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# Three-Year Exclusivity

## Exclusivity for New Clinical Investigations

**George O'Brien**

Partner, FDA Regulatory
+1 202 263 3302
gobrien@mayerbrown.com

**Ryan Babcock**

Associate
+1 212 506 2197
rbabcock@mayerbrown.com

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**George O'Brien**
Partner, FDA Regulatory
+1 202 263 3302
gobrien@mayerbrown.com

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.

**Ryan Babcock**
Associate
+1 212 506 2197
rbabcock@mayerbrown.com

Ryan T. Babcock is an associate in Mayer Brown's New York office and a member of the Intellectual Property practice. Ryan is registered with the U.S. Patent Office. His practice focuses on intellectual property transactional work as well as complex patent litigation matters related to the pharmaceutical and biotechnology industries, both in district courts and before the USPTO. He also assists pharma and biotech clients with strategic IP agreements, IP due diligence, IP licensing and FDA-facing regulatory issues. Ryan received a JD, magna cum laude, from Fordham University School of Law, and a Bachelor of Science degree in Biochemistry, magna cum laude, from Villanova University.

# Introduction

- Welcome to Mayer Brown's FDA Lifecycle Management webinar series
  - Monthly installments addressing issues affecting lifecycle of pharma and biotech products
  - Today's webinar addresses 3-Year "New Clinical Investigation" Exclusivity
- Next installments will cover additional types of regulatory exclusivity and related issues
  - *Orange Book* Patent Listing (June 15, 2023)

# Today's Agenda

- What is 3-year exclusivity?
  - How do you obtain it?
- What is its scope?
  - Which products are blocked?
- Leading court cases
- Other important precedents
- Key takeaways

# THREE-YEAR EXCLUSIVITY

## HOW TO OBTAIN IT

# What Is 3-Year Exclusivity?

- Incentive to the further clinical development of ***previously approved drugs***
  - Protects new indications, dosage forms, strengths, dosing regimens, and other new conditions of use approved in new drug applications (NDAs)
- Blocks the ***approval*** of abbreviated new drug applications (ANDAs) and 505(b)(2) NDAs with the same "***conditions of approval***"
  - Does not block the submission of these applications
  - Does not block approval of a 505(b)(1) NDA
- Limited to ***innovations*** based on "***new clinical investigations*** (other than bioavailability studies) ***essential to the approval*** of the application and ***conducted or sponsored by the applicant***" FDCA 505(c)(3)(E)(iii),(iv) and (j)(5)(F)(iii), (iv)
  - Not every change or new approval will qualify

# Regulatory Definitions: "Clinical Investigation"

- ***Clinical investigation***: "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects" 21 CFR 314.108(a)
  - The investigation must "be of the type necessary to support approval of the proposed change" 54 FR 28872, 28899 (July 10, 1989)
    - A single investigation can qualify for 3-year exclusivity
  - What about pharmacokinetic endpoints?
  - Safety studies?

# Regulatory Definitions: "New Clinical Investigation"

- ***New clinical investigation:*** "an investigation in humans (other than bioavailability studies) the results of which ***have not been relied on by FDA*** to demonstrate ***substantial evidence of effectiveness*** of a previously approved drug product for any indication or of ***safety for a new patient population*** and does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product" 21 CFR 314.108(a)
  - FDA's Exclusivity Checklist: "does not redemonstrate something the agency considers to have been demonstrated in an already approved application"
  - "Data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new." 59 FR 50338, 50369 (Oct. 3, 1994)

# Regulatory Definitions: "Essential to Approval"

- ***Essential to approval:*** "there are no other data available that could support approval of the application"
  - FDA's Exclusivity Checklist: the agency "could not have approved the application or supplement without relying on that investigation"
  - NOT essential if:
    - No clinical investigation is necessary to support the supplement or application in light of previously approved applications (*i.e.*, the information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA for 505(b)(2) application because of what is already known about a previously approved product), or
    - There are published reports of studies ... or other publicly available data that independently would have been sufficient to support approval of the application

