INNsight article by Aaron Lukas – December 2011

Aaron Lukas is an associate in Duane Morris's ANDA litigation practice group, which represents a wide range of generic drug companies in district court litigations and appellate proceedings at the U.S. Court of Appeals for the Federal Circuit. He also has extensive experience drafting and prosecuting patents before the U.S. Patent and Trademark Office. Previously, he worked as a research scientist in the chemical industry and is an inventor on more than 10 issued U.S. patents.

Case Study: *Unigene v. Apotex* (2011)
A New Test for Obviousness of Pharmaceutical Formulations in the U.S. Federal Circuit

Introduction

A recent decision by the Federal Circuit adopted a rigid framework for evaluating the obviousness of pharmaceutical formulations that conflicts with a more flexible approach taken by the U.S. Supreme Court on such issues in prior decisions. As noted below, the Federal Circuit has, in its analysis, conflated the FDA's requirements for generic drug approvals with the statutory requirements for patentability. In doing so, the court foreclosed the consideration of other factors which well may have led to a different result on the question of "obviousness."

Earlier this year, the U.S. Court of Appeals for the Federal Circuit decided Unigene v. Apotex ("Unigene"), which affirmed summary judgment of non-obviousness of a patent directed to a nasally administered pharmaceutical formulation of salmon calcitonin. A three-judge panel found that the defendants had not established that the patent-in-suit would have been obvious to a person of ordinary skill in the art.

The Federal Circuit analyzed the obviousness of the pharmaceutical formulation using a modified "lead compound" test adopted from cases that evaluated the obviousness of chemical compounds. In adapting this test to pharmaceutical formulations, the Federal Circuit first identified a "reference composition" that a person of ordinary skill in the art would have been motivated to modify in view of prior art teachings.

The reference composition test set forth in Unigene is inconsistent with a U.S. Supreme Court decision in an earlier case, KSR, to evaluate obviousness using a "flexible test" supported by certain factual inquiries. A proper obviousness analysis in Unigene should have relied more clearly on these factors, with a particular focus on the scope and content of the prior art and differences between it and the claimed invention. The "reference composition" test as applied in Unigene may obscure relevant facts and conflate patentability requirements with the U.S. Food and Drug Administration's ("FDA's") requirements for drug approval.

I. Background of the Patent in Suit

The dispute in Unigene arose from Apotex's filing of an Abbreviated New Drug Application ("ANDA") under the Hatch-Waxman amendments to the FDA statute. Apotex sought to market a generic version of Unigene's FORTICAL® (salmon calcitonin) nasal spray, and asserted that Unigene's patent covering this drug product was invalid as obvious. Unigene filed suit against Apotex in the Southern District of New York.

The district court granted Unigene's motion for summary judgment, finding that the patent-in-suit would not have been obvious at the time of invention. The Federal Circuit affirmed the district court's judgment.

When Unigene filed its FDA application for Fortical®, the FDA had already approved a salmon calcitonin nasal spray product marketed by Novartis as Miacalcin®. Rather than file a stand-alone application with the FDA, Unigene made use of FDA provisions that allowed its Fortical® application to rely upon Miacalcin® as the reference-listed drug. Thus, instead of performing its own full safety and efficacy analysis, Unigene chose to seek approval for Fortical® by demonstrating it was bioequivalent to Miacalcin®. While Miacalcin® contained benzalkonium chloride as a preservative, absorption enhancer and surfactant, Unigene formulated Fortical® differently to include citric acid (as an absorption enhancer and stabilizer/buffer), polyoxyethylene monooleate (as a surfactant) and phenylethyl alcohol and benzyl alcohol (as preservatives). Unigene also filed a patent application for its FORTICAL® formulation at the USPTO. The question put before the Federal Circuit panel was whether the patent for FORTICAL® would have been obvious at the time it was filed.

