#1346

PARLODEL

Public Citizen

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Joan Claybrook, President

August 16, 1994

David Kessler, M.D., J.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Dear Dr. Kessler:

Today, Public Citizen's Health Research Group and the National Women's Health Network are filing suit in the U.S. Court of Appeals for the District of Columbia to force the FDA to begin the process of banning the widely-used drug Parlodel (bromocriptine) for the benign, self-limited condition of post-partum breast engorgement (PPBE). This long-overdue FDA action is urgently needed because of an ever-increasing number of serious injuries such as strokes and heart attacks including many deaths in otherwise healthy young women associated with the use of Parlodel.

Although Sandoz, the manufacturer of Parlodel, must bear the primary responsibility for this tragedy, the FDA has clearly been complicit in allowing these deaths and injuries to continue. It is more than five years since, following our petition to the FDA to stop this use of Parlodel and other drugs for the treatment of PPBE, an FDA advisory committee in June 1989 recommended that this use of Parlodel and other drugs be banned. Shortly thereafter, the FDA Commissioner, Dr. Frank Young, concurred (all companies but Sandoz have withdrawn such drugs for this use). It is also almost a year since the September 2, 1993 reminder petition from Public Citizen's Health Research Group, upon receipt of which you convened a meeting to discuss this serious problem and, the same day, reporters were told by the FDA that the agency would publish its intentions to ban this use of Parlodel in the *Federal Register*. No such action has occurred.

Increasing Toll of Deaths and Serious Injuries

Based on data we have obtained from the FDA, from the time Parlodel was first approved as a lactation suppressing drug in 1980 through June 1994, there have been 531 adverse reaction reports in women ages 15 through 45 who have used Parlodel, including 32 deaths involving 14 with strokes, 5 with heart attacks, and 8 with hypertension. In addition to the deaths, there have been 36 additional reports listing strokes, 14 with heart attacks, 73 with hypertension and 98 with seizures, none of which were immediately fatal but a number of which were

permanently disabling.

Of the above total, 264 -- almost half of the reports in women ages 15 through 45 -- were received since the June 1989 FDA "decision", as yet unaccompanied by any action, to stop the use of Parlodel for PPBE. Of these 264, 19 were fatalities (over half of the total deaths since marketing for PPBE began).

In the last year alone, from June 1993 through June 1994, there have been 44 more reports of adverse reactions in women 15 through 45, including 6 additional deaths in women aged 17, 23, 24, 31, 35 and 39. Three additional non-fatal strokes, 5 seizures, 2 heart attacks and 4 cases of hypertension were also reported in the last year. The FDA and others who have studied adverse drug reaction reporting estimate that only 1 in 10 adverse reactions which actually occur are reported to the FDA since it is voluntary on the part of doctors as to whether they file such reports. Thus, the toll of deaths and serious injuries is much higher than the reported number of cases indicates.

Continuing Sales of Parlodel

According to various estimates, each year at least 300,000 women get Parlodel for treatment of PPBE, at a return to Sandoz of approximately $12.5 million a year. Thus, since June 1989, when the process of banning the drug for this indication should have occurred, approximately 1.5 million more American women have been exposed to this dangerous, too often deadly drug, which major medical centers including Yale, Johns Hopkins, the University of North Carolina and others have long since stopped using for PPBE. Sandoz during this interval has sold approximately $62.5 million of Parlodel for this purpose, generating, in addition to this sizeable flow of cash, the additional deaths and injuries in the young, previously healthy victims of this drug.

Recent Jury Verdict

In the first case of death or injury caused by Parlodel to be adjudicated (several others have resulted in reportedly large settlements), the jury in a Kentucky District Court awarded $2.1 million, in a July 20, 1994 judgement, to the family of Rosemary Roberts, a 31 year old woman who suffered a severe stroke on December 1, 1988 shortly after being prescribed Parlodel for PPBE after delivering a baby boy. She currently has left-sided paralysis with severe limitation of use of her left hand and foot.

Nine of twelve jurors agreed that "Parlodel as manufactured and marketed by Defendant Sandoz...for the suppression of post-partum lactation...was in a defective condition unreasonably dangerous, which was a substantial factor in causing Rosemary Roberts' stroke...". Nine jurors also agreed, referring to the company's previous marketing strategy for routine use of

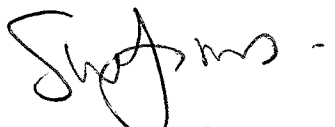
Parlodel, that Sandoz "acted with malice in the sale and promotion of Parlodel for the suppression of lactation for women electing not to breast feed with conduct that was flagrantly indifferent to the rights of Rosemary Roberts and with subjective awareness that such conduct would result in human death or bodily harm...".

