

# Challenges to Innovation in Developing Drugs & Biologics

Time, Scope of Exclusivity, & Properly Identifying Competitors

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# Time - Adequate for an Return of Investment (“ROI”)?

- ▶ An ROI of at least **10** years is preferred
- ▶ Patents naturally expire **20 years** from filing
  - ▶ Drugs & Biologics often take 12+ years to get to market
  - ▶ Diligence at PTO may add term (Patent Term Adjustment - “**PTA**”)
  - ▶ Diligence in Clinic can add term (Patent Term Extension - “**PTE**”)
    - ▶ PTE requires diligence, issued patent, & IND being filed
- ▶ Patent term **starts upon filing** of a non-provisional application
  - ▶ If can delay filing can extend term so monitor third parties & control publication - some secret activity (e.g. sales) can set bar dates
- ▶ Regulatory Exclusivity starts upon product approval
  - ▶ New Chemical Entity (**NCE**) - 5 years and potential 30 month injunction - 7.5 years
  - ▶ Clinical Investigation (**CI**) - 3 years and injunction
  - ▶ Orphan Drug Exclusivity (**ODE**) - 7 years
  - ▶ Biologics (**BLA**) - 12 years but scope of exclusivity can be an issue

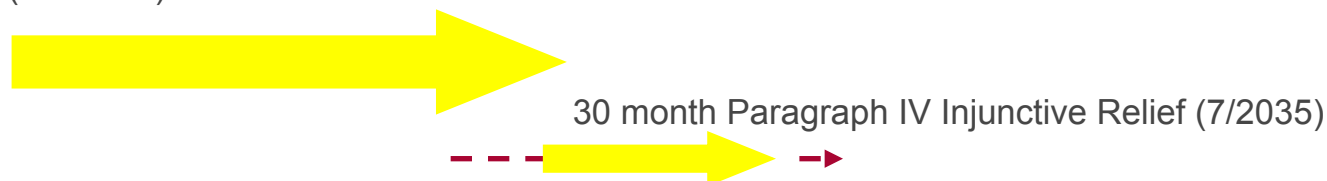
# Scope of Exclusivity - Is it sufficient to block?

- ▶ Do not be enamored by any one form of protection - consider “Matryoshka” model - layers or concentric circles
- ▶ Patent **Claims** define metes and bounds - they are a right to exclude - not a license to do anything
- ▶ **New Chemical Entity** status - prevents an abbreviated pathway for bio equivalent - does not prevent someone from spending resources required to go through unabbreviated pathway - NDA
- ▶ **Orphan Drug Exclusivity** - prevents approval for same indication, abbreviated or unabbreviated pathway, unless a “clinically superior” product comes along
- ▶ **Clinical Investigation** - Largely co-extensive with clinical work conducted but scope is now in flux
- ▶ Explore other exclusivities - **Pediatric** (+6 months); **QIDP** (+5 yrs)
- ▶ Consider **other forms** of exclusivity - sole source, economic advantage, manufacturing secrets

# U.S. Exclusivity Timeline - Patent Term

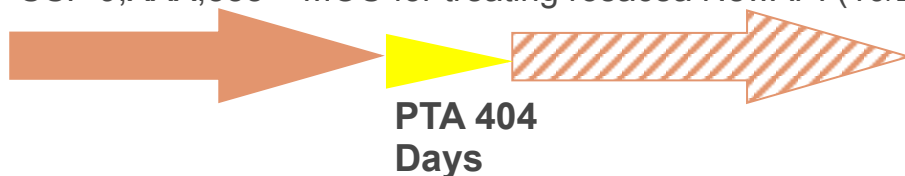
## Regulatory Exclusivity

New Chemical Entity (NCE) Exclusivity prevents filing of any ANDA/505(b)(2) for same active moiety for 5 years (~ 1/2033)



## Patent Exclusivity

USP 9,XXX,888 – MOU for treating rosacea NewAPI (10/2031) Potential PTE ~ 4 years (10/2035)



Base Assumptions:

