Dormant Therapies

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What Are Dormant Therapies?

- Dormant therapies are:
  - compounds with potentially valuable therapeutic uses
  - that have not yet been approved by the FDA for medical use,
  - but lack adequate patent protection,
  - which deters firms from investing in their development.

How The Novelty Rule Creates Dormant Therapies

- § 102: Anything that discloses the idea of a drug will prevent it from later being patented, even if that drug has not yet been developed for medical use
  - Ultracet®: combination analgesic drug
    - Invalidated by an old patent that mentioned the combination (476 F.3d 1321)
  - Nabumetone (Relafen®): anti-inflammatory drug
    - Invalidated by article that merely disclosed the compound (154 F. Supp.2d 157)
  - Finasteride (Proscar®) as a treatment for prostate cancer
    - Invalidated by prior patent rejected for insufficient evidence of utility (413 F.3d 1318)
  - 3-hour Taxol® regimen
    - Invalidated by an article saying the 3-hour regimen is ***ineffective*** (246 F.3d 1368)
  - Paroxetine (Paxil®): a treatment for depression
    - Invalidated by an earlier-known process that, in retrospect, inevitably produced trace, undetectable amounts of the not-yet-discovered drug (403 F.3d 1331)

How The Obviousness Rule Creates Dormant Therapies

- §103: A drug is obvious if there was a "reasonable expectation" it "would work for its intended purpose" when invented and it doesn't show "unexpectedly superior results." (480 F.3d 1348)
- "Obvious" new drugs still require extensive clinical testing for FDA approval, and thus generally need a patent to be developed
- Under §103, therefore, we deny patents to drugs because they seemed likely to work when invented, even though we probably won't get them as a result!!!
  - e.g., courts refused a patent on an analgesic because its "substantially greater effectiveness" was "suggested" by prior art (345 F.2d 1013)
- Problematic for combination drugs and new drugs created by modifying older compounds to enhance their effects
  - Moduretic®, a combination diuretic: patent invalidated because its beneficial effects weren't "unexpectedly good" (874 F.2d 804)
  - Norvasc®, a hypertension drug: patent invalidated because it was created with "a well-known problem-solving strategy" (480 F.3d 1348)

There's A Vast & Growing Number Of Potential New Drugs That Are Unpatentable

- There are millions of compounds of potential therapeutic valuable disclosed in old patents, none of which can be patented again
  - Between 2000 & 2009 alone, the large drug companies disclosed 791,722 unique compounds in 14,335 drug-patents compared to the 230 NDAs approved for NMEs over the same period.
  - Firms pursue the compounds that they think are most promising, but drug R&D is highly unpredictable, and good drugs can be overlooked
- Potentially valuable drugs are sometimes disclosed in journal articles without being patented, especially by academics
  - 82% of universities were unable to patent at least one life-science invention the prior year due to early disclosure, and 71% could not find a commercial partner to develop an invention for the same reason (Campbell & Bendavid '03)
- Advances in the science of drug discovery can make drugs "obvious"
  - Anything that make it easier to identify promising drug candidates based on their physical structure will cut against the patentability of those compounds
- Compounds found in nature??? (waiting for *Myriad*)

Should We Be Worried?

- Are we losing valuable new therapeutics as a result of these coverage gaps in the patent system?
  - It is well known that firms will rarely invest to develop a new drug without a strong patent on it.
  - Yet the patent system leaves many compounds unprotected despite (or perhaps because of) their potential therapeutic value.
  - If the patent system is causing valuable drugs to be left on the laboratory shelf, the resulting harm to the public could be massive.
  - This harm is difficult to see, however, because dormant therapies have not been developed for medical use, and so we don’t know what drugs we are missing.
  - Do we have reason to believe that the coverage gaps in the patent system are causing a serious problem?

