CLINICAL INNOVATION: Fair & Effective Incentives for New Uses of Established Drugs

A critical review of the current landscape
Presentations

Presenters:
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Second Medical Use Patents:

Regulatory Framework and Enforcement in Germany

SMU conference
Washington, D.C., Feb 8, 2018
Christoph de Coster
The Agenda

- Distribution of drugs in Germany
- Substitution rules/practice
- Case law in Germany
- Guidance/Problems
- Conclusions
Distribution/Payment of drugs in Germany

- SHIs
- Pharmacies
- Wholesalers
- Manufacturers
- Patients
- Physicians

Rebate contracts (tender process)
Rebate payments
Payment for drug
Dispensing the drug
Prescriptions

SHIs → Pharmacies → Wholesalers → Manufacturers

Patients → Physicians

Payment for drug
Dispensing the drug
**Substitution in Germany**

**General rule:** Substitution is possible, if
- a physician allows it and
- products are substitutable (same API and one identical indication)

<table>
<thead>
<tr>
<th>Physician</th>
<th>Information</th>
<th>Obligations/Incentives</th>
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<tbody>
<tr>
<td></td>
<td>Patient and indication</td>
<td>Under control and budget pressure of the SHIs</td>
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<td>Available products (software)</td>
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<td>Pharmacist</td>
<td>Prescription</td>
<td>Obligation to dispense the substitutable product which is</td>
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<td></td>
<td>Patient/SHI but no indication</td>
<td>under a rebate contract with SHI</td>
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<td></td>
<td>Substitutable products (software)</td>
<td>otherwise one of the three cheapest on the market</td>
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<td></td>
<td>Rebate contracts of SHIs</td>
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85% of the prescriptions allow substitution

**Conclusion:** Regulatory system promotes wild substitution (cross-label)
German case law

> Pregabalin (Rebate tenders)

- DC Hamburg (2015: Patent Chamber): Gx have to indicate limitations of their tender offer (not for protected indication)

- CoA Dusseldorf (2016: Procurement Division): SHIs have to split tender for APIs into a tender for the protected indications and a tender for the non-protected indications; Social security law does not have priority to patent protection

> Fulvestrant (Liability of Gx despite skinny label)

- CoA Dusseldorf (2017: Patent Division): Direct infringement is possible, if
  > product is suitable for infringing use
  > Gx knows or should know that wild (and infringing) substitution occurs in practice to a relevant extent
Guidelines and remaining problems

1. Rebate Tender

- SHIs have to split tender offer
- Gx cannot participate with skinny label products in an unrestricted tender

**Problem:** Even if different rebate contracts for the same API but different indications exist, pharmacist still does not know which one applies to a certain prescription.

2. Wild Substitution

- Gx are potentially liable for wild substitution as soon as it becomes relevant and obvious

**Problem:** Which measures have to be taken and who is responsible?

- Limited measures available since the Gx have limited influence on behaviour of SHIs/physicians
- Still unclear who (the patentee or the Gx) is responsible for identifying reasonable measures
Conclusions

- The regulatory framework in Germany promotes cross-label (wild) substitution

- German courts cannot solve but just mitigate the dilemma

- Within the current regulatory framework the problem can be mitigated, if physicians do not allow substitution in case
  - the prescription is for a still protected indication of the API and
  - the other available products have carved out this indication

  **But:**
  - SHIs have to promote such practice under their cost efficiency control and
  - physicians need sufficient information

- **Proposal:** Agreement between Association of SHIs and the Association of physicians providing an up-to-date list of products for which substitution should be excluded for certain (still protected) indications plus software implementation
A Critical Review of the Current Landscape

Patents and Practice in the U.S.

Elaine Herrmann Blais
Goodwin Procter LLP
February 8, 2018
Overview: Protection for Additional Uses

• Regulatory exclusivities – Dan Kracov’s presentation

• Method-of-Use Patents
  - Companies manufacturing generic versions of drugs can either:
    ▪ Wait for the patent to expire (“Paragraph III” or “PIII”),
    ▪ Challenge the patent (“Paragraph IV” or “PIV”), or
    ▪ Carve-out the patented use (“Section viii carve-out”)
  - Carve-out means: not seeking FDA approval on the patented use
    ▪ The patented use will be “carved-out” from the generic label; the resulting label will be a “skinny label” omitting information about the patented use
Overview: Method-of-Use Patents

• Method-of-use patents ("MOU" patents) cover new indications/uses for a drug

• No direct infringement
  - Drug manufacturers are not treating patients or practicing the patented method

• Indirect infringement
  - Contributory infringement
    ▪ defeated if there is a substantial noninfringing use, which the remaining labeled (first) use often is
  - Induced infringement
    ▪ requires showing specific intent and active steps taken to cause direct infringement
Overview: Prescribing, Dispensing, Reimbursement

- **Doctors** prescribe drugs
  - Doctors can prescribe either by brand name or active ingredient, and can optionally further specify to “dispense as written”

- **Pharmacies** dispense drugs
  - Automatic substitution laws: unless doctor specifies “dispense as written,” a generic will be automatically substituted for the brand drug
  - Indications play no role in generic dispensing
    - Pharmacies dispense AB-rated generics for all uses regardless of label carve-outs
    - Pharmacies typically do not know (a) what indications are in a generic label, and/or (b) which condition the product was prescribed to treat

- **Insurers** determine costs of drugs
  - Prescription filled with an AB-rated generic: **low copay**
  - Prescription filled with brand drug, when an AB-rated generic version is available: **higher copay, or no coverage at all**
Implications for Patent Litigation

- Inducement infringement requires **specific intent** and **active steps** taken to **cause** direct infringement

