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

A critical review of the current landscape
Presentations

Presenters:

- **Christoph de Coster** *Taylor Wessing LLP*
- **Elaine Herrmann Blais** *Goodwin Procter LLP*
- **Daniel Kracov** *Arnold & Porter Kaye Scholer LLP*
- **Gareth Morgan** *CMS Cameron McKenna Nabarro Olswang LLP*

Second Medical Use Patents:

Regulatory Framework and Enforcement in Germany

SMU conference

Washington, D.C., Feb 8, 2018

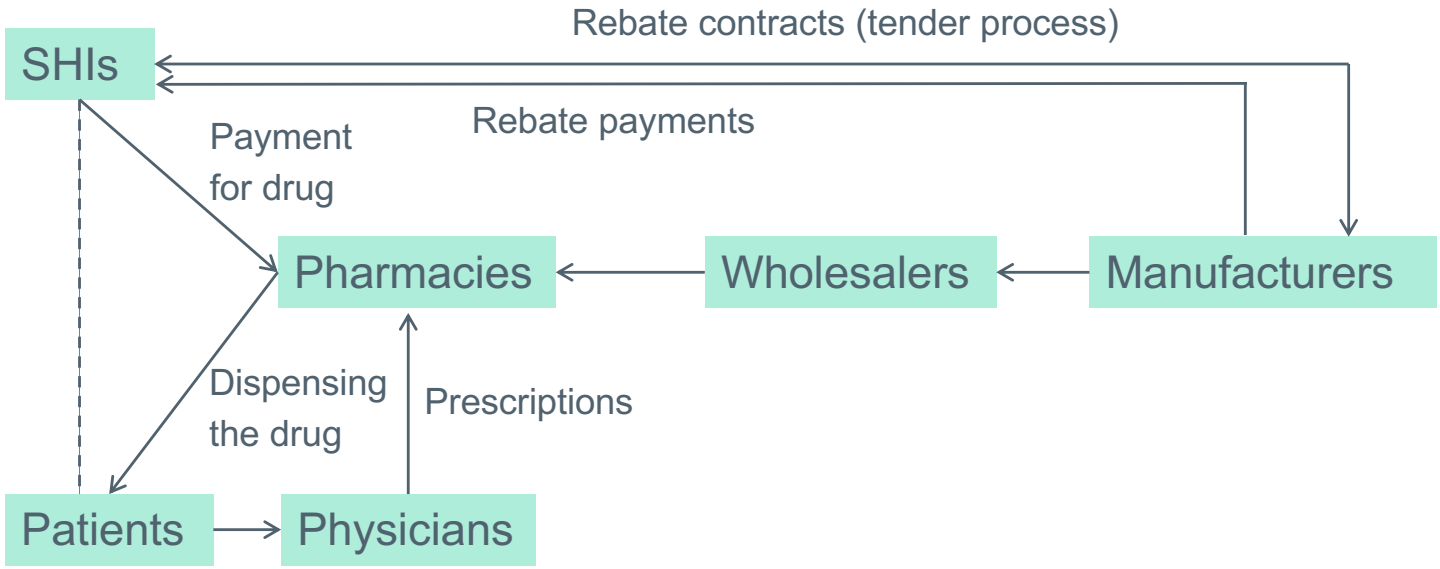
Christoph de Coster

TaylorWessing

The Agenda

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

Distribution/Payment of drugs in Germany



Substitution in Germany

General rule: Substitution is possible, if

- a physician allows it and
- products are substitutable (same API and **one** identical indication)

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

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	
Incentivize research and development of ***new uses*** for ***old drugs***	Incentivize use of ***lower-cost drugs*** for ***off-patent treatments***
↓ Award patents on new uses	↓ Allow generics to be used for old/non-patented uses

Who are the stakeholders?
Where are the action points?
Who decides whether these solutions work with each other?

Arnold & Porter

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)