Unreasonable Delay

The legal basis for our lawsuit against the FDA is that the agency has unreasonably delayed, for five years, formally initiating the process of banning the use of Parlodel for treatment of PPBE. Bromocriptine is appropriately indicated for the treatment of a variety of other conditions, such as Parkinson's Disease, acromgaly and hyperprolactinemic states and therefore we are not proposing a complete ban on Parlodel. Following our September 2, 1993 letter to you, I was told by FDA officials that the *Federal Register* notice beginning the banning process would be published by the end of October 1993. Later, I was told, it would be published by the end of 1993. To date, the notice has still not been published.

But beyond the persuasive legal basis for you to have taken this action is the human imperative. Instead of banning a drug which is used to treat a benign, self-limited condition in otherwise healthy women who have just delivered a baby, you and the FDA have recklessly allowed Sandoz to continue selling this drug which keeps killing and maiming more and more women. In effect, by protecting Sandoz from the loss of tens of millions of dollars of sales of Parlodel, you are endangering hundreds of thousands of women who continue to get the drug each year. It is time to put a stop to this deadly delay.

Sincerely,



Sidney M. Wolfe, M.D.
Director, Public Citizen's
Health Research Group

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

In re: PUBLIC CITIZEN HEALTH RESEARCH GROUP and NATIONAL WOMEN'S HEALTH NETWORK,	)	No. 94-1565
Petitioners.	)	

PETITION FOR A WRIT OF MANDAMUS

Public Citizen Health Research Group and the National Women's Health Network hereby petition this Court to issue a Writ of Mandamus, pursuant to its authority under Federal Rule of Appellate Procedure 21, the All Writs Act, 28 U.S.C. § 1651(a), and the Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, compelling Respondents, the Food and Drug Administration ("FDA") and David A. Kessler, M.D., Commissioner of the FDA, to cease their unreasonable delay in acting to withdraw approval of bromocriptine mesylate, marketed under the name Parlodel, for use as a lactation suppressant.

In support of this petition, Petitioners submit the following materials: (a) a memorandum of law, including an appendix of relevant statutory provisions, (b) a motion for expedition, requesting that the Court direct Respondents to reply promptly and that the Court set this case for argument as expeditiously as its calendar permits, and (c) a declaration of Sidney M. Wolfe, M.D.

Dated: August 16, 1994

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Attorneys for Petitioners

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 94-

In re PUBLIC CITIZEN HEALTH RESEARCH GROUP
and NATIONAL WOMEN'S HEALTH NETWORK,

Petitioners.

On Petition For A Writ Of Mandamus
Compelling Respondents The Food and Drug Administration
and David A. Kessler, M.D., Commissioner of the FDA,
To Take Agency Action Unreasonably Delayed

MEMORANDUM IN SUPPORT OF PETITION FOR MANDAMUS

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August 16, 1994

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In re PUBLIC CITIZEN HEALTH RESEARCH GROUP and NATIONAL WOMEN'S HEALTH NETWORK,	)	No.
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MEMORANDUM IN SUPPORT OF PETITION FOR MANDAMUS

Introduction

Petitioners Public Citizen Health Research Group and National Women's Health Network seek a writ of mandamus compelling Respondents, the Food and Drug Administration and David A. Kessler, M.D., Commissioner of the Food and Drug Administration (collectively referred to as the "FDA"), to take prompt action to protect over 300,000 new mothers each year who are prescribed bromocriptine mesylate ("bromocriptine")--a drug used to suppress the benign and temporary conditions of postpartum lactation and breast engorgement.[1]

Nearly six years ago, on November 29, 1988, Public Citizen's Health Research Group petitioned the FDA to revoke or amend the New Drug Application approvals for all medications then in use to treat postpartum breast engorgement ("PBBE"), including bromocriptine. Declaration of Sidney M. Wolfe, filed concurrently herewith, ¶ 3 ("Wolfe Decl."). In June, 1989, an FDA Fertility and Maternal Health Drugs Advisory Committee convened to consider the benefits

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[1] Bromocriptine is marketed by Sandoz Research Institute under the name Parlodel.

