predecessor in Interest, or Other Related Entity)"
  - Predecessor in interest: any entity that the sponsor has taken over, merged with, or purchased, or that has granted the sponsor exclusive rights to market the biological product, or had exclusive rights to the data underlying that application
  - Licensor: any entity that has granted the sponsor a license to market the biological product, regardless of whether such license is exclusive
  - Related entity:
    - (1) either entity owns, controls, or has the power to own or control the other entity (either directly or through one or more other entities) or
    - (2) the entities are under common ownership or control,
    - And, maybe, "certain commercial collaborations"

Reference Product Exclusivity: FDA's Draft Guidance

- "Modification to the Structure of the Biological Product"
  - Are there products with the same "principal molecular structural features" and that affect the same molecular target?
    - Compare to orphan drug regulations and guidance
  - Are these products owned by the same sponsor or related entity?
  - FDA will consider differences in amino acid sequence, infidelity of translation or transcription, glycosylation patterns, tertiary structures, and post-translational events (e.g., chemical modification)
    - Not necessarily material, however
    - Different cell line does not necessarily mean structural modification
- **REMEMBER**: this only matters if you are the "same sponsor" as previously approved product

Reference Product Exclusivity: FDA's Draft Guidance

- "Results in a Change in Safety, Purity or Potency"
  - If FDA concludes there has been a structural modification, the agency will determine whether the modification results in a change to the safety, purity, or potency
    - "Case-by-case" and data-driven
  - FDA has stated that preclinical or clinical data of measurable effects will generally be needed to show a change in safety, purity, or potency
  - Presumption of a change in safety, purity, or potency if modified structure and sponsor can show that its product affects a different molecular target
    - "A molecular target can be any molecule in the body whose activity is modified by the product, resulting in a desirable therapeutic effect. Such molecular targets can include receptors, enzymes, ion channels, structural or membrane transport proteins, nucleic acids, and pathogens, among others."

Reference Product Exclusivity: Limited Precedent

- Perjeta (pertuzumab): approved in June 2012; listed with 12-year exclusivity
  - Similar structure to Herceptin (trastuzumab), also from Genentech
  - Difference in certain complimentary determining regions
  - Both target the HER2 receptor extracellular domain, but bind to different subdomains
- Granix (tbo-filgrastim): approved in August 2012; listed with 12-year exclusivity
  - Same amino acid sequence as Neupogen (filgrastim), but different sponsor
- These are the only two CDER-regulated BLAs with an exclusivity dates listed in the Purple Book.
  - No publicly available record of either determination

Reference Product Exclusivity: Limited Precedent

- Indicia from orphan drug determinations
  - FDA has looked to the definition of "same drug" for large molecule products from the orphan drug regulations, for purposes of 12-year exclusivity
  - Guidances on orphan "sameness" for monoclonal antibodies and gene therapy products
- Products that are not the "same drug" for orphan purposes
  - E.g., Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel)
- Several "negative precedents," where no orphan exclusivity has been granted
- Lots of uncertainty and few public determinations

Reference Product Exclusivity: Fixed-Dose Combinations?

- Genentech has developed fixed-dose combination products containing its previously approved products Herceptin (trastuzumab) and Perjeta (pertuzumab):
  - Herceptin Hylecta (trastuzumab and hyaluronidase-oysk)
  - Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf)
  - Addition of hyaluronidase allows for subcutaneous administration
  - No new biological substances
- Uncertain whether either will get additional exclusivity
  - 42 USC 262(k)(7) is silent about fixed-dose combinations
  - Compare orphans and NCE
  - What if the product included one new biological substance?

Reference Product Exclusivity: Antibody-Drug Conjugates?

- Each component (i.e., antibody, linker, and drug) seems to be part of the active biological substance
  - Covalent bonds
  - In the orphan drug mAb guidance, FDA indicated that ADCs differ from unmodified mAbs, due to additional functional element
  - E.g., Kadcyla (ado-trastuzumab emtansine), which links trastuzumab with cytotoxic drug
- Is a change in one element sufficient?

Strategic Considerations

- Know the structure and the science
- Clear communications with FDA
  - Educate the agency, as needed
- Fewer inflection points
  - Orphan drug determinations remain critical
  - Will FDA permit sponsor to leverage data from previously approved product?
- Research precedent as much as is possible
- These determinations are precedent-setting for FDA
  - Policy implications
  - Broader impact

Citations

- NCE Exclusivity
  - 21 USC 355(c)(3)(E)(ii) (exclusivity provision for 505(b)(2) NDAs)
  - 21 USC 355(j)(5)(F)(ii) (analogous provision for ANDAs)
  - 21 CFR 314.108(a), (b)(2) (NCE exclusivity regulations)
  - 21 CFR 314.50(j) (exclusivity request regulations)
  - Final Guidance, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products (Oct. 2014)
- Reference Product Exclusivity
  - 42 USC 262(i), (k)(7) (exclusivity provision for BLAs)
  - Draft Guidance, Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Aug. 2014)
  - Final Guidance, Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations (Apr. 2014)

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