# Regulatory Definitions: "Conducted or sponsored by"

- ***Conducted or sponsored by:*** an investigation is conducted or sponsored by the applicant if "before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application [IND] under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation"
  - If no IND (such as a foreign study), need certified statement from a certified public accountant to show "substantial support," *i.e.*, greater than 50%
  - Other explanations possible if less than 50%

## Submitting an Exclusivity Request

- Submission of an Exclusivity Request as part of an NDA or supplement (sNDA) is an important tool to assist the agency and to advocate for exclusivity
- "Required" by 21 CFR 314.50(j), which provides additional detail
  - Certification by sponsor; list of studies; identification of IND number
- Not strictly speaking required, but always worth doing
  - Generally, the tricky issue is whether the study is a "new clinical investigation," *e.g.*, if the study has pharmacokinetic (PK) endpoints
  - *See, e.g.*, testosterone products, where PK endpoint qualified for exclusivity

# SCOPE OF 3-YEAR EXCLUSIVITY

## STANDARDS AND PRECEDENT

# Scope of 3-Year Exclusivity

- Statutory Standard
- Leading Court Cases
  - *Veloxis v. FDA* (Astagraf XL and Envarsus XR)
  - *Otsuka v. Price* (Abilify Maintena and Aristada)
  - *Braeburn v. FDA* (Sublocade and Brixadi)
- Other Important Precedents
- Key Takeaways

# Scope of 3-Year Exclusivity

- ***Statutory standard***: If FDA approves an NDA "for a drug..." and if such application earns 3-year exclusivity, the agency may not ***approve*** an ANDA or 505(b)(2) NDA "for the ***conditions of approval*** of ***such drug*** in the approved [NDA] ... before the expiration of three years from the date of the approval of the application." FDCA 505(c)(3)(E)(iii),(iv) and (j)(5)(F)(iii), (iv)
  - "Conditions of approval" is not defined by statute or regulation
  - Slightly different language for sNDAs: "...for a change approved in the supplement..."
    - FDA nevertheless interprets this to mean "conditions of approval"
- *Zeneca Inc. v. Shalala*, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. FDA*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (not all changes made in supplement qualify for exclusivity)

# FDA Exclusivity Determinations

- FDA awards 3-year exclusivity at the time of approval of the NDA or supplement
- Typically appears with the product listing when first published in the *Orange Book* (generally the end of second week of following month) as one of several 3-year exclusivity codes, *e.g.*,
  - New Combination (NC), New Dosage Form (NDF), New Product (NP), New Patient Population (NPP)
  - M-290: Information added to section 8.4 of the labeling to include the result of study HZA114971
  - I-907: To increase bone density in men with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapy
- FDA considers these codes to be informative rather than determinative and won't make a determination about the scope unless and until another application is eligible for approval

# Scope of 3-Year Exclusivity in Practice

- **ANDAs**
  - Almost always blocks ANDAs, because generics must be pharmaceutically equivalent and have the same "conditions of approval" as the NDA that is the "reference listed drug" (RLD)
  - 3-year exclusivity on a second indication is often not effective to block approval of ANDA, where the exclusivity-protected information can be "***carved out***" of the generic's labeling (unless the new information is essential to the safe or effective use of the drug for the remaining conditions of use)
- **505(b)(2) NDAs**
  - Much more difficult to apply because 505(b)(2) products are ***inherently different*** from approved RLD: When do they have the same conditions of approval? Do differences matter?
  - Series of key cases and precedents over last 10 years

