DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

October 16, 1991

REGISTERED MAIL
RETURN RECEIPT REQUESTED

Chaovanee Aroonsakul, M.D.
Ave.

Dear Dr. Aroonsakul:

Re: Notice of Disqualification to Receive Investigational New Drugs

I have reviewed the record of the regulatory hearing conducted by Freddie Ann Hoffman, M.D., Presiding Officer, on April 23, 1990, concerning your eligibility to receive investigational new drugs. The report of the Presiding Officer which was sent to you on May 11, 1991, provided a 30 day period within which you could submit any comments you had on the report. On June 3, 1991, your counsel, H. Nasif Mahmoud, requested a 60 day extension of time to comment on the Presiding Officer's report. On June 7, 1991, Dr. Hoffman granted a 30 day extension. The original 30 day time period and the 30 day extension have passed and the Presiding Office has not received any comments from you or your counsel. Thus, you had a full opportunity to comment on that report but chose not to do so.

Therefore, I am affirming and adopting the May 1991 Report of the Presiding Officer and have determined that you have repeatedly and deliberately failed to comply with the regulatory requirements regarding investigational new drugs. Specifically:

1. You violated 21 C.F.R. § 312.42(a) by administering the investigational new drug, human growth hormone, to study subjects after your notice of claimed investigational exemption for a new drug (IND) was placed on clinical hold.

2. You failed to obtain review and approval of the proposed IND study from an institutional review board as required by 21 C.F.R. § 312.66.

3. You failed to obtain informed consent from the IND study subjects as required by 21 C.F.R. § 50.20.

ecutive
secretariat
Tracking
9104895

4. You failed to maintain adequate records showing the receipt of investigational new drugs as required by 21 C.F.R. § 312.57.

5. You promoted the investigational new drug, human growth hormone, as an effective treatment for Alzheimer's disease in violation of 21 C.F.R. 312.7.

In accordance with 21 C.F.R. § 312.70(b), you are hereby advised that you are no longer eligible to receive investigational new drugs. All such drugs in your possession should be promptly returned to their supplier.

Sincerely,

David A. Kessler, M.D.
Commissioner of Food and Drugs

cc: Cathy Grimes
Office of the General Counsel, GCF-1
Food and Drug Division
Department of Health and Human Services
5600 Fishers Lane
Rockville, Maryland 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

CHAOVANEE AROONSAKUL, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

REPORT OF THE PRESIDING OFFICER

I. INTRODUCTION

Pursuant to 21 C.F.R. Parts 16 and 312, on April 23, 1990, the Food and Drug Administration ("FDA") conducted a hearing to consider the proposal of the Center for Drug Evaluation and Research ("Center") to disqualify Dr. Chaovanee Aroonsakul from receiving investigational new drugs. The Center contended that Dr. Aroonsakul should be disqualified because she administered the investigational drug or "human growth hormone" after FDA imposed a clinical hold prohibiting the administration of to study subjects. The Center also contended that Dr. Aroonsakul failed to comply with regulations regarding clinical investigations in 21 C.F.R. §§ 312.7, 312.57, 312.62(a), 312.62(b), 312.66 and 50.20.

This document constitutes my report on the hearing. See 21 C.F.R. § 16.60(e). This report, along with the parties' comments with respect thereto and the administrative record, will be referred to the Commissioner for a final determination on this matter. See 21 C.F.R. § 16.95.

II. BACKGROUND

A Notice of Claimed Investigational Exemption for a New Drug ("IND")[1] was submitted to FDA by cover letter dated July 29, 1985, from an attorney, on behalf of Dr. and Dr. Chaovanee Aroonsakul. The IND stated that the "[s]ponsor wishes to test the effects of human Growth Hormone (hGH) on the clinical course of subjects with senile dementia, including diagnosed cases of Alzheimer's disease." Center Exhibits ("CX") 1. The IND listed both "Growth

---

1/21 C.F.R. § 312.20 requires a sponsor to "submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 21 C.F.R. § 312.2(a)." A clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." See 21 C.F.R. § 312.3(b). An investigational new drug is defined as "a new drug, antibiotic drug, or biological drug that is used in a clinical investigation." See 21 C.F.R. § 312.3(b). A new drug is defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act, and includes an approved drug that is proposed for a new use. See 21 C.F.R. § 310.3.