**ENJOY FULL 7.5 YRS OF NCE**

IND filed 2021

NDA approved 2028

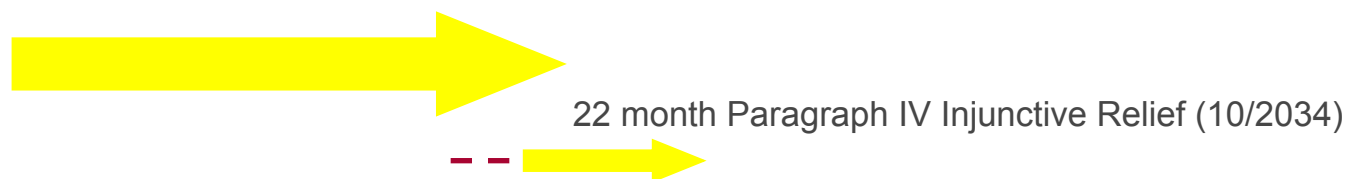
If IND filed and Patent Issued 1/2 days in clinic and day for day in front of FDA



# Late IND (Lose 8 months of Exclusivity)

## Regulatory Exclusivity

New Chemical Entity (NCE) Exclusivity prevents ANDA/505(b)(2) for same active moiety - 5 years (~ 1/2033)



## Patent Exclusivity

USP 9,XXX,888 – MOU for treating rosacea NewAPI (10/2031) Potential PTE ~ 3 years (10/2034)



Base Assumptions:

**Is 6yrs 10 months enough?**

IND filed 2023

NDA approved 2028

If IND filed and Patent Issued 1/2 days in clinic and day for day in front of FDA



# Late NDA - Lose 8 months (& 2 years later launch)

## Regulatory Exclusivity

New Chemical Entity (NCE) Exclusivity prevents any ANDA/505(b)(2) for same active moiety 5 years (~ 1/2035)



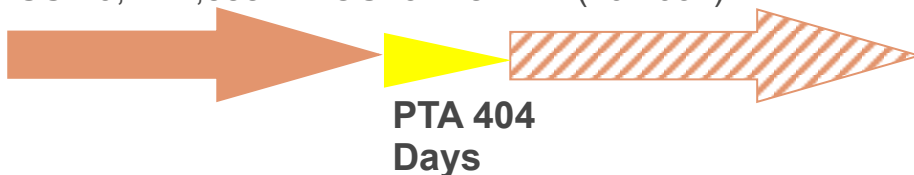
22 month Paragraph IV Injunctive Relief (10/2036)



## Patent Exclusivity

USP 9,XXX,888 – MOU for NewAPI (10/2031)

Potential PTE ~ 5 years (10/2036)



## Base Assumptions:

IND filed 2021

NDA approved 2030

IND filed & Patent Issued 1/2 days in clinic and day for day in front of FDA



# Similar Patent Claims Different Results - New API

- ▶ 1) A composition **comprising** a New API
- ▶ 2) A composition **consisting essentially** of a New API
- ▶ 2) A composition **consisting** of a New API
- ▶ 3) A method of **preventing** rosacea by administering an effective amount of a New API
- ▶ 4) A method of treating rosacea by administering an effective amount of a New API **topically**
- ▶ 5) A method of treating rosacea by administering an effective amount of a **beta-2 agonist**, wherein the beta-2 agonist is a New API. - **Questionable Value**
- ▶ 6) A method of **manufacturing** a topical dosage form of an effective amount of a New API - **Not Orange Book Eligible**

# Consider your Competition's Burden

- ▶ Less concerned about Multiple Innovators racing to “cure” an indication
  - ▶ Later approved innovator has to consider timing of first innovator becoming generic
- ▶ The first layer of competition are Generics - Hatch Waxman or Drug Price Competition and Patent Term Restoration Act
  - ▶ Abbreviated New Drug Application (“ANDA”) - 505(j) provides Mechanism whereby bio equivalent generic is approved solely in the manner that Innovator is approved
- ▶ Bio-equivalence requirements for topicals different than systemic exposure - often rely on FDA Guidance Documents
- ▶ 505b(2) - Rely on data of Innovator or others for abbreviated pathway - involves cost that generics generally avoid
- ▶ Compounding Pharmacies -
  - ▶ Telemedicine and 503A Pharmacies are interesting
  - ▶ Bulk (503B) Pharmacies are limited to APIs approved for bulk compounding by the FDA (and are subject to FDA jurisdiction)



# Troutman Pepper Hamilton & Sanders

“Troutman Pepper”

AmLaw 50

National Presence

1100+ lawyers

# Background - Drug Patents and the Orange Book

# 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
- ▶ Incentive of receiving marketing exclusivity for generic

**PROZAC**<sup>®</sup>  
fluoxetine hydrochloride



# Orange Book Listable Patents



APPROVED DRUG PRODUCTS  
With Therapeutic Equivalence Evaluations



The "Orange Book"

- 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 is a fertile ground for extending exclusivity
  - OB-ineligible patents may still be asserted against generic, but not until actual launch and no automatic 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 bio-equivalency (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



# Types of Regulatory Exclusivities available in the United States

# 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

# Patent Term Extension

# 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 =  $\frac{1}{2}$  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:
  - $RRP - PGRRP - DD - \frac{1}{2}(TP - PGTP)$ ;
    - 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.

