Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

Modern Bio/Pharma Patent Prosecution Strategies

Andy Brookes
Danielle Pasqualone
Paul A. Calvo
Marsha Rose Gillentine
Eric K. Steffe

MIND + MUSCLE

September 15, 2017

SKGF.COM

Par Pharm., Inc v. TWi Pharms. Inc.

Representative Claim at Issue:

- Claim 1 (of '576 patent): A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
  a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
  b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and
  c) the administration is once daily;
     – wherein after a single administration in a human subject of the formulation there is no substantial difference in the Cmax of megestrol when the formulation is administered to the subject in a fed versus a fasted state,
     – ***wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.***

Par Pharm., Inc v. TWi Pharms. Inc.

Prior art taught:

- Micronized megestrol
- Use of nanoparticle technology in drug formulation

Par argued it was unexpected that there was a reduced food effect which led to increased weight gain for patients dosed with the nanosized megestrol formulations

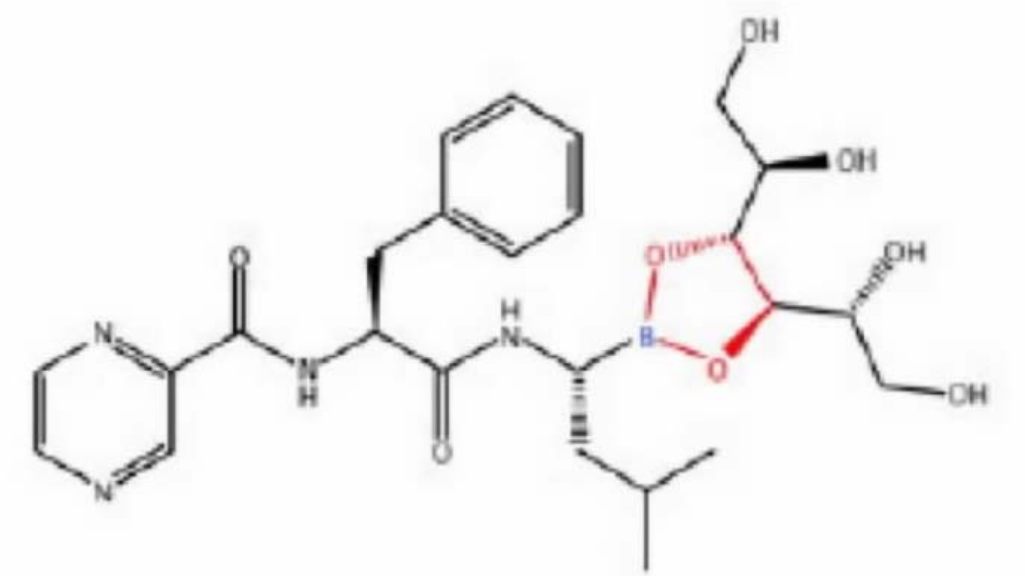
Federal Circuit :

- Not sufficient evidence on record establishing “food effect” is natural result flowing from nanosized megestrol particles
- Unexpected results were not entitled to substantial weight when factored into the overall obviousness analysis

Millennium Pharma, Inc. v. Sandoz, Inc.

- VELCADE®—approved for treatment of oncology disease

- Claim: the lyophilized ester of bortezomib and D-mannitol



Millennium Pharma, Inc. v. Sandoz, Inc.

- Bortezomib was known in prior art (the Adams patent)
- But was very unstable—countless liquid formulations failed; never approved
- Switched to lyophilized formulations, experimented with multiple variables that affected lyophilization, including bulking agents such as mannitol
- Adams patent did not disclose laundry list of dosage forms
- Discovered new chemical compound was formed (mannitol ester of bortezomib)—very stable and effective pro-drug of bortezomib
- FDA approval in record time

Millennium Pharma, Inc. v. Sandoz, Inc.

- Question on appeal—would a POSA obviously produce the previously unknown bortezomib ester?
- Applied lead compound analysis—bortezomib was the undisputed lead compound
- Reason to modify with a reasonable expectation of success? – NO!
  - No teaching of the new compound in the prior art
  - No reason in the art to make the same
  - No evidence that the compound would actually form
  - No teaching that the new compound would have the desired properties (solution to instability)
  - No teaching to use mannitol to form the ester
  - Also found teaching away

Millennium Pharma, Inc. v. Sandoz, Inc.

Objective Indicia

- Unexpected results—greatly improved stability, solubility, and dissolution
- Did not buy the argument that “because its an inherent result, its not unexpected”
- Bortezomib was the closest prior art; no requirement to “create prior art”
- Long felt need, commercial success—bortezomib alone was not an available product

Hypothetical

Claim 1: A method of treating a subject in need of treatment for diabetes comprising

treating the subject in need thereof with a therapeutically effective amount of drug A, wherein the therapeutically effective amount of drug A is about 200 mg per day.

- Prior art
  - Phase II clinical trial results in which patients with diabetes were administered 100 mg or 300 mg drug A per day
  - Patients administered 100 mg per day did not see statistically significant improvement over placebo
  - Patients administered 300 mg per day exhibited significant improvement

Hypothetical con't

Evidence of unexpected results from Phase III clinical trials:

- Patients administered 200 mg per day drug A exhibited same therapeutic efficacy as patients administered 300 mg per day

- Patients exhibited fewer side effects at 200 mg daily dose as compared with 300 mg dose