

**UNITED STATES DEPARTMENT OF JUSTICE  
DRUG ENFORCEMENT ADMINISTRATION**

**IN THE MATTER OF** )

**Docket No. 05-16**

**Lyle E. Craker, Ph.D.** )

**GOVERNMENT'S FOURTH SUPPLEMENTAL  
PREHEARING STATEMENT**

The Government, by and through the undersigned attorney, respectfully submits the following fourth supplemental prehearing statement and a motion for leave of court to file this fourth supplemental prehearing statement, as follows.

**SUPPLEMENTAL PREHEARING STATEMENT**

**DOCUMENTS** [Additional document]

92. Copy of an affidavit by Douglas C. Throckmorton, M.D., Acting Deputy Director, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA) (7 pages)

**MOTION SEEKING LEAVE TO FILE SUPPLEMENTAL  
PREHEARING STATEMENT**

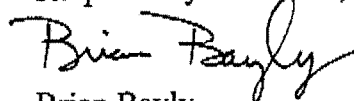
The Government seeks leave to file the above Fourth Supplemental Prehearing Statement based upon the following. The affidavit, a copy attached herein, is not voluminous and is more informational than adversary by virtue of the fact that Dr. Throckmorton is explaining the FDA process for approving drugs. The affidavit liberally cites to FDA statutes and regulations, and both parties will have an opportunity at any time to ask the Administrative Law Judge to take administrative notice of the

applicable statutes and regulations relevant to the affidavit or to cite to such statutes and regulations in their briefs.

The undersigned was in contact with FDA representatives on June 6, 2005. The undersigned was directed to have DEA supervisory personnel send a letter to FDA personnel in order to seek information from FDA that would be relevant to this litigation. This letter was sent on June 20, 2005. A copy of this letter was forwarded to FDA counsel by the undersigned sometime between July 6 and July 8, 2005. Because of the numerous obligations that FDA had, they were not able to complete this affidavit until August 17, 2005.

The Government will fax this pleading to Respondent's counsel in order to see if Respondent has no objection, objects without filing a response, or objects and seeks to file a response explaining the objection(s). Furthermore, because this supplemental is submitted just before the first hearing, the Government will not attempt to introduce this affidavit until the September or December portion of the hearing, which should give Respondent reasonable time to put forth rebuttal material if any.

Respectfully submitted,



Brian Bayly  
Senior Attorney  
Office of Chief Counsel

Dated: August 18, 2005

**CERTIFICATE OF SERVICE**

On August 18, 2005, I sent, via facsimile machine, (202) 661-4810, a copy of the foregoing to Julie M. Carpenter, Esq., Jenner & Block, 601 13<sup>th</sup> St., NW, Suite 1200 South, Washington, D.C. 20005, Amherst, Massachusetts 01003, and filed the original and two copies of the foregoing at the DEA Office of Administrative Law Judges by hand delivery.

  
\_\_\_\_\_  
Brian Bayly

**Declaration of Douglas C. Throckmorton**

I, Douglas C. Throckmorton, M.D., declare as follows:

1. I am the Acting Deputy Director, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA). In that capacity I am responsible for oversight of daily operations at CDER.
2. The responsibilities of my position require that I be familiar with and knowledgeable about the legal requirements of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 301-97, and the FDA's regulations pertaining to "drugs" and "new drugs."
3. The Act, 21 U.S.C. § 321(g), defines the term "drug" in relevant part as (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C) . . . ."
4. The Act, 21 U.S.C. § 321(p), defines the term "new drug" in relevant part as:
  - (1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . or

- (2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.
5. In order to be generally recognized as safe and effective (GRAS/E) within the meaning of 21 U.S.C. § 321(p), a drug must satisfy three criteria. First, the drug's reputation must be based on adequate and well-controlled studies that establish that the drug is safe and effective. See 21 C.F.R. § 314.126. Second, those studies must have been published in the scientific literature so that they are available to qualified experts. Third, qualified experts must generally recognize, based on those published studies, that the drug is safe and effective for its intended use.
  6. Even if an active ingredient in drug product "A" has been previously approved as safe and effective in drug product "B", drug product "A" is considered a new drug if its particular formulation of active and inactive ingredients has not been previously approved or has not been found to be GRAS/E.
  7. Any drug product derived in whole or in part from marijuana is a new drug within the meaning of 21 U.S.C. § 321(p). Further, I am not aware of any evidence that any drug product derived in whole or in part from marijuana is exempt from the new drug requirements of the Act.
  8. No new drug product may be legally introduced into interstate commerce unless it has an approved new drug application (NDA), an approved abbreviated new drug application (ANDA), or a valid investigational new drug application (IND). See 21 U.S.C. § 355.

