The Chemistry of Patent and Regulatory Exclusivity for Drugs and Biologics in the U.S.

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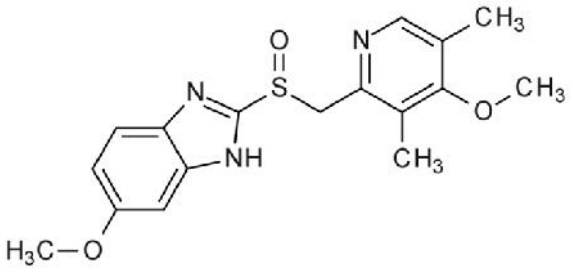
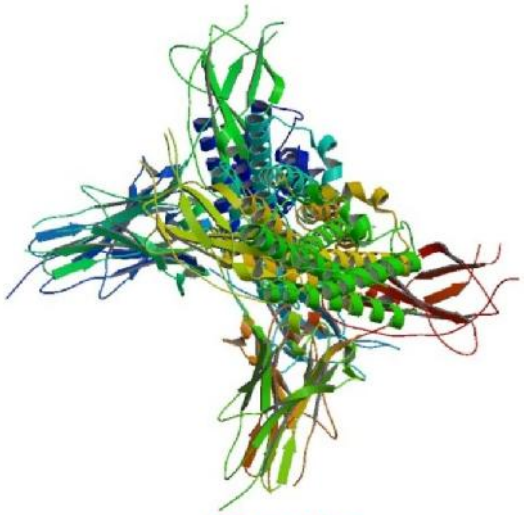
Outline

- Drugs v. Biologics
- Drugs- Patents, Exclusivity and The Orange Book
- Biologics- Patents, Exclusivity and The Purple Book
- Patent Term Extensions

Drugs v. Biologics

- Drug- a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body
  - Chemically synthesized
- Biologic- a virus, therapeutic serum, toxin, antitoxin, vaccine, blood or components, allergenic product, protein (except any chemically synthesized polypeptide), and applicable to the prevention, treatment, or cure of a disease or condition of human beings
  - Biologically synthesized
  - Certain “drugs” are being transition to biologics through 2020
- *every similarity, there is a difference*





Filgrastim
Molecular Formula: $C_{845}H_{1343}N_{223}O_{243}S_9$
Average mass: 18.8 Da
Chemical name: Filgrastim

For Every Similarity, There is a Difference

Drugs	Biologics
Innovator, generic, orphan and pediatric exclusivities	Same
505b2 / ANDA	aBLA
Orange Book patent listing; certification by generic	Confidential Exchange of information
Automatic 30 month stay	No automatic stay

Drug Patents, Exclusivity and the Orange Book

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Hatch Waxman Act

- Governs process of how a generic may obtain marketing approval on same drug as an innovator
- Innovators may receive marketing exclusivity and patent term extension
- Statutory exemption from patent infringement for acts reasonably related to seeking FDA approval
- Generic may obtain FDA approval by relying on safety and efficacy data of innovator
- Provisions for challenging the enforceability, validity, or infringement of drug patents
- May receive marketing exclusivity for generic

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Orange Book Listable Patents

- Applicant shall list any patent that claims the drug or a method of using the drug that is the subject of the application
  - Drug- drug substance (active ingredient), drug product (formulation and composition), polymorph, approved method of use
  - Not listable- packaging, intermediates, metabolites, methods of synthesizing
- Submit at time file NDA application, NDA approval or within 30 days of issuance of patent

- Drug label- fertile ground for extending exclusivity
- OB-ineligible patents may still be asserted against generic, but not until actual launch and no 30 month stay

Generic Drug Approval Process

- Generic- product that contains the same active ingredient of Innovator
  - same dosage form, route of administration, strength, quality, pharmacokinetics and use
  - FDA allows for standard, deviations in the non-active ingredients of a generic formulation
- Abbreviated New Drug Application (ANDA)
  - Demonstrate bioequivalency (rate and extent of absorption) to reference drug (Innovator)
  - Applicant relies upon FDA's earlier finding that the reference drug is safe and effective
- 505(b)(2) Application (Paper NDA)
  - Includes full pre-clinical and clinical data, but not all of which was developed by Applicant
    - published scientific data and/or reference drug data

Patent Certifications

- ANDA/505(b)2 Applicant must certify its position with respect to each patent listed in the Orange Book for the drug it seeks to market