# *Veloxis v. FDA*: Astagraf XL and Envarsus XR

- Astellas' Astagraf XL (tacrolimus) ER capsules
  - Approved for ***once-daily dosing*** for prophylaxis of organ rejection in kidney transplant patients in July 2013, based on a clinical study in ***de novo patients*** (patients who had not previously received the drug)
  - Once-a-day extended release, 0.5, 1.0 and 5 mg capsules
  - "Relied on" Astellas' Prograf (tacrolimus) IR tablets, dosed 2 times per day
  - Awarded 3-year "New Dosage Form" exclusivity expiring July 2016
- Veloxis' Envarsus XR (tacrolimus) ER tablets
  - 505(b)(2) referencing Astellas' Prograf (tacrolimus) IR tablets, did not reference Astagraf
  - Once-a-day extended release, 0.75, 1.0 and 4 mg tablets
  - Included ***both de novo and conversion patient studies***

# *Veloxis v. FDA*: Astagraf XL and Envarsus XR

- FDA determined that Envarsus XR was blocked by Astagraf XL's exclusivity for ***once-daily dosing of de novo transplant patients with tacrolimus***
  - "Astellas' innovation for Astagraf XL was the ER nature of its dosage form that permitted once-daily dosing …. The new clinical investigations essential to this innovation studied Astagraf XL for the prophylaxis of organ rejection in *de novo* kidney transplant patients. Astellas' exclusivity is circumscribed by the scope of these new clinical investigations and cannot extend beyond this condition of approval."
  - Permitted Envarsus XR to be approved for conversion patients only
- Key Takeaways
  - ***No need for direct reliance*** for exclusivity to block approval of a 505(b)(2)
  - Exclusivity blocks approval of a product that shares the ***same "conditions of approval," despite other differences***

# *Otsuka v. Price*: Abilify Maintena v. Aristada

- Otsuka's Abilify Maintena (aripiprazole) ER injectable for suspension
  - Approved on February 28, 2013 for the treatment of schizophrenia
  - Relied on Otsuka's Abilify (aripiprazole) IR tablets; 505(b)(1) NDA
  - Received 3-year "New Dosage Form" exclusivity expiring February 28, 2016
- Alkermes' Aristada (aripiprazole lauroxil) ER injectable suspension
  - Relied on Abilify as a listed drug; plus additional studies conducted by Alkermes
- Otsuka submitted citizen petition to FDA seeking to block approval of Aristada
  - FDA denied petition and approved NDA for Aristada on October 5, 2015
  - 3-year exclusivity awarded for studies of a single-entity drug product will not block approval of a product for a different active moiety

# *Otsuka v. Price*: Abilify Maintena v. Aristada

- Both the district court and the DC Circuit affirmed FDA's conclusion
  - July 28, 2016: District court granted FDA's MSJ, finding the agency's approach reasonable at *Chevron* Step 2. (*Otsuka Pharm. Co., Ltd. v. Burwell*, 2016 WL 4098740 (DDC 2016))
  - August 29, 2017: DC Cir. affirms. (*Otsuka Pharm. Co., Ltd. v. Price*, 2017 WL 3708609 (DC Cir))
- Key Takeaway
  - The scope of 3-year exclusivity for an NDA or sNDA does not extend beyond the active moiety (or moieties) approved in that NDA or sNDA

# *Braeburn v. FDA*: Sublocade and Brixadi

- Both Braeburn and Indivior manufacture drug products using buprenorphine, a safer alternative to methadone, to treat moderate-to-severe opioid use disorder ("OUD")
- Indivior's Sublocade (buprenorphine) is an injectable depot that releases buprenorphine over a one-month period; approved November 30, 2017
  - Two initial monthly doses of 300 mg, followed by 100 mg monthly maintenance doses
- Two new clinical investigations were essential to Sublocade's approval
  - The first tested how well Sublocade inhibited the subjective effects of opioid use over a 29-day period, after stabilization on daily buprenorphine product
  - The second investigation tested the efficacy, safety, and tolerability of multiple Sublocade injections over a 24-week period
- 3-year "New Product" exclusivity, expiring November 30, 2020