and risks of such drugs to postpartum women who do not breastfeed. The committee concluded that the drugs had not been demonstrated to be safe and effective for treatment of the symptoms of PBBE and unanimously recommended that the drugs, including bromocriptine, not be used to treat PBBE. On July 13, 1989, FDA Commissioner Young instructed the Director of the FDA's Division of Metabolism and Endocrine Drug Products to proceed with the implementation of the committee's recommendations. The FDA then made informal requests, in meetings with bromocriptine's manufacturer, Sandoz Research Institute ("Sandoz"), and in writing, that Sandoz voluntarily withdraw the indication for the use of bromocriptine for PBBE. Sandoz "respectfully decline[d]" to do so. Wolfe Decl., Exh. G at 2.[2]

Today, more than five years after the FDA's advisory committee recommended withdrawal of approval of bromocriptine for treatment of PBBE, the FDA has taken no action to effectuate that recommendation. The first step would be to publish a Notice of opportunity for Hearing in the Federal Register. See 21 U.S.C. § 355(e). The FDA has not taken this step, despite statements to Petitioner Public Citizen Health Research Group that it would issue the notice by the end of October, 1993, and later that it would issue the notice by the end of 1993, and later that it was working on the notice in February, 1994. Wolfe Decl., ¶ 15. See also id. at ¶ 14.

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[2] Withdrawal of the "indication" means that the drug could no longer be used for PBBE, that is, that the label would not indicate PBBE as an approved use of the drug.

Accordingly, without this Court's intervention, the agency will almost certainly continue to delay commencement of the withdrawal process. Because healthy new mothers are paying for the FDA's delay with their well-being and, in some cases, with their lives, this Court should compel the FDA to take prompt action. Specifically, Petitioners seek an order directing the FDA to publish a notice of opportunity for hearing in the Federal Register stating the FDA's intention to withdraw approval for the indication for the use of bromocriptine for PBBE within 30 days of the Court's order, to hold any hearing requested within 60 days of receiving such a request, and to issue its final decision with 60 days of the conclusion of such hearing. Petitioners also request that this Court retain jurisdiction and order the FDA to provide monthly status reports to the Court and to Petitioners, to ensure compliance with the timetable imposed by the Court.

QUESTION PRESENTED

Whether the FDA has unreasonably delayed revoking the approval for bromocriptine, where (a) the FDA's own advisory committee recommended in June of 1989 that bromocriptine not be used to treat PBBE, (b) the Commissioner of the FDA has at least twice, on July 13, 1989, and on February 5, 1990, authorized the relevant division director to take steps to withdraw the indication, (c) although PBBE is a benign, self-limited condition, postpartum women treated with bromocriptine are at risk of a range of adverse reactions to the drug, including strokes, heart attacks, and even death, and (d) the FDA has repeatedly stated over the past year that it would soon

publish a notice of opportunity for hearing proposing that the indication be withdrawn.

STATUTES

The pertinent provisions of the Administrative Procedure Act, the All Writs Act, and the Food, Drug, and Cosmetic Act are set out in the addendum to this memorandum.

JURISDICTION

This Court has jurisdiction over this petition for mandamus under the All Writs Act, 28 U.S.C. § 1651(a), the Administrative Procedure Act, 5 U.S.C. §§ 555(b) and 706(1), and the judicial review provision of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(h). Telecommunication Research and Action Center v. FCC, 750 F.2d 70, 75, 79 (D.C. Cir. 1984) ("TRAC").[3]

STATEMENT OF THE CASE

Bromocriptine is a prolactin inhibitor, i.e., a drug that inhibits the hormone that promotes lactation. It also acts in the central nervous system like a type of chemical transmitter known to affect neurologic function and is known to cause low blood pressure. A.E. Mehta & G. Tolis, Pharmacology of Bromocriptine in

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[3] Section 355(h) provides that appeals from the agency's withdrawal of approval may be taken by the applicant by filing a written petition that the application be set aside in the United States Court of Appeals for the circuit wherein the applicant resides or has its principal place of business or in the United States District Court for the District of Columbia. Accordingly, because this petition "might affect the Circuit Court's future jurisdiction," it is "subject to the exclusive review of the Court of Appeals." TRAC, 750 F.2d at 78-79. See American Foreign Service Ass'n v. Baker, 895 F.2d 1460, 1461 (D.C. Cir. 1990) ("TRAC stands for the proposition that cases should be brought in the same judicial forum whether the complaint is about agency action or failure to act.").