9. 21 U.S.C. § 355(b)(1) states that an NDA is required to contain the following:
- (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;
  - (B) a full list of the articles used as components of such drug;
  - (C) a full statement of the composition of such drug;
  - (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
  - (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and
  - (F) specimens of the labeling proposed to be used for such drug.
10. The regulations, 21 C.F.R. Part 314, set out in detail the required content and format of an NDA and ANDA.
11. To develop the necessary reports of investigations that show that a particular drug product is safe and effective for a specific indication, an NDA sponsor must complete certain clinical investigations of that drug product. A clinical investigation is any experiment in which the drug is administered or dispensed to, or used involving one or more human subjects. Clinical investigations of unapproved new drugs are required to be conducted under valid INDs. See 21 U.S.C. 355(i) and 21 C.F.R. Part 312.
12. A sponsor who intends to conduct a clinical investigation is required to submit an IND. 21 C.F.R. 312.23 sets out the information required to be contained in an IND. This information includes the name of the drug and all active ingredients, the structural formula of the drug, the formulation of the dosage form to be used, the route of administration, a brief summary of previous human experience with the drug, a brief description of the overall plan for investigating the drug product for the following year, and a protocol for the study. INDs are generally required to have a section describing the composition, manufacture, and control of the drug

product. In each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug product. FDA recognizes that modifications to the method of preparation of a new drug substance and dosage form are likely as the investigation progresses. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

13. The clinical investigation of a previously untested drug product is generally divided into three phases. See 21 C.F.R. 312.21. These phases are generally conducted sequentially, however they may overlap. The three phases of an investigation are as follows:

- (1) Phase 1: Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are designed to determine the metabolism and pharmacologic actions of the drug product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence of effectiveness. The total number of subjects generally ranges from 20 to 80. During this phase, information about the drug product's pharmacokinetics and pharmacological effects should be obtained to permit the design of a well-controlled, scientifically valid Phase 2 study.
- (2) Phase 2: Phase 2 includes the controlled clinical studies conducted to explore the effectiveness of the drug for a particular indication and to determine the common short-term side effects and risks of the drug product. Phase 2 studies usually involve no more than several hundred subjects.
- (3) Phase 3: Phase 3 studies are expanded controlled and uncontrolled clinical trials that are performed after preliminary evidence suggesting effectiveness of the drug product has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to

evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for labeling. Phase 3 studies generally include several hundred to several thousand subjects.


14. An IND goes into effect 30 days after FDA receives the IND unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold or the FDA notifies the sponsor that the investigations may begin earlier than 30 days after receipt of the IND. 21 C.F.R. 312.40.
15. A clinical hold is an order issued by FDA to delay or suspend a clinical investigation. The bases for clinical hold are set out in 21 C.F.R. 312.42.
16. The Act, 21 U.S.C. 355(d), provides the grounds under which FDA must refuse to approve an NDA. See also 21 C.F.R. § 314.125.
17. Botanical products are finished, labeled products that contain vegetable matter as ingredients. Botanical products that meet the definition of a drug under 21 U.S.C. 321(p) are subject to regulation as a drug. However, botanical drug products have certain unique characteristics that are taken into account in the application of FDA regulations. For instance, because of the complex nature of a typical botanical drug and the lack of knowledge of its active constituent(s), FDA may rely on a combination of tests and controls to ensure the identity, purity, quality, strength, potency, and consistency of botanical drugs. For more information about FDA's current approach to the regulation of botanicals see the Guidance For Industry Botanical Drug Products, [www.fda.gov/cder/guidance/4592fnl.htm](http://www.fda.gov/cder/guidance/4592fnl.htm). This guidance discusses several areas in which, because of the unique nature of botanicals, FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic, semisynthetic, or otherwise highly purified or chemically modified drugs.

18. The term "orphan drug" refers to a specific drug product that treats a rare disease or condition. The Orphan Drug Act was signed into law on January 4, 1983 and is codified at 21 U.S.C. § § 360aa - 360dd. The term "rare disease or condition" means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from U.S. sales of such drug.
19. The intent of the Orphan Drug Act is to stimulate the research, development, and approval of drug products that treat rare diseases, through, among other things, tax incentives for clinical research and a grant of seven years of marketing exclusivity after approval of an orphan drug product. Orphan drug designation is given to a particular active moiety for a particular indication. If an orphan-designated drug is approved for the designated indication, FDA is prohibited for 7 years from approving the same drug for the same indication for which the orphan drug approval was granted. Determinations regarding orphan designation are made on the basis of the facts and circumstances as of the date the request for orphan designation of the drug is made.
20. Dronabinol, a synthetic version of THC that is the active moiety in Marinol, was given orphan designation for the stimulation of appetite and the prevention of weight loss in patients with a confirmed diagnosis of AIDS, on January 15, 1991. See the list of Orphan Products Designations available at [www.fda.gov/orphan/designat/alldes.rtf](http://www.fda.gov/orphan/designat/alldes.rtf). This designation does not have any bearing on whether other drugs containing synthetic or natural THC, or any component of cannabis will receive orphan designation. In addition, because the determination of orphan drug status is made at the time the request for designation is made, it is possible that what is considered a "rare disease or condition" at a given point in time may at some point no longer continue to meet this definition

because of factors such as growing prevalence of a disease or condition in the United States.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on August 17, 2005.



Douglas C. Throckmorton, M.D.  
Acting Deputy Director  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration