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Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Re: GONAL-F, follitropin alpha/beta

FDA Docket No. 98E-0488

Dear Mr. Wilson:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,156,957. The application was filed on November 28, 1997, under 35 U.S.C. § 156.

A copy of the application has been previously forwarded to the Food and Drug Administration (FDA) with a request for assistance. In reply, in a letter dated December 14, 1998, the FDA stated that the product had been subject to a regulatory review period before its commercial marketing, but that the approval was not the first permitted marketing or use of the product.

The term "drug product" is defined in 35 U.S.C. § 156(f)(2) as the active ingredient of "a new drug, antibiotic drug, or human biological product...as a single entity or in combination with another active ingredient."

The active ingredient in the approved product is follitropin alpha/beta (recombinant).[1] As noted in the above FDA letter, this product, follitropin alpha/beta, has been previously approved for commercial use or sale. The human drug products Humegon, Pregonal and Repronex all contain the active ingredient monotropins (which is naturally occurring and a combination of follicle simulating hormone (FSH) and luteinizing hormone (FH)).[2] FSH contains follitropin alpha/beta.[3] Humegon, Pregonal and Repronex were approved for commercial marketing on September 1, 1994, May 20, 1985, and January 30, 1997, respectively,[4] which was prior to the approval of the applicant's product, i.e., September 27, 1997. In addition, the human drug product Fertinex

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[1]The application for patent term extension incorrectly states that 37 CFR 1.740(a)(4) does not apply. The active ingredient, follitropin alpha/beta, has been previously approved as discussed in this letter.

[2]See the USP Dictionary of USAN and International Drug Names, 98, page 450.

[3]See the USP Dictionary of USAN and International Drug Names, 98, page 325.

[4]Approved Drug Products with Therapeutic Equivalence Evaluations, 18th Edition, 1998 (Orange Book), Prescription Drug Product List, page 3-209.

contains highly purified, naturally occurring FSH,[5] and was approved as early as September 18, 1986.[6] Recombinant follitropin alpha/beta is understood to have an amino acid sequence that is indistinguishable from natural follitropin alpha/beta.[7] Applying the definition of "product" provided in section 156(f) to the extension requirement of § 156(a)(5)(A), applicant's approval of GONAL-F does not qualify as the first permitted marketing or use of the product, since the recombinant form of follitropin alpha/beta is the same as the natural products that were previously approved.

However, 35 U.S.C. § 156(a)(5)(B) provides that:

> in the case of a patent which claims a method of manufacturing the product which primarily uses recombinant DNA technology in the manufacture of the product, the permission for the commercial marketing or use of the product after such regulatory period is the first permitted commercial marketing or use of a product manufactured under the process claimed in the patent;

U.S. Patent No. 5,156,957 claims a method of manufacturing a product, GONAL-F, which primarily uses recombinant DNA technology[8]. As a result, the '957 patent is eligible for extension if the approval of GONAL-F was the first permitted commercial marketing or use of a product manufactured using the recombinant DNA techniques claimed in the patent. Follitropin alpha/beta, as made by the process claimed in the patent, has not been shown to have been previously approved. The product FOLLISTIM™ (recombinant follitropin beta)(Organon) was

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[5]See the USP Dictionary of USAN and International Drug Names, 98, page 771.

[6]See Urofollitropin, Prescription Drug Product List, page 3-320.

[7]FDA regulations related to orphan drugs define two drugs as the same even if there are minor differences in the amino acid sequence. See 21 C.F.R. 316.3(b)(13)(ii)(A). But see Genentech, Inc. v. Bowen, 676 F. Supp. 301 (D.D.C. 1987). (A recombinant DNA-derived drug having the same amino acid sequence as the naturally occurring form is a different drug.)

[8] For example, claim 9 of U.S. Patent No. 5,156,957 states:

A method for producing the biologically active human fertility hormone FSH comprising culturing host mammalian cells in accordance with claim 1.

Claim 1 states:

A mammalian cell comprising a transformed cell transformed by at least a first expression vector, said transformed cell being capable of producing a biologically active heterodimeric human fertility hormone comprised of an alpha subunit and a beta subunit, each said subunit being encoded in nature by a distinct rRNA, said hormone being human FSH, the alpha subunit of said hormone being encoded by said first expression vector by which said transformed cell is also transformed, or progeny of said transformed cell containing the genetic information imparted by said vector or vectors.

also approved on September 29, 1997,[9] but this date is the same date, not before, the date of approval of GONAL-F. Thus, the contemporaneous approval of FOLLISTIM™, albeit a recombinant DNA product, does not preclude patent term extension based upon the regulatory review period of GONAL-F and the '957 patent is considered to be eligible for extension.

As a result, a determination by your office of the applicable regulatory review period is necessary. Notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Telephone inquiries regarding this matter should be directed to the undersigned at (703)306-3159.

Karin Tyson
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Roger L. Browdy
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Attachments

[9]See the application for patent term extension of U.S. Patent No. 5,270,057; FOLLISTIM™, and "Two new fertility drugs offer convenient self-administration," Drug Topics, Oradell, November 3, 1997.