Global Pharmaceutical Patent Protection in Practice

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Research support from the National Foreign Trade Council is gratefully acknowledged.
Acknowledgements

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Background

• Before 1995, many developing countries did not issue patents on pharmaceuticals.
• Under the 1995 TRIPS agreements, all WTO members were required to provide patent protection on drugs, with less developed countries given a 10 year compliance grace period to 2005.
• Controversial – access and pricing issues, differential pricing, incentives to innovate,...
Limitations of TRIPS Agreement

• Drug products protected by patents with priority dates before 1995 are not affected – are exempted
• Due to long development times for drugs, only drugs launched since mid-2000s are likely to have any degree of patent protection
• Given grace period, many emerging countries have only begun to issue drug product patents since 2005
Getting Around TRIPS

Countries have found ways to limit the impact of TRIPS. Several countries have:
- Invoked compulsory licenses on public health grounds
- Allowed parallel imports from countries with lower prices
- Restricted scope of patentable subject matter (e.g. India Section 3(d))
- Have been unable to examine pending applications in a timely manner (Brazil)
- Have limited ability or willingness to enforce patent rights in their national court systems
Circumventing TRIPS

• Section 3(d) of India’s new patent law prevents patenting of new uses of known compounds, or salts, esters, polymorphs, metabolites, isomers, or other derivatives or combinations

• Brazil has linked patentability decisions to determination by health and safety regulatory body (ANVISA), and is thought to have as many as 150,000 pending patent applications and a ten-year delay in examination decisions [OAS(2008)]
Our Focus Here

• Lots of heat, but little factual quantitative evidence on originators’ ability to obtain/maintain market exclusivity

• Here we examine “de facto exclusivity” for a particular set of countries – the extent to which pharmaceutical products are supplied by a single seller, based on data from the IMS Health Midas database

• What portion of the new drugs launched around the world since 2000 do not appear to have effective patent protection in various countries?
De facto vs. de jure exclusivity

• Originators of drugs rely on market exclusivity to generate returns on R&D
• But filing of domestic patent applications, or even issuance of a patent may be of little help in some countries
  – Difficult to get patents granted
  – Opposition proceedings
  – Difficult to enforce even when granted
• We focus here on de facto exclusivity -- as determined by the number of sellers of a new drug in a given country
Data and Methods: I

• We examine 155 NMEs launched in the US market between 2000 and 2009
• Exclude biologics (complex IP, not listed on Orange Book), diagnostic or imaging agents, and drug products with a first world-wide launch date reported before 1995
• Launch dates verified using FDA and EMEA listing of new drug approvals, data in Lanjouw [2005], and by the PharmaProjects data base
Data and Methods: II

• Determining earliest world-wide patent priority date involves much manual labor
• Took all patents listed for each drug in the US Orange Book or Health Canada Patent Register
• Obtained worldwide “patent family” (corresponding patent applications in different countries which claim the same priority and which normally disclose the same invention) from European Patent Office ("EPO") International Patent Documentation Center (INPADOC) and the EPO’s DocDB database
Data and Methods: III

- Among all patent family members, we identify the earliest patent application date.
- In principle, this allows us to determine which drugs are eligible for patent protection in countries affected by the TRIPS agreement.
- Looked at sales 2004-2009 for a range of nine countries from the OECD, Asia, Eastern Europe and Latin America:
  - Brazil, China, Germany, India, Korea, Mexico, Poland, Spain and the US.
Data and Methods: IV

• We focus on the number of distinct sellers of each drug in each country in a given year
  – “de facto” exclusivity
• Categorize drugs as single/dual source (one, or two related sellers, latter allowing for licensing and co-marketing) vs. multisource (two or more unrelated sellers, “genericized”)
• Issue: Could an apparently dual sourced product be an originator plus a single generic entrant?
Data and Methods: V

• In apparent dual source situations, we searched a variety of commercial databases (MedTrack, Biopharm Insight, PharmaProjects), trade press, news releases, company websites, and websites indexed by Google for information on licensing, partnership, or co-marketing agreements.

