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Forum on Drug Discovery, Development, and Translation*

*Financial Incentives to Support Unmet Medical Needs
for Central Nervous System Disorders*

An Overview of Current Intellectual Property Protections: Patents and Data Package Protection

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The Way It Was...

- Medicines could be approved without any demonstrated efficacy—relatively little time and relatively little cost to get to market (pre-1962).
- No abbreviated regulatory approval pathways—no substitutability of “generic” versions of new drugs.
- Patents were sought by the originator of a new drug to secure pipeline exclusivity from other R&D-based enterprises’ pipeline medicines.
- Trade secrecy = “data package protection.”
- Patent expiration typically had little market impact.

The Way It Is...

- Prolific, expensive, high-risk investments needed to establish safety and effectiveness before a new medicine can be approved for marketing.
- Abbreviated regulatory approval pathways exist—drugs are approved as bioequivalent substitutes without any safety/effectiveness testing.
- Patents and patent litigation typically define the onset of generic drug-biosimilar competition.
- Limited “data package protection” periods.
- Patent expiration typically ends commercial life.

Patents Alone Define Most of Biopharma Market Capitalization?

<http://www.reuters.com/article/2015/01/07/pharmaceuticals-haymancapital-idUSL3N0UM42O20150107>

US hedge fund plans to take on big pharma over patents

Wednesday, 7 Jan 2015 | 2:49 PM ET



U.S. hedge fund manager Kyle Bass, who won fame for predicting the subprime mortgage crisis in 2008, plans to take on some of the world's biggest drug producers by challenging the patents of their top brands, he said on Wednesday.

Bass, the founder of Dallas-based Hayman Capital Management, L.P., said some drug firms were hanging onto patents in questionable ways and he planned to take around 15 firms into a so called Inter Partes Review (IPR) process created by the America Invents Act. in 2012.

"We are going to challenge and invalidate patents through the IPR process ... (and) we are not going to settle," Bass said in a presentation in Oslo, Norway's capital.

"The companies that are expanding patents by simply changing the dosage or the way they are packaging something are going to get knee capped," he said.

Challenging Patents Could Reduce Biopharma Market Cap By ½ ?

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U.S. hedge fund manager Kyle Bass, who won fame for predicting the subprime mortgage crisis in 2008, plans to take on some of the world's biggest drug makers, he said on Wednesday.

Bass, the founder of Hayman Capital, said some of the firms he planned to challenge were on the list of the U.S. Patent and Trademark Office's (PTO) "Patent Review (PR) Pilot Program."

"We are going to challenge the process... in Oslo, Norway," he said.

"The companies that are going to get their dosage or the way they are packaging something are going to get knee capped," he said.

Bass said the firms he planned to challenge had a combined market capitalization of \$450 billion and if he succeeded that could halve, benefiting his investments and reducing medicine prices in the United States.

"This is going to lower drug prices for Medicare and for everyone," he said.

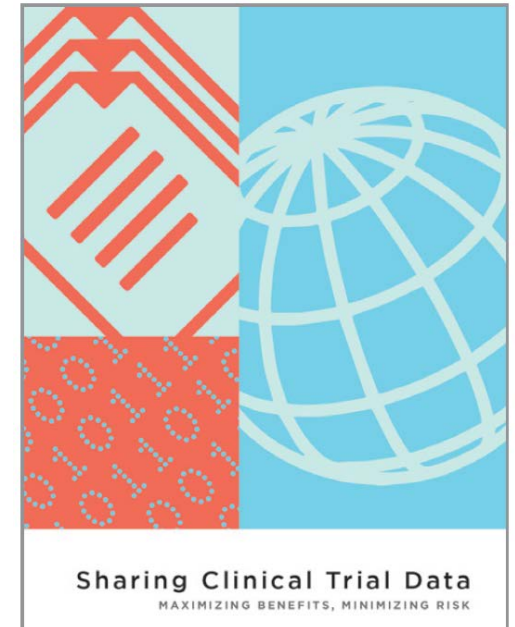
Why “Data Package Protection”?

