Overview of Administrative Law, Drug and Medical Device Regulation

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Reminders

• Updated syllabus online:

New Readings

• October 28th, Science-Based Regulation
  [Image]

Online Resources

• For the Opioids sessions, videos are available from the HarvardX MOOC, “The Opioid Crisis in America,” http://bit.ly/OpioidX.

Debates

• Debate 1: Prescription Drug User Fees (September 11, 2019)
• Debate 2: Off-Label Promotion (September 23, 2019)
• Debate 3: OTC Naloxone (October 16, 2019)
• Debate 4: Should the FDA be independent? (October 28, 2019)

• All students should come to class prepared to debate if called upon

DEADLINE CHANGE!

• E-mail me a 3-4 sentence description of your final paper topic by the end of the day on Friday, September 6th. I will reply promptly with feedback.
  • Don’t begin flushing out the proposal until you get the go-ahead on the topic.
  • Describe legal arguments and policy solutions. Focus on how your proposal differs from existing published work.

• Deadline for paper proposal will now be September 16th.

• TWO SAMPLE PAPER PROPOSALS ARE NOW UP ON THE SYLLABUS PAGE
Public Comment Brief


• Consult relevant legal, regulatory, and public health material to educate yourself about the context and implications for the proposed action.

• A structured “public comment” brief (5-6 pages) will be due before the start of class on Wednesday, October 2, 2019.
**Current Events in Drug Law**

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**#NUSLD璟DrugLaw on Twitter**

- Be sure to tag the following in your tweets: @DrSinhaEsq #NUSLD璟DrugLaw
- Need help getting started on Twitter? Schedule time during office hours!

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**Patents vs. Exclusivity**

Patent granted by USPTO, with a range of requirements and benefits
- can be granted and can expire anywhere along the course of the drug development process
- must be submitted with all new drug applications (NDA)

Exclusivity granted by FDA upon approval based on its regulatory jurisdiction
- Orphan Drug (ODE) - 7 years
- New Chemical (NCE)- 5 years
- "Other" Exclusivity - 3 years for a "change"
- Pediatric Exclusivity (PED) - 6 months added

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**Requirements for Patentability**

- Patentable subject matter: (35 U.S.C. § 101)
- Utility: usefulness (35 U.S.C. § 101)
- Novelty: not anticipated in "prior art" (35 U.S.C. § 102)
- Non-obviousness: non-trivial extension of the known (35 U.S.C. § 103)
- Disclosure and enablement: must describe invention with sufficient particularity to enable one skilled in the art to "practice" it (35 U.S.C. § 112)

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**Patents vs. Trademarks**

- Patents
  - Four conditions for patentability (really, five)
  - 20-year exclusivity
  - Not affected by "lawful use in commerce" rule
- Trademarks
  - Word, name, symbol, or device, or any combination thereof
  - Identifies and distinguishes a maker’s goods from those manufactured or sold by others.
  - Subject to “lawful use in commerce” rule
Key Domestic Legislation/Case Law

1836: Patent Office, patent bar created
1861: Extension 14 to 17 years
1983: Boyh-Doyle Amendment changes ownership of federally-funded inventions
1984: Hatch-Waxman Amendments extend patent protection for FDA-approved products
1995: Extension 17 to 20 years
2011: Leahy-Smith America Invents Act: “first to file” framework

- Diamond vs. Chakrabarty (1982)
- Myriad Genetics (2013)

The Market Exclusivity Floor: Regulatory Exclusivity

Traditional (Hatch-Waxman) Drug
- 5-year baseline
- 6-7 years

Orphan Drug
- 7-year baseline
- 8-9 years

Antibiotic Drug
- 10-year baseline
- 11-12 years

Biologics
- 12-year baseline
- 13-14 years

New formulation of existing drug
- 3-year baseline
- 4-5 years

Patent Term Restoration

- Pharmaceutical manufacturers petition the government to extend the term of one key patent by one-half the time from the initiation of clinical trials to the filing of the new drug application (NDA), plus the full time the FDA took to review the NDA.

- Patent term restoration is capped at 5 years and the resulting patent term cannot extend more than 14 years after the date of the drug’s FDA approval for the basic patent.

Patent Term Restoration

- For the top 170 drugs (by sales) in the US, 2000-2012:
  - 83% received PTR (49%)
  - Nearly all (93%) pertained to active ingredient patents
  - Median PTR duration was 2.75 years (interquartile range 1.5 – 4.0 years)
  - Majority of PTR periods reach the maximum allowed (70% reached the 14-year limit, 30% reached the 5-year limit)
  - Median time to generic entry among these drugs: 13.75 years
    - This means that approximately HALF had market exclusivity longer than the 14-year threshold
Unapproved Drugs Initiative

• Hundreds of drugs developed before the FDA was established were “grandfathered” onto the market, meaning they never received approval from the FDA.