• If covered by such provisions, or when names of both sellers were identifiable as originator (R&D based) companies, it was designated to be in the single/dual source category, else multisource.
Data and Methods: VI

• Re “parallel trading” in EU (transshipping of drugs among member countries to take advantage of wholesale price differences – see Kyle [2010]) which shows up as a patent-protected drug having n or more sellers (n > 1) – we remove these entities from consideration based on their IMS parallel trade flag designation, and confirm by checking company websites

• If IMS/we miss some seller(s), this biases results away from finding a drug to be multisource
Diffusion of New Drugs

• Noting that our sample of drugs is admittedly US-centric, let’s first look at how large are the differences across countries in the number of distinct new drugs available relative to the US – by year and then focus on the last year – 2009

• Differences across countries on access to new drugs is remarkably large...
<table>
<thead>
<tr>
<th>Year</th>
<th>Brazil</th>
<th>China</th>
<th>Germany</th>
<th>India</th>
<th>Korea</th>
<th>Mexico</th>
<th>Poland</th>
<th>Spain</th>
<th>US</th>
<th>Any country</th>
</tr>
</thead>
<tbody>
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<td>25</td>
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<td>44</td>
<td>64</td>
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<td>2005</td>
<td>51</td>
<td>36</td>
<td>81</td>
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<td>53</td>
<td>57</td>
<td>54</td>
<td>74</td>
<td>101</td>
<td>111</td>
</tr>
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<td>2006</td>
<td>57</td>
<td>45</td>
<td>92</td>
<td>48</td>
<td>63</td>
<td>68</td>
<td>70</td>
<td>84</td>
<td>118</td>
<td>126</td>
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<tr>
<td>2007</td>
<td>64</td>
<td>60</td>
<td>106</td>
<td>58</td>
<td>79</td>
<td>71</td>
<td>82</td>
<td>94</td>
<td>131</td>
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<tr>
<td>2008</td>
<td>75</td>
<td>64</td>
<td>117</td>
<td>70</td>
<td>85</td>
<td>80</td>
<td>93</td>
<td>111</td>
<td>137</td>
<td>152</td>
</tr>
<tr>
<td>2009</td>
<td>82</td>
<td>69</td>
<td>126</td>
<td>84</td>
<td>89</td>
<td>92</td>
<td>103</td>
<td>119</td>
<td>149</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Availability of New US Drugs, By Country and Year
FIGURE 1

Fraction of Drugs Available
(as % of number launched worldwide to date)
Market Characteristics of Availability

- Next let’s examine the market characteristics of drugs that are available – among those drugs that are available, how many (or what proportion) are multisource vs. single/dual source?
Table 2: Country-specific *de facto* exclusivity by year

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
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<th></th>
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<th>2007</th>
<th></th>
<th>2008</th>
<th></th>
<th>2009</th>
</tr>
</thead>
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<tr>
<td></td>
<td># drugs multi-source</td>
<td>Total # drugs on sale</td>
<td># drugs multi-source</td>
<td>Total # drugs on sale</td>
<td># drugs multi-source</td>
<td>Total # drugs on sale</td>
<td># drugs multi-source</td>
<td>Total # drugs on sale</td>
<td># drugs multi-source</td>
<td>Total # drugs on sale</td>
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</tr>
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<td>6</td>
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<td>11</td>
<td>64</td>
<td>11</td>
<td>75</td>
<td>12</td>
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<td>China</td>
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<td>25</td>
<td>12</td>
<td>36</td>
<td>18</td>
<td>45</td>
<td>21</td>
<td>60</td>
<td>24</td>
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<td>5</td>
<td>82</td>
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<td>93</td>
<td>8</td>
<td>107</td>
<td>9</td>
<td>119</td>
<td>10</td>
</tr>
<tr>
<td>India</td>
<td>25</td>
<td>32</td>
<td>32</td>
<td>43</td>
<td>36</td>
<td>49</td>
<td>42</td>
<td>59</td>
<td>49</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td>Korea</td>
<td>3</td>
<td>45</td>
<td>5</td>
<td>53</td>
<td>7</td>
<td>63</td>
<td>8</td>
<td>79</td>
<td>9</td>
<td>85</td>
<td>11</td>
</tr>
<tr>
<td>Mexico</td>
<td>3</td>
<td>52</td>
<td>5</td>
<td>58</td>
<td>5</td>
<td>69</td>
<td>6</td>
<td>71</td>
<td>6</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>Poland</td>
<td>4</td>
<td>44</td>
<td>3</td>
<td>55</td>
<td>4</td>
<td>71</td>
<td>6</td>
<td>83</td>
<td>6</td>
<td>94</td>
<td>8</td>
</tr>
<tr>
<td>Spain</td>
<td>4</td>
<td>64</td>
<td>5</td>
<td>74</td>
<td>5</td>
<td>84</td>
<td>8</td>
<td>95</td>
<td>10</td>
<td>112</td>
<td>11</td>
</tr>
<tr>
<td>US</td>
<td>.</td>
<td>88</td>
<td>1</td>
<td>103</td>
<td>2</td>
<td>119</td>
<td>6</td>
<td>132</td>
<td>10</td>
<td>138</td>
<td>12</td>
</tr>
</tbody>
</table>
Figure 2
Single/Dual vs. Multisource Drugs in 2009
Based on 155 new drugs launched 2000-2009
Findings – Figure 2

