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Litigation Webinar Series

Hatch-Waxman 301: Proving Infringement in a Hatch-Waxman Case



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Patenting the Label

Objective

- Presentation of strategies for adding patentable subject matter to drug labels to protect brand investments and market share.

Summary of Strategic Considerations

- Drug labels generally — purposes, opportunities for patent protection, sources of protectable information.
- Drug description claims evidence of direct infringement.
- Method of use claims — evidence of induced infringement.
- Label sections where patent protected information can appear.
- Understanding the generic labeling “sameness” rule and its exceptions.
- New FDA rules on OB listing of method patents and use codes.
- Label “ever-greening” strategies.
- Implementing good patent-labeling practices.
- Recent patent developments involving method of treatment claims.

Drug Labels Generally

- Pre-clinical data.
- Information obtained from clinical studies:
 - Phase I — metabolic actions, pharmacological actions, drug metabolism, safety, side effects, structure-activity relationships, mechanism of action.
 - Phase II — effectiveness for targeted indications and uses, side effects, risks.
 - Phase III — side effects, drug interaction, population-specific data.
 - PMR (post approval) information.
- Spontaneous reports from physicians, hospitals, patients.
- Useful information for patients and healthcare providers.
- Safety concerns (duty to warn).
- Note: label language is a negotiation with FDA.

Drug Description Claims – Evidence of Direct Infringement

- Formulations.
- pH levels.
- Stability characteristics.
- Impurity levels.
- Molecular structures (hydrates, solvates, polymorphs).
- Analytical standards.
- Molecular weight.
- Process of making (not OB listable).
- Product by process (OB listable).
- Sterilization data.
- Metabolites (not OB listable).

Drug Description Claims (cont'd)

➤ Biomarker information on labels:

- Genetic v. non-genetic.
- Disease related v. drug related.
- Informational labeling (dose adjustment or side effects based on genotype).
- Therapeutic labeling (ID patients at risk; ID patient responders; choosing dosing schedule).

➤ Examples of biomarkers on approved labels:

- Maraviroc (first approved biomarker test 2007) — genetic test to determine mutation of HIV virus.
- Gleevec — test to identify patients that over-express a particular protein, to treat GIST.
- Revlimid — test for cytogenetic abnormality, to treat transfusion dependent anemia.
- Warfarin — genotype test to identify SNPs, for accurate dosing of Coumadin.
- Ziagen — test for alleles to calibrate dosing.
- Plavix — genotype test to identify patients who may not respond to the drug.
- Elitek — test for enzyme deficiency to determine patient monitoring.
- Herceptin — test for over-expression of protein to identify cancer patients eligible to take the drug.

Method of Use Claims – Evidence of Inducement

- Indications.
- Dosage and administration.
- Precautions.
- Warnings.
- Contraindications.
- Adverse drug reactions.
- Companion diagnostics (biomarker testing).
- Combination therapies.

Sections Of Label Where Patent-Protected Information May Be Located

- Description (drug identify and characteristics).
- Indications and usage.
- Dosage and administration (including monitoring recommendations, food effects, etc.).
- Dosage forms and strength.
- Contraindications.
- Warnings and precautions.
- Adverse reactions.
- Drug interactions (including absence of interactions).
- Use in specific populations (e.g., pregnancy, pediatric use, geriatric use).
- Drug abuse and dependence.
- Over-dosage.
- Clinical pharmacology (including microbiology, mechanism of action).
- Non-clinical toxicology.
- How supplied/storage and handling.
- Patient counseling information (e.g., pregnancy, nursing mothers).
- Other FDA-required information for certain types of drugs or drug substances.
- Optional labeling permitted on animal pharmacology and clinical studies.

Drug Description Patents - Examples

➤ Formulation:

- **Label:** Nexium® is supplied as a delayed-release capsule containing the Mg²⁺ salt of omeprazole with an enteric coating.
- **Claim:** A pharmaceutical preparation comprising
(a) a core comprising an alkaline omeprazole salt; and
(b) an outer layer comprising an enteric coating.

➤ Impurity levels:

- **Label:** No more than 2% of the drug compound X is in the form of the R-stereoisomer.
- **Claim:** A compound X composition wherein at least 98% of the compound X is the S-stereoisomer.

Drug Descriptions Patents (cont'd)

➤ Analytical standards:

- **Label**: 15-25% of the polysaccharide chains of Lovenox[®] enoxaparin have a 1,6 anhydro ring structure on the reducing end, when analyzed by the following method:
- **Claim**: Method of analyzing for polysaccharides with 1,6 anhydro ring structure on the reducing end.