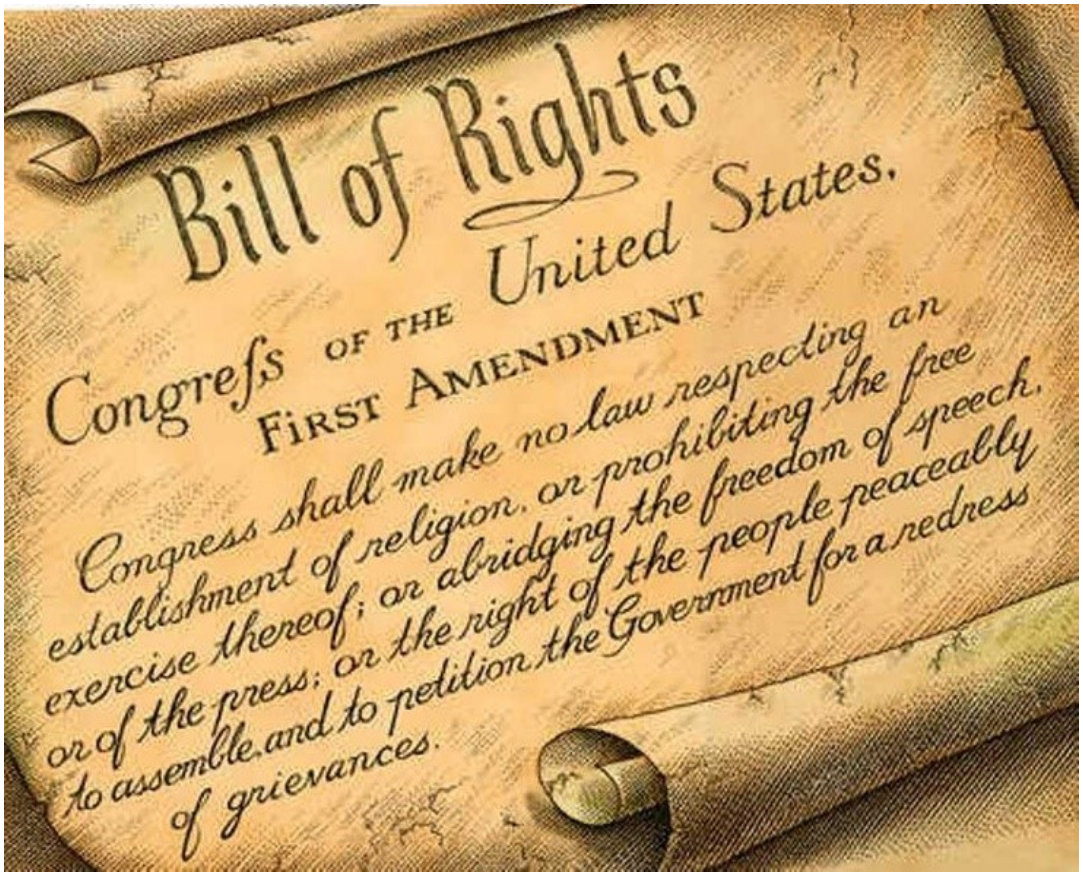
Biologics (BLAs)

- 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

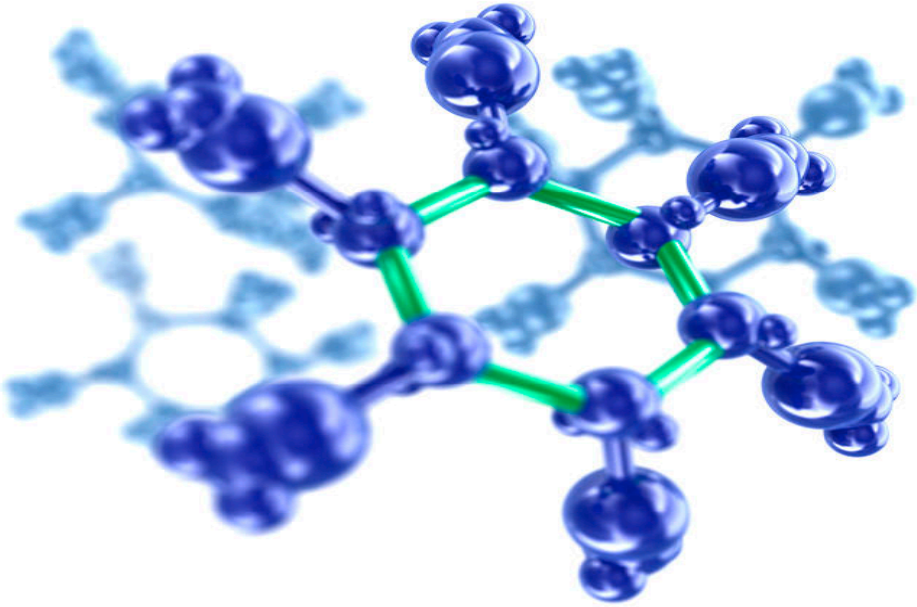
daniel.kracov@arnoldporter.com
202-942-5120

Your World First

C/M/S/
Law.Tax

UK drug markets and SMU patents

Gareth Morgan



SMU Conference Washington - Session 1E | 8 February 2018

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 is 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