• The 2006 Unapproved Drugs Initiative (UDI) required manufacturers to remove these drug products from the market or to obtain FDA approval by demonstrating evidence of safety and efficacy.

• Once the FDA acts against an unapproved drug, fewer manufacturers remain in the market, potentially enabling drug price increases and greater susceptibility to drug shortages.
Unapproved Drugs Initiative

- Systematic review of all prescription drugs targeted by the UDI between 2006 and 2015 showed that the price of these drugs increased by a median of 37% after UDI regulatory action or approval.
- The number of drugs in shortage increased from 17 (50%) to 25 (74%) during the 2 years before and after UDI regulatory action or approval, and the median shortage duration increased from 31 days to 217 days.
- Nearly 90% of previously unapproved drugs with a drug product that received FDA approval through the UDI were supported by literature reviews or bioequivalence studies, not new clinical trial evidence.

The Pediatric Knowledge Gap

Historically, drugs have been used in children WITHOUT the same level of evidence as in adults.

Study of drugs in children was discouraged:
- Children cannot volunteer or give consent (though they can assent)
- Fear of harm to healthy children enrolled in studies
- Increased liability (?)
- Why bother? Children are just little adults!

Inherent difficulties in conducting pediatric trials
- Limited populations for certain conditions
- Lack of infrastructure and technical expertise
- Logistical challenges: whole family involved in coordinating care
- Many age groups to study
  - Common ranges: 0-30 days, 1-24 mo, 2-5 years, 6-11 years, 12-17 yrs

Importantly:
- Lack of regulation/legislation to incentivize or require drug companies to conduct pediatric trials

Impact of Pediatric Knowledge Gap

- Many children did not have access to potentially lifesaving or otherwise beneficial therapeutics
- Some children received therapeutics (off-label, with limited or no pediatric evidence) with occasionally disastrous results:
  - **Elixir sulfanilamide** — liquid formulation of antibiotic (diethylene glycol, a sweet-tasting compound, was added to mask the drug's bitter taste)
    - Diethylene glycol is a toxic agent (similar to ethylene glycol, or antifreeze)
    - Over 100 people died in 1937, including many children
  - **Chloramphenicol** — widely used in adults in the 1950s to treat infections resistant to penicillin
    - Many newborns died after receiving the drug (immature livers can't break down the drug)

Pediatric Exclusivity

- 6-month exclusivity extension for branded drugs
- Sponsors may submit a proposed pediatric study request, but FDA must issue a formal Written Request to qualify for the extension
- 6-month exclusivity is awarded regardless of study outcome

Importantly:
- Pediatric studies are conducted for a particular formulation and a particular indication for the drug
- BUT 6-month extension attaches to BOTH patent and non-patent exclusivity for ALL protected indications and formulations of the sponsor’s drug

Over a 20-year period:
- $13.9 billion in additional expenditures
- $29.6 billion to innovator drug firms in sales revenues
- $10.7 billion in lost generic sales
- $4.9 billion in lost retail pharmacy sales

As of April 2017:
- 938 Proposed Pediatric Study Requests (PPSRs) received from manufacturers
- 508 pediatric Written Requests (WRs) issued
- 428 WRs with PPSRs
- 80 WRs without PPSRs

As of March 2017:
- 221 total pediatric exclusivity grants

Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

- Over 600 products now contain pediatric information on the label (~1/3 BPCA, ~2/3 PREA)
- Sponsors subject to PREA mandates can request pediatric exclusivity
- Increased workload for FDA review
- NIH Pediatric Trials Network (Duke)
- Goal: issue Written Requests earlier in development

Pediatric Exclusivity

Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012

Michael S. Srinu, MD, JD, MPH; Mendel N. Szollosi, PhD; Elisabeth A. Rajasingh, BA; James Lowe, MA, MPH; Aaron S. Kesselheim, MD, JD, MPH
Data Sources

Pediatric Clinical Trial Data
- 54 pediatric exclusivities granted (September 27, 2007 – December 31, 2012, duration of FDAAA)
- 48 had accessible revenue data in the relevant time period
- FDA Medical Review documents
- FDA pediatric Written Request letters
- 9/48 drugs had not lost market exclusivity as of December 31, 2017