• India markedly different from all other countries considered – 72% (61/85) of new drugs on sale in India are multisource

• China second highest multisource at 38% (26/69), Brazil third at 15% (12/82), and Korea fourth at 12% (11/89)

• Contrast with other countries is striking – Mexico 6% (6/93), Poland 8% (8/106), Spain 9% (11/120), Germany 8% (10/128) and US 8% (12/149)
Obvious caveat

- Relatively slow and incomplete diffusion of new drugs launched in the US and Europe could be due to differences in
  - Disease incidence
  - National medical practice
  - Other “technological” factors

Hence certain drugs would have a very limited market in some of these countries regardless of the commercial environment
Interpretation

• We suspect the primary reason for relatively high rates of multisource entry in India, China and Brazil is that patent protection is absent – product grandfathered in from the pre-TRIPS period, not patentable under local law, patent issued but invalidated by opposition or legal action, or because originator company hasn’t even attempted to obtain or enforce patent protection
Pre-TRIPS vs. Post-TRIPS Drugs

• If grandfathering from pre-TRIPS era accounts for differences, we should see differential multisource entry for pre-TRIPS drugs (those with a world-wide priority date before 1996) vs. post-TRIPS drugs (having a world-wide priority date in 1996 or thereafter) – Table 3 shows sample splits about 2/3 pre-TRIPS and 1/3 post-TRIPS

• Finding: No large differences in any country between the two samples in the fraction of drugs on sale in 2009 that are multisource
Table 3: De Facto Exclusivity By Cohort

<table>
<thead>
<tr>
<th>Country</th>
<th>Pre-TRIPS</th>
<th>Post-TRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of drugs</td>
<td>% multi-source</td>
</tr>
<tr>
<td>Brazil</td>
<td>57</td>
<td>14.0%</td>
</tr>
<tr>
<td>China</td>
<td>54</td>
<td>40.7%</td>
</tr>
<tr>
<td>Germany</td>
<td>89</td>
<td>7.9%</td>
</tr>
<tr>
<td>India</td>
<td>61</td>
<td>72.1%</td>
</tr>
<tr>
<td>Korea</td>
<td>62</td>
<td>11.3%</td>
</tr>
<tr>
<td>Mexico</td>
<td>65</td>
<td>6.2%</td>
</tr>
<tr>
<td>Poland</td>
<td>73</td>
<td>8.2%</td>
</tr>
<tr>
<td>Spain</td>
<td>49</td>
<td>9.6%</td>
</tr>
<tr>
<td>US</td>
<td>100</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Based on 155 new drugs launched in the US 2000-2009. Pre-TRIPS means the world-wide priority date is before 1996.
Potential Market Size Differential for Drugs Available and Not Available?

• Using US sales as a measure of market size, let’s compare US sales averaged over drugs that are and that are not available in each country.

• Table 4 indicates that relative market size is strongly associated with whether or not a drug is available in each country.

• On average, US sales are three to five times greater for drugs on sale in a country in 2009 compared to those that were not available – for India the ratio is almost six times.
# Table 4: Global Diffusion and US Market Size

<table>
<thead>
<tr>
<th>Country</th>
<th>Average US Sales $MM</th>
<th>Drugs not available in that country</th>
<th>Drugs available in that country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>$133.4</td>
<td>$515.8</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>$171.8</td>
<td>$548.8</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>$104.5</td>
<td>$386.8</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>$93.0</td>
<td>$538.8</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>$109.4</td>
<td>$502.1</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>$102.2</td>
<td>$489.4</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>$156.5</td>
<td>$426.4</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>$103.4</td>
<td>$409.0</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td></td>
<td>$341.3</td>
<td></td>
</tr>
</tbody>
</table>
Potential Market Size Predictor of “Genericized” or Multisource Drugs?