- Doctors **prescribe** drugs – practice of medicine
- Pharmacies **dispense** drugs – automatic substitution laws
- Insurers determine **costs** of drugs – copay schedule depends on availability of generic

**How do these legal and practical contexts inform induced-infringement cases?**

- Is mere knowledge of how a generic might be dispensed and/or used for a patented method enough to show inducement?
- What factors should be considered in demonstrating specific intent and active steps taken to induce infringement?
  - pre-launch: inducement based on label only
  - post-launch: other activities (e.g. marketing) may come into play
- What factors should be considered in attributing causation?
  - What influences doctors to make their prescribing decisions? Medical journals? Practice guidelines? Brand promotional activity? Generic promotional activity?
## Competing Incentives, Competing Solutions

### Competing Incentives in the U.S. System

<table>
<thead>
<tr>
<th>Incentivize research and development of <strong>new uses</strong> for <strong>old drugs</strong></th>
<th>Incentivize use of <strong>lower-cost drugs</strong> for <strong>off-patent treatments</strong></th>
</tr>
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<tbody>
<tr>
<td>Award patents on new uses</td>
<td>Allow generics to be used for old/non-patented uses</td>
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Who are the stakeholders?
Where are the action points?
Who decides whether these solutions work with each other?
A Critical Review of the Current Landscape:

Current U.S. Regulatory Incentives and Expedited Programs

Daniel Kracov

Clinical Innovation:
Fair and Effective Incentives for New Uses of Established Drugs
February 8, 2018
The 505(b)(2) Application

- Type of new drug application (NDA) – not an abbreviated new drug application (ANDA)
- Relies, in part, on published information or FDA's past finding of safety and efficacy for which the 505(b)(2) sponsor does not have a right of reference
  - Application containing "investigations . . . relied upon by the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." FDCA Sec. 505(b)(2)
- Sponsor typically needs to submit new studies to support change
- Pathway can reduce development time and costs
When is it Used?

- When the proposed drug product is different from the Reference Listed Drug
  - New dosage form (e.g., tablet, capsule)
  - New indication
  - Different strength
  - Different route of administration
  - Different active ingredient (e.g., enantiomer, racemate, salt, ester)
  - Substitution of active in combination product
  - Rx-to-OTC switch
  - Formulation changes outside 505(j)/ANDA limits
  - Naturally-derived v. recombinant active ingredient
When is it Not Used?

- Cannot be used when
  - The proposed drug product could be submitted for approval by the 505(j) ANDA pathway
  - Only difference is the extent to which the active ingredient that is absorbed is less than the RLD
  - Only difference is that the rate that the active ingredient is absorbed is unintentionally less than the RLD
505(b)(2) — Patent Considerations

- Hybrid patent requirements
- Must comply with patent certification and notice requirements (like ANDAs)
  - Must address all patents listed in the Orange Book for the RLD upon which the applicant relies
  - May be delayed from FDA final approval by the existence of blocking patents for the RLD
- Still subject to patent listing requirement (like NDAs)
Regulatory Incentive Provisions

**Drugs (NDAs)**
- 5-year exclusivity for new chemical entities (NCEs)
- 3-year exclusivity
  - New indications, clinical exclusivity, etc.
- 7-year orphan drug exclusivity
- 6-month pediatric exclusivity
- 5-year QIPD exclusivity (antibacterials/antifungals)

**Biologics (BLAs)**
- 12-year reference biologic exclusivity
- 7-year orphan drug exclusivity
- 6-month pediatric exclusivity
Expedited Programs

- Breakthrough Therapy designation
- Regenerative Medicine Advance Therapy (RMAT) designation
- Fast Track
- Accelerated Approval
- Priority review vouchers (6 month review)
  - Rare Pediatric Disease
  - Tropical Disease
  - Medical countermeasures (chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases)
- For antibacterial and antifungal drugs:
  - Qualified Infectious Disease Product (QIDP) designation
  - Limited Population Pathway
First Amendment Developments and SMUs
Questions?

Dan Kracov

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UK drug markets and SMU patents

Gareth Morgan
Overview of UK P&R

- Drug Tariff works to maintain drug price competition
- Category C includes pre-generic innovative products
- Price set in accordance with the PPRS
- Upon generic entry drugs usually undergo reclassification
- Category A includes readily available generics
- Pricing then becomes set by DoH (based on average wholesaler/generic company prices)
Overview of UK generic approvals

- Where SMU patents exist generic companies will “carve out”
- Removal of protected indications from product literature
- Gives rise to “skinny labels”
- Risk this runs is these products are nevertheless used “off-label”
- UK prescriptions do not carry intended use so the pharmacist dispenses blind
Resulting situation

- So on generic entry:
  - Reclassification occurs in the Drug Tariff
  - Takes a number of months
  - Price is set by DoH
  - Reflects generic pricing
  - Therefore leads to a rapid decline

- Regulators practice of approving “skinny labels” creates a dual product market in terms of labelling

- Drug Tariff does not recognise the products as being different

- Therefore protected indications are exposed to generic competition from first generic product entry into an unprotected indication
How have the markets/courts reacted?

- Some companies have succeeded in creating a dual market
- Glivec has generic competition in its CML indication but GIST is protected by a SMU patent
- Product is supplied direct into the hospital market
- NHS in the UK splits hospital tenders for Imatinib between CML (with generic competition) and GIST (no generic competition)
How have the markets/courts reacted?

- Lyrica is more complex - no ability to create a split tender market

- Courts have indicated certain steps have to be followed in order to satisfy patentee generics are attempting to avoid the protected SMU

- NHS has implemented prescribing guidance but this is not binding and not “hardwired” into P&R

- Comes down to individual prescribing physicians

- That is the point the generic prescription for the protected SMU occurs