

A CHANGE IN PHARMACEUTICAL PROSECUTION PRACTICE

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August 22, 2003

A recent decision from the Federal Circuit, Schering Corp. v. Geneva Pharmaceuticals, Inc.,¹ has changed pharmaceutical patent prosecution practice before the United States Patent and Trademark Office (“USPTO”).

Prior to this decision, the common practice for pharmaceutical companies was to first file patent applications directed to a drug and later to the metabolite.² Frequently, the metabolite is not identified for years after the drug was discovered; an application directed thereto is subsequently filed. Since the metabolite was not described per se in the earlier patent application and since it usually is a novel compound and is more active than the drug in vivo, the USPTO has granted patents to metabolites.

Obtaining patent protection to the metabolite is important since it prevents others from making, using and selling any drug converted in vivo to the metabolite. Furthermore, if a competitor obtained a patent on the metabolite, then the drug owner would be precluded from practicing its own invention.

However, this decision has changed the practice. Schering held that a patent on a drug that does not explicitly describe a metabolite inherently discloses the metabolite if it teaches, in an enabling manner, the administration of the drug to a patient and it necessarily

¹ 2003 WL 21767852 (Fed. Cir.); hereinafter (“Schering decision”).

² “Metabolite”, as used herein, refers to active metabolite, i.e., the active form of the drug converted in vivo in the patient’s body.

follows that the metabolite is formed, even if the metabolite is not described or disclosed in the patent. As a result, the patent inherently anticipates claims directed to the metabolite in a patent application filed more than one year after the issuance of the patent to the drug, even if the metabolite was not publicly known until after the filing of the metabolite application.

The relevant facts are as follows:

Schering Corporation (“Schering”) filed an application, which matured into U.S. Patent No. 4,282,233³, that encompassed the antihistamine, loratadine, the active component in CLARITIN™. More than one year after the issuance of the ‘233 patent, Schering filed an application directed, *inter alia*, to the metabolite of loratadine, identified as descarboethoxyloratadine (“DCL”). This application matured into U.S. Patent No. 4,659,716.⁴

The ‘716 patent contains several claims; Claims 1 and 3 were directed to generic and subgeneric formulae, respectively, which encompass DCL. The chemical structure of DCL is structurally similar to loratadine; DCL differs by the absence of an ester functionality, i.e., the carboethoxy substituent (COOEt).

³ Hereinafter “‘233 patent”.

⁴ Hereinafter “‘716 patent”.

The defendants were generic drug companies who sought to market the generic version of loratadine. They waited until the expiration of the ‘233 patent before seeking FDA approval to market the generic version. They each filed an abbreviated New Drug Application (ANDA) with the FDA,⁵ and asserted that the claims in the ‘716 patent were invalid in a Paragraph IV certification.

Schering filed suit for patent infringement of the ‘716 patent. The defendants filed a summary judgment motion that Claims 1 and 3 were anticipated by the ‘233 patent under 35 U.S.C. §102(b).⁶

The district court construed Claims 1 and 3 to encompass DCL in any form, including metabolized and synthetically produced and isolated forms. The district court found that the ‘233 patent did not explicitly teach or disclose DCL, or discuss any compound identifiable as DCL. Yet, the district court found that DCL was inherently formed as a metabolite by carrying out the process in the ‘233 patent and concluded that the ‘233 patent anticipated Claims 1 and 3. The Federal Circuit affirmed.

In the opinion of the author, two factors affected the Court’s decision.