Hormone (biosynthetic methionyl human growth hormone)" and as the name of the investigational drug.[2] CX 1. The IND listed the ("Foundation")[3], Dr. and Dr. Chaovanee Aroonsakul as the sponsors of the IND. The IND listed both Dr. and Dr. Aroonsakul as clinical investigators. CX 1. FDA received the IND on August 5, 1985, and sent a routine acknowledgement letter, dated August 13, 1985, to Mr. CX 2.

The IND was reviewed by the Center's Division of Neuropsychopharmacological Drug Products. Dr. S.W. Blum, chemist, reviewed the IND for chemistry and manufacturing controls. CX 3, Trans. at 15. Dr. Glenna G. Fitzgerald reviewed the pharmacology and toxicology portion of the IND. CX 4, Trans. at 16. Dr. Peggy A. Hanson, medical officer, reviewed the IND clinical protocol and clinical plan. CX 5, Trans. at 16,

---

2/The product (biosynthetic methionyl human growth hormone), is manufactured by . CX 1. At the time the IND was submitted the product was not yet approved for marketing and was only available for investigational use. The product was approved by FDA on October 30, 1985, for the treatment of dwarfism in children. The product is also referred to as " ," " " " " and " ." CX 3,4,5,19.

3/Dr. Aroonsakul is the founder and president of the Foundation. CX 1, 18.

17. The reviewers unanimously recommended that the IND be placed on "clinical hold."[4]

Laurie Macturk, Consumer Safety Officer, FDA, contacted Dr. by telephone on August 23, 1985, and advised him that the IND had been placed on hold for "chemistry, pharmacology and clinical reasons" and that the IND "needed [the drug] supplier['s] state[ment] to complete the agency review." CX 6, Trans. at 18. In follow up, FDA sent Dr. a letter dated September 23, 1985, to advise him that he could not proceed with the proposed IND study due to deficiencies in the chemistry and clinical portions of the IND. CX 7.

In response to FDA's letter dated September 23, 1985, a revised protocol dated January 22, 1986, was submitted to the IND by Dr. and Dr. Aroonsakul. Trans. at 19. Dr. Elizabeth B. Rappaport, medical officer for the Center's

---

4/21 C.F.R. § 312.42(a) defines "clinical hold" as "an order issued by FDA to the sponsor [of an IND] to delay a proposed clinical investigation or to suspend an ongoing investigation. . . ." When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. . . ." 21 C.F.R. § 312.42(b) sets out the grounds for the imposition of a clinical hold which include safety reasons as well as deficiencies in the protocol for the investigation.

5/At the time of the IND submission, FDA designated Dr. as the sponsor of the IND since his name appeared first on the IND application. CX 2. See also footnote 6.

Division of Neuropsychopharmacological Drug Products, reviewed the revised protocol and continued to recommend that the clinical trial not proceed under the IND because of deficiencies in the protocol. CX 8, Trans. at 19-20. FDA sent a letter dated March 18, 1986, to Dr. advising him that the IND remained on clinical hold for chemistry and clinical deficiencies. CX 9, Trans. at 20-21.

In June 1986, FDA initiated a directed inspection of Dr. Aroonsakul as a result of a letter that was sent by the Foundation to the governor of North Dakota. CX 17. The North Dakota State Laboratories Department brought this letter to FDA's attention. CX 46. The letter stated that Dr. Aroonsakul had developed an "effective treatment" for Alzheimer's disease and that FDA had "approved" the treatment and had assigned an IND for the second phase of research and development.

