El Lunes de Patentes (Patent Mondays)

Barcelona, Spain

September 29, 2008

AstraZeneca v. Mylan and Esteve
The Omeprazole II US Patent Case
An Eight Year Patent Conflict About a Best-Selling Prilosec® (Losec® in Europe) Drug

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Overview

• Chronology of the case

• Design around avoids infringement

• Foreign supplier liability – before launch and after launch

• Foreign supplier discovery issues – as non-defendant third party and as defendants

• Testing finished products and intermediates

• “At Risk” sales prior to adjudication
## Chronology of the Case

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 7, 2000</td>
<td>Complaint Filed</td>
</tr>
<tr>
<td>April 3 – June 14, 2006</td>
<td>Trial</td>
</tr>
<tr>
<td>May 31, 2007</td>
<td>Trial Court Decision</td>
</tr>
<tr>
<td>May 6, 2008</td>
<td>Oral Argument CAFC</td>
</tr>
<tr>
<td>June 10, 2008</td>
<td>CAFC Decision</td>
</tr>
</tbody>
</table>
The Mylan/Esteve Defendants

API

Laboratorios Dr. Esteve, S.A.

Pellets

Holding Company

Capsules
Esteve carefully reviewed the Astra patents 15 years ago to develop a non-infringing formulation that is independently protected by two U.S. patents (5,626,875 and 6,780,436)
The Problem Solved by Astra’s Patents

- Omeprazole is acid labile
- There must be protection from stomach acids
- Enteric coat prevents exposure in stomach
- Because enteric coat is itself acidic, to protect omeprazole
  - add alkaline reacting compound (“ARC”) to omeprazole
  - put a protective layer containing, e.g., HPMC between omeprazole and enteric coat
- Protective layer protects omeprazole from acids in enteric coat and protects enteric coat from ARC drug layer.
We claim:

1. An oral pharmaceutical preparation comprising
   (a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;
   (b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and
   (c) an outer layer disposed on said subcoating comprising an enteric coating.

TABLE 6

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Capsule</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>010</td>
<td>024</td>
</tr>
<tr>
<td>20</td>
<td>010</td>
<td>024</td>
</tr>
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<td>25</td>
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</tr>
<tr>
<td>65</td>
<td>010</td>
<td>024</td>
</tr>
</tbody>
</table>

*Note: The oral concentrations listed are the mean single dose of omeprazole given in food-gland coated according to Example 5 and 5a, a preparation comprised of polymeric and inert excipients.*
Examples Of ARCs – Do Not Include Talc, HPMC or TEA

to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other 50 suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as Al₂O₃.6MgO.-CO₂.12H₂O, (Mg₆Al₂(OH)₁₆CO₃.4H₂O), MgO.Al₂O₃.- 2SiO₂.nH₂O or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline

Also included into the coating layer:
- In case of gelatin capsules the gelatin capsule itself
- In case of PVP-coated pellets or microgranules
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The Patents Distinguish Talc From “ARCs”

Enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>10</td>
<td>9</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Excipient</td>
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<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
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<td>40</td>
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<tr>
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<td>40</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pH 7.5</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
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<tbody>
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</tr>
</tbody>
</table>

The tablets that obtained were stored in open form under so-called accelerated conditions, that is 40°C,
Esteve Design Around

- Esteve project leaders used patent disclosures to carefully avoid ARCs and instead included HPMC and talc in the Omeprazole layer.

- Esteve formulation relies on limiting exposure to moisture, including effective physical barriers, for stability – not chemical stabilization.

- Esteve received ‘875 Patent for its novel ARC-free formulation.
Impact of Design Around

- The selection and location of the ingredients forced Astra to make inconsistent and indefensible arguments

- It asserted that the HPMC and Talc in the active ingredient core provided impurities that are ARCs to that layer but it also argued that the very same HPMC and Talc that are in the protective subcoating met the patent’s limitation for that layer that they be inert!