II. Federal Circuit's Obviousness Analysis

The Federal Circuit in Unigene made much of the fact that the FDA application for Fortical® utilized Miacalcin® as the reference-listed drug. The court's obviousness analysis in Unigeneturned on whether it would have been obvious to a person of ordinary skill in the chemical arts to have modified Miacalcin® to arrive at the claimed formulation for Fortical®. This is a new analytical framework for evaluating the obviousness of pharmaceutical formulations under which a defendant must first identify a reference composition and then look to the prior art for a teaching, suggestion or motivation ("TSM") to modify the reference composition to arrive at the claimed formulation.

III. Unigene The Federal Circuit's Analysis in Unigene Appears to Depart from the Supreme Court's Obviousness Test

KSR International Co. v. Teleflex, Inc. ("KSR") made clear that obviousness in all patent cases should be evaluated by a flexible test, and rejected the Federal Circuit's TSM test as the sole framework for evaluating obviousness.

Notwithstanding its departure from KSR, the panel in Unigene relied on certain language in KSRas grounds for using the reference composition test. Unigene quoted the passage from KSRdiscussing when a design need or market pressure can provide motivation to solve a problem. However, KSR discussed real-life scenarios where there is "a design need or market pressure to solve a problem and there are a finite number identified, predictable solutions" leading to a solution that is "obvious to try."

Under KSR, "obvious to try" is the proper standard for obviousness when there is a design need and a finite number of identified, predictable solutions that satisfy it. Unlike KSR, no factual finding in Unigene supported that there were "a finite number of identified, predictable solutions" for improving the bioavailability of salmon calcitonin. Not surprisingly, the Unigene court concluded that the challenged formulation would not have been obvious to try. It utilized a reference composition test limiting the obviousness analysis to an examination of whether functional alternatives to the ingredients in a reference composition existed. Viewed through KSR, the Federal Circuit's conclusions of non-obviousness based on the reference composition test do not demonstrate that the claimed formulation was non-obvious, but merely that the court utilized an improper standard for evaluating obviousness.

Under KSR, the question of whether a person of ordinary skill would have viewed citric acid as a functional alternative to benzalkonium chloride would have been among the facts related to an obviousness analysis, but certainly not, in itself, determinative of non-obviousness. In Unigene, a highly relevant fact would have been whether a person of ordinary skill would have looked beyond a salmon calcitonin formulation that was already approved by the FDA as a starting point for a new formulation.

IV. Unigene Improperly Considered Drug Approval Factors Over Patentability Requirements

FDA's approval of a new drug requires protocols for manufacturing, shelf-life stability, sterility, product packaging and labeling, in addition to clinical proof of pharmacology, toxicity, efficacy and safety—or in the case of Unigene's FORTICAL®, bioequivalence. However, none of these requirements are required for patentability. A new pharmaceutical product may be "patentable," but may fail to obtain FDA approval because of the FDA's stringent safety, bioequivalence and efficacy requirements.

By framing the obviousness analysis as whether a salmon calcitonin formulation that was bioequivalent to

MIACALCIN® would have been obvious, the Unigene panel required the prior art to disclose the functional equivalents of a buffer, pH adjuster, preservative, surfactant and absorption enhancer—despite the fact that such functional limitations appear nowhere in the claims of the patent-in-suit and are a result of Unigene's decision to file an application with FDA that required bioequivalence with a product containing these components.

In Unigene, the closest prior art cited by defendants taught the use of citric acid in the context of enhancing bioavailability for orally administered or injectable salmon calcitonin. Under the reference composition test applied by the Federal Circuit, this evidence was discounted as not relevant "to human use in a liquid pharmaceutical formulation." However, a fact finder may have considered such evidence relevant utilizing the proper analytical standards of KSR and other Supreme Court precedent unconstrained by the reference composition test. At a minimum, such additional evidence taking a broader, multi-factorial view of prior art beyond the simplistic reference composition test likely would have made summary judgment unavailable to Unigene.

Aaron Lukas
December 2011
ASLukas@duanemorris.com