Health and Disease," 17 Drugs 313 (1979). Thus, bromocriptine was initially used in treating Parkinson's disease.

In 1980, the FDA approved bromocriptine's use for suppression of lactation. Since that time, the drug has been prescribed to millions of postpartum women. At a June 2, 1988 hearing of the FDA's Fertility and Maternal Health Drugs Advisory Committee, Dr. Dianne Kennedy of the FDA staff estimated that between 480,000 and 939,000 postpartum women were prescribed bromocriptine each year.

At the time of its approval, the FDA and Sandoz, the drug's manufacturer, failed to assess the drug adequately on two counts: 1) the seriousness of the side-effects in the face of a benign self-resolving indication, and 2) the degree of efficacy as compared to alternate therapies. Since 1980, testing and experience have shown that the risks far outweigh the uncertain efficacy of the drug.

A. Bromocriptine Poses Serious Dangers To Postpartum Women.

Bromocriptine carries with it numerous potential side-effects including sharp decreases in systolic blood pressure, headaches, nausea, dizziness, vomiting, and rashes. In fact, the number of women with significant side-effects is equal to or greater than the number of women who would have marked discomfort from breast engorgement and soreness without treatment. Wolfe Decl., ¶ 7.

Equally important, indications of serious life-threatening adverse reactions have been evident ever since 1980, when the FDA approved the indication for use of bromocriptine to treat PBBE. In May, 1980, the FDA received the first report of a fatal adverse

drug reaction in a 30 year old woman who received bromocriptine and died following a cerebral hemorrhage. Id. at ¶ 16. As experience with the drug has grown, cases of stroke, heart attacks, seizures, and hypertensive crises in young women have multiplied. Since 1980, the FDA has received, in regard to women between the ages of 15 and 45, 50 reports of stroke, 14 of which were fatal; 19 reports of heart attacks, five of which were fatal; 104 reports of seizures, six of which were fatal and others of which resulted in permanent neurologic impairment; and 91 cases of hypertension, eight of which were fatal.[4] Id. at ¶ 16.

The FDA approved labelling for bromocriptine in the 1993 Physicians' Desk Reference lists the following adverse drug reactions associated with bromocriptine use: symptomatic hypotension (low blood pressure); 50 cases of hypertension; 38 cases of seizures, "occurring mostly in postpartum patients up to 14 days after initiation of treatment;" 15 cases of stroke, "mostly in postpartum patients whose prenatal and obstetric course had been

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[4] In addition, bromocriptine has been associated with induction of postpartum psychosis in both well individuals and women with a history of psychiatric illness. See, e.g., R. Canterbury, et al., Postpartum Psychosis Induced by Bromocriptine, 80 Southern Medical Journal 1463 (1987); J. Johnson, Treated Mania exacerbated by bromocriptine, 138 American Journal of Psychiatry 980 (1981); K.C. Pearson, Mental Disorders from Low Dose Bromocriptine, 305 New England Journal of Medicine 173 (1978). Because postpartum depression, manic depressive disorder, and schizophrenia are common conditions in females of childbearing age (up to 10 percent may be affected, see L. Robins, et al., Lifetime Prevalence of Specific Psychiatric Disorders in Three Sites, 41 Archives of General Psychiatry 949 (1984)), the wide-spread use of a drug known to exacerbate or induce psychosis in postpartum women is particularly problematic because the postpartum period is a time when women are subject to the additional stress and responsibility of a newborn infant.

uncomplicated;" and four cases of acute myocardial infarction (heart attack), "including three cases receiving Parlodel for the prevention of physiologic lactation." Physicians' Desk Reference 2116 (47th ed. 1993).[5]

Medical journals continue to publish case reports detailing accounts of women injured by using bromocriptine for lactation suppression. For example, an article published in 1993 discussed the case of a 32-year-old woman who experienced a heart attack while using bromocriptine. She experienced a 70 percent narrowing of the right coronary artery one month after discharge from the hospital, when tested two hours after ingesting bromocriptine. The authors concluded that she may have been experiencing bromocriptine induced vasospasm (intermittent contraction of the blood vessels). The patient also experienced visual hallucinations and severe headaches with bromocriptine use. F. Larrazet, et al., Possible bromocriptine-induced myocardial infarction, Annals of Internal Medicine 118, 199-200 (1993).

