Evergreening: Patents and Money

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Points to Cover

• Short history of drug patenting in Canada
  – Compulsory licensing, Bills C-22 and C-91
• Evergreening
  – Why it’s important to companies
  – Methods to extend effective patent life
• Costs of evergreening
• Further questions
Patents and Drug Prices in Canada

• 3 reports in the early 1960s:
  – Special Committee of the House of Commons on Drug Costs and Prices
  – Restrictive Trade Practices Commission
  – Royal Commission on Health Services

• Canadian drug prices among the highest in the world
The Cause??

- Drug patents which gave companies monopolies
The Solution?

• Since 1923 Canadian legislation allowed compulsory licensing to manufacture
  – Not very useful because of the economics of the relatively small Canadian market
• Compulsory licensing to import (Bill C-102)
• Passed in 1969 by Liberal government under Pierre Trudeau
Compulsory license to import, 1969-1987

- Able to import active ingredients
- Approval of patent holder not required
- Royalty of 4% to patent holder
Savings due to compulsory licensing, 1983

1.5 billion

0.211 billion

Drug sales
Savings

Eastman, 1985
Rate of return on capital employed, before taxes, 1970-1983

<table>
<thead>
<tr>
<th>Year</th>
<th>Pharmaceutical industry (%)</th>
<th>All manufacturing (%)</th>
<th>Rank out of 87 manufacturing industries</th>
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</table>
What Changed After 1985?

- Election of Canadian Conservative government committed to free trade with the U.S.
- Pharmaceutical industry heavily involved in determining U.S. trade policy
- Intellectual property protection became key part of U.S. trade policy
- Politics of Canadian unity
## Canada and Trade Agreements

<table>
<thead>
<tr>
<th>Trade Agreement</th>
<th>Date entered into force</th>
<th>Parties</th>
<th>Accompanying change in Canadian patent law</th>
<th>Date law took effect</th>
<th>Main features</th>
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</thead>
<tbody>
<tr>
<td>Free Trade Agreement (FTA)</td>
<td>1987</td>
<td>Canada, United States</td>
<td>Bill C-22</td>
<td>1987</td>
<td>New drugs exempt from compulsory licensing for 7 years; exemption extended to 10 years if active ingredient manufactured in Canada</td>
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<td>North American Free Trade Agreement (NAFTA)</td>
<td>1994</td>
<td>Canada, United States, Mexico</td>
<td>Bill C-91</td>
<td>1993</td>
<td>Compulsory licensing abolished (retroactive to Dec. 1991); patent life changed from 17 years from date patent granted to 20 years from date patent filed for (retroactive to Oct. 1, 1989)</td>
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<td>Trade Related aspects of Intellectual Property Rights (TRIPS)</td>
<td>1995</td>
<td>Worldwide</td>
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Bill C-22

- New drugs exempt from compulsory licensing for 7-10 years
- Industry promised increased R&D (at least 10% of sales versus previous ~6.5%)
- Creation of Patented Medicine Prices Review Board to control prices
Bill C-91

• Compulsory licensing abolished
• Patent life 20 years from date of filing instead of 17 years from date patented granted
• Notice of Compliance (NOC) regulations established
  – Generic drugs could not receive a NOC until it was established that there was no valid patent on the brand-name drug
Patent Disputes

• European Union complaint to WTO
  – Canadian “Bolar” provisions illegal
    • Stockpiling by generic companies stopped
    • Generic entry delayed by 3-6 months

• United States complaint to WTO
  – Patents not retroactively extended to 20 years
    • Patent extension for 30+ drugs
    • Additional $40 million in drug costs
Evergreening

• Attempts by brand name companies to extend effective patent protection
  – Molecular manipulation
  – Intellectual property rights
Molecular Manipulation

• As patents expire on original product companies introduce a new patent protected version and attempt to switch prescribing before generics arrive
  – Racemic isomers
  – “New, improved” versions of drugs (capsules instead of pills, once a day instead of three times a day)
  – Combining two drugs into one
Intellectual Property Rights

• Filing additional patents once a drug is marketed
• Notice of compliance linkage regulations
• Data exclusivity
1.5 to 3 Years – Chemical and Biological Design and Synthesis
From 10,000 molecules which are chemically or biochemically synthesized and tested.

1.5 to 3 Years - Preclinical Research
Twenty chemical substances show sufficient promise to proceed to detailed safety effectiveness studies. An Investigational New Drug Submission is filed with Health Canada.

2 years - Clinical Trials - Phase I
Five chemical substances move on to safety and dosage range studies in approximately 20-100 healthy volunteers.

2 years - Clinical Trials - Phase II
Four chemical substances pass into early safety and efficacy studies with approximately 100-300 patients suffering from the illness the medicines are intended to treat.

2 to 3 years - Clinical Trials Phase III
Two chemical substances go on to large scale comparative studies in 1,000 to 5,000 patient volunteers. Only one of the original 10,000 molecules may prove its worth as an effective therapy. A New Drug Submission is filed with Health Canada.