- DPP is defined as the period after the approval of a new medicine (or use) during which regulatory approval of a copied version, under an abbreviated approval pathway, is barred even if some or all safety/effectiveness information has become public.
- DPP is the *inherent result* of creating new abbreviated regulatory approval pathways.
 - Hatch-Waxman “generic drug” approval process in 1984.
 - Biologic Price Competition and Innovation Act (Biosimilars Act) process for biosimilar approval in 2010.
- *Important to encourage public disclosure of safety and effectiveness data, not maintain their trade secrecy.*

Sharing Clinical Trial Data

Maximizing Benefits, Minimizing Risk

Clinical trials are essential to determining the safety and efficacy of new health treatments, but limited data sharing prevents maximum utilization of knowledge gained. In short, the current system fails to provide an adequate return on the investments of trial participants, investigators, and sponsors. Greater data sharing could enhance public well-being by accelerating the drug discovery and development process, reducing redundant research, and facilitating scientific innovation. Before these benefits can be realized, however, stakeholders must confront significant risks and challenges. In *Sharing Clinical Trial Data*, the IOM committee provides a practical and ethical framework to help stakeholders navigate this complex terrain. 26



Decisions about the timing of data sharing should balance several goals:

1. allow a fair opportunity for clinical trialists to publish results before secondary investigators gain access to the data;
2. allow secondary investigators to access unpublished trial data after a fair period has passed or reproduce the findings of a published analysis; and
3. protect the commercial interests of sponsors in gaining regulatory approval for a product so that they receive fair financial rewards for their investment.

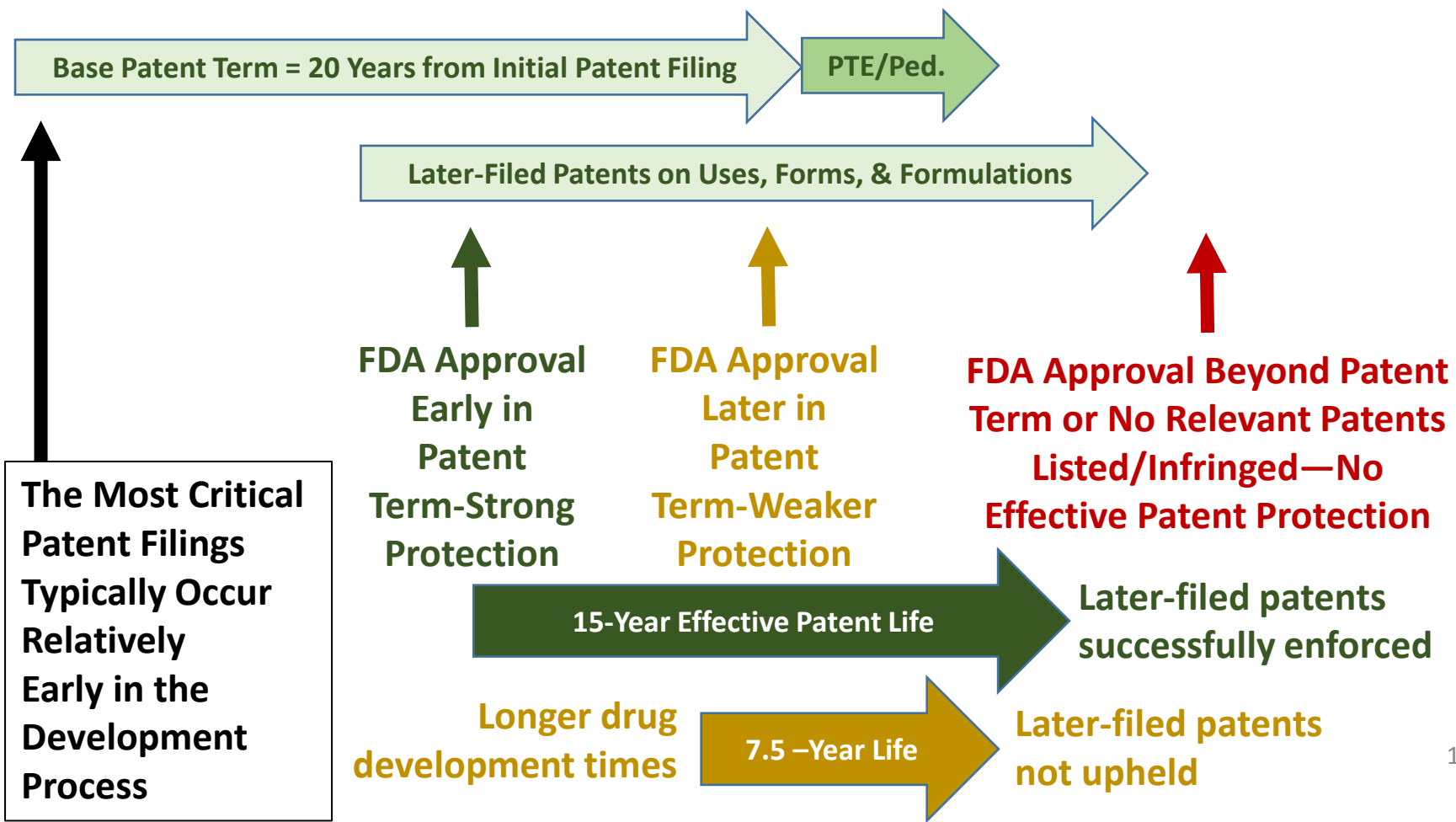
Hatch-Waxman Aligns “Data Package Protection” To Patent Life