Another article reported the case of a 19 year old woman who experienced new onset of seizures and hypertension four days postpartum and three days after starting bromocriptine. Magnetic resonance imaging ("MRI") revealed a hemorrhage into the pituitary gland. The authors stated that the case illustrated possible

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[5] The 1993 edition lists the same number of adverse events as the 1989 edition, which indicates that the listing has not been updated since 1989 to reflect more recent reported incidents of severe patient injuries and deaths, examples of which are discussed below.

"Physiologic lactation" refers to lactation in postpartum women.

connection between the use of bromocriptine for PBBE and the onset of hypertension, seizures, and intracranial hemorrhage. D. Gittleman, Bromocriptine associated with postpartum hypertension, seizures, and pituitary hemorrhage, 13 General Hospital Psychiatry 278-280 (1991).

The 531 adverse drug reaction reports filed with the FDA between 1980 and June 1994, regarding bromocriptine use by women under age 45, demonstrate that otherwise healthy women have been and continue to be injured and killed by the drug. Thirty-two of the 531 reports are cases of patient deaths. Wolfe Decl., ¶ 16.

B. Alternate Therapies Are Superior To Bromocriptine In Suppressing Lactation And Reducing Breast Engorgement.

Postpartum women who do not breastfeed begin lactation, which may include breast pain and engorgement, within two to seven days of giving birth. Traditional therapies to relieve such discomfort include breast support, cold packs, and over the counter pain relievers such as acetaminophen. Wolfe Decl., ¶ 4. Without treatment, only eight to 33 percent will ever develop significant symptoms. The symptoms dissipate on their own, and 90 percent of all women who do not breastfeed are free of all significant symptoms within eight days. Id., Exh. A at 6-7 (summarizing studies) & Exh. B.

In contrast, the FDA approved bromocriptine as a 14-day course of treatment for PBBE. Yet the FDA's summary basis for approval in 1980, based on studies done prior to that time, reported that up to 71 percent of women who took bromocriptine for the recommended two-week period of treatment experienced some breast soreness, leaking,

and/or engorgement after they stopped taking the drug. Id., Exh. A at 6-7 & Exh. B.

Thus, at the end of two weeks, women who have not taken bromocriptine are symptom-free, while up to 40 percent of the women who have taken the drug may begin experiencing breast discomfort. Since at least 1989, no study reported in the medical literature indicates that bromocriptine is any more effective than alternate therapies, such as breast supports and over-the-counter pain relievers. The efficacy of bromocriptine in relation to its dangers renders its use inappropriate for treating PBBE, as the FDA itself has recognized by pledging to take the drug off the market.

C. The Regulatory History Of Bromocriptine Is Replete With Illustrations Of FDA Concern Regarding The Safety Of The Drug In Treatment Of PBBE.

The FDA approved the indication of bromocriptine for lactation suppression in 1980. By February 1983, the number and severity of side-effects reported to the FDA were mounting. Correspondence from the FDA to Sandoz in August of 1983 stated that there was cause for concern about the safety of Parlodel in the treatment of physiologic lactation. The letter noted that while many cases were inconclusive, in the aggregate they were compelling. Wolfe Decl., Exh. A at 7. The FDA directed Sandoz to change Parlodel's labelling and reminded it that, under FDA regulations, Sandoz should "include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; causal relationship need not be proved." Id. Nonetheless, Sandoz did not make the labelling change until December 1984--almost two years

later. Id.

Again in February 1987, the FDA directed Sandoz to make a labelling change based on a review of reported adverse drug reactions. The FDA also requested that Sandoz list uncontrolled hypertension as a contraindication to use of the drug and to report to the FDA the number of reported incidents of hypertensive crises, strokes, and heart attacks occurring subsequent to the 1984 labelling change. In addition, the FDA requested that Sandoz send a "Dear Doctor" letter to all obstetricians and family practitioners alerting them to the health risks associated with use of bromocriptine in the postpartum period. Id., Exh. A at 8.

On June 2, 1988, a representative of Public Citizen Health Research Group addressed an FDA Fertility and Maternal And Child Health Advisory Committee regarding concerns about bromocriptine's safety and efficacy as a treatment for PBBE. Wolfe Decl., ¶ 3. On November 29, 1988, Public Citizen Health Research Group, along with the National Women's Health Network, petitioned the FDA to revoke or amend the New Drug Application approvals for all medications then in use to treat PBBE, including bromocriptine. The petition was based on the growing number of reports of dangerous side-effects associated with the use of bromocriptine and other lactation suppressants by postpartum women. Id. at ¶ 3 & Exh. A.

