Patents and pharmaceuticals

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23 April 2015
Introduction – the importance of patents in pharmaceuticals

Source: Cohen et al. (2000).
• How does the patent system work for pharmaceuticals?

• Gilead’s **Sofosbuvir**
Introduction – Sofosbuvir

• Sofosbuvir is a nucleotide analogue prodrug that acts as a viral replication inhibitor
Introduction – Sofosbuvir


**United States**

**Patent Application Publication**

**Sofia et al.**

**Pub. No.: US 2011/0257122 A1**

**Pub. Date:** Oct. 20, 2011

**NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS**

**Inventors:** Michael Joseph Sofia, Doylestown, PA (US); Jinfu Du, New Hope, PA (US); Peiyuan Wang, Glen Rock, NJ (US)

**Assignee:** Pharmasset, Inc., Princeton, NJ (US)

**Appl. No.:** 13/099,671

**Filed:** May 3, 2011

**Abstract**

Disclosed herein are phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomer, salt (acid or basic addition salt), hydrate, solvate, or crystalline form thereof, represented by the following structure:

Also disclosed are methods of treatment, uses, and processes for preparing each of which utilize the compound represented by formula I.
Introduction – Sofosbuvir

- Sofosbuvir approved in U.S. by FDA in early September 2013
- Antiviral company Idenix filed two patent infringement suits in the U.S. shortly before FDA approval
- Idenix (+ University of Cagliari, French National Centre for Scientific Research (CNRS) and Montpellier 2 University) claim Gilead’s sofosbuvir infringes on US6914054, US7608597, US7608600
- Merck and Isis Pharmaceuticals asked Gilead for 10% royalty on net sales of sofosbuvir for infringing US7105499 and US8481712 – Gilead sued for declaratory action for non-infringement and invalidity
- Roche claims right to exclusive license of sofosbuvir because of previous collaboration with Pharmasset (which is at the origin of sofosbuvir and which was bought by Gilead) that developed an inhibitor that Roche claims to be the basis for the sofosbuvir prodrug

专利纠纷：起源者的专利争端
- Astra Zeneca’s Nexium
Nexium is proton pump inhibitor that blocks production of stomach acid

Nexium sales before 2008 US$5.6 billion

Astra Zeneca settles patent dispute with Ranbaxy Laboratories in 2008, with Teva in 2010, with Dr. Reddy’s Laboratories in 2011

Settlement grants license to Ranbaxy, Teva, and Dr. Reddy’s Laboratories taking effect in mid-2014

In 2013, insurance companies and union health plans in the U.S. sued Astra Zeneca, Teva, Dr. Reddy’s Laboratories and Ranbaxy

Pay-for-delay settlements anti-competitive?

Patent protection vs generic entry
Introduction – Glivec

- Novartis’s Glivec
**Introduction – Glivec**

- U.S. patents on Novartis’s *Glivec* (FDA’s Orange Book)

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Introduction – Glivec

- Indian Natco Pharma’s Glivec...called Veenat
Introduction – Glivec

- India’s Glivec decision, 1 April 2013
  - Novartis’s patent application on Glivec (Gleevec) in India rejected by Supreme Court for obviousness (critical issue Section 3d of India’s Patent Act)
  - Crucial issue: are new forms (beta crystalline form) of known substances (imatinib mesylate) patentable?
  - Novartis’s reaction: ‘cautious’ about introducing new drugs to India, undertaking new investments, and conducting R&D in India

- Brazil’s Projeto de Lei no 5.402/2013 includes provision similar to 3d of India’s Patent Act

- South Africa’s proposed National Policy on IP: [Legislation] should exclude diagnostic, therapeutic and surgical methods from patentability, including new uses of known products, as is the case under the TRIPS agreement.