- The sponsor of a new drug must list each relevant patent in its New Drug Application. (*Orange Book*)
- The FDA is barred from approving generic drugs before the expiration of all the relevant patents, absent a challenge to the patent’s validity or infringement.
- Once a patent challenge is initiated in a timely manner, generic drug approval is automatically stayed to allow the lawsuit to be decided.
- Generic drug approval under Hatch-Waxman typically awaits the outcome of patent litigation.

Doubling Down on Patents: Patent Term Extension Under Hatch-Waxman

- Hatch-Waxman created a complicated formula for extending the patent life for a single patent for a new drug or new biologic product.
 - Can add up to 5 additional years of patent life,
 - But not to exceed a total of 14 years of patent life,
 - Based upon the clinical testing and FDA review period,
 - But deducting $\frac{1}{2}$ of the clinical testing period,
 - Not counting any of the lost patent term before issuance and excluding any previously extended patent.
- Ca. 30% of new drugs qualify for a patent extension yielding a 14-year patent life.

Factors Producing Variability in Patent Life for a New Drug



Patent Reality Check

- Nothing in the patent law works to assure strong patent protection can be secured for the most promising ideas for new medicines.
- Inherent uncertainties in the ability to successfully enforce patents disproportionately impact investments in medicines that are the riskiest and take the longest to develop. (*Risk-stacking effect.*)
- Patents provide inherently perverse protection—the longer and more difficult the anticipated road to market, the relatively weaker the resulting patent protection that can be expected upon approval.

Potential “Patent Life” for New Drugs Often Exceeds 14 Years—

2013 Drugs Approved	Date-FDA Approval	Listed Pats	Last Expiring	Expiration Date	Pot. Life
Mekinist	5/29/2013	4	8,580,304	1/28/2032	18.7
Pomalyst	2/8/2013	18	8,828,427	6/21/2031	18.4
Imbruvica	11/13/2013	11	8,754,090	6/3/2031	17.6
Sovaldi	12/6/2013	5	8,618,076	12/11/2030	17.0
Tafinlar	5/29/2013	2	8,415,345	1/20/2030	16.6
Gilotrif	7/12/2013	4	8,545,884	12/19/2029	16.4
Invokana	3/29/2013	4	7,943,582	2/26/2029	15.9
Olysio	11/22/2013	5	8,148,399	9/5/2029	15.8
Tivicay	8/12/2013	1	8,129,385	10/5/2027	14.1

Source: FDA “Orange Book” Patent Listings for Selected New Drugs Approved in 2013 as Addressing an “Unmet Medical Need” (Fast-Track Approvals).

Patent settlements and first-filers' 180-day generic monopoly period

- Generic drug manufacturers first to challenge listed patents for a new drug—
 - Can bar FDA approval for all competing generic drug manufacturers for 180 days after marketing commences for first generic drug.
 - Subject to a series of “forfeiture” provisions on this 180-day generic drug monopoly period.
- First-filers and originators can secure mutual benefits by settling H-W patent lawsuits—
 - To preserve 180-day monopoly rights and
 - To extend duration of the patent life for the innovator.

Adding 6 More Months of Patent Life Through “Pediatric Exclusivity”

- Best Pharmaceuticals for Children Act—
 - FDA “requests” pediatric studies be done by sponsor.
 - Sponsor completes studies in a timely manner.
 - All listed patents get additional 6 months of patent life.

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Hatch-Waxman Operation Absent Any Originator-Listed Patents

- If no patents are listed for an NME new drug—
 - A generic drug application cannot be filed seeking approval for 5 years. (“ANDA filing moratorium” period)
 - Pediatric exclusivity can extend the period to 5.5 years.
 - If patents had been listed, the 5-year period reduces to a 4-year moratorium period on an ANDA filing, but subject to a 3.5 year additional litigation stay on ANDA approval.
 - Extremely rare for a new drug, even an orphan drug, to have no listed patents.
- For a non-NME drug approved for a new indication for use, a 3-year moratorium on ANDA approval for the same drug/same indication can apply.