# *Braeburn v. FDA*: Sublocade and Brixadi

- Braeburn's product, Brixadi (buprenorphine) is also an extended-release injectable depot that releases buprenorphine over either a weekly or monthly period for the "treatment of moderate to severe ... OUD in adults"
  - Unlike Sublocade, Brixadi comes in both a weekly and monthly depot version
- Braeburn's application for approval of Brixadi relied on three of its own clinical investigations
  - The first study involved administering Brixadi Weekly for seven weeks following stabilization
  - The second study involved treating patients first with Brixadi Weekly and then transitioning to Brixadi Monthly; no dose stabilization
  - A third study confirmed the safety of Brixadi Weekly and Monthly over an extended period
- FDA concluded that Brixadi Monthly was blocked by Sublocade's exclusivity until November 30, 2020; granted tentative approval in 2018 for both Brixadi Weekly and Monthly

# *Braeburn v. FDA* – FDA's Letter Decision

- FDA determined that the 3-year exclusivity for Sublocade blocks approval of Brixadi
  - **Step 1**: For a single entity drug to be barred by three-year exclusivity, it must contain the ***same active moiety*** as the protected drug → Both contain buprenorphine
  - **Step 2**: The scope of the new clinical investigation determines the "***conditions of approval***" for which subsequent applications may be barred. Thus, what was the "***innovation***" for which a new clinical investigation was essential to the approval of Sublocade?
    - FDA: Sublocade's innovation was the dosing interval provided by the monthly depot product to treat moderate to severe OUD
    - Exclusivity was not tied to a particular treatment initiation/stabilization regimen, dose adjustment schedule, or strength
- FDA: A second-in-time drug can be blocked if it "shares the 'innovation' supported by the first drug product's 'new clinical investigation essential to approval'"

# *Braeburn v. FDA* – District Court Decision

- Braeburn sued FDA under Administrative Procedures Act (APA), arguing that FDA ignored critical limitations on the conditions of approval of Sublocade:
  - (1) It is approved for use only in patients who have undergone a period of initial treatment and dose adjustment with oral buprenorphine for minimum 7 days
  - (2) Sublocade was only studied in patients new to treatment, and not in patients already clinically stable on another buprenorphine treatment
- The district court found the meaning of "conditions of approval" to be ambiguous (*Chevron* Step 1), and so looked to whether FDA's interpretation of this term was reasonable (*Chevron* Step 2)
  - Court: tying "conditions of approval" to "innovation" and scope of studies is sensible, except that the agency has not articulated any legal or scientific principle for identifying what is an "innovation"
  - "[T]he FDA's standard simply supplants the ambiguous phrase 'the conditions of approval' for the ambiguous term 'innovation.'"

# *Braeburn v. FDA* – FDA Decision on Remand

- The district court vacated FDA's exclusivity determination and remanded back to the agency
  - On remand, FDA reached the same conclusion, that 3-year exclusivity for Sublocade precluded final approval of Brixadi Monthly until November 30, 2020
- To identify the "innovation," FDA will determine "what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use do the new clinical investigations essential to approval answer for the first time?"
  - FDA must determine "whether the relevant characteristics of the drug studied are ***clinically meaningful***," *e.g.*, "significantly changes the population or use for which the drug is appropriate … or would otherwise be expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient"
  - "Thus, the conditions of approval to which exclusivity applies are the product's innovation for which new clinical investigations were essential, as defined by clinically meaningful characteristics of the product supported by the new clinical investigations essential to its approval."

# 3-YEAR EXCLUSIVITY

## WHICH “DRUGS” ARE BLOCKED?

# Prodrugs with Same Active Moiety

- FDA addressed whether 3-year exclusivity for Valcyte (valganciclovir HCl, NDAs 22257 and 21304) blocked the approval of Ganciclovir injection 500mg/250ml (NDA 209347) (February 16, 2017)
  - "Although Valcyte and Exela's Ganciclovir have different active ingredients—valganciclovir HCl and ganciclovir, respectively—the products have the ***same active moiety***, ganciclovir. Because the two products at issue contain the same active moiety, Exela's Ganciclovir could potentially be barred by Valcyte's unexpired 3-year exclusivity."
- Ultimately:  Not blocked based on different indications/patient populations
- Corollary to *Otsuka* case

