Intellectual Property and Regulatory Incentives to Protect Innovation

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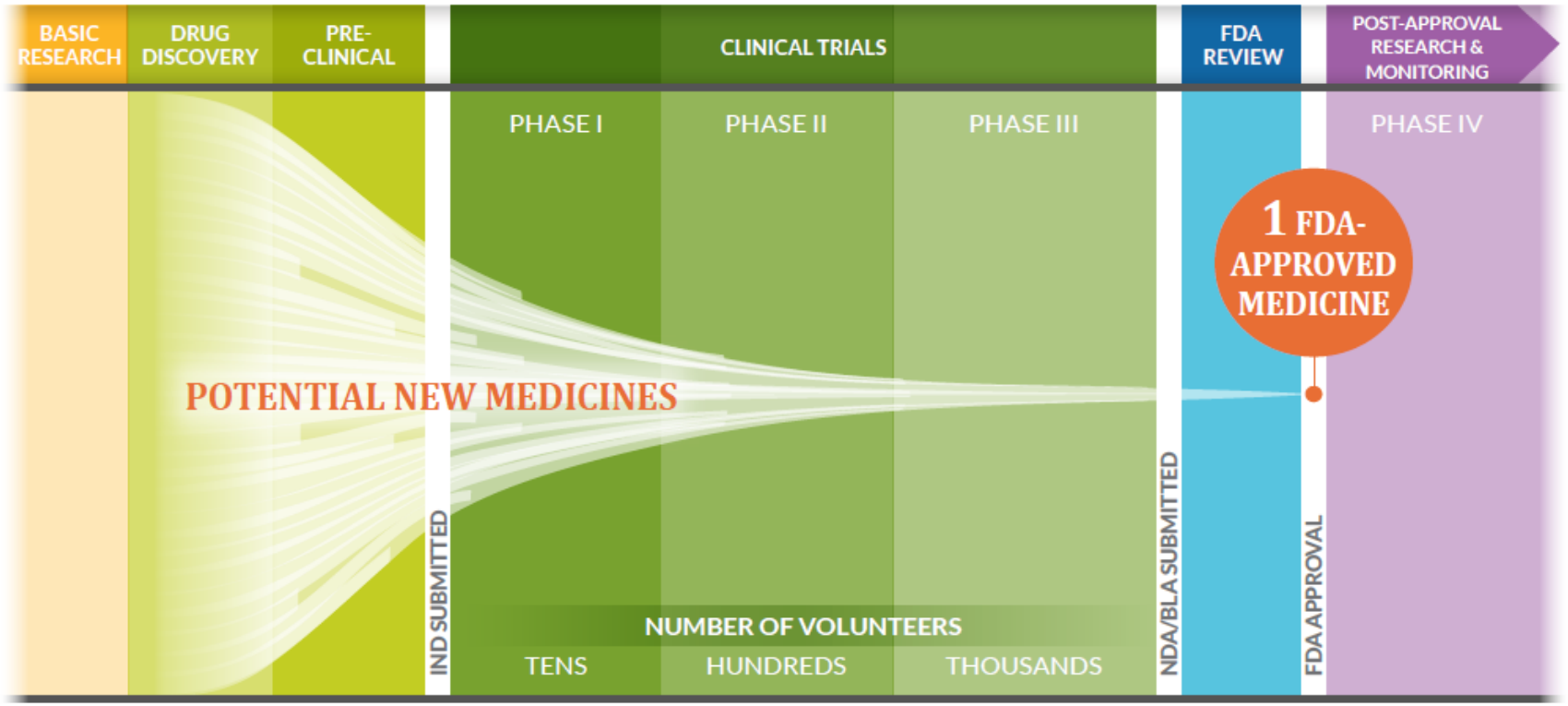
Agenda

- Patent Term Restoration/Extension
- Five- and Three-Year Exclusivity
- 180-Day Exclusivity
- Pediatric Exclusivity
- Orphan Drugs
- Priority Review Vouchers (PRVs) (Tropical Disease, Rare Pediatric Disease, and Medical Countermeasures)
- Biosimilars: Intersection of Regulatory Exclusivity and Patent Exclusivity

The Lengthy, Costly, and Uncertain Biopharmaceutical Research and Development Process

From drug discovery through FDA approval, developing a new medicine on average takes 10 to 15 years and costs $2.6 billion.* Less than 12% of the candidate medicines that make it into phase I clinical trials are approved by the FDA.



Key: IND=Investigational New Drug Application, NDA=New Drug Application, BLA=Biologics License Application

*The average R&D cost required to bring a new FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Sources: PhRMA adaptation of DiMasi JA et al.; Tufts CSDD; FDA[7]

Patents and Patent Term Restoration

- Property right issued by USPTO to an inventor “to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States” for a limited time, in exchange for public disclosure of the invention when the patent is granted.
- Generally, the term of a new patent is 20 years from the date on which the application for the patent was filed in the United States.
- Patents and FDA Approval are unrelated. A company may apply for a patent at any time in FDA approval timeline.
- Patents are *distinct from statutory exclusivities,* and run in parallel.