Yes, Because The PTO Seems To Be Denying A Lot Of Drug Patents

- For example, it denied patents on drugs intended to treat
  - **HIV** (*e.g.*, Williams, 2005-0902; Hofmann, 1996-0729; Stapleton, 2005-1797; Murrer, 95-2603; Maury, 2007-1621)
  - **Cancer** (*e.g.*, MacLeod, 2001-1651; Cuthbertson, 2007-1140;Behr, 2006-2417; Rajopadhye, 2007-0856; Chen, 2006-3290, Barbera-Guillem, 2006-2466; Shawver, 2004-0005; Linnenbach, 2001-1258; Rosenblatt, 2004-1505; Bianco, 1996-0756)
  - **Diabetes** (*e.g.*, Sander-Struckmeier, 2005-1150; Schmitke, 2007-0854)
  - **Strokes** (*e.g.*, Bennett, 2003-1678; Childers, 2003-0890)
  - **Hypertension** & **Cholesterol** (*e.g.*, Pershadsingh, 95-0885; Picard, 95-2879)
  - **Tuberculosis** (Horwitz, 2002-1740)
  - **Malaria** & **Diarrhea** (D'Antonio, 1998-1987; Bergeron, 2004-1008)
- Just the tip of the Iceberg: these rejections are only visible when the applicant appeals the examiner's decision

Yes, Because Drugs Are Often Screened Out Of R&D Due To Weak IP

- Firms regularly inspect the patentability of their drug candidates to screen out unpatentable drugs
  - Medicinal chemists screen out non-novel lead compounds because, “needless to say, the lead structure series must be patentable” (deStevens ’90)
  - When lead compounds progress into drug candidates, firms screen them again as they begin filing their patents
  - Before a drug enters clinical trials, firms thoroughly check its patents as a “gatekeeping event,” usually dropping compounds if their IP is weak
- Translational research programs at universities also assess the patentability of their discoveries, and “applications without identifiable IP are not funded” (Pienta ’10; Coller & Califf ‘09)
- Industry insiders, venture capitalists, academics and medicinal chemists all report that inadequate IP is a common reason for passing on a drug

Yes, Because Drugs Are Often Screened Out Of R&D When Their Remaining Patent Life Is Inadequate

- Longer development times & delays in R&D reduce time on the market before generics enter, making it harder to earn a profit
  - Preclinical & clinical development takes 8-15 years on average
  - Firms file patents early in R&D & the 20-year clock starts at filing
  - Patent-term extensions only partially compensate for time lost
    - ½ of the time spent in clinical trials + the entire length of FDA review
    - total extension cannot exceed 5 years
- This policy is **dumb** because drugs with longer development times usually have higher costs, and thus need more protection, not less
- Firms drop drugs from their pipeline when the remaining patent life isn't sufficient to recoup the expected R&D costs
  - Unforeseen delays in R&D cause firms to drop potentially good drugs
  - Firms ignore drugs that sit on the shelf for too long
  - Firms ignore therapies that require lengthy clinical trials
    - e.g., treatments for early-stage disease and preventative therapies, where it can take much longer to observe outcomes in clinical trials
  - Drugs that fail in phase III trials for reasons related to trial design (rather than safety/efficacy) are often just dropped, not retested

Yes, Because Redesigning Old Compounds To Make Them Patentable Adds Cost, Time & Risk To R&D

- When firms are confronted by these patent problems, they sometimes alter the old compound's structure to create a new compound that is patentable
- This is an imperfect and costly reaction to the problem of unpatentable drugs
  - Drug-redesigns are not always successful
    - Redesign risks making the compound less safe or effective
      - rising molecular weight of drugs candidates (Walters, J.Med.Chem. '11)
    - Redesigned drugs may be "obvious" under §103
  - Drug-redesigns are costly and time-consuming
    - Firms waste money redesigning perfectly good compounds
    - Time spent in the lab delays the introduction of new drugs
    - The redesign stops firms from relying on preclinical & clinical data related to the original compound, which would save money and speed up development