- Paragraph I: no patent information
- Paragraph II: patent already expired
- Paragraph III: date the patent will expire
- Paragraph IV: patent is invalid or will not be infringed

  or
- Section viii Statement (skinny labeling/use codes)

Paragraph IV Certification

- Paragraph IV Certification
  - an act of infringement 35 U.S.C. § 271(e)(2)
- Notice to Patentee and NDA holder with detailed statement of why invalid or not infringed
- ANDA Generic entitled to 180 days of exclusivity
  - subject to certain limitations/requirements
- If Patentee takes no action within 45 days of receipt, application may be approved

Paragraph IV Certification

- If Patentee commences an infringement suit within 45 days of receipt, automatic stay of FDA approval for longer of (i) 30 months or (ii) 7 ½ years from NCE NDA approval
  - unless court decision prior to 30 months that extends or shortens stay
  - usually, only one 30 month stay per ANDA/505(b)2 App
    - no “late listing” for additional 30 month stays
  - Patentee can obtain preliminary injunction after automatic stay
- If litigation still on-going after stay, generic may launch “at risk”
  - damages- lost profits, treble damages, attorney fees, price erosion

U.S. Exclusivity for Drugs

- New Chemical Entity (NCE) Exclusivity- encourage development of drugs with new actives
- Clinical Investigation Exclusivity- encourage development of drugs for new indications etc.
- *Orphan Drug Exclusivity- encourage development of drugs for rare diseases*
- *Pediatric Exclusivity- encourage development of information related to use of drug in pediatric population*
- QIDP Exclusivity- encourage development of drugs to treat serious or life threatening infectious diseases

NCE Exclusivity

- Any drug with an active moiety that has not been previously approved by FDA in a NDA
  - active moiety- molecule or ion responsible for the drug's physiological or pharmacological action (not salt or ester)
  - special qualifiers: fixed dose combos, enantiomers, non-ester prodrug, poorly characterized mixtures
- For 5 years, FDA may not *review or approve* an ANDA or 505(b)2 for same active moiety (regardless of indication)
  - 30 months average ANDA approval time
- However, if there is an OB Listed patent, ANDA/505(b)(2) *may* be submitted with Para IV Cert at year 4
  - Recall: If Innovator asserts OB Listed patent within 45 days of Para IV Cert, approval of ANDA/505(b)(2) stayed until 30 months from cert or 7 ½ years from NDA approval (if brought in Y4) 21 CFR 314.07(b)(3)(i)(A) and (B)
- While unlikely, NDA may be reviewed and approved by FDA during this time

Clinical Investigation Exclusivity

- Any drug that has been previously approved by FDA, but the application contains a new clinical investigation that was necessary for approval
  - e.g., new indication, dosage form, script to OTC
  - NDA or supplemental NDA
  - no bioavailability study
- For 3 years, FDA may not *approve* an ANDA or 505(b)2 application for same active moiety containing the new clinical investigation
  - FDA can review during this time
- ANDA/505(b)(2) may be submitted at any time
- If Innovator asserts OB listed patent within 45 days of Para IV Cert, approval of 505(b)2/ANDA stayed 30 months from cert (non-NCE)
  - Can run concurrently with 3 year CI Exclusivity
  - 30 months average ANDA approval time in 2012

Orphan Drug Exclusivity

- Any drug intended to treat a disease that affects less than 200K U.S. citizens ("medically plausible" subset)
- For 7 years, FDA may not *approve* a NDA, ANDA or 505(B)2 application for same active moiety for the same indication
  - FDA can review during this time
- However, FDA can review and approve if "clinical superiority"
  - third party product is safe, more effective or MCPC
  - only after any applicable NCE exclusivity expired
- FDA can review and approve same active moiety for different indication
  - Could be used off-label for the Orphan disease

Pediatric Exclusivity

- If Applicant conducts a study in pediatric population as requested by FDA through a formal Written Request

- *6 month add-on* to any *existing* marketing and Orange Book listed patent exclusivity
  - the study itself may entitle it to CI exclusivity
  - attaches to all of the applicant's products containing the active moiety (all dosage forms, all indications)
  - attaches to the END of exclusivity

QIDP Exclusivity (antibiotics and antifungals)

- Any drug that is designated as a qualified infectious disease product when application filed
  - e.g. resistant gram positive pathogens, multi-drug resistant gram negative bacteria (Pseudomonas), multi-drug resistant tuberculosis, C diff
  - once a drug is designated as a QIDP, can't revoke