Drug Revenue Data
- Corporate annual reports, including filings with the US Securities and Exchange Commission (SEC)
- Press releases from generic manufacturers entering the market, which often provided IMS Health revenue data
- For drugs with unexpired patents, used 2016 revenue as a proxy

Pivotal Clinical Trial Costs

Trial Costs (2017$):
- $4.9 billion for 54 drugs
- Median $16.4 million [IQR $16.6m - $100.6m]
- 8 drugs <$10 million
- 30 drugs >$25 million

Pivotal Efficacy Trial Cost:
- $19.0 million (IQR $12.2 to $33.1 million)

Mylan Receives Final Approval for First-to-File Generic Version of Antiepileptic Keppra® and Launches Immediately

Drug Revenue Data

Total 6-month gross revenues (48 drugs): $29.0 billion

- $29.6 billion in sales revenues

5-year period (2007-2012):
- $29.0 billion in sales revenues

Equations:
\[ R_{2017} = R \times (1 + \beta)^{17} \]
\[ AR = R_{2017} \times GMS \times (1 - GP) \]
\[ CT = \frac{\text{No. of patients phase 1 \times phase 1 per-patient estimate \times (1 - \text{phase 1 deflator})}}{\text{No. of patients phase 2 \times phase 2 per-patient estimate \times (1 - \text{phase 2 deflator})}} \]
\[ C_{2017} = CT \times (1 + \gamma)^{17} \]
\[ C = C_{2017} \times (1 + C) \times (1 + CQ)^{14} \]
NR = (AR-CI): $176.0 million [IQR $47.0m - $404.1m]
NR/CI: 680% [IQR 80% - 1270%]

Federal funding of trials?
- Median trial cost: $36.4 million
- Pediatric exclusivity produced $29.0 billion additional gross revenues for 48 drugs (~40% government-funded)
- For that amount, could have studied ~800 drugs in pediatric populations
- In comparison, one study found that FDA (or predecessor agency) approved 1453 drugs from 1827-2013

Pediatric Exclusivity
- When six-month patent extensions are earned for completion of pediatric trials under the Best Pharmaceuticals for Children Act (BPCA), it applies to ALL patents in the product portfolio, not just the primary patent (as with patent term restoration)

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Promoting Pediatric Drug Research and Labeling — Outcomes of Legislation

Florence T. Bourgeois, M.D., M.P.H., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

Table 1: Legislation to Promote Pediatric Drug Development and Research.

<table>
<thead>
<tr>
<th>Legislation</th>
<th>Year</th>
<th>Provision</th>
<th>Scope and implementation</th>
</tr>
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<tbody>
<tr>
<td>Best Pharmaceuticals for Children Act</td>
<td>2002</td>
<td>States require drug manufacturers to:</td>
<td>The FDA may issue written requests for studies involving children regarding approved or unapproved indications to test products of different development phases in a more efficient and economical manner. The inclusion of new restrictions on the use of the drug is not required, and the drug can be marketed for a new indication on the basis of the results of a confirmatory study.</td>
</tr>
<tr>
<td>Pediatric Research Equity Act</td>
<td>2003</td>
<td>requires the FDA to expand the performance of studies involving children</td>
<td>The FDA may issue written requests for studies involving children regarding approved or unapproved indications to test products of different development phases in a more efficient and economical manner. The inclusion of new restrictions on the use of the drug is not required, and the drug can be marketed for a new indication on the basis of the results of a confirmatory study.</td>
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Table 2: Policy Proposals Affecting Market Exclusivity Periods for Prescription Drugs

<table>
<thead>
<tr>
<th>Proposal</th>
<th>States</th>
<th>Details</th>
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<tbody>
<tr>
<td>Patent extension provision</td>
<td></td>
<td>Recipients of a geographic area's' approval will be able to file for up to an additional 2 years of market exclusivity.</td>
</tr>
<tr>
<td>Regulatory exclusivity provision for drug manufacturers</td>
<td></td>
<td>Recipients of a geographic area's' approval will be able to file for up to an additional 2 years of market exclusivity.</td>
</tr>
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<td>5-Months patent expiration for rare disease approvals</td>
<td></td>
<td>Recipients of a geographic area's' approval will be able to file for up to an additional 2 years of market exclusivity.</td>
</tr>
<tr>
<td>5-year “new drug” exclusivity for fixed-dose combination drugs</td>
<td></td>
<td>Recipients of a geographic area's' approval will be able to file for up to an additional 2 years of market exclusivity.</td>
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Any questions?

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