Potential Solutions

- Changes to the patent laws – highly unlikely
- Public funding to develop unpatentable drugs – unlikely
- Lengthening the existing period of data-exclusivity provided under Hatch-Waxman (Roin ‘09)
  - The main reason why firms need a lengthy period of exclusivity is because of the FDA
    - we require firms to produce safety & efficacy data before marketing their drugs, which costs hundreds of millions of dollars, while we exempt generic competitors from those requirements
  - Since firms won’t pay for the clinical trials necessary for FDA approval unless they expect a lengthy period of exclusivity afterwards, we should guarantee a sufficient exclusivity period for all drugs that successfully complete those trials
  - The existing 5-year period is clearly insufficient, since firms systematically drop unpatentable drugs from development
  - We should lengthen that period to somewhere between 10 and 14 years, the average monopoly period for patented drugs
    - maybe using longer or shorter periods for different types of drugs?

The MODDERN Solution: Dormant Therapy Exclusivity

- New drugs receive 15 years of market exclusivity if they:
  - contains no active moiety previously approved by the FDA
    - this excludes new uses of existing drugs
  - have less than 14 years of patent life remaining at approval, and
  - satisfy an “unmet medical need,” i.e., they offer some meaningful improvement over existing therapies for some class of patients
- In exchange, firms must agree to waive any patent rights over the drug when their exclusivity period ends
- Compared to lengthening the Hatch-Waxman exclusivity periods, the MODDERN Cures Act
  - Prevents firms from getting protection on simple re-designs of existing drugs that will likely have similar therapeutic effects: i.e., it excludes “me too” drugs
  - But we need to ensure that the FDA doesn’t make overly burdensome demands for comparative-efficacy evidence, or require comparative-trials against recently approved therapies

Looking Forward: How to Address the Problem Of New Uses Of Existing Drugs

- Dormant new uses of existing drugs
  - compounds that are approved by the FDA for one or more therapeutic uses,
  - but may have other valuable therapeutic uses that have not yet been adequately tested in clinical trials,
  - and there is little or no life remaining on any of the patents that would block generic versions of the compound
  - thereby deterring firms from funding the clinical trials needed to test the safety and efficacy of those new uses.

Modern Medicine's Low-Hanging Fruit

- Once a new drug reaches the market, physicians and researchers often discover potential new uses for it
- Without rigorous clinical trials to test these new uses, one of two things happens
  - Many physicians don't use them, which is bad if the new use turns out to be effective
  - Or many physicians do use them, which is bad if the new use turns out to be ineffective
- Testing these new uses is much less expensive and risky than developing a new drug
  - Oftentimes there is already some clinical evidence suggesting that the new use will be effective
  - The drug's safety profile is known, which can allow drug companies to proceed directly to phase II or III trials
  - Mass production of the drug makes the raw materials for the trials inexpensive

The Patent System Fails Again

- Once the patent on a drug expires or nears the end of its term, firms won't finance rigorous clinical trials to test a new use for it
- Even if a firm can get a patent on that newly discovered use of the drug, those patents have very little value
  - New uses of existing drugs are patentable
    - although firms may encounter the problems with the novelty and nonobviousness requirements discussed above.
  - However, once the patents expire that cover the drug's chemical structure and at least one of its FDA-approved uses, that drug "goes generic."
  - Patents covering new uses of the drug will not stop generics from entering the market; only from listing the patented new uses on their label.
  - Drug companies would need to enforce their new-use patents against prescribing physicians and patients, which they won't do because those people are their customers.

Are There Any Solutions To The Problem Of New Uses?

- Patent-term extensions (e.g., pediatric exclusivity)
  - But these incentives are not tied to the value of the new use
- Public or charitable funding: e.g., GlobalCures Inc.
  - Finding the money is hard
- Forcing insurers to pay drug companies when doctors prescribe off-patent drugs for a patented new use
  - The computerization of medicine makes it conceivable that we could track the intended therapeutic use behind many drug prescriptions
    - Computerized prescribing creates reviewable records
    - Some insurers already ask doctors to report the intended therapeutic purpose of some prescriptions
  - Would doctors be honest in their reporting?
  - Would drug companies be willing to sue insurers when doctors misreport the intended purpose of their prescriptions?