- The court did not accept this argument
Enteric Coating

* Methacrylic Acid Copolymer
* Triethylcitrate
* Talc

Protective Subcoating

* HPMC
* Talc
* Titanium Dioxide

Inert Core

* Sucrose
* Starch

Active Coating

* Omeprazole
* HPMC
* Talc

See 490 F. Supp. 2d 381, 425 (2007)
Liability Of The Foreign Supplier Before Launch
Hatch-Waxman Act

- Statutory safe Harbor for activities relating to submission for FDA approval
  
  35 U.S.C. 271(e)(1)

- Filing ANDA creates artificial act of infringement
  
  35 U.S.C. 271(e)(2)(A)

- Limited Pre-launch Remedies
  - court order prohibiting FDA approval before patent expiration
  - injunction against commercial activities
  
  35 U.S.C. 271(e)(4)(A), (B)
Liability Of The Foreign Supplier **Before** Launch
Inducing Infringement

- “Whoever actively induces infringement of a patent shall be liable as an infringer.” -- 35 U.S.C. 271(b)

- Supplier of a product or component may be liable for inducing infringement if the patentee shows:
  - there has been direct infringement; and
  - the supplier knowingly induced the infringing acts with the specific intent to encourage the direct infringement
Liability Of The Foreign Supplier Before Launch
Mylan/Esteve’s Omeprazole Case

- **Sep 2000:** Astra sued Mylan based on filing ANDA
- **Jan 2003 (pre-launch):** Astra sought consent to add EQ and LDE as parties – Mylan refused
- Astra moved to amend its complaint to add EQ/LDE as parties – motion denied
Liability Of The Foreign Supplier Before Launch
Astra’s Theory of Inducement

- Submission of omeprazole DMF and authorization for Mylan to reference the DMF in the ANDA
- Collaboration with Mylan in developing the ANDA product
- Providing assistance to Mylan in preparing its ANDA
- Supplying raw materials and pellets to be used in the ANDA product
- Providing raw materials and documentation used to support the ANDA batches relied on for FDA approval
## Liability Of The Foreign Supplier Before Launch

**Case Law as of 2003**

<table>
<thead>
<tr>
<th>YES</th>
<th></th>
<th>NO</th>
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<tbody>
<tr>
<td>• <em>SmithKline Beecham Corp. v. Pentech Pharms., Inc.</em>, 2001 WL 184804 (N.D. Ill. Feb. 20, 2001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“There is no doubt that Astra’s proposed complaints sufficiently allege that [EQ and LDE] significantly and intentionally aided Mylan . . . in the preparation of [its] ANDA and would likely participate in the manufacture of the proposed product if approved.”

BUT . . .

“[T]he appropriate question in an inducement inquiry brought under section 271(b) with respect to an ANDA filing is whether the drug, if approved, will induce infringement of the plaintiff’s patents. Therefore, the Court finds that an action for inducement for aiding and abetting the filing of an ANDA is unavailable.”

_AstraZeneca AB v. Mylan Labs., 265 F.Supp.2d 213 (S.D.N.Y. 2003)_
Liability Of The Foreign Supplier Before Launch
Federal Circuit 2007: *Forest Labs*

- District court permitted addition of foreign API supplier as a party; issued injunction against both ANDA applicant and supplier

- Majority: “Cipla has therefore actively induced the acts of Ivax that will constitute direct infringement upon approval of the ANDA, and it was thus not inappropriate for the district court to include Cipla within the scope of the injunction.”

  *Forest Labs, Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007)

- Dissent (Schall, C.J.): Cipla’s activities of contributing to the ANDA fell within the 271(e)(2) safe harbor and thus should have been immune from suit
Liability Of The Foreign Supplier **Before Launch**
Impact of *Forest Labs*

- Foreign suppliers less likely to avoid being brought into ANDA litigation
- Involvement in the ANDA submission triggers potential liability
- Scope of injunction against API supplier should be narrowly tailored
- U.S. subsidiary/affiliate of foreign supplier may be at risk if it was involved in the ANDA filing process or will be involved in importing, selling, manufacturing, or marketing of the future product
Liability Of The Foreign Supplier After Launch

