



7 3 2 3 '02 JUL 24 P1:46

July 24, 2002

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket No. 01E-0363  
Determination of Regulatory Review Period for  
Purposes of Patent Extension, MIFEPREX®

### **CITIZEN PETITION**

#### ***A. Specific Regulatory Action Requested***

Corcept Therapeutics Incorporated ("Corcept") submits this citizen petition pursuant to Section 4(d) of the Administrative Procedure Act, 5 U.S.C. § 553(c); Section 156 of the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman"), 35 U.S.C. § 156(d)(2)(B); and regulations established by the Food and Drug Administration ("FDA") governing due diligence petitions, codified at 21 C.F.R. § 10.30 and § 60.30.

In accordance with 21 C.F.R. § 60.30, we respectfully request FDA to initiate an investigation, to determine that The Population Council did not act with due diligence during the regulatory review period for MIFEPREX (mifepristone), and revise accordingly the period eligible for patent extension.

#### ***B. Statement of Factual and Legal Grounds***

##### **1. Factual Background and Standard for Diligence**

On January 25, 2002, FDA published a Federal Register notice announcing the agency's determination of the regulatory review period for MIFEPREX.<sup>1</sup> The agency concluded that the regulatory review period for MIFEPREX began on August

<sup>1</sup> 67 Fed. Reg. 3724 (January 25, 2002).

4, 1994 and extended for 2,249 days.<sup>2</sup> Of this time, the agency concluded that 593 days had occurred during the testing phase of the regulatory review period, while the approval phase had consumed 1,656 days.

In August 1994, The Population Council amended IND No. 22,047 to include studies testing the combination of mifepristone and misoprostol.<sup>3</sup> The Population Council submitted a new drug application ("NDA") for MIFEPREX on March 18, 1996. Shortly after submission of the NDA, the agency reclassified the MIFEPREX submission from a "standard" application, to a "priority" application, based on the fact that it would have been the first drug proposed for its indication. This designation placed MIFEPREX on an expedited, six-month review schedule.

On September 18, 1996, FDA issued an approvable letter for MIFEPREX. Due in part to the Population Council's failure to secure an adequate or appropriate manufacturing source for mifepristone, final approval for MIFEPREX was not granted until September 28, 2000. While FDA's initial review of the mifepristone NDA was expedited and took only six months, the Population Council took *over four years* to provide the agency with complete answers to the issues raised in the 1996 approvable letter.

Pursuant to 35 U.S.C. §156, The Population Council has requested an extension of the MIFEPREX patent for the period of time the drug was subjected to regulatory review. The applicable statute requires that the regulatory review period eligible for restoration be reduced by "any period... during which the applicant... did not act with due diligence."<sup>4</sup> Both the statute and regulations define "due diligence" as "that degree of attention, continuous directed effort and timeliness as may be expected from, and are ordinarily exercised by a person during a regulatory review period."<sup>5</sup>

## 2. Patent Term Restoration Is Intended to Compensate for Time Used by Regulatory Agency, Not by Applicant

---

<sup>2</sup> In a separate petition filed June 10, 2002, Corcept requested that FDA revise its determination of the start date for the regulatory review period to reflect the clear fact that IND No. 22,047 was made effective on May 3, 1983, not August 4, 1994. The Population Council submitted its response to this petition on July 2, 2002. Corcept filed additional comments regarding this issue on July 17, 2002.

<sup>3</sup> For purposes of this due diligence petition, Corcept does not take issue with use of August 4, 1994 as the start of the regulatory review period. If FDA rejects our request for revision and affirms its previous determination that the regulatory review period began in 1994, the diligence of the Population Council prior to that date would not be relevant to this action. However, a favorable ruling on our petition would establish 1983 as the start of the regulatory review period and result in a reduction of the patent restoration period for MIFEPREX from five years to two years, a reduction that would be commensurate with any reduction that might be required for lack of diligence.

<sup>4</sup> 35 U.S.C. §156(c)(1).

<sup>5</sup> 35 U.S.C. §156(c)(3); 21 C.F.R. § 60.36(a).

Patent term restoration is not designed to compensate drug sponsors for their manufacturing, licensing, or political problems, however serious and unfortunate they might be. An examination of the congressional intent underlying the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman") illustrates that, at its core, Hatch-Waxman was intended to restore some of the patent life that is eroded by the government regulatory review process.