# Pharmacy Compounding – An emerging concern for Specialty Pharmaceuticals and Dermatology Products

# Why Care about Pharmacy Compounding Now?

- ▶ Competitive concerns raised by Innovators, VCs and investors
  - Annual Growth Rate of ~ 9%; expected to reach \$14–20B by 2020, ~2% of pharmaceutical market
  - Diverting clinical trial candidates
  - Adverse events- reporting, impact on reputation
  - Impact on innovator exclusivity
  - Impact on innovator pricing, consumer expectations
- ▶ Emergence of telemedicine, personalized medicine and integrated care
- ▶ Creation of new 503B Outsourcing Facilities
  - 503A- traditional compounding pharmacies
  - 503B- outsourcing facilities-quasi-drug manufacturers
- ▶ Compounded drugs are not FDA-approved drug products
  - no evaluation of the safety, efficacy or quality

# 503A and 503B- Key Parameters

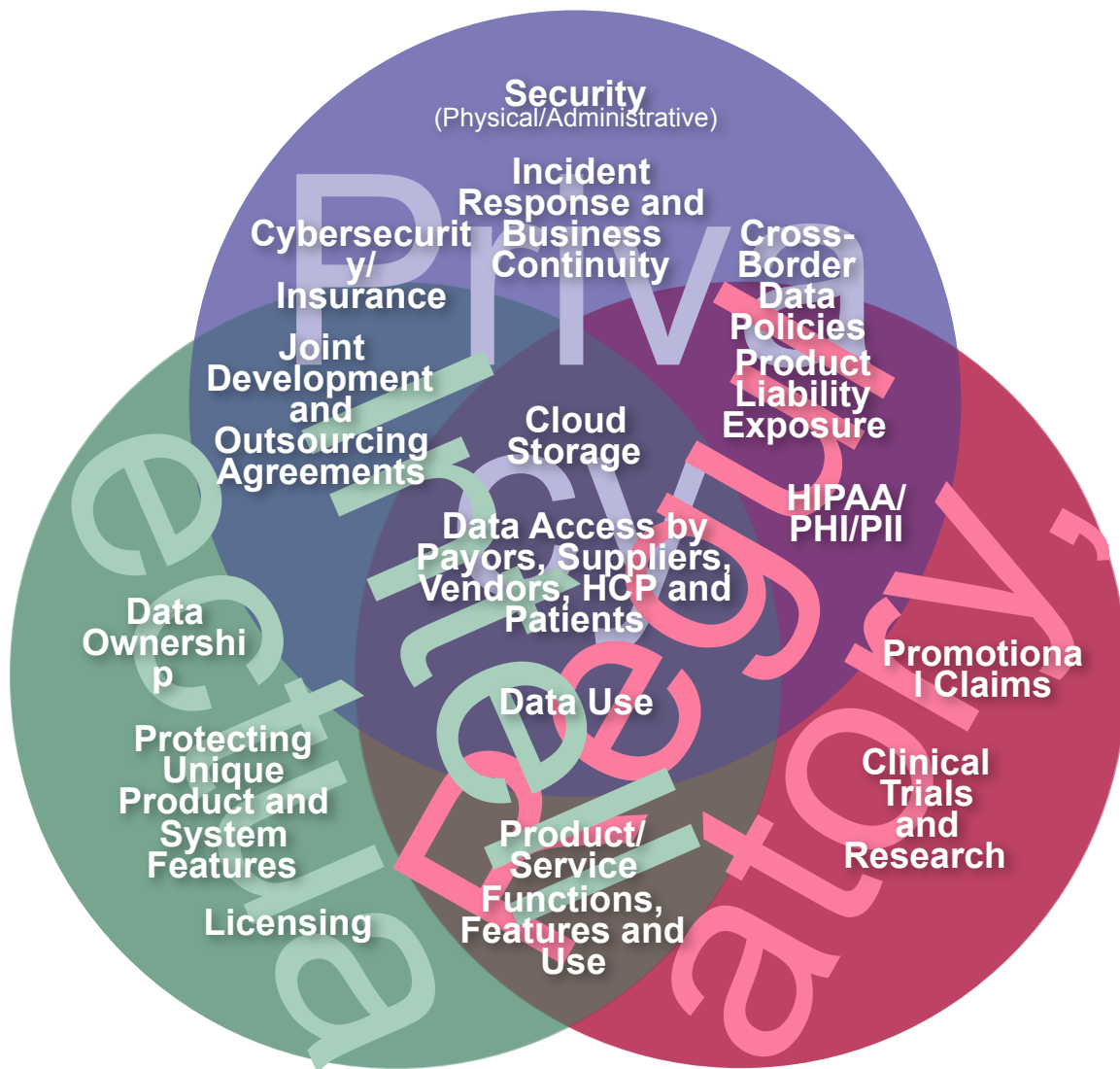
	503A	503B
Types of compounders	Licensed pharmacist or physician	Licensed pharmacist (or direct supervision)
Location of compounding	Pharmacy or federal facility	Outsourcing Facility
Prescription	Valid script for patient required, indicating necessary for patient (or in limited quantities, based upon history)	No script required, unless dispense directly to patient
Bulk Drug Substances	<ul style="list-style-type: none"><li>• Complies with USP compounding chapter</li><li>• If USP/NF monograph, complies; if not, is component of FDA approved drug; if not, on FDA 503A Bulk List</li><li>• Manufactured by registered establishment with CoA</li></ul>	<ul style="list-style-type: none"><li>• On FDA 503B Bulk List or Shortage List</li><li>• If USP/NF monograph, complies</li><li>• </li><li>• </li><li>• Manufactured by registered establishment with CoA</li></ul>