- The 5 year exclusivity of NCE, the 3 year exclusivity of CI or the 7 year exclusivity for OD is *extended an additional 5 years*

- Fast-track review and approval

Biologic Patents, Exclusivity and the Purple Book

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Biologics Price Competition and Innovation Act

- Created a biologics data exclusivity for new biologic products
- Created an abbreviated approval pathway for biosimilars
  - Biosimilar- highly similar, with no clinically meaningful differences from the reference product in terms of safety, purity or potency (safety & effectiveness)
  - Interchangeable- expected to product the same clinical result as the reference product in any given patient; substitutable without MD intervention
- *Optional* patent dance
  - Earlier resolution of any patent disputes vis-à-vis biosimilar market entry
- 11 biosimilars approved to date
  - none designated as interchangeable

Biosimilars Approval Process

- Abbreviated Biologics License Application (aBLA)
  - Demonstrate it is highly similar via analytical studies, animal studies and at least one clinical study (tox, PK / PD, immunogenicity)
  - Utilize the same MOA (if known)
  - Same route of administration, dosage form and strength
  - Applicant relies upon FDA's earlier finding that the reference biologic product is safe and effective

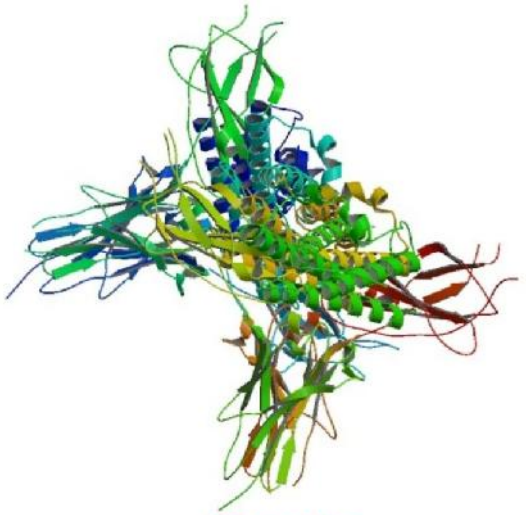
Optional Patent Dance

- Upon filing of an aBLA, the aBLA applicant may elect to resolve any potential patent infringement via the “Patent Dance”

- Exchange of detailed, confidential information between the reference product manufacturer and the aBLA applicant regarding potentially applicable patents and copy of aBLA application
  - Exchange of information includes in-house and outside counsel NOT involved in patent prosecution matters

Biologic Patent Claims

- Because of the non-identical nature of biosimilars, patent portfolio should focus on product and obvious variations and design arounds
- Label is still important
- Where to look
  - Development Stage
    - compound, uses, dosage forms
  - Clinical Stage
    - new dosage formulations, combos, interactions, PK
  - Post-approval Stage
    - line extensions, new uses, improved formulations, improved synthesis



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U.S. Exclusivity for Biologics

- Reference Biologic Product Exclusivity- encourage development of new biologic products
- Orphan Drug Exclusivity- encourage development of biologics for rare diseases
- Pediatric Exclusivity- encourage development of information related to use of a biologic in pediatric population
- Interchangeable Biosimilar- encourage development of interchangeable biologic products

Biologics Reference Product Exclusivity

- Approval of a biosimilar or interchangeable biologic product may not be made until 12 years after the date on which the reference biologic product was *first licensed*
  - aBLA may be filed after 4 years

- Only first licensures are eligible
  - Does not apply to supplemental BLA
  - Subsequent BLA by same sponsor that is merely for a change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system/device or strength, UNLESS it is a modification to the structure of the biological product that changes its safety purity or potency

Orphan Biologic Exclusivity

- Any biologic intended to treat a disease that affects less than 200K U.S. citizens ("medically plausible" subset)
- For 7 years, FDA may not *approve* a BLA or aBLA for same *principal molecular structural features* for the same indication
  - FDA can review during this time
  - Guidances to help define what is the same principal molecular structural features
    - E.g., protein- minor differences in AA sequence or post-translational events
- However, FDA can review and approve if "clinical superiority"
  - third party product is safe, more effective or MCPC
  - only after any applicable biologic reference product exclusivity expired
- FDA can review and approve same principal molecular structural features for different indication
  - Could be used off-label for the Orphan disease

Pediatric Biologic Exclusivity

- If Applicant conducts a study in pediatric population as requested by FDA through a formal Written Request

- *6 month add-on* to any *existing* marketing exclusivity
  - attaches to the END of exclusivity
  - No 6 month extension on patents