- No safe harbor -- importation, sale, etc. are subject to liability
- Post-launch remedies include
  - pre-launch remedies (injunction/stay of FDA approval) -- 35 U.S.C. 271(e)(4)(A), (B)
  - monetary relief (e.g., damages) -- 35 U.S.C. 271(e)(4)(C)
- Direct and indirect infringers are jointly and severally liable
- No less than a reasonable royalty -- 35 U.S.C. 284
- Lost Profits
- Enhanced damages for willfulness -- 35 U.S.C. 284
Foreign Third-Party Discovery Generally

- U.S. discovery rules permit broad discovery of information within the “possession, custody and control” of parties and non-parties that are within the federal courts’ jurisdiction

- Discovery from foreign third parties located outside the U.S. is governed by international treaty (e.g., Hague Convention)

- Letter of Request limits permissible discovery, e.g., requests for documents may be prohibited (as in Spain); deposition questions must be disclosed in advance
Some Discovery Considerations For The Non-Party Foreign Supplier

• Potential discovery under Hague Convention
• Consideration of voluntary compliance with discovery requests issued to ANDA applicant
• Potential inability of ANDA applicant to rely on incomplete information or information not produced during discovery (e.g., underlying test data; partial test results produced)
• Potential that supplier will eventually be added as a party
• Potential requirement for expedited discovery to catch up in a consolidated action
• Potential that document production will lead to identification of additional witnesses for depositions
Discovery Issues For The Foreign Supplier As A Party

• Full discovery under the U.S. Federal Rules
  – Paper Documents/Samples/Site Inspections
  – Electronic Discovery
  – Depositions
  – Interrogatories
  – Requests for Admissions
• Discovery and use of information from prior litigations
• Privilege and immunity issues
  – Attorney-Client Privilege
  – Work Product Immunity
  – Joint Defense
  – Common Interest
Discovery Of Esteve In The Omeprazole Case

- Dec 2002: Astra seeks documents from Esteve’s files from Mylan -- Esteve produces limited voluntary discovery through Mylan
- May 2003: Court denies Astra’s motion to compel production
- May 2003: Court denies Astra’s motion to add Esteve as party
- May 2003: Astra submits motion for Letter of Request to take depositions of Esteve witnesses in Spain – granted in June
- Jul 29, 2003: Esteve depositions in Court of First Instance 24 Barcelona
- Aug 4, 2003: Mylan launches product
- Aug 8, 2003: Astra files separate lawsuit against Esteve
- Dec 03 – Apr 04: Expedited discovery of Esteve in Spain and U.S.
Testing of Finished Product and Intermediates

- Hundreds of samples produced by Mylan/Esteve
- Finished Product (capsules) – Mylan
- Intermediates (pellets at each coating level) – LDE
- Raw Materials (API and 9 excipients) – EQ, LDE and Mylan
Some Samples Production Issues

- Chain of custody
- Complications of shipping samples overseas
  - Shipping/storage conditions
  - Customs issues
- Sufficient supply of materials for counter-testing
- Representativeness of samples
  - Expiration/Degradation
  - Changes in specifications or manufacturing process
Some Testing Issues In Mylan/Esteve’s Case

• “Alkaline Reacting Compound” = (1) pharmaceutically acceptable alkaline compound that (2) stabilizes the omeprazole [in the formulation] by (3) reacting to create a “micro-pH” around the omeprazole particles of not less than 7

• Astra alleged that every component of Mylan/Esteve’s omeprazole-containing layer met the “ARC” requirement

• At least four potential areas for testing
  – presence of alleged ARC
  – pH of alleged ARC
  – stabilization by alleged ARC
  – “micro-pH” around omeprazole

• Astra presented some test evidence purporting to establish each of the above but focused mainly on pH and “micro-pH”
Astra’s Battery of “ARC” Testing