Lessons from 30 Years of the Hatch-Waxman Act: New Drugs

- Originators of new medicines appear today to focus R&D pipelines largely on molecules that can secure strong patent protection.
- The prospect of strong patent protection decreases the longer the development time, disadvantaging—
 - Unprecedented mechanisms of action.
 - Other higher-risk or highly novel therapies.
 - Chronic, rather than acute, conditions.
 - Preventative medicines, rather than disease treatment.
- The best medicines for patients may not always be the medicines with the best patents.

Market Entry for Biosimilar Versions of Biologic Products

- Patent-agnostic, not patent-centric FDA approval.
- DPP = 12 years; approvals under the biosimilars pathway are barred during the 12-year DPP period.
- Pediatric exclusivity → 12.5 years of DPP instead of 12 years.
- “Patent dialogue” required with exchange of patent lists, but no impact on FDA approval of biosimilars.
- *Marketing of biosimilars may still be enjoined after 12/12.5 years pending outcome of patent litigation.*

Orphan Drug Exclusivity

- Applies to both new drugs and biologics.
- Enacted in 1983 and extended to include patented orphan drugs in 1985.
- Core IP protection: 7-year period during which same molecule cannot be approved for the “orphan indication.” *Provides registration exclusivity.*
 - Seldom important for NME drugs or biologics—Hatch-Waxman and Biosimilar Act provide longer DPP.
 - Limited importance for medicines also approved for non-orphan indications due to substitution with non-orphan products.
 - Can produce bizarre market results in the case of orphan approvals for pre-1962 drugs. (Colchicine , discussed at <http://www.nejm.org/doi/full/10.1056/NEJMp1003126>.)

GAIN Act Exclusivity for Qualifying Infectious Diseases Product (QIDP)

- Adds 5 additional years for QIDP on top of—
 - Hatch-Waxman 3-, 4-, or 5-year moratorium periods.
 - ~~Orphan Drug 7-year registration exclusivity period.~~
- Additional 6-month pediatric exclusivity may apply.
- GAIN effectively reproduces the 12- to 12.5-year DPP period under the Biosimilars Act for QIPDs.
 - ~~ODA+GAIN+Pediatric → 7+5+0.5 = 12.5 years.~~
 - H-W+GAIN+Pediatric → 5+5+0.5+2 = 12.5 years, assuming no patents and a 2-year period for generic drug (ANDA) approval.
 - H-W+GAIN+Pediatric → 4+3.5+0.5 = 12.5 years, assuming patent listings and 42-month stay of generic drug approval.

Antibiotics are not
approved for
orphan indications.

MODDERN Cures Act/Dormant Therapies Act (113th Congress)

- Originator can opt out of all other IP protection regimes for an NME medicine being investigated to address an unmet medical need.
- Fixed, 15-year IP protection period (IPPP) applies.
 - DPP fixed at 15-years; pediatric exclusivity inapplicable.
 - All shorter-lived relevant patents in effect at approval are extended to expire at the end of the 15-year IPPP.
 - Originator's rights under any longer-lived patents must be waived beyond the end of the 15-year IPPP.
- Generic drug/biosimilar market entry can take place immediately after 15-year period ends.

Rationale for Fixed, 15-Year IPPP for Addressing Unmet Medical Needs

- Equivalent to the IP protection currently available for any medicine with strong patent protection.
- Approximates the historic 13- to 16-year “break-even” period for a typical new medicine. (Grabowski, *Nature Reviews*, 2008).
- Approximates the Hatch-Waxman patent extension, pediatric exclusivity and generic monopoly period of 14 years + 6 months + 180 days.
- Economically essential for medicines that are typically the most challenging to develop—NME medicines being studied to address unmet medical needs.
- No patent litigation and no patent settlements as predicate to generic drug entry.

Conclusions

- Abbreviated approval pathways for copiers and more arduous approval pathways for originators have brought IP protection to the fore as a limiting factor in the ability to invest in the creation of a new medicine.
- Patent variability—and patent perversity—work to particularly disadvantage making investments to develop the highest-risk medicines, *e.g.*, those to address unmet medical needs.
- New incentives should allow R&D focus on the best medicines, not medicines with the best patents.

Backup

Typical Intellectual Property Inputs into Biopharmaceutical Pipeline Decisions—