Patent Term Extension for Drugs and Biologics

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Patent Term Extension- General

- PTE only available for a patent that has been issued during clinical development and/or regulatory review period for the first approved commercial use of a drug, biologic or medical device product. 35 U.S.C. § 156
  - patent claims product, method of using a product or method of manufacturing a product
  - term of patent not expired before PTE application submitted
  - term of patent not previously extended
  - first permitted commercial marketing or use of product under which regulatory review period occurred
  - must submit application within 60 days of FDA approval
- Extension = ½ clinical development time + NDA/BLA/PMA review/approval time
  - Max extension is 5 years; and 14 years total patent term from FDA approval

Products Eligible for PTE

- Patent claims a product, method of using a product, or method of manufacturing a product
- Application submitted by the owner of the patent or its agent
  - patent owner or agent must be the holder of regulatory approval
  - the marketing applicant must serve as the patent owner's agent if it applies for a PTE
- PTEs are granted only for "the first permitted commercial marketing or use of the **product**"
  - the "product" is the active ingredient, including or any salt or ester of the active ingredient
    - *e.g.*, if a salt has been previously approved, a patent on its **acid** is not eligible for PTE (same product);
    - if an acid has been previously approved, a patent on its **salt or ester** is eligible for PTE (different products);
    - *and* if only the salt of an acid has been previously approved, an **ester of the same acid** is eligible for PTE (different products)
  - combination product where both components were previously approved is not eligible (*e.g.*, hydrocodone/ibuprofen combination not eligible); combination where only one component was previously approved is eligible, but only as to patent on previously unapproved component
- Class III medical devices are eligible (devices receiving review under FDCA section 515); Class I and II devices are not.

Rights Derived from PTE

- Term of the entire patent is extended, not just the individual claims
- But only as to the FDA-approved uses, not other commercial uses
- Extension applies to any new salt or ester of the acid, but not vice-versa (if patent otherwise encompasses the same)

Calculating the Regulatory Review Period

- Extended patent term will be the shortest of:
  - RRP – PGRRP – DD – ½(TP-PGTP);
    - RRP = regulatory review period
      - If multiple INDs filed, begins on the date of first exemption of the approved product (even if different indication)
    - PGRRP = pre-grant regulatory review
    - DD = time during which applicant did not act with due diligence
    - TP = regulatory review period which is testing phase
    - PGTP = pre-grant testing phase
  - 14 years of total exclusivity; or
  - 5 years from end of patent term under 35 U.S.C. § 154.

Case Study: Ampyra® (dalfampridine)

Ampyra (dalfampridine) 10 mg extended release tablet for oral administration, twice daily, to improve walking in patients with multiple sclerosis

- NDA Approved 1/22/2010
- NCE- 1/22/2015
- Orphan Drug- 1/22/2017
- 4 Orange Book listed patents (2024-2027)
  - 1 with PTE
  - Generic entry after OB listed patents found invalid in 2018

Case Study: Rhofade® (oxymetazoline)

Rhofade (oxymetazoline)1% cream for topical administration once daily for the treatment of persistent facial erythema associated with rosacea in adults

- NDA Approved 1/18/2017
- CI- 1/18/2020
- 5 Orange Book listed patents (2024-2031)
  - no PTE

Case Study: Eskata® (hydrogen peroxide)

Eskata (hydrogen peroxide) 40% topical solution for the treatment of seborrheic keratoses that are raised

- NDA Approved 12/14/2017
- CI- 12/14/2020
  - NCE reconsideration request pending before FDA exclusivity board
- 4 Orange Book listed patents (2022-2035)
  - PTE application pending

Case Study: Solosec® (secnidazole)

- Solosec (secnidazole) 2 g granules for oral administration for the treatment of bacterial vaginosis in adult women

- NDA approved 9/15/2017
- NCE + GAIN- 9/15/2027
- Currently, no Orange Book listed patents

The Chemistry and Take Homes

- Patents play a critical role in the life cycle of a therapeutic
- “Secondary” patents can provide equally important protection against generic/biosimilar entry as composition of matter
- Patent exclusivity is only as strong as its validity and scope; regulatory exclusivity is more of a certainty
- While Hatch-Waxman and the Biologics Price Competition Acts were meant to strike a balance
  - Push by FDA to approve more generics / biosimilars
- U.S. less aggressive statutory protection for innovative drugs
- Life cycle management occurs much earlier
  - introduce improvement prior to generic/biosimilar entry to keep market share

What's the take home?