# 503A and 503B- Key Parameters

	503A	503B
Essentially Copies	Not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug product	Drug is not essentially a copy of one or more approved drugs -if OTC monograph drug, shortage is not an exception
Interstate Distribution	Limited to 5% or less of the total scripts dispensed by such pharmacy, unless state has MOU with FDA	No limits
Other	Not Applicable	<ul style="list-style-type: none"> <li>CGMP, federal registration, reporting, AE reporting, labeling</li> </ul>
Exempt from	<ul style="list-style-type: none"> <li>502(f)(1) labeling with adequate directions for use</li> <li>505 NDA requirements</li> <li>501(a)(2)(B)- cGMP</li> </ul>	<ul style="list-style-type: none"> <li>502(f)(1) labeling with adequate directions for use</li> <li>505 NDA requirements</li> <li>582 drug supply chain security</li> </ul>

# Integrated Healthcare Requires Integrated Counseling

- ▶ Pepper has created an interdisciplinary team of practitioners to address this important emerging issue
- ▶ What tools are available to address concerns?





# Implications for Innovators

- ▶ Patent exclusivity
  - Composition of Matter v. Method of Use v. Formulation
    - Manufacturers of bulk drug substance
    - 503B Outsourcing Facilities (FDA publishes annual list)
    - 503A State Licensed Pharmacies
  - For MOU- identify documentary evidence to establish intent required to establish induced infringement
    - Prior Authorization submitted to insurance company (503A) or communications between “prescriber” and OF when ordering (503B) or Directions for Use (503B)
- ▶ Inform patients, prescribers, insurance companies, pharmacies and outsourcing facilities
  - Lack of insurance reimbursement for compounded products; insurance fraud
  - Potential medical malpractice claims for off-label use
  - Potential safety and efficacy concerns/inferiority

# Implications for Innovators

- ▶ Reporting to FDA or State Boards of Pharmacy
  - Report compounding non-compliance to FDA or State Boards
    - 503A- 5% interstate distribution limitation, *source* of bulk drug substance, advance compounding, “need” for compounded drug not identified on scripts
    - 503B- not cGMP, reporting, registration, labeling requirements, *source* of bulk drug substance
  - Report adulteration or misbranding to FDA
  - Report breach of exclusivity to FDA
    - If awarded NCE, CI or Orphan Drug exclusivity, report breach of exclusivity to FDA
    - Consider enforcement action against FDA for failure to enforce exclusivity provisions.

# Changes in case law and government regulations impacting pharmaceutical development

# Capabilities

## Best Lawyers

More than 70 lawyers listed, including 5 as Lawyer of the Year

## 100+

lawyers highly rated by **Super Lawyers** and **Rising Stars**

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PHARMACEUTICAL AND MEDICAL DEVICE  
RETAIL  
TECHNOLOGY  
TRANSPORTATION