Although Petitioners did not receive a formal response to the petition, the FDA's Fertility and Maternal Drugs Advisory Committee conducted a two-day hearing on June 1 and 2, 1989. At the conclusion of the hearing, the committee unanimously recommended

that lactation suppressants, including bromocriptine, concluded that the drug had not been demonstrated to be safe and effective for treatment of symptoms of PBBE and recommended that these drugs not be used for this indication. Id., Exh. D at 5-6. On July 13, 1989, Frank Young, M.D, Ph.D., then-commissioner of the FDA, approved the request of the Director of the FDA's Division of Metabolism and Endocrine Drug Products, to proceed with implementation of the Committee's recommendations. Id., Exh. E at 5. The three-phase implementation procedure was to include 1) meeting informally with drug sponsors requesting the withdrawal of the indication, 2) if companies refused voluntary withdrawal, sending letters to them again requesting withdrawal, and 3) if companies continued to refuse, publishing the FDA position in the medical literature, sending letters regarding the agency's position to physicians, and issuing a notice of opportunity for hearing in the Federal Register proposing that the indication be withdrawn. Id. at 3. Publishing such a notice is the necessary first step in withdrawing approval. 21 U.S.C. § 355(e).

In informal meetings, Sandoz refused voluntarily to withdraw the indication. Wolfe Decl., ¶ 10 & Exh. F. Accordingly, on September 13, 1989, the FDA wrote to Sandoz and requested voluntary withdrawal of the indication of bromocriptine for PBBE. Id., Exh. F at 1-2. On October 25, 1989, Sandoz wrote to the FDA in response that the company "respectfully decline[d]" to withdraw the indication. Id., Exh. G at 2. In contrast, all other producers of drugs used for treatment of PBBE voluntarily complied with the

FDA's request. Id., Exh. H.

On January 12, 1990, the Director of the Division of Metabolism and Endocrine Drug Products sought approval to undertake the final step of the process of implementing the advisory committee's June 1989 recommendation, that is, to "issuing an NOOH [notice of opportunity for hearing] that the indication be withdrawn." See id. On February 5, 1990, the Acting Commissioner approved such action. Id. at 2.

Today, nearly five years after Sandoz's refusal to act voluntarily, the FDA has yet to publish the notice of opportunity for hearing. As a consequence, well over one million additional women have received bromocriptine for PBBE. The FDA received 264 additional reports of adverse drug reactions associated with bromocriptine use in women under 45 during these years, including reports of severe injuries and 19 deaths. Id. at ¶ 16. Even more troubling, the FDA estimates that, in general, actual incidents of adverse drug reactions are ten times the number of reported cases. Id. at ¶ 17.

ARGUMENT

THE FDA'S FAILURE TO ACT IS UNREASONABLE UNDER THE APA AND FDC ACT.

This Court should issue a writ of mandamus to compel unreasonably delayed action by the FDA in failing to publish the notice of opportunity for hearing required to start the withdrawal process for the indication. The FDA has long acknowledged the dangers of bromocriptine for postpartum use, as demonstrated by its 1984 and 1987 requests to Sandoz regarding labelling changes, its

1987 request that Sandoz send a "Dear Doctor" letter, and its 1989 committee recommendation and subsequent instruction that the recommendations be implemented. Despite repeated statements over the years indicating imminent publication of a notice of opportunity for hearing regarding proposed withdrawal of the indication for PBBE, see Wolfe Decl., ¶¶ 14-15, the FDA has failed to take even the threshold step of publishing this notice.

Where unreasonable delays in agency action adversely affect the interests served by government regulation, this Court has held that it will compel the agency to take necessary action. See Cutler v. Hayes, 818 F.2d 879, 894-99 (D.C. Cir. 1987); TRAC, 750 F.2d 70, 76-77, 79 (D.C. Cir. 1984); Public Citizen Health Research Group v. FDA, 740 F.2d 21, 32, 33 (D.C. Cir. 1984) ("PCHRG v. FDA"); Public Citizen Health Research Group v. Auchter, 702 F.2d 1150, 1153-54 (D.C. Cir. 1983) ("PCHRG v. Auchter"); infra at 19 (citing cases). These cases are based on the unambiguous language of the Administrative Procedure Act, 5 U.S.C. §§ 555(b) and 706(1). As this Court has stated, an unjustified agency delay is "an outright violation of 5 U.S.C. § 555(b)'s mandate that agencies decide matters in a reasonable time . . . ." TRAC, 750 F.2d at 79. Moreover, Congress, in 5 U.S.C. § 706(1), has specifically "instructed statutory review courts to compel agency action that has been unreasonably delayed." Id.; see generally Sierra Club v. Thomas, 828 F.2d 783, 792-96 (D.C. Cir. 1987).