- While Hatch-Waxman and the Biologics Price Competition Acts were meant to strike a balance
  - Significant push by FDA to approve more generics and more biosimilars
- Compare U.S. to other countries, less aggressive statutory protection for innovative drugs results in a dearth of new drugs
  - consider extended either regulatory exclusivity or PTE
- Life cycle management occurs much earlier
  - introduce improvement prior to generic/biosimilar entry to keep market share

Questions & Answers

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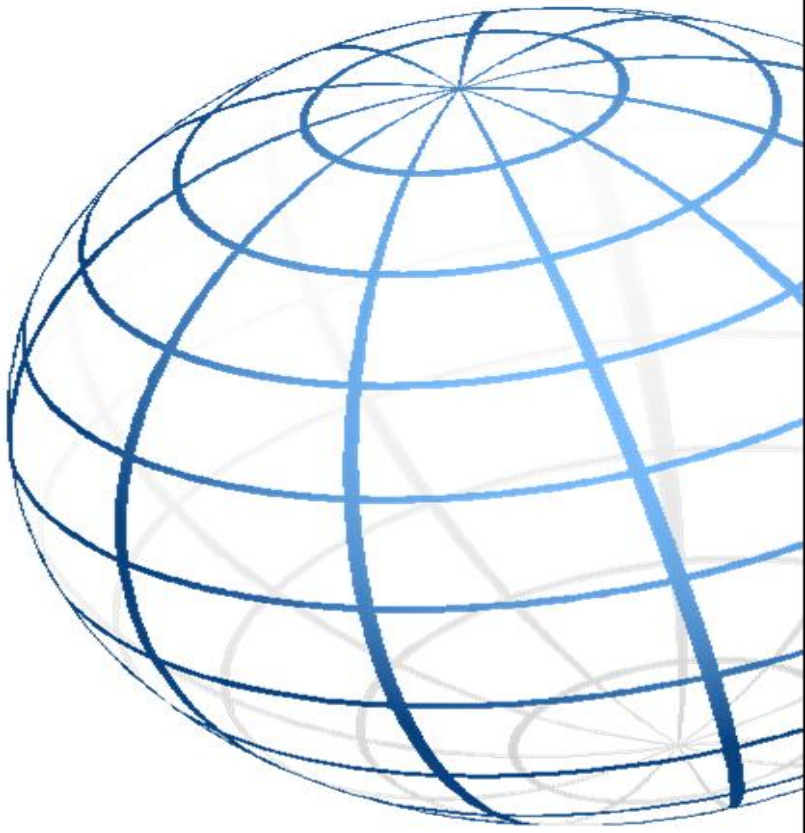

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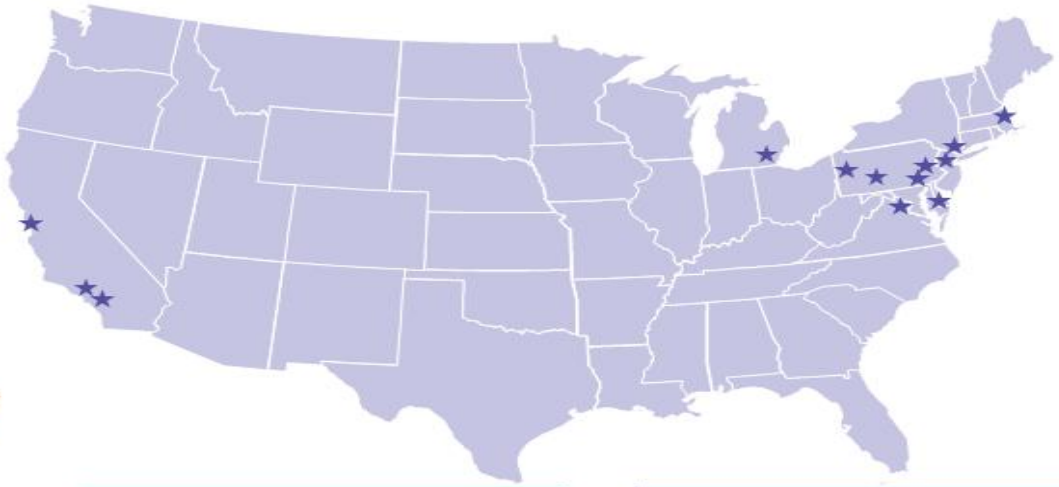

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