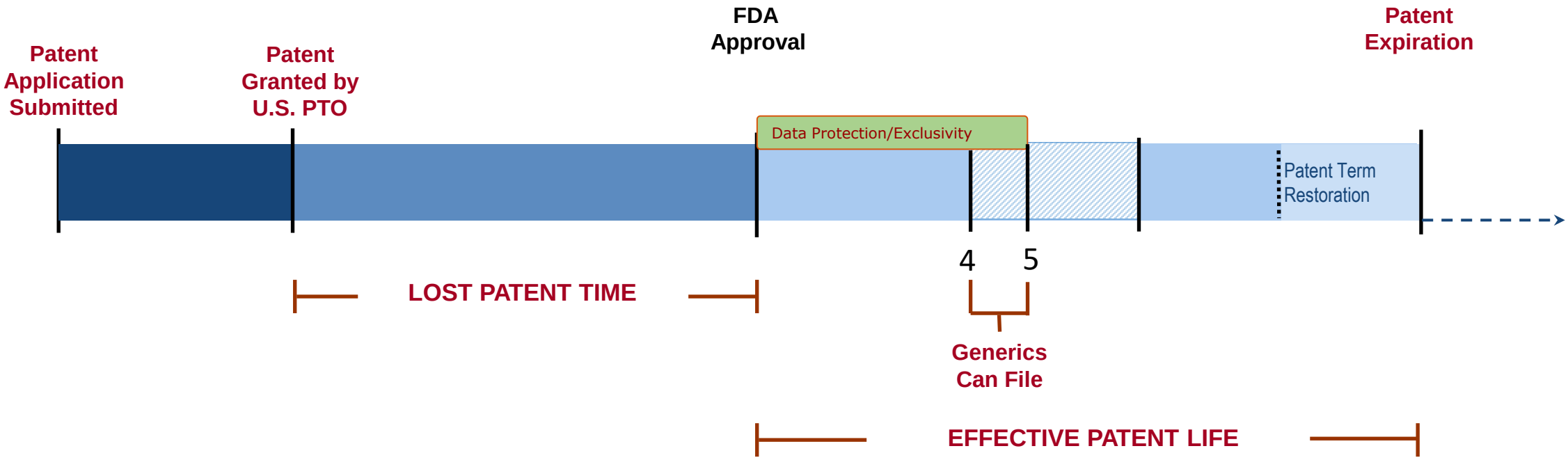
Patents and Patent Term Restoration

- Patent term restoration established in 1984 Hatch-Waxman Act to "restore . . . some of the incentive for innovation which has weakened as Federal pre-market approval requirements have become more expensive and time-consuming."
- Effectively allows for restoration of patent term "lost" during regulatory review
- Basic limitations:
  - One patent extension per product
  - One product per patent extension
  - One patent extension per patent

Patents and Patent Term Restoration

- 35 U.S.C. § 156 governs patent term restoration.
- Basic requirements:
  - Product has been subject to regulatory review period
  - Regulatory approval results in *first* commercial marketing of product
  - Patent has not been previously granted PTE
  - Patent “claims” the product, method of using, or method of manufacturing
  - PTE application filed within 60 days of approval
  - PTE application filed before patent expires

Illustrative IP Timeline – After Hatch-Waxman



Five-Year Exclusivity

- Established as part of Hatch-Waxman Act
- Also called “New Chemical Entity” (NCE) exclusivity
- Applies to new drugs “no active ingredient (including any ester or salt of the active ingredient)” of which has previously been approved
- Blocks *submission* of application referencing the new drug application for five years from approval
  - Note: For ANDAs/(b)(2)s with Paragraph IV certification (i.e., patent challenge), may submit after *four* years
- Provides “umbrella exclusivity,” meaning supplements to NDA with NCE exclusivity similarly share in the 5-year exclusivity

Hypothetical #1

- Sponsor A obtains approval for Drug X, with new active ingredient Y.
- Several years later, sponsor B submits application for Drug A, with active ingredient Y.
- Is FDA required to refuse submission of sponsor B's application?

1- Yes

2- No

3 - It depends

Answer

- 3 – It Depends
- Relevant considerations:
  - How many years has it been since approval of Drug X?
    - If less than 5 years, 5-year exclusivity would preclude submission of ANDAs and 505(b)(2) applications referencing Drug X
      - Or 4.5 years if Sponsor B included Paragraph IV certification
  - What type of application does Sponsor B plan to submit?
    - 5-year exclusivity applies against ANDAs and (b)(2) applications

Three-Year Exclusivity

- Established as part of Hatch-Waxman Act
- Applies to applications for approved active ingredients that contain reports of “new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant”
- Blocks ANDAs and 505(b)(2) applications for three years with respect to the “conditions of approval” qualifying for 3-year exclusivity

Hypothetical #2

- Sponsor A submits sNDA to drug X seeking new use in patients with breast cancer.
- 2 year later, sponsor B submits ANDA referencing drug X.
- Can FDA approve Sponsor B's submission?