⁵ Although an understanding of the Hatch-Waxman Act is not necessary to understand the Decision, a summary of the mechanics relevant to this decision is provided. When a company seeks to market a new drug, it must first obtain approval from the FDA by filing a New Drug Application (NDA) which includes, inter alia, clinical studies relating to the safety and efficacy thereof. When the NDA is filed, the owner of the drug also provides the FDA with information regarding the patents that cover the product which is the subject of the NDA. Upon approval of the NDA, the patents are listed in what is called the “Approved Drugs with Therapeutic Equivalence Evaluations” (the “Orange Book”). As the NDA owner obtains patents which it alleges also includes the drug within its scope, the Orange Book also lists those additional patents. Pursuant to the Hatch-Waxman Act, when a generic company wishes to obtain approval of a generic version of the NDA owners product, it files an abbreviated New Drug Application (ANDA), in which the ANDA applicant must show, inter alia, that its product is bioequivalent to the reference NDA drug and that the generic product has the same active ingredients and dosage form as the NDA owners brand product. In addition, the ANDA applicant must also review the Orange Book listing of the drug, and as part of the application, make one of four possible certifications. Three of those certifications, Paragraphs I, II or III do not challenge the patents listed in the Orange Book. The Paragraph IV certification alleges that the generic drug does not infringe any patent listed in the Orange Book covering the drug and/or the patent is invalid. If a generic company files a Paragraph IV certification, the ANDA applicant is to provide a detailed statement of the factual and legal basis for its assertion regarding invalidity of or non-infringement of the patent, a copy of which is forwarded to the NDA owner. Although it is not considered an act of patent infringement for the ANDA applicant to conduct its tests and experiments on drugs covered by unexpired patents listed in the Orange Book relating to the submission of information to the FDA, it is considered an act of patent infringement to file an ANDA on a product protected by an unexpired patent listed in the Orange Book. Once the NDA owner is provided notice of an ANDA filing, he has 45 days to file suit for infringement. If suit is filed within 45 days, the FDA stays approval of the ANDA for 30 months unless the patent expires prior to the expiration of the 30 months or a court of competent jurisdiction determines either non-infringement or patent invalidity.

⁶ 35 U.S.C. §102(b) states in pertinent part: A person shall be entitled to a patent unless.... (b) the invention was patented or described in a printed publication in this or a foreign country... more than one year prior to the date of the application for patent in the United States.

First, although not discussed, it is the opinion of the author that the Court felt that the practice of obtaining patent protection for the metabolite unfairly extended the term of the patent to the drug. Even after the patent of the drug expires, no one can make, use or sell the drug without infringing the patent to the metabolite.⁷

The second factor was the overwhelming evidence that the metabolite was always formed upon administration of the drug to patients. For example, Schering and the defendants provided data from studies on 144 and 864 patients, respectively, that showed that DCL was formed in measurable amounts when loratadine was administered. Further, DCL was recognized in the art as the metabolite of loratadine, and even Schering so admitted. The Schering Court noted that the district court found no reports in any of the studies of any individual who did not metabolically produce DCL following administration of loratadine. The Court held that it necessarily follows that when DCL is administered to patients, DCL is produced and that no reasonable jury could not find that DCL was not produced when a human ingests loratadine.

The '233 patent was prior art to the '716 patent under 35 U.S.C. §102(b) since it issued more than one year prior to the filing of the underlying application of the '716 patent. The Court found that since the '233 patent discloses, in an enabling way, the administration of loratadine, and since loratadine would necessarily metabolize in vivo to DCL, the '233 patent inherently disclosed DCL. It is of no import, according to the Court, that DCL did not become publicly known until after the filing date of the underlying application of the '716 patent. What is critical, the Court held, is that the '233 patent discloses in an enabling manner the administration of loratadine to patients and that DCL necessarily and inevitably forms in

⁷ Whether it was equitable or not, this was not unique in U.S. practice heretofore. For example, patents of selection are quite common, wherein a patent directed to a species, later filed, may be considered patentably distinct from patents earlier filed, which generically covered the species within its scope, provided it could be shown that the species had unexpected properties. Thus, when the generic patent expired, as long as the separate patent to the species was still in effect, no one could make, use or sell the species without authorization from the patentee thereof.

measurable quantities from the administration of loratadine to patients, so that its formation is a necessary consequence, regardless of when DCL became publicly known.

What are some ramifications of this decision?

(1) Consistent with the Schering decision, patent applications or articles disclosing the administration of a drug to subjects in an enabling way and published more than one year prior to the filing of a patent application to the metabolite may also inherently anticipate the metabolite if it necessarily follows that the metabolite is formed in vivo, even if the existence of and identity of the metabolite becomes publicly known after the filing of the metabolite application.

(2) Furthermore, a competitor of the patent owner is prevented from obtaining a patent to the metabolite per se as the published application or patent or article disclosing the drug in an enabling way will be prior art to any such application filed by the competitor.

(3) Schering does not preclude all protection of metabolites of known drugs. The Court stated, in dicta, that the metabolite may be claimed “in its pure and isolated form or as a pharmaceutical composition” or as a method of administering or utilizing the metabolite.⁸

(4) The Schering decision did not address the situation when the metabolite application is filed within one year of the issuance or publication of the drug application, whichever is first. Thus, it still is possible to obtain patent protection of the metabolite per se if the metabolite application is filed within a year of the publication or issuance, whichever occurs first, of the application describing the drug.