This Court has identified three guidelines to aid reviewing courts in determining whether an agency has engaged in unreasonable

delay. First, the court should "ascertain the length of the time that has elapsed since the agency came under a duty to act and should evaluate any prospect of an early completion." Cutler v. Hayes, 818 F.2d at 897; see also PCHRG v. FDA, 740 F.2d at 32 ("There must be a 'rule of reason' to govern the time limit to administrative proceedings") (citation omitted).

Second, "[t]he reasonableness of the delay must be judged 'in the context of the statute' which authorizes the agency's action." Cutler v. Hayes, 818 F.2d at 897 (quoting PCHRG v. Auchter, 702 F.2d at 1158 n.30; National Congress of Hispanic American Citizens v. Marshall, 626 F.2d 882, 888 (D.C. Cir. 1979)). As part of this inquiry, the court "must also examine the extent to which the delay may be undermining the statutory scheme . . . by frustrating the statutory goal . . . ." Id. at 897-98. Here, where the "agency is charged with the administration of a statutory scheme whose paramount concern is protection of the public health, the pace of agency decisionmaking must account for this statutory concern." PCHRG v. FDA, 740 F.2d at 34.

Finally, "and perhaps most critically, the court must examine the consequences of the agency's delay." Cutler v. Hayes, 818 F.2d at 898. "The deference traditionally accorded an agency to develop its own schedule is sharply reduced when injury likely will result from avoidable delay." Id. Accordingly, "[d]elays that might be altogether reasonable in the sphere of economic regulation are less tolerable when human lives are at stake." Id. (quoting PCHRG v. Auchter, 702 F.2d at 1157).

Here, application of these guidelines demonstrates that the FDA's failure to proceed with the approval withdrawal process constitutes unreasonable agency delay. Measuring the FDA's response from September 20, 1989, when Sandoz informed the agency in writing that it would not voluntarily remove the indication for PBBE--as opposed to measuring from the mid-1980s when the FDA first became of aware of serious dangers posed by bromocriptine to postpartum women, Wolfe Decl., Exh. A at 7-8; or from June 1988 when Petitioners first formally addressed the agency regarding the dangers of bromocriptine to such women, id. at ¶ 3; or from November 1988, when Petitioners petitioned the FDA to withdraw the indication, id.--there has already been four years and 11 months of delay. Accordingly, the "prospect of an early completion" is nonexistent. Far too many years have already passed without action. See PCHRG v. Brock, 823 F.2d at 628 ("With lives hanging in the balance, six years is a very long time."); see also Midwest Gas Users Ass'n v. FCC, 833 F.2d 341 (D.C. Cir. 1987) (citing MCI Telecommunications Corp. v. FCC, 627 F.2d 322, 340 (D.C. Cir. 1980) ("Although the issue of whether delay is unreasonable necessarily turns on the facts of each particular case, this court has stated generally that a reasonable time for an agency decision should encompass 'months, occasionally a year or two, but not several years or a decade.'").

Assessing "the reasonableness of the delay . . . 'in the context of the statute,'" the agency again falls short. The Food, Drug, and Cosmetic Act includes provisions for withdrawal of

approval of an application if clinical or other experience or data show the "drug is unsafe for use under the conditions of use upon the basis of which the application was approved." 21 U.S.C. § 355(e). Although this provision of the Act does not set forth a time period within which the agency must act, "[w]hen the public health may be at stake, the agency must move expeditiously to consider and resolve the issue before it." PCHRG v. FDA, 740 F.2d at 34. Accord PCHRG v. Brock, 823 F.2d at 629 ("When lives are at stake, as they assuredly are here, OSHA must press forward with energy and perseverance . . . ."). Despite section 355(e)'s grant of authority to withdraw approval, the agency simply has refused to act on that authority in this case. Meanwhile, women have died after taking a drug solely to alleviate two weeks of discomfort caused by a benign condition--childbirth, and better treated through safe means.[6]

The fatal consequences of the agency's delay are readily

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[6] Under § 355(c), the agency has 180 days from the filing of a new drug application to either approve an application or to "give the applicant notice of an opportunity for hearing." Although this period may be extended by agreement of the agency and the applicant, the statute's six-month period for action on new applications provides a sharp contrast to the five-year (and growing) period at issue here.