Mr. Richard Kingdon, the FDA investigator, had several discussions with Dr. Aroonsakul, representatives of the Foundation, and physicians and pharmacists connected with Dr. Aroonsakul. He obtained information regarding Dr. Aroonsakul's operation and the sources from which she obtained human growth hormone. Dr. Aroonsakul informed Mr. Kingdon that the letter sent to the governor of North Dakota

was sent to the governors of all the states in an attempt to raise money to fund her research on Alzheimer's disease. Mr. Kingdon issued Dr. Aroonsakul an inspectional observation report (FDA Form 483) which advised her that the letter contained material which represented that Dr. Aroonsakul's treatment of patients under the IND had received FDA approval, when in fact the IND was on clinical hold, and that this misrepresentation violated the regulation prohibiting a sponsor from disseminating promotional material about an investigational drug. CX 46. Representatives of Dr. Aroonsakul indicated that they might send a corrective letter to all governors who received the letter in question. CX 46. FDA did not take any further action against Dr. Aroonsakul based on this investigation.

In July 1986, Dr. Aroonsakul submitted two clinical protocols to the IND. These protocols were for a "model project" and a "double blind" randomized study involving human growth hormone manufactured by CX 12, Trans. at 22. Dr. Peggy A. Hanson reviewed the protocols and recommended that the IND continue on hold because of deficiencies in the protocols. CX 13.

FDA sent a letter dated October 31, 1986, to Dr. Aroonsakul[6], to advise her that the IND remained on clinical hold. CX 48. Dr. Aroonsakul sent a letter dated December 22, 1986, to FDA requesting that the agency provide a "formal explanation" to a drug manufacturer regarding why the project with human growth hormone was on clinical hold.[7] CX 69.

In August and September 1988, FDA conducted another directed inspection of Dr. Aroonsakul as a result of information regarding her treatments with human growth hormone received from the Drug Enforcement Administration. CX 68. Based on the inspection, Mr. Richard Kingdon and Ms. Doralee Segal, the FDA investigators, advised Dr. Aroonsakul that they found the following fourteen violations: 1) Dr. Aroonsakul dosed patients with human growth hormone in 1986 and 1987 after her IND was placed on clinical hold; 2) Dr. Aroonsakul's curriculum vitae misrepresented her qualifications by stating that she had an appointment as an assistant professor at the University of Illinois College of Medicine where she had no

---

6/Based on conversations and letters from Dr. Aroonsakul and Dr. (CX 10, 11), FDA recognized Dr. Aroonsakul as the sponsor of the IND. Therefore, future correspondence regarding the IND was directed to her.

7/The letter from Dr. Aroonsakul indicated that she proposed to use a synthetic growth hormone made by A representative of that drug manufacturer had requested a formal explanation of why Dr. Aroonsakul's project was on clinical hold.

such appointment; 3) Dr. Aroonsakul made claims in a brochure that she had permission from FDA to conduct the study, when in fact the IND was placed on clinical hold; 4) Dr. Aroonsakul changed the order of laboratory values diagnosing the serum for human growth hormone response on the data sheets for three patients; 5) Dr. Aroonsakul graphed the somatomedin-C level for her provocative test as "cholineacethylesterase;" 6) Dr. Aroonsakul failed to submit her IND study protocol to an Institutional Review Board for review and approval; 7) the consent forms submitted for the IND did not identify the investigational drug or its risks; 8) Dr. Aroonsakul did not have FDA approval to charge for the drug; 9) Dr. Aroonsakul included a diabetic patient in her study for whom there were greater theoretical risks; 10) Dr. Aroonsakul's records failed to show the quantity of the investigational drug administered or the dates and quantities of human growth hormone received, stored and dispensed; 11) the consent forms submitted for the IND included exculpatory provisions; 12) the consent forms submitted for the IND failed to include any reference to human growth hormone and its risks, a description of the route of administration for the drug, a description of any benefits to study subjects that could reasonably be expected from the research, a disclosure of alternate treatments, if any, and a statement describing the extent to which records would be maintained

confidential; 13) Dr. Aroonsakul misrepresented that the University of would participate in her somatotropin study; and 14) Dr. Aroonsakul's records failed to show that she had submitted an updated IND form FDA 1571, FDA 1572 or FDA 1573 for the study. CX 47.