- Why do emerging economies impose restrictions on patentability of pharmaceuticals?
  - Patent eligibility of pharmaceutical “innovation”
Background – drug development

- The development of a new drug takes on average 12-15 years and requires a minimum investment of US$800 million
- 3 phases
  1. Development of compound
  2. Safety and efficacy studies:
  3. Pre-clinical trials: 3-5 years, in-vitro tests and with animals
  4. Clinical trials
     - Phase I: 1-3 years, drugs administered to healthy individuals
     - Phase II: 2-5 years, drugs administered to ill individuals
     - Phase III: 2-4 years, drugs administered to healthy and ill individuals
     - Phase IV: usually conducted after a drug has been marketed
- Results are submitted to health regulator (FDA in U.S.) with a new drug application
- Estimates suggest 1 out of 5,000 compounds that enter the pre-clinical trial phase is eventually approved for therapeutic use
- Once approved, WHO assigns international non proprietary name (INN)
Extensive regulatory interference

- In the U.S. (since Hatch-Waxman in 1984):
  - Patent term extension (of max 5 years)
  - *New chemical entity exclusivity* (5 years)
  - *Data exclusivity* (5 years)
  - *Pediatric exclusivity* (6 months)
  - But generics can obtain abbreviated new drug approval (no clinical trials needed) if they can show that the generic drug has the same active ingredient, route of administration, dosage form, and strength as originator drug. Must also demonstrate bioequivalence (rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the listed drug when administered at the same dosage) with the originator drug.
Extensive regulatory interference

- Challenge exclusivity through patent certifications:
  - Paragraph I: no relevant patent information listed in the Orange Book
  - Paragraph II: patent has expired
  - Paragraph III: patent will expire on a particular date
  - Paragraph IV: patent is invalid or noninfringed

- First generic producer to file a Paragraph IV challenge entitled to 180-day exclusivity

- Bolar exemption/safe harbor
Pharmaceutical patents

- Active ingredients identified by International Nonproprietary Name (INN)
- Patents use IUPAC (International Union of Pure and Applied Chemistry) classification
- Example: INN denomination for the active ingredient Imatinib (Glivec) is imatinib mesylate and its IUPAC is 
  4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-yl]aminophenyl)benzamide
- In patents active ingredients often described by Markush structure which comprises many functionally equivalent active ingredients
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- In patents active ingredients often described by Markush structure which comprises many functionally equivalent active ingredients
- IUPAC in contrast represents an individual active ingredient
- Challenges:
  - Find IUPAC that corresponds to INN
  - Determine which active ingredient is claimed by the patent – need to look at Markush formula in combination with examples provided in the patent application
• During the development phase of new drugs, commonly large numbers of patents are filed on modifications of a given active ingredient

• Patents on active ingredients filed during the first stage of the drug development process

• During the pre-clinical trial phase, methods, formulations and dosages patented

• Later on (e.g. in Phase IV) patents on new production methods and second uses may appear

• Research progress reflected in type of patent filings?

• Or is there scope for strategic behavior?
Pharmaceutical patent claim types

- **Chemical Compound**: active ingredients
- **Processes/production methods**
- **Formulation**: combination of known excipients (inactive substance) and active ingredients
- **Concentrations/dosage**: therapeutic methods
- **Salts**: “straightforward” derivatives of known active ingredients
- **Isomers**: same molecular structure but different chemical structures
- **Polymorph**: variations of known active ingredient with distinct physical properties (can only be discovered, not ‘invented’)
- **Enantiomers**: non-identical mirror images of known active ingredients
- **Treatment methods**: use of a compound for treating a disease
- **Second use**: different therapeutic use than originally intended
- **Active metabolites/prodrugs/ester**: drugs that is broken down inside the body to form an active drug (including modification of original active ingredient)
Pharmaceutical patent types

• Legal questions:
  • Which patent types are patent eligible?
  • Which patent types are patentable?
  • How to examine the different patents in practice?

