Has the EU Incentive for Drug Repositioning been Effective? An Empirical Analysis

CIPIL Spring Conference

7 March 2020
The Plan

Background
- Definitions
- Incentives and the “repositioning problem”
- Procedural aspects and historical notes on the +1

Method & Results
- Has the +1 increased the proportion of repositioned drugs?
- Has the +1 increased the number of times drug are repositioned?

Conclusion
- Policy implications and reform options
Background
• Drug repositioning: developing new uses (medical indications) for (already) authorised drugs
  • Not rescuing

• Why do we care about repositioning?
  • Cheap(er), fast(er), safe(r)

• What is a new indication?
  • Conditions, including diseases
  • Indications are often very specific
The “Repositioning Problem”

- Repositioned-drug (second medical use) patents are weak
  - Claims have narrow protection and are often invalid
  - And, if valid, are challenging to enforce
    - Cross-label use


Breckenridge & Jacob (2019) argue we should: i) reform to dispensing; and ii) extend regulatory exclusivities.
Incentives

• What are the incentives and competitive advantages?
  
  • Patents, market demand, scientific lead time, distribution networks, obliged drug surveillance, relationships with regulators, relationships with reimbursement authorities, trade secrets, brand power
  
  • $8 + 2 + 1$
• Regulation 726/2004 art. 14(11):
  - Market protection for authorised drugs shall be extended by an extra year IF
    - during the first eight years of market protection,
    - the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications
    - which … bring a significant clinical benefit in comparison with existing therapies.
Historical notes on the +1

- No incentive for repositioning prior to Regulation 726/2004 (*R v The Licensing Authority*, 1998)

- A 2000 EU Commission report expressed concern about “lack of protection” for “significant new indications”

- BUT the report admitted that there was “little hard evidence” to support implementing an incentive for repositioning

- EP Commissioner Liikanen argued the “+1” was the “right balance” between innovators and generics
Procedural Aspects of the +1

- The +1 is only available for drugs applied for AFTER 20 November 2005 (primary authorisation)
- Drug authorisation holders must apply for the +1 when they apply to reposition drugs
- The +1 can only be obtained once per drug
Method & Results
Method: First Stage

- Downloaded EMA database of all medicinal products authorised in the EU via “centralised procedure” (pan-EU rights, began in 1995; 1565 products)
- Remove irrelevant entries (e.g. generics, veterinary drugs, diagnostics etc.), leaving 742 drugs
- The EMA maintains web-based European Public Access Report (EPAR) for each drug.
  - Comb each EPAR for details of repositioning
Method: Second Stage

1. Evaluating whether the +1 increased the proportion of repositioned drugs?
   - Divide the data into two groups:
     a. Drugs applied for **before** 20 Nov 2005 (1/1/95 to 20/11/05)
     b. Drugs applied for **after** 20 Nov 2005 (21/11/95 to 31/12/2010)
   - Count the proportion that are repositioned **at least once** in each group
     - Repositioning only counts if it occurred within 8 years

2. Evaluating whether the +1 increased the number of times drugs are repositioned?
   - Use the same grouping (**before** and **after**)
   - Count: average number of times a drug is repositioned (if it is repositioned)
Crowd Participation (avoiding hindsight bias)

1. Has the +1 increased the proportion of repositioned drugs?
   a. Increased, steady, decreased

2. What proportion of drugs were repositioned in the “after” sample?
   a. 0–12.5%   b. 12.5–25%   c. 25–37.5%   d. 37.5–50%
   e. 50–62.5%   f. 62.5–75%   g. 75–100%.
Results: 1. Has the +1 increased the proportion of repositioned drugs?

<table>
<thead>
<tr>
<th>Time Frame</th>
<th># Primary Drug Authorisations</th>
<th># Repositioned Drugs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>256</td>
<td>108</td>
<td>42.2</td>
</tr>
<tr>
<td>After</td>
<td>125</td>
<td>56</td>
<td>44.8</td>
</tr>
</tbody>
</table>

- A difference of 2.6%; ~ 3 “extra” repositioned drugs
- Not statistically significant ($\chi^2$ test; not close).

<table>
<thead>
<tr>
<th>Year</th>
<th># Primary Drug Authorisations</th>
<th># Repositioned Drugs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>12</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>2004</td>
<td>30</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>2005</td>
<td>18</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>2006</td>
<td>38</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>2007</td>
<td>34</td>
<td>19</td>
<td>56</td>
</tr>
<tr>
<td>2008</td>
<td>30</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>2009</td>
<td>42</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>2010</td>
<td>19</td>
<td>5</td>
<td>37</td>
</tr>
</tbody>
</table>
Results: 2. Has the +1 increased the number of times drug are repositioned?

<table>
<thead>
<tr>
<th>Time Frame</th>
<th># Repositioned Drugs</th>
<th># Repositioning Events</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>108</td>
<td>215</td>
<td>2.0</td>
</tr>
<tr>
<td>After</td>
<td>56</td>
<td>103</td>
<td>1.8</td>
</tr>
</tbody>
</table>

- A difference of 0.2; ~9 “less” times drugs were repositioned.
- Not statistically significant (T-Test; not close).

An explanation:
- “Before” includes two drugs that were repositioned 9x (Remicade and Humira) AND another two that were repositioned 8x
- “After” has no drugs repositioned 6x or more.
Policy Implications
Why has the +1 had no impact?

I. The +1 is an *insufficient* incentive?
   a. Other incentives or competitive advantages are more important, market demand, first mover advantage and patents (original molecule, SPCs, formulation claims, first medical use claims, second medical use claims, drugs linked to diagnostics or delivery mechanisms)

II. We already see high rates of repositioning? ~45%

III. Cross-label use undermines the +1?
   a. How important exactly?
      • Many drugs do not have generics; originator companies sometimes produce their own generic drugs; originator drugs continue to sell; dosage or pharmaceutical form (e.g. cream, tablet, IV) prevents cross-label use.
Conclusion: Reform?

- Increase the +1? +3? More?
  - The +1 didn’t have an affect, why should +3?
  - At what cost? 14 drugs obtained the +1, and the data indicates they probably would have repositioned the drugs without the incentive.
  - Should avoid increasing unless cogent evidence says it will spur innovation that wouldn’t otherwise occur. Cost effectively

- Repeal the +1?
  - What does it cost? 10–100s €/£ of millions
  - Confirm it isn’t spurring “extra” innovation
  - What is the impact of cross-label use?
Thanks & Acknowledgements

- Co-authors
  - Kathy Liddell
  - Mateo Aboy

- Funder