As the official congressional reports accompanying the legislation's introduction indicate, Hatch-Waxman's incentive "is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval."<sup>6</sup> Further, the report described some of the pharmaceutical testimony preceding the legislation's passage as expressing a need for "compensation for the loss of patent term *due to government review*."<sup>7</sup> The emphasis on compensation due to government review, which is largely out of the control of drug sponsors, is seen in the structure of Hatch-Waxman. The patent restoration provisions calculate a patent term extension by rewarding drug sponsors for only half the time spent in the drug sponsor's investigational testing of the product, a process which is largely within the control of the sponsor. In contrast, the statute restores to the patent all of the time spent in the agency's formal review of an NDA, a process which is largely out of the control of the sponsor.

In the case of MIFEPREX, the lengthy time spent in the review phase was not due to FDA's review of the data. Nor was it due to a request for extensive additional clinical work that required years to complete. Instead, the extensive delay in converting the agency's "approvable" designation to full approval of MIFEPREX was caused by The Population Council's failure or inability to complete the chemistry, manufacturing, and control (CMC) portion of the NDA.

Completion of the CMC portion of an NDA is generally expected at the time an NDA is submitted. Minor changes and modifications are not unusual, but are usually resolved prior to receiving an initial approvable letter. It took the Population Council almost four years after FDA completed the bulk of its review to develop and submit a CMC package adequate to support approval. During this time period, the "loss of patent term" was not "due to government review," but rather was due to the applicant's failure to complete the critical components of the NDA necessary to allow the agency to conclude its review. Allowing patent restoration for this period of time unjustly advantages the Population Council and contravenes the intent of Congress.

---

<sup>6</sup> Drug Price Competition and Patent Term Restoration Act of 1984, H. Rept. 98-857, Part I (June 21, 1984) at page 15.

<sup>7</sup> *Id.*, at p. 18, *emphasis added*.

3. The Population Council Did Not Exercise Due Diligence in Developing the CMC Section of the MIFEPREX NDA.

In 1994, The Population Council obtained expansive rights to mifepristone through a unique agreement with Roussel-Uclaf. The agreement arranged for Roussel-Uclaf to transfer patent rights and all of its technology to the Population Council, without any remuneration from the Population Council.<sup>8</sup> In addition, the product had an extensive marketing history in France (where it had been marketed since 1988) and The Population Council was given the rights to cite the research used for approval in France to bolster the data already generated pursuant to IND No. 22,047. More importantly, this transaction would allow The Population Council to seek marketing approval at a time during which the Executive Branch and its agencies openly encouraged American market entry of mifepristone – known then as RU-486.

Despite all of these favorable indicators, MIFEPREX was not approved until September 2000. The Population Council had entered into a series of convoluted licenses, sublicenses, and contractual arrangements to manufacture, market, and distribute MIFEPREX. When disputes arose among these parties, the Population Council and its partners wasted years in litigation and negotiations while FDA awaited the submission of acceptable CMC data.

The Population Council had initially licensed the U.S. manufacturing and distribution rights for mifepristone to Advances in Health Technology (“AHT”), another nonprofit organization. AHT subsequently sub-licensed the manufacturing and distribution rights for mifepristone to NeoGen Industries. NeoGen was headed by Joseph Pike, a disbarred lawyer and businessman who was a convicted felon and involved in various lawsuits alleging, among other things, fraud, breach of fiduciary duty, fraudulent concealment, breach of contract, and unfair business practices. NeoGen in turn sublicensed its rights to Danco Laboratories. Shortly after submission of the NDA, the Population Council and AHT became enmeshed in a licensing dispute. In November 1996, the nonprofit groups sued Pike, charging him with fraud and financial improprieties. After months of legal maneuvering, the Population Council and Pike settled their legal issues in early 1997, leaving in place the sublicenses that Pike had issued to Danco Laboratories.

Later in 1997, Gedeon Richter, Ltd., the Population Council’s manufacturing partner, announced plans to terminate its agreement to manufacture bulk mifepristone. Danco Laboratories, the domestic marketer and distributor of the drug, filed suit against Gedeon Richter for breach of contract. More than two years elapsed before Danco announced, at the end of 1999, a replacement for Gedeon Richter. Final approval of MIFEPREX was granted in September 2000.

---

<sup>8</sup> In return, Roussel-Uclaf immunized itself from product liability claims, anti-abortion protests, and the political scrutiny that had followed its introduction of mifepristone (RU-486) in France.