# Drug-Drug Combination v. Single Entity Product

- FDA determined that the 3-year exclusivity for Bunavail (buprenorphine; naloxone) buccal film was to the ***combination of active moieties***
  - 3-year exclusivity for Bunavail did not block the approval of Narcan (naloxone) nasal spray
  - 3-year exclusivity will generally apply only against products that contain the same combination of active moieties because the clinical investigations that earn exclusivity generally support approval of the combination described in the application
- Other examples
  - Belbuca (buprenorphine HCl) not blocked by Bunavail (buprenorphine HCl; naloxone HCl)
  - MorphaBond (morphine sulfate) ER tablets not blocked by Embeda (morphine sulfate; naltrexone hydrochloride) ER capsules
  - Targiniq (oxycodone hydrochloride; naloxone hydrochloride) ER tablets not blocked by Troxyca ER (oxycodone hydrochloride; naltrexone hydrochloride) ER capsule

# 3-YEAR EXCLUSIVITY

## NARROWING OF EXCLUSIVITY OVER TIME

# Narrowing of Exclusivity Over Time

- "[T]he scope of 3-year exclusivity for a drug product may be affected by a previous approval for a drug product containing the same active moiety or moieties. The exclusivity protected condition of approval, and thus the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for a condition(s) of approval that differs from the conditions of approval of the earlier-approved drug product. In sum, because 3-year exclusivity generally covers only a different condition(s) of approval from any previously approved product with the same active moiety or moieties, as a practical matter a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously with the same active moiety or moieties."

# Too Much Narrowing? Amphetamine Products

- CDER Exclusivity Board Memorandum, Whether the 3-year exclusivity for Dyanavel XR (NDA 208147) or Mydayis (NDA 022063) blocks the approval of Adzenys ER (NDA 204325) (Sept. 15, 2017
  - "The Board has determined that Dyanavel XR's exclusivity-protected condition of approval for which new clinical investigations were essential to approval is the oral ER suspension formulation associated with its drug release profile. Similarly, the Board concludes that Mydayis's exclusivity-protected condition of approval is the oral ER capsule formulation associated with its drug release profile. Because Adzenys ER comprises a different formulation that results in a drug release profile different from that of Dyanavel XR and Mydayis, the Board recommends that the approval of Adzenys ER should not be blocked by the exclusivity for Dyanavel XR or Mydayis."

# Balance Exclusivity

- Balance Exclusivity is to 3-Year Exclusivity as Umbrella Exclusivity is to 5-Year Exclusivity
  - "If an application or supplement earns 3-year exclusivity because it is approved based on new clinical studies that are essential to approval conducted by or for the applicant and the same applicant subsequently obtains approval of an additional application or supplement that references those same clinical studies, technically the studies are no longer `new' for purposes of the second supplement and the change approved in the subsequent application or supplement is not eligible for its own exclusivity period. Under FDA's longstanding practice, however, if the studies are essential to the approval of the subsequent application or supplement, the subsequent application or supplement would be eligible for the balance of the previously awarded exclusivity period such that its 3-year exclusivity will end on the same date as that of the application or supplement that obtained the original exclusivity period."
- Plan B Exclusivity Memo
  - Study supporting OTC use for ages 15-16 also essential to later approval for age 14 and below
  - Memo cites other precedents

# 3-Year Exclusivity Summary

- ***Applies to ANDA generics but …***
  - Virtually always blocks ANDAs
  - For initial NDA approval, often too short to be relevant
  - For sNDA changes, usually can be carved out unless critical to general use of product
- ***Applies against competing 505(b)(2) products …***
  - That have the same active moiety
    - Even those who do not rely on the exclusivity-protected product
  - Same innovative "conditions of approval," notwithstanding other differences
    - Clinically meaningful and commensurate with scope of underlying studies
  - Can be very important in a "505(b)(2) horserace"
  - But also can be significantly narrowed at the last minute by FDA

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