- pH Testing: talc, HPMC, omeprazole, mixtures
- “micro-pH” testing: active layer material from pellet intermediates
- “Acid Challenge” tests and pH titrations: talc, HPMC
- EDX and FTIR spectroscopy: carbonates in talc
- “Stability” tests: active layer coating suspensions
- GC/MS: carbonates in HPMC
- Selected Mylan/Esteve early R&D and regulatory data
How Mylan/Esteve Overcame Astra’s Tests

• Introduced contradictory test results
  – Samples testing by Mylan/Esteve’s pH expert
  – Data submitted in previous litigation against Esteve in Europe

• Introduced credible expert testimony of pH and organic chemistry experts who pointed out inconsistencies and unsupported assumptions in opposing expert testimony/test evidence

• Highlighted inconsistency in testing of co-defendant’s formulated pellet for presence of impurity while failing to use the same test on Mylan/Esteve’s pellet to test for the same alleged impurity (the “super sniffer”)

How Mylan/Esteve Overcame Astra’s Tests

• Highlighted prior rulings in “First Wave” case
• Attacked relevance of Astra’s testing
  – Design around theme (deliberate avoidance of “ARCs”)
  – Patent disclosures (HPMC and talc not “ARCs”)
  – Prior admission in EPO counterpart (talc not an “ARC”)
  – Use of tests predating change in specifications
• Used simple, yet effective, in-court demonstration by organic chemistry expert to attack trace impurity stabilization theory
• Presented stability data for talc-free versions of Mylan/Esteve formulation
How Mylan/Esteve Overcame Astra’s Tests

• Highlighted selective reliance on tests that did not represent Mylan/Esteve product
  – Early stability data for non-US versions of Esteve’s products having different structures and specifications
  – Esteve’s early pH testing predating change to pH specification for HPMC for Mylan/Esteve product

• Presented credible fact testimony about Esteve’s product development

• Attacked failures of proof on multiple levels: presence of alleged ARC in raw material, presence of ARC in final product, presence of stabilizing amount in final product
Sales “At Risk” Prior To Adjudication
Risk/Reward Balancing

• Value of early market entry
  Versus
• Potential for considerable damages exposure
  – Damages not less than a “reasonable royalty”
  – Potential lost profits (multi-billion dollar, high margin product)
  – Potential enhanced damages (up to 3x actual)
  – Potential attorneys fees in “exceptional case”
  – Even if prevail at trial, damages accrue while decision is on appeal
• Mylan/Esteve’s omeprazole launch in 2003 is believed to be first generic at-risk launch prior to a favorable trial court decision
Sales “At Risk” Prior To Adjudication
Likely Trend: More At-Risk Launches

- Reduced risk of willfulness finding under recent Fed. Cir. case law
- Increasingly competitive market environment
- Waning number of blockbuster drugs
- Consolidation and growth of generic industry
- Increase in authorized generics
- Recent change in law regarding obviousness
- Previously feared doomsday scenario has not occurred
Some Concluding Points

• A good pre-litigation design-around story can have significant impact (e.g., avoidance of ARCs)

• Changes in an accused product or process even after start of litigation can have significant impact (e.g., HPMC specification)

• Counter testing, while not required, can tip the balance (e.g., “micro-pH”)

• Discovery of previous litigation positions and foreign counterpart prosecution histories can reveal critical admissions (e.g., talc is not an ARC; Esteve’s omeprazole is acidic)

• Avoiding discovery from non-party collaborator could prevent assertion of potential defenses (e.g., talc-free stability studies)
Some Concluding Points

- Common issues in consolidated case may be a significant advantage or disadvantage (e.g., the “super sniffer”)
- Reliance on non-representative data and/or cherry-picking documents produced by the other side can damage credibility (outdated pH testing/inapplicable stability studies)
- Multiple level attacks can expose critical failures of proof (e.g., presence of alleged ARC in raw material, presence of ARC in final product, presence of stabilizing amount in final product)
- Early involvement of both local counsel and U.S. counsel in projects likely to lead to litigation helps reduce litigation risks and provides an invaluable liaison to U.S. litigation counsel when litigation occurs