For almost two years after receiving notice that the NDA was approvable, the CMC section of the MIFEPREX NDA sat idle while The Population Council devoted its resources and attention to resolving disputes with business partners and negotiating terms with a new manufacturer. In its application for patent restoration, The Population Council chronicled its communications with the agency and submissions to the NDA. The attached excerpt of the correspondence and communications specifically regarding to the CMC data indicates that The Population Council took no action concerning outstanding CMC issues from April 24, 1996 to August 5, 1997, a period of over 15 months (including 12 months of inactivity following receipt of the approvable letter). After a meeting with FDA in August 1997, there was no activity on CMC issues for another year, from September 24, 1997 through October 1, 1998.

Due to over two years of inactivity in resolving a critical portion of the NDA, the agency was unable to finalize its review of the application and approve MIFEPREX. The Population Council failed to exercise due diligence because it did not sustain the kind of "continuous directed effort... ordinarily exercised" by an applicant during the regulatory review period. As discussed above, the purpose of patent restoration is to compensate an applicant for patent life lost due to government action, not for an agency's inability to complete its review due to the applicant's inaction. Consequently, the period of time for which MIFEPREX is eligible for patent restoration should be reduced by at least two years.

### ***C. Environmental Impact***

The action requested is subject to a categorical exclusion from environmental assessment under 21 C.F.R. §25.30(h).

### ***D. Economic Impact***

Pursuant to 21 C.F.R. §10.30(b), we will provide data concerning the economic impact of the action requested should such information be requested by FDA.

### ***E. Certification of Service***

The undersigned certifies that a true and complete copy of this petition has been served upon The Population Council, through its counsel, by personal delivery.

Dockets Management Branch (HFA-305)

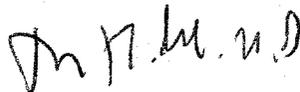
July 24, 2002

Page 6

*F. Certification*

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. K. Belanoff, M.D.", written in a cursive style.

Joseph K. Belanoff, M.D.  
Chief Executive Officer

## Timeline of CMC-related Submissions and Communications with FDA

| Date               | Event   |
|--------------------|---|
| May 3, 1983        | Date of receipt by FDA, assignment of IND No. 22,047  |
| October 3, 1983    | FDA request for CMC information and investigational labels  |
| December 1, 1983   | Reply to FDA's request of October 3, 1983 with CMC information  |
| February 15, 1984  | Reply to FDA's request of October 3, 1983 with CMC information  |
| June 27, 1985      | Information amendment – CMC   |
| August 3, 1994     | Protocol amendment – new protocol, new investigator<br>Information amendment – clinical, CMC                                      |
| September 1, 1994  | Information amendment – CMC   |
| October 6, 1994    | Protocol amendment – change in protocol, new investigators<br>Information amendment – clinical, CMC                               |
| February 9, 1995   | Protocol amendment – additional information on investigators<br>Information amendment – CMC updated information on study supplies |
| October 27, 1995   | Information amendment – CMC   |
| March 8, 1996      | Information amendment – CMC   |
| March 14, 1996     | NDA mailed  |
| March 15, 1996     | Information amendment – CMC, clinical   |
| March 18, 1996     | NDA date of receipt by FDA  |
| April 19, 1996     | Information amendment – CMC, clinical   |
| April 24, 1996     | FDA facsimile regarding CMC matters   |
| September 18, 1996 | FDA Approvable Letter   |

|                    |   |
|--------------------|---|
| August 5, 1997     | Amendment 008 to NDA (inadvertently identified as amendment 006) – proposed agenda for August 11, 1997 meeting with FDA including amended CMC section   |
| August 11, 1997    | FDA meeting   |
| September 24, 1997 | Amendment 009 to NDA – CMC information  |
| October 1, 1998    | Amendment 016 to NDA – request for meeting with FDA and request for written report from FDA on CMC matters  |
| November 2, 1998   | FDA meeting   |
| December 18, 1998  | Information amendment – CMC   |
| January 27, 1999   | FDA comments and requests for CMC information regarding submissions dated August 5 and September 24, 1997   |
| February 22, 1999  | Amendment 019 to NDA – response to FDA letter of January 27, 1999 and correspondence regarding teleconference call of February 10, 1999   |
| June 3, 1999       | Amendment 025 to NDA – CMC section for drug substance   |
| June 15, 1999      | Amendment 026 to NDA – proposed drug product manufacturing procedure  |
| November 8, 1999   | FDA advises that no further CMC information is necessary for use of drug substance provider's product for compassionate use program   |
| January 28, 2000   | Amendment 040 to NDA – CMC response to information request of December 14, 1999   |
| July 5, 2000       | Amendment 050 to NDA – briefing package for July 19, 2000 Meeting: revised distribution plan, revised labeling (prescribing information, patient information, and patient agreement), CMC and inspection issues, Phase IV studies |