

## **When Does “A Little” Equal “Enough”?**

Development and filing of an ANDA to market a generic drug requires many considerations. One important consideration concerns the evaluation of the patent landscape protecting the brand name product. An initial patent evaluation typically begins with patents listed in the Orange Book for the brand name product. Patents listed in the Orange Book may be directed to: i) the “drug substance” (active ingredient); ii) the “drug product” (formulation and composition); and iii) the approved method(s) of use. It is recommended that the generic company also search for and analyze any non-Orange Book patents (i) owned by the brand manufacturer (which may include process patents, method of treatment patents for non-approved uses, and patents directed to alternative formulations), and (ii) patents owned by third parties which might be relevant to the generic drug product.

Typically, the generic drug company is not manufacturing the active pharmaceutical ingredient (API) that is to be included in its proposed generic product. Instead, it obtains the API from a third party source and relies on that third party to have sufficiently characterized its API and evaluated and cleared its API with respect to any patents covering the same.

At the same time, in many situations the NDA holder is the brand manufacturer who undertook the initial development of the API and still produces the API for inclusion in the brand product(s). A natural consequence is that the brand manufacturer has had a long period of time to characterize and study the API, and may have obtained patents directed not only to the chemical structure of the API, but also to polymorphs, metabolites, pro-drugs, isomers, anhydrates and hydrates, and different salt forms, for example. This is particularly the case where the patents covering the chemical entity itself are either expired or will expire in the foreseeable future, leaving the valuable brand name product with less than optimal patent coverage. In response to such patents, third party manufacturers of the API may seek to design around such patents. Examples of

design around strategies would include using a different polymorph, or a different hydrate of a specifically claimed polymorph or hydrate of the API in question.

What if the API in the ANDA product contains substantially all API in a non-infringing form, but also may contain minor amounts of API in a form that falls within the claim of a patent (and even more critically, an Orange Book patent)? Can an ANDA product be found to infringe a patent that claims a specific species of the API where the ANDA filer's proposed generic formulation contains small amounts, trace amounts or even undetectable amounts of the claimed species of the API? This question demands serious consideration by companies during the development of an ANDA product.

### **Trace Amount of a Claimed Species of API**

The issue of whether a trace amount of a claimed species of API contained in a proposed ANDA product would infringe the NDA holder's Orange Book patent that specifically claims that species has recently been considered. *SmithKline Beecham Corporation and Beecham Group PLC v. Apotex Corp., Apotex, Inc., and Torpharm Inc.*, 365 F.3 1306 (*Fed. Cir.* 2004). In this case, SmithKline Beecham ("SKB") sued Apotex for patent infringement under Hatch-Waxman<sup>1</sup> asserting that Apotex's ANDA filing for generic paroxetine constituted an infringement of SKB's U.S. Patent No. 4,721,723 directed to crystalline paroxetine hydrochloride hemihydrate.

Paroxetine was developed in the 1970's and was the subject of U.S. Patent No. 4,007,196 that claimed certain 3-substituted 4-phenylpiperidines and salts thereof. The '196 patent was owned by a British Company, Ferrosan, that developed the process for the preparation of crystalline paroxetine hydrochloride. The '196 patent technology was later licensed to SKB who eventually developed a new crystalline form of paroxetine believed to be more stable than the hydrochloride form. This new crystalline form was crystalline paroxetine hydrochloride hemihydrate, which became the subject matter of

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<sup>1</sup> 35 U.S.C. § 271(e)(2)

U.S. Patent No. 4,721,723 assigned to SKB. The ‘723 patent, which was not set to expire until June 29, 2007<sup>2</sup> contained claims directed to the hemihydrate salt, a process for its preparation, an antidepressant formulation and to a method of treating depression. The ‘723 patent was Orange Book listed as covering SKB’s marketed paroxetine formulations.

Apotex filed an ANDA for generic paroxetine identifying the active ingredient as paroxetine hydrochloride *anhydrate*. Apotex submitted a paragraph IV certification in view of the Orange Book listed ‘723 patent asserting that the ‘723 patent was invalid or non-infringed by Apotex’s proposed formulation. SKB subsequently filed an infringement action against Apotex asserting that Apotex’s paroxetine hydrochloride anhydrate “necessarily contain[ed], by a conversion process... at least trace amounts of PHC [paroxetine hydrochloride] hemihydrate.”<sup>3</sup>

Claim 1 of the ‘723 patent recites:

1. *Crystalline paroxetine hydrochloride hemihydrate.*

The District Court records indicated that during the litigation, the court considered claim 1 of the ‘723 patent to be indefinite and therefore considered claim 1 to be limited to commercially significant amounts of the hemihydrate.<sup>4</sup> The District Court based this decision on uncontested testimony that a paroxetine hydrochloride anhydrate-hemihydrate composition would require “high double digits” of the hemihydrate in order for the composition to have any commercial value.<sup>5</sup>

On Appeal, the Court of Appeals for the Federal Circuit (“CAFC”) disagreed with the District Court. The CAFC held the language of claim 1 is not ambiguous and that the record showed skilled artisans would understand the meaning of the claim to embrace

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<sup>2</sup> The patent term of the ‘723 patent was extended 6-months for pediatric exclusivity.