1 to 2 years - Review and Approval
All the information gathered by the company, including chemical structure and properties, production details, preclinical and clinical studies are evaluated by Health Canada.
Market Loss

• When generics appear brand-name companies don’t compete on price
If there were 4 or more generic competitors then price of brand-name product rose, otherwise no change in price of brand-name drug.
Market Loss

• Once generics are available, the structure of provincial drug plans means that pharmacists don’t dispense brand-name products:
  – Novo-venlafaxine XR: $220,826,000
  – Effexor XR (original brand): $67,664,000

• Significant loss in market share
Market Loss

• Lipitor (atorvastatin) – best selling drug in Canada
  – Sales $1,423,170,000 (2009)
  – Revenue per day $3,899,000
Racemic Isomers

• Many drugs are two molecules
  – Mirror images – one is active, one is inactive
  – Easier to produce the racemic mixture
  – Active isomer is marketed as an alternative to mixture
  – No more effective & no safer

• Losec (omeprazole) vs. Nexium (esomeprazole)

• Celexa (citalopram) vs. Lexapro (escitalopram)
Other Types of Molecular Manipulation

• Long acting versus short acting
  – Diltiazem, diltiazem ER, diltiazem LA, diltiazem SR

• Combining two drugs into one
  – Atorvastatin (Lipitor) + amlodipine (Norvasc) = Caduet
Filing Additional Patents

- Lipitor
  - Original patent filed July 17, 1990
  - Expiry July 17, 2010
  - Additional patents added as late as May 21, 2002, (expires May 21, 2022)
Patents per Drug

![Bar Chart showing the number of medicines and patents per drug. The chart has two y-axes: one for the number of medicines and another for the number of patents. The x-axis represents the number of patents, ranging from 1 to 22. The highest bar indicates that 248 medicines have one patent each, while the majority have no patents.](image-url)
Data Protection

• In order to market a brand name drug company must produce evidence that drug is safe and effective (big clinical trials)
• Once a drug is known to work and be safe unethical to ask a generic company to repeat the same tests
• When Health Canada received a submission from a generic company it would rely on safety and effectiveness data from the brand name company
SECTION 7: PROTECTION OF UNDISCLOSED INFORMATION
(TRIPs Agreement)

Article 39

3. Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.
Data Protection

“Unfair commercial use”

• Not further defined in TRIPs

• Member countries (in WTO) can determine
  – When such a use exists
  – Means of protection

• No minimum term for data protection
Data Protection

• Until 2006 Health Canada gave 5 years of protection for data

• Since 2006 Health Canada is prohibited from using this data for 8 years after the brand name drug appeared on the market
  – Generic companies cannot submit an application for 6 years

• Companies given additional 6 months of data protection if they study drug in children
  – Doesn’t matter how useful drug is for children
Costs of the Patent System

• Companies take out multiple patents on drugs
  – May inhibit others from doing research since it would violate patents
• Legal costs in filing patents and fees involved in patent fights between brand name and generic companies
• Government costs in administering patent system for drugs
NOC Regulations

• “Balance effective patent enforcement over new and innovative drugs with the timely market entry of their lower priced generic competitors.”

• Before generic company allowed to market a drug all patents have to be expired

• If brand name company claims an existing patent there is an automatic 24 month delay on marketing drug
  – Stay expires either at the end of 24 months or when a court decision has resolved the issue
NOC Regulations

- US only other country with the equivalent mechanism
- Ties approval for marketing which is suppose to be a scientific decision to intellectual property
- Brand-name companies could file additional patents at any time
  - 2006 federal government amended legislation so that brand-name companies could not file new patents once a generic company had submitted application for approval of its product
NOC Regulations and Legal System

• The Supreme Court of Canada has held that the automatic stay issued to patentees under the NOC Regulations is an ‘extraordinary’ remedy, not available to patentees in any industry outside of the pharmaceutical industry.

• Each year generic companies send out about 54 notices that they intend to market a product & 41 court cases launched each year.

• 2008: team of approximately 30 Federal Court judges devoting some or all of their time to about 350 separate drug patent cases.
### Outcome of Court Cases, 1998 - 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Court applications commenced</td>
<td>447</td>
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<tr>
<td>Partial prohibitions granted (more than one patent disputed but prohibition didn’t apply to all patents)</td>
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<tr>
<td>Prohibitions pending resolution of court case</td>
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<tr>
<td>Prohibitions discontinued</td>
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<tr>
<td>Prohibitions granted</td>
<td>48</td>
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<tr>
<td>Prohibitions dismissed</td>
<td>97</td>
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</table>
Cases Can Take Longer

• 2004
  – Ratiopharm challenged Pfizer’s patent on Amlodipine

• 2006
  – Ratiopharm successful at Federal Court
  – Pfizer later appealed the decision and won

• 2009
  – Ratiopharm won the case against Pfizer invalidating the Amlodipine patent on all grounds
And Costs Can Be Considerable If Generics Are Not Available

• Amlodipine cost to Ontario Drug Benefit Formulary 2003-2008
  – $422 million

• Minimum savings if generic version available
  – $106 million
Costs of Evergreening

• Drug costs
  – Paying brand-name prices instead of generic prices while NOC linkage regulations cases are being fought in court
  – Doctors prescribing newer brand-name drugs instead of older ones that have been genericized

• Indirect costs
  – Costs of litigation
  – Costs of maintaining NOC linkage regulations
  – Costs of patent system to drug companies, federal and provincial governments
Issues That Need Research

- How might the position of PhRMA (body representing US brand-name companies) regarding the Canadian IP legislation affect overall trade relations between Canada and the United States?
- Do IP rules affect investment decisions by either generic or brand-name companies?
- Do IP rules discourage generic companies from introducing some drugs?
- Do IP rules affect the value of drugs exported from or imported into Canada?
- Do IP rules lead to R&D investment into ways of modifying products with a view to “evergreening” as opposed to investment in innovative products?