• Potential market size might also be a good predictor of which molecules are more likely to be “genericized” where patent protection is weak or unavailable – results given in Table 5

• Differences in single/dual vs. multisource less dramatic, but with the exception of Korea, in each country drugs which have been genericized have substantially greater US sales than those that remain single/dual sourced
# Table 5: Genericization and US Market Size

<table>
<thead>
<tr>
<th></th>
<th>US Sales $MM</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single/Dual</td>
<td>Multi-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>source drugs</td>
<td>source</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>477.89</td>
<td>734.08</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>334.31</td>
<td>909.09</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>384.51</td>
<td>412.76</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>422.57</td>
<td>586.04</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>503.97</td>
<td>488.59</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>466.91</td>
<td>812.46</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>405.33</td>
<td>674.56</td>
<td></td>
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<tr>
<td>Spain</td>
<td>373.84</td>
<td>744.36</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>330.81</td>
<td>461.07</td>
<td></td>
</tr>
</tbody>
</table>
Limitations

• Although we have undertaken extensive searches, it is possible (but *a priori* unlikely) that some of the drugs we have designated as multisource are in fact fully licensed by the originator company to multiple local sellers.

• IMS Midas sales data base may not capture all distribution channels, but unclear how this would bias our findings qualitatively.
Conclusions: I

• Many of new drugs launched in the past decade do not have *de facto* market exclusivity in emerging country markets such as those in India, Brazil, China and Korea.

• The Indian market remains particularly difficult for originator companies, with almost ¾ of those drugs in our sample that were on sale in India in 2009 apparently being genericized, multisource drugs.

• The little difference between pre-TRIPS and post-TRIPS drugs suggests that the post-TRIPS policy regime has yet to “bite” to any meaningful degree.
Conclusions: II

• While statutory *de jure* patent protection may be present, particularly in Brazil, India, China and Korea, weak *de facto* protection of new drugs limits their diffusion.

• In 2009 residents of China, India, Brazil, Korea and Mexico have access to less than 60% of the 155 new drugs launched in the US since 2000.

• Drugs with “smaller” US sales are less likely to be launched in emerging countries, whereas drugs with “larger” US sales are more likely to be genericized multisource drugs.
Conclusions: III

• Thus, while competition in the supply of drugs within countries with weak patent protection may result in lower domestic prices than would prevail if the originator company had market exclusivity, any such gains to consumers— and profits to generic manufacturers – may be coming at the cost of limited availability of new drugs for patients that need them – that’s the trade-off
Additional Analyses: I

• Have not controlled for drug-specific characteristics, such as therapeutic class and vintage – extent of competitive incumbent drugs could affect entry decisions

• Might also want to undertake multivariate regression analyses with country characteristics (e.g., population, GDP, national health care expenditures) as explanatory variables, and number of companies selling drug in country as dependent variable, conditional on the drug being available at all
Additional Analyses: II

• In fact, we have just published results of such additional analyses; see Ernst R. Berndt, Nathan Blalock and Iain M. Cockburn, “Diffusion of New Drugs in the Post-TRIPS Era”, *International Journal of the Economics of Business*, 18(2):203-224, July 2011.

• Find that the country and market size effects on availability and genericization of new drugs that we have discussed today are qualitatively robust to various alternative model specifications.
Possible Future Research Directions

• Interview legal/regulatory officials in originator companies, verify unauthorized multisource entry, lack of incentives to enter given weak IP protection

• Extend to other countries, find instances of “natural experiments” and analyze effects on changes in single/dual vs. multisource entry

• Undertake detailed analyses of effects of entry on prices of incumbent and newly entering drugs
We all know that generic medications offer safe, high-quality medicine at a fraction of the cost of a brand-name drug. In fact, once a generic medication hits the market, prices tend to fall by 60-80%. The problem is that many of the drugs we rely on today are not yet available generically in the US. The good news is that this is not the case in India! The law in India allows generic medications to enter the market nearly 20 years sooner than in the US. As a result, generic medications are available for virtually every brand-name drug.

Founded in 2004, Global Pharmacy Canada, Inc. fills over 100,000 prescriptions per year, with over 20,000 satisfied customers in the United States. We deal exclusively in generic medications from India's world-renowned drug manufacturers. Not sure about India? India's pharmaceutical industry is the fourth largest in the world. (Read more about India on page 4 of this letter)

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New customers only

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See FAQ on page 4
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“Founded in 2004, Global Pharmacy Canada, Inc. fills over 100,000 prescriptions per year, with over 20,000 satisfied customers in the United States. We deal exclusively in generic medications from India’s world-renowned drug manufacturers. Not sure about India? India’s pharmaceutical industry is the fourth largest in the world. (Read more about India on page 4 of this letter)” (italics added)
“India is the largest producer of generic medications in the world....

Many of the generic drugs on the shelves at your local US pharmacy come from drug companies in India – the same drug companies Global Pharmacy Canada buys from.

Every year, thousands of American citizens travel to India to receive world-class medical care....

38% of doctors in America are Indian.”