• Economics questions:
  • What is the purpose of granting patents on the different types of pharmaceutical ‘inventions’?
  • Is there a trade-off between encouraging follow-on innovation and granting exclusivity?
Total pharmaceutical patent filings by residents and non-residents in Chile
Total pharmaceutical patent grants & filings in Chile by foreign (1991-2008)
What explains the application/grant gap in Chile?
• **Multiple functions of patents:** ensure freedom to operate, bargaining etc
• Are patents used to keep other originators at bay?
• Are patents also used to block/delay entry of generics and avoid loss of (broad) exclusivity?
• Possible strategies:
  - **Blanketing/Flooding:** cover in unsystematic ways
  - **Fencing/Surrounding:** different technological solutions for similar functional outcomes, surround patent on basic inventions with other patents
  - **Networking:** create overlapping portfolio
• Important factors:
  - Legal complementarity vs legal substitutability of patents on “same” invention
  - Economic complementarity vs economic substitutability of patents on “same” invention
• Regardless of strategy, result is more patents on a given invention
Primary vs secondary patents

- Primary: active ingredient
- Secondary: alternative forms of existing molecules, new formulations, dosing regimens, new uses

What is the role of secondary patents?

- Extend patent life
- Increase patent breadth

Challenge: how to distinguish from follow-on innovation – evergreening vs life cycle management
• Patent cluster to extend lifetime
Secondary patents: breadth

- Patent cluster to extend breadth

![Diagram showing relationships between Process, Dosage, Formulation, Crystalline form, and Salt surrounding an Active ingredient.]
[A] striking example is the strategy to defend the originator’s sales of Cipramil (active ingredient citalopram hydrobromide), a drug for which patent protection was filed in 1976 and having an SPC expiry date in January 2002. Facing the looming expiry of the SPC, the originator filed approximately 30 patent applications between 1999 and 2002 covering the preparation and/or composition of citalopram. (EGA 2008: p. 13)
We were recently successful in asserting the crystalline form patent in [name of country], where we obtained an injunction against several generic companies based on these patents by 'trapping' the generics: they either infringe our crystalline form patent, or they infringe our amorphous form process patent when they convert the crystalline form to the amorphous form. (Anonymous pharmaceutical company quoted in EU Commission, 2009)
The entire point of the patenting strategy adopted by many originators is to remove legal certainty. The strategy is to file as many patents as possible on all areas of the drug and create a ‘minefield’ for the generic to navigate. All generics know that very few patents in that larger group will be valid and infringed by the product they propose to make, but it is impossible to be certain prior to launch that your product will not infringe and you will not be the subject of an interim injunction. (Anonymous generic producer quoted in EU Commission, 2009)
Secondary patents: empirical evidence

- EU Commission (2009):
  - primary to secondary patent ratio 1:7
  - pending patents 1:13
  - granted patents 1:5
  - Disproportionately more secondary patents after product launch

- Kapczynski et al. (2012):
  - Of new drugs with FDA in 1991-2005: 56% formulation, 24% salts, crystalline forms etc., 63% methods of use (secondary patents)
  - Secondary patents filed after FDA approval and extend exclusivity lifetime by 4-5 years
  - More secondary patents the higher is the branded drugs sales
Secondary patents: empirical evidence

Source: Amin and Kesselheim (2012).
Conclusion

• Plenty of patent battles also in pharmaceuticals – among originators and between originators and generics producers

• Plenty of strategic patenting

• Secondary patents as strategic patenting
  • Secondary patents account for the majority of patents on a given drug
  • Secondary patents extend patent protection in length and breadth
  • Secondary patents create uncertainty
  • Validity of secondary patents often decided in litigation (not in examination)

• Do we want to limit originators’ ability to obtain secondary patents?

• Some evidence that generic entry reduces innovation in the long run (Branstetter et al., 2012)
• Amin Tahir and Aaron S. Kesselheim (2012): Secondary Patenting of Branded Pharmaceuticals: A case study of how patents on two HIV drugs could be extended for decades, Health Affairs, Vol. 31(10), pp. 2286-2294.


• Branstetter Lee, Chirantan Chatterjee, and Matthew J. Higgins (2012): Starving (or Fattening) the Golden Goose? Generic Entry and the Incentives for Early-Stage Pharmaceutical Innovation, mimeo