1- Yes

2- No

3 - It depends

Answer

- 3 – It Depends
- Relevant considerations:
  - What exclusivities apply here?
    - Does Drug X have 5-year exclusivity?
      - If so, FDA could not accept submission of ANDA referencing Drug X
    - Does Drug X have 3-year exclusivity?
      - If so, FDA may still approve the ANDA, but may “carve out” labeling for uses protected by 3-year exclusivity
      - Were the clinical studies essential to approval?
      - Were the studies conducted by, or for, Sponsor A?

Orphan Exclusivity

- Applies to active ingredients (in drugs and biologics) designated to treat a “rare” disease defined as fewer than 200,000 persons in the U.S. or for which the manufacturer cannot hope to recover development costs
- Precludes FDA approval of the “same drug” for the same indication for seven years
  - FDA has interpreted “same drug” in its regulations such that a drug with the same active ingredient but that is shown to be “clinically superior” is not considered the “same drug.”
- Additional incentives for orphan drugs:
  - 25% tax credit for qualified incentives
  - Application fee waiver

Hypothetical #3

- Sponsor A obtains orphan designation for Use Y for Drug Z
- FDA approves Sponsor A's application for Drug Z for Use Y
- 6 years later, Sponsor B submits NDA for Drug Z containing entirely new studies and not referencing Sponsor A's application
- Can FDA approve Sponsor B's submission?

1- Yes

2- No

3 - It depends

Answer

- 3 – It depends
- Critical question is whether Sponsor B's application is for the "same drug"
  - Orphan exclusivity applies against all applications for the "same drug," regardless of whether the application references the exclusivity-protected drug.

Pediatric Exclusivity

- Applies to products that receive a “written request” from FDA for studies that may produce “health benefits” in a pediatric population
  - A sponsor can propose these studies in a Proposed Pediatric Study Request
- Provided the sponsor conducts studies that “fairly respond” to the written request, FDA will confer a six month extension to any other exclusivity and listed patents
  - Note: Studies need not be successfully in order to qualify for exclusivity

Hypothetical # 4

- Sponsor A conducts study of drug X in pediatric patients
- Study fails to meet endpoints
- Is Sponsor A eligible for pediatric exclusivity?

1- Yes

2- No

3 - It depends

Answer

- 3 – it depends
  - Did FDA issue a written request?
  - Did the study “fairly respond” to the request?
    - Note: Does not matter if study was not “successful”
  - Are there remaining patents or exclusivity?

180-day Exclusivity

- Grants 180-day exclusivity to first ANDA sponsor to file a substantially complete ANDA containing a Paragraph IV certification (i.e., patent challenge to reference drug)
- Exclusivity applies against other ANDAs
- Note: Can be multiple ANDAs with 180-day exclusivity if filed on same day

Rare Pediatric Disease Vouchers

- Applies to new products that treat serious diseases affecting fewer than 200,000 US children
- Approval confers a transferable priority review voucher for a future application
- Vouchers have sold for between $67 million and $350 million

Tropical Disease Vouchers

- Applies to a new product that treats any of 24 listed diseases that affect the developing world (e.g. Malaria, Leprosy, Zika,etc.)
- Potential to add other diseases with “no significant market in developed nations and that disproportionately affects poor and marginalized populations…”
- Earns a transferable priority review voucher

Medical Countermeasure Voucher

- Applies to products for conditions associated with “chemical, biological, radiological, and nuclear threats and emerging infectious diseases
- Eligible conditions are listed by the Secretary of Homeland Security
- Approval confers a transferable priority review voucher
- Note: FDA recently granted MCM voucher for Velkury (remdesivir)

Biosimilars: Intersection of Regulatory Exclusivity and Patent Exclusivity

- Biologics Price Competition and Innovation Act passed in 2010 as part of ACA
- What is a “biosimilar”?
  - “Highly similar” to reference product with “no clinically meaningful differences”
- Demonstrating biosimilarity typically requires analytical, animal, and clinical data
  - Note: FDA may waive any of these requirements
  - Must show that biosimilar has same mechanism of action as reference product, same “conditions of use”, same strength, dosage form, and route of administration
  - Biosimilar application must also include manufacturing and facilities information

Biosimilars: Intersection of Regulatory Exclusivity and Patent Exclusivity

- Biosimilars may also be “interchangeable” if FDA determines that the biosimilar:
  - Can be expected to produce the same clinical result as the reference product in any given patient; and
  - For a biological product administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch
- Interchangeable biologics may be substituted for the reference product without the intervention o the health care provider who prescribed the reference product.

Biosimilars: Intersection of Regulatory Exclusivity and Patent Exclusivity

- **Reference Product Exclusivity (12-year exclusivity)**
  - Precludes submission of biosimilar application referencing biological product for 12 years from date of first licensure
- **180-day Interchangeability Exclusivity**
- **Patent Exchange Process**
  - Establishes patent exchange process for biosimilar applications
  - Biosimilar applicant may submit application 4 years after first licensure of reference product
  - BPCIA sets forth elaborate process for exchanging and litigating patents
    - Note: Process *not* mandatory (*Amgen v. Sandoz*)
  - Unlike Hatch-Waxman, no 30-month stays or patent linkage