If the applicant files an application to the drug only in the USPTO, then the applicant may file the application directed to the metabolite within a year of the issuance of the

⁸ The Schering Court indicated that the ‘233 patent did not disclose the isolation of the metabolite or the direct administration of the metabolite to the patient.

patent.⁹ If the applicant files in the U.S. and in foreign jurisdictions, then the application describing the drug publishes within 18 months of its filing, and the published application would not be prior art under 35 U.S.C. §102(b) if the metabolite application is filed within the year of the publication, i.e., thirty months after filing the application to the drug. Further, to maximize the term of patent protection for the drug, the metabolite application should be filed as a provisional application, since the twenty-year term of a patent is measured from the date of filing of the application for examination and not the provisional application. Thus, it may be possible to extend patent protection to the drug by an additional 42 months, provided the metabolite application claims priority to the provisional application and does not claim benefit of the drug application.¹⁰

Frequently, the applicants who invented the drug are the same inventors who discover the metabolite. If the inventive entity for the metabolite application is the same as that for the drug application, then the metabolite application would not be “to another”. Consequently, such drug application or patent would not be prior art under 35 U.S.C. §102(a) or (e).¹¹

Further, since the metabolite is not identical to the drug, there would be no 35 U.S.C. §101 double patenting concerns. Moreover, obviousness double patenting is obviated if it

⁹ This assumes that the drug application did not publish prior to its issuance.

¹⁰ Please note that the author does not suggest that the applicant should wait thirty months after the filing of the application to the drug to file an application to the metabolite if the identity of the metabolite is known to the applicant at the time of the filing of the application on the drug. On the contrary, the application to the metabolite should be promptly filed after the discovery of the metabolite to avoid issues of potential abandonment under 35 U.S.C. §102(c) or issues of abandonment, concealment or suppression under 35 U.S.C. §102(g). The point is that the applicant may have a maximum of thirty months after the filing of the application to the drug to discover the identity of the metabolite and file an application thereon.

¹¹ The relevant portions of 35 U.S.C. §102(a) and (e) reads as follows:

A person shall be entitled to a patent unless:

(a) the invention was known or used by others in the country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the application for patent.

(e) the invention was described in (1) an application for patent published under Section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of the subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

could be shown that the metabolite has unexpected properties relative to the drug, such as significantly enhanced efficacy in vivo, bioavailability, less toxicity or some other unexpected result, which usually is the case.

(5) Frequently, the identity of the metabolite may not be discovered within thirty months after the filing of the drug application. If a finite number of candidate metabolites are identified, it would be propitious to file application(s) directed to the various proposed metabolites within a year of the publication of the application or issuance of the patent on the drug, whichever comes first. If one of those candidates is the metabolite, then the applicant will enjoy the advantages described in item (4). If, upon further research, the metabolite is not one of those candidates, a patent directed to the isolated metabolite, as described in item (3), may still be obtained.

(6) It is clear from the Schering decision that the published patent or application describing the drug is material¹² to the examination of the metabolite application, especially if the patent or application describing the drug was first published more than one year prior to the filing of the metabolite application. To comply with the duty of disclosure in the metabolite application, it would be prudent to cite the published drug application or patent in an Information Disclosure Statement, since in accordance with the Schering decision, the publication is relevant art that could affect the scope of the claims that may eventually issue. Furthermore, if the drug application is pending, it may also be prudent to advise the USPTO of the existence of the metabolite application, especially if the claims to the metabolite raise issues of obviousness-type double patenting relative to the claims in the drug application.

¹² Under 37 C.F.R. §1.56(b), information is material when it is not cumulative of information already of record or being made of record in the application and (1) establishes by itself or in combination with other information a prima facie case of unpatentability of a claim or (2) it refutes or is inconsistent with, a position the applicant takes in (i) opposing an argument of unpatentability relied on by the USPTO or (ii) asserting an argument of unpatentability.

These are just a few of the ramifications resulting from the Schering decision.

This decision has changed the strategies of drafting and claiming metabolites in pharmaceutical applications and requires the applicant to consider additional issues when prosecuting such applications.