The Act further provides that where the Secretary "finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection." 21 U.S.C. § 355(e). Congress, having authorized the agency to act "immediately" when faced with a serious problem, surely did not contemplate five-year delays in cases where lives are at risk. The availability under the Food, Drug, and Cosmetic Act of the process for immediate action renders the five-year delay even more egregious.

apparent. In the last year alone, the FDA has received 44 reports of adverse reactions to bromocriptine by women between the ages of 15 and 45, including six deaths, four cases of stroke, eight cases of seizure, three cases of heart attack, and six cases of hypertensive episode. Wolfe Decl., ¶ 16. Reports to the FDA from 1980 through June 1994 indicate 531 adverse reactions to bromocriptine by postpartum women between the ages of 15 and 45, including 32 deaths, 50 cases of stroke, 104 cases of seizure, 19 cases of heart attack, and 91 cases of hypertensive episodes. Id. Because these women take bromocriptine to alleviate a benign condition, limited by the women's own biology to less than two weeks, and treated equally or more effectively by alternate therapies, each of these injuries and each of these deaths was entirely avoidable.

The FDA has repeatedly stated its intention to begin the process of withdrawing approval for the indication for bromocriptine, Wolfe Decl., ¶¶ 14-15 & Exhs. E & H, thus recognizing that postpartum women prescribed bromocriptine are entitled to the protections of section 355 of the Food, Drug, and Cosmetic Act. Therefore, this Court need not determine for itself whether withdrawal of the indication for bromocriptine is needed. See Cutler v. Hayes, 818 F.2d at 895 & n.138; cf. PCHRG v. FDA, 740 F.2d at 33 (declining to evaluate scientific evidence before agency in order to draw conclusion about whether evidence mandated finding that aspirin products are misbranded). In this case, the Court need only let the FDA know that "enough is enough." PCHRG v.

Brock, 823 F.2d at 627 ("we have seen it happen time and time again, that agency action Congress has ordered for the protection of the public health all too easily becomes hostage to bureaucratic recalcitrance, factional infighting, and special interest politics. At some point, we must lean forward from the bench to let an agency know, in no uncertain terms, that enough is enough.")

Accordingly, Petitioners ask the Court to declare that the FDA has unreasonably delayed far too long in implementing its decision, made five years ago, to take action to withdraw approval for the indication for the use of bromocriptine for PBBE. Petitioners also ask that this Court order the FDA to publish a notice of opportunity for hearing with 30 days of the Court's order, to convene any hearing requested within 60 days of receiving the request, and to issue a final decision within 60 days of the hearing. Ample precedent gives this Court the authority to grant the relief requested. See, e.g., Environmental Defense Fund v. EPA, 852 F.2d 1316 (D.C. Cir. 1988) (ordering EPA to issue proposed rules within 33 days and final rule three months later); Public Citizen v. Heckler, 602 F. Supp. 611, 614 (D.D.C. 1985) (finding that FDA had unreasonably delayed responding to petition concerning pasteurization of raw milk and directing agency to publish proposed rule reflecting its decision within 60 days). See also TRAC, 750 F.2d at 81 (retaining jurisdiction, ordering agency to inform court of its timetable within 30 days, and requiring progress report every 60 days thereafter). The Court should also retain jurisdiction to monitor the FDA's compliance with the Court's order

and should require the FDA to submit monthly reports to the Court and to Petitioners every 90 days to ensure that Respondents abide by the timetable imposed by the Court.

CONCLUSION

For more than five years, the FDA has recognized the dangers that bromocriptine poses to postpartum women. Yet for five years, the FDA has delayed acting to prevent perfectly healthy women from suffering injury and death through treatment for a benign condition. Accordingly, the Court should compel the FDA to publish, within 30 days of the Court's order, a notice of opportunity for hearing in the Federal register, in which it indicates its intention to withdraw approval of bromocriptine for use in treating PBBE. The Court should further order that the FDA convene any hearing requested pursuant to that notice within 30 days of receiving the request and that it issue its final decision within 10 days of the hearing. In the interim, the Court should retain jurisdiction and require the FDA to submit monthly status reports to the Court and to Petitioners.

Dated: August 16, 1994

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