<sup>3</sup> *SmithKline Beecham Corporation and Beecham Group PLC v. Apotex Corp., Apotex, Inc., and Torpharm Inc.*, 365 F.3 1306 at 1309, April 23, 2004 (CAFC).

<sup>4</sup> *Id.* at 1310.

<sup>5</sup> *Id.*

paroxetine hemihydrate without further limitation.<sup>6</sup> The CAFC further noted that nothing in the specification limited the hemihydrate to commercial applications and that “nothing in the prosecution history defined the invention in terms of commercially significant quantities.”<sup>7</sup>

In an important aspect of its decision, the CAFC maintained that indefiniteness of a claim “does not depend on a potential infringer's ability to ascertain the nature of its own accused product to determine infringement, but instead on whether the claim delineates to a skilled artisan the bounds of the invention.”<sup>8</sup> The Court appears to be taking the position that it may be permissible for the patent holder to evaluate the accused ANDA product using new or more sensitive technology to determine the presence of the claimed API species.<sup>9</sup>

In the end, the CAFC held that Apotex’s proposed paroxetine hydrochloride anhydrate formulation infringed claim 1 of the ‘723 patent. However, the CAFC also held that claim 1 of the ‘723 patent was invalid in view of SKB’s public use more than one year prior to the filing of the application that issued as the ‘723 patent.<sup>10,11</sup> This result leaves open the possibility that a proposed ANDA product could be held to infringe a patent claiming a species of the API, even if that ANDA product contains trace amounts of that species of API.

In determining whether trace amounts of a claimed API species are present in an alleged infringing compound, the presence of such a substance can only be excluded up to the relevant limit of detection. The burden of proving the presence of such trace amounts rests upon the patent holder.<sup>12</sup> Consider the situation where the API as tested by

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<sup>6</sup> Id. at 1313.

<sup>7</sup> Id.

<sup>8</sup> Id. at 1315.

<sup>9</sup> See the District Court’s decision in *SmithKline Beecham Corporation and Beecham Group PLC v. Apotex Corp.*, 247 F.Supp.1011, 1032 (D.Ill. 2003), *aff’d*, *SmithKline Beecham Corporation and Beecham Group PLC v. Apotex Corp.*, 365 F.3rd 1306 (Fed. Cir. 2004).

<sup>10</sup> 35 U.S.C. § 102(b)

<sup>11</sup> See my previous article in the July/August issue of *Drug Delivery Technology* entitled “Loss of Patent Rights: “Experimental Use” Versus On-Sale Bar/Public Use”.

<sup>12</sup> *Glaxo Inc., v. Novopharm Limited*, 931 F. Supp 1280 at 1286.

the ANDA filer (or its supplier) does not contain any detectable amount of the claimed API species. Could the patent holder nevertheless contend that the API species is still present and bring a Hatch-Waxman (ANDA) litigation? That remains to be seen, but it is not hard to imagine that such a situation (e.g., where the patent holder alleges some basis for its contention) may indeed lead to the initiation of an ANDA litigation.

In addition to its contention that the Apotex product directly infringed the '723 patent, SKB also had contended that ingestion of Apotex's paroxetine hydrochloride anhydrate formulation by a patient would ultimately result in conversion of the anhydrate to the claimed hemihydrate. The CAFC never decided this issue as they held claim 1 to be invalid for public use. However, the CAFC in a 1993 decision held that a claim to a compound (descarboethoxyloratidine) was anticipated because evidence showed that a prior art substance (loratidine) was metabolized into the claimed compound upon ingestion by a patient. *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 1993).

### **Conclusion**

Companies that are seeking to bring generic products to the market should focus on the possible assertion of any and all patents which may be pertinent to the ANDA formulation. This focus should include the API itself. In situations where patents exist on specific forms of the API, the advice of patent counsel concerning the applicability of such patents to the API should be sought. These issues should optimally be addressed early in the development process of a generic product rather than later.

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