➤ Molecular weight:

- **Label**: Ferrlecit[®] (sodium ferric gluconate complex in sucrose injection) is a stable macromolecular complex with an apparent molecular weight *on gel chromatography* of 350,000 ± 23,000 daltons.
- **Claim**: Method for producing gluconate complex comprising: evaluating apparent molecular weight of the complex *on gel chromatography*, and discarding preparations where the apparent molecular weight is not between 300,000 and 400,000.

Drug Descriptions Patents (cont'd)

➤ Product by process:

- **Label**: [Approved HRT product] is a complex mixture of hormones A, B, C and unidentified metabolites, purified from pregnant mare urine by the following process . . .
- **Claim 1**: A process for extracting a hormonal mixture from urine, the process comprising . . .
- **Claim 2**: A product made by a process comprising. . .

Methods of Use Patents - Examples

➤ Indication:

- **Label**: Tamoxifen is indicated for treatment of breast cancer in women who do not have the CYP2D6*4/*4 genotype.
- **Claim**: A method of treating a breast cancer patient comprising:
 - determining that a patient has breast cancer and does not have the CYP2D6*4/*4 genotype; and
 - administering tamoxifen to the patient.

Methods of Use Patents (cont'd)

➤ Dosage and administration:

Antibiotic X previously limited to use on an empty stomach; now found that it doesn't matter.

- **Label**: Antibiotic X tablets can be taken with or without food.
- **Claim**: A method of administering Antibiotic X comprising administering Antibiotic X tablets to a subject who has recently eaten food.

Methods of Use Patents (cont'd)

➤ Precautions:

INOmax[®] (inhaled NO gas), a known treatment for pulmonary hypertension in neonates, found to trigger pulmonary edema in neonates who have left ventricular dysfunction.

- **Label**: Patients with left ventricular dysfunction treated with INOmax[®] may experience pulmonary edema. . . . Discontinue INOmax[®] while providing symptomatic care.
- **Claim**: See patented claims on next two slides.

Methods of Use Patents (cont'd)

➤ Precautions example:

US 8,431,163

1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:
 - (a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;
 - (b) determining that the patient identified in (a) has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
 - (c) excluding the patient from inhaled nitric oxide treatment, based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

Methods of Use Patents (cont'd)

Precautions example:

US 795,741

1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:
 - (a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;
 - (b) determining that a first patient of the plurality does not have left ventricular dysfunction;
 - (c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;
 - (d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and
 - (e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

Methods of Use Patents (cont'd)

➤ Warnings:

Thalomid® (thalidomide)

- **Label**: WARNING: Thalidomide causes birth defects and is approved for marketing only under a special restricted distribution program approved by the FDA.
- **Claim 1**: Method for distributing a teratogenic drug comprising. . .

Methods of Use Patents (cont'd)

➤ Contraindications:

Vaccine X appears to have caused an adverse reaction in one patient who years earlier received a liver transplant.

- **Label**: Vaccine X should not be given to patients who received a liver transplant.
- **Claim**: A method of administering Vaccine X comprising
 - a) identifying a patient in need of immunization with Vaccine X;
 - b) determining whether the patient has ever received a liver transplant; and
 - c) if the patient has never received a liver transplant, administering Vaccine X.

Methods of Use Patents (cont'd)

➤ Contraindications:

Drinking grapefruit juice alters metabolism of felodipine and may cause overdose symptoms.

- **Label**: Patient should not drink grapefruit juice within four hours before or after taking felodipine.
- **Claim**: A method for prescribing felodipine comprising
 - a) Identifying a patient in need of felodipine;
 - b) Prescribing that the patient take felodipine; and
 - c) Advising the patient not to drink grapefruit juice within four hours before or after taking felodipine.

Methods of Use Patents (cont'd)

➤ Adverse drug reactions:

Tamiflu®

- **Label**: Children who are taking Tamiflu® should be closely monitored for signs of abnormal behavior, such as delirium.
- **Claim 1**: A method of treatment comprising
 - a) administering Tamiflu® to a child in need thereof; and
 - b) monitoring the child for symptoms of delirium associated with the use of Tamiflu®.
- **Claim 2**: A method of treatment comprising
 - a) prescribing Tamiflu® treatment for a patient in need thereof; and
 - b) instructing the patient's caregiver to monitor the patient for symptoms of delirium during treatment with Tamiflu®.

Generic Labeling Sameness Requirement

- General rule: ANDA label must be same as brand.
- Exceptions to sameness rule (21 CFR 314.94(a)(8)(iv)): changes in formulation, bioavailability, pharmacokinetics, indications/uses protected by patent.
- Under FDA rules, polymorph with bioequivalence showing constitutes “same AI” as in brand drug.

OB Listing Rules for Use Patents (Form 3542)

- Identification of claim #s that read on label.
- Identification of label location(s) on which the patent claims read.
- Use code language protected by patent for which a section viii “carve out” statement rather than a patent certification can be filed.

FDA 2016 Update to Use Code Rules

- Use code must describe only the specific approved method of use claimed by the patent.
- Note that H-W statute requires listing of use patents that claim a method of using such drug for which a claim can reasonably be asserted.
- New rule also says that if patent claim does not cover an indication or other approved condition of use in its entirety, then the use code must describe only the specific approved method of use claimed by the patent.
- FDA decides whether to allow a partial overlap of label and use code.
- Example of UC carve out problem:
 - Drug approved to “treat pain” based on a neuropathic study and a nociceptive study.
 - Patent claims use of the drug to “treat neuropathic pain.”
 - Sale of drug to “treat pain” will inevitably be prescribed/used to treat neuropathic pain as well as nociceptive pain.
 - But FDA’s new rule says use code must only read “treatment of neuropathic pain.”
 - ANDAs will be allowed to carve out the neuropathic study under a section viii statement, obtain FDA approval and launch generic before the brand can litigate its patent.

Exception to Section viii Carve Out Rule (S&E Evaluation)

- Use code can be carved out only if the generic drug is as S&E as the brand for all remaining non-protected conditions of use.
- Foreseeability of use is not relevant.
- Minor language changes allowed in carved out label for clarity.
- Examples of how carve out exception operates:
 - Drug X approved to treat Indication A (not patented) and for patients with [a certain genotype], to treat Indication B (patented). Generic seeks to carve out Indication B. FDA would find Generic as S&E as Pioneer for treating Indication A and would allow the carve out.
 - Drug X approved to treat Indication A. Warning on label requires patients with genotype Y to lower dosage due to known adverse effects. OB patent claims a method of testing for genotype Y and lowering dosage to avoid adverse effects. If Generic seeks to carve out patented warning information, FDA would find it less safe than Pioneer for treating A in patients with genotype Y. FDA would not allow the carve out.

Ever-Greening the Label

- Label updates: PMR data; spontaneous reports from doctors/patients in the field; REMS reports.
- Amending the label (annual reports, Change Being Affected (CBE), CBE-30, Prior Approved Supplement).
- Generics required to copy brand label amendments.
- Importance of communications between Regulatory and Patent departments during clinical trials; post approval reporting; labeling changes.
- Teach regulatory people:
 - What to look for in patenting opportunities.
 - Importance of protecting confidentiality.
 - What not to say to FDA (“expected” results).
 - Documentation discovery dates, inventors.
 - Communicate data to patent attorney immediately.

Ever-Greening the Label (cont'd)

- Teach patent people:
 - What language can and can't go on drug labels.
 - Marketing and strategic considerations governing label language.
 - Crafting/drafting claims that track label language.
 - Creative ways to claim new categories of inventions and even trivial discoveries.
 - Should review clinical trial publications before they are published.
 - Inventorship issue – invention/discovery may involve several parties; scientists, academics, CRO, physicians, patients.

Patent Issues Relevant to Labeling

- Patent eligible subject matter:
 - Claim drawn to new and useful end as opposed to “law of nature” or “abstract idea.”
 - Active treatment as opposed to merely detecting or observing a phenomenon.
 - Active treatment as opposed to avoiding treating a patient at risk for a side effect.

Patent Issues Relevant to Labeling (cont.)

➤ Inherency:

- Existing drugs have lots of prior art describing actual and speculative uses.
- Newly discovered use necessarily occurring during a prior art use(?)
- Add a claim step to overcome inherency (select a patient subset, test, consult, monitor, observe improvement, etc.) and make sure that step is reflected on the label.

Patent Issues Relevant to Labeling (cont.)

➤ Joint/divided Infringement:

- Precision medicine: multiple actors involved in testing, diagnosing, administering, monitoring; no single actor responsible for infringement.
- Single entity is responsible when it directs or controls method steps performed by others, or where actors form a joint enterprise.
- “Directing or controlling” occurs when participation in activity or receipt of benefit (1) is conditioned on performance of patented method steps and (2) establishes manner or timing of that performance.
- Entire label may be used as evidence of infringement.
- Mere suggestions on label may not be enough; mandatory language for direction or control by single entity (e.g. physician).

Questions?

Thank you!



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