In accordance with 21 C.F.R. § 312.70, by letter dated March 14, 1989, the Center offered Dr. Aroonsakul an opportunity to respond to the violations at an informal conference or in writing. CX 55. Dr. Aroonsakul responded by letter dated April 11, 1989, in which she addressed the above issues by alleging that she never conducted a clinical investigation with pursuant to IND but in fact, was practicing medicine. CX 55. The Center, by letter dated June 27, 1989, rejected this explanation for the conduct and advised Dr. Aroonsakul of the opportunity to withdraw the IND to terminate further administrative action against her. The Center also advised Dr. Aroonsakul that if she did not withdraw the IND, the Center would forward to the Commissioner its recommendation that the regulatory process be continued against Dr. Aroonsakul to find her ineligible to receive investigational new drugs. CX 55.

The Center, by letter dated July 21, 1989, advised Dr. Aroonsakul that since she had not agreed to withdraw the IND,

it was forwarding to the Commissioner its recommendation that she be disqualified from receiving investigational new drugs. CX 56. Dr. Aroonsakul sent FDA a letter dated July 21, 1989, in which she alleged that she was not conducting research under the IND. CX 50. The Center advised Dr. Aroonsakul by letter dated August 14, 1989, that her letter dated July 21, 1989 did not present any new information that would cause it to cancel its recommendation to the Commissioner. The Center again advised Dr. Aroonsakul of the opportunity to withdraw the IND and terminate the regulatory process. CX 56.

On November 24, 1989, Ronald Chesemore, then Acting Associate Commissioner for Regulatory Affairs, FDA, issued a notice of an opportunity for hearing ("NOOH") under Part 16 procedures to Dr. Aroonsakul. She requested a hearing, and that hearing was held on April 23, 1990.

III. CHARGES

The Center made the following charges in the NOOH in support of its proposal that Dr. Aroonsakul be disqualified from receiving investigational new drugs:

Charge #1: Dr. Aroonsakul violated 21 C.F.R. §312.42(a) by dosing subjects 33, 36, 37, 38, 39, 40, 41, and 42 with the

investigational new drug in 1986 and 1987, after FDA imposed the "clinical hold" prohibiting her from administering the investigational new drug, human growth hormone, to study subjects.

Charge #2: Dr. Aroonsakul failed to obtain approval from an Institutional Review Board as required by 21 C.F.R. § 312.66.

Charge #3: Dr. Aroonsakul failed to obtain informed consent from study subjects as required by 21 C.F.R. § 50.20.

Charge #4: Dr. Aroonsakul failed to maintain adequate records showing the receipt of the investigational new drug, as required by 21 C.F.R. § 312.57.

Charge #5: Dr. Aroonsakul failed to maintain adequate records to show the quantity and identity of the investigational new drug dispensed to study subjects as required by 21 C.F.R. § 312.62(a).

Charge #6: Dr. Aroonsakul failed to maintain adequate and accurate case histories as required by 21 C.F.R. § 312.62(b).

Charge #7: Dr. Aroonsakul promoted the investigational new drug, human growth hormone, as an "effective treatment" for Alzheimer's disease in violation of 21 C.F.R. § 312.7.

The Center's charges against Dr. Aroonsakul are fully described in the NOOH letter dated November 24, 1989 to Dr. Aroonsakul from Mr. Ronald Chesemore.

To support the charges against Dr. Aroonsakul, the Center presented three witnesses, Dr. Russell Katz, Deputy Director of the Center's Division of Neuropharmacological Drug Products, FDA (Trans. at 10-31); Ms. Doralee Segal, Division of Scientific Investigations, FDA (Trans. at 102-181); and Mr. Richard Kingdon, FDA investigator (Trans. at 44-67).

Dr. Aroonsakul testified in her own behalf. Dr. Aroonsakul testified as to her administration of the drug human growth hormone and alleged that the drug was administered in the practice of medicine, and not in a clinical investigation. (Trans. at 258-348). She presented no other witnesses.

IV. REGULATORY FRAMEWORK

FDA's regulations governing the clinical evaluation of investigational new drugs are set forth in 21 C.F.R. Part

312. Regulations regarding informed consent and institutional review boards applicable to clinical investigations are set forth in 21 C.F.R. Parts 50 and 56.

Section 312.70 of the regulations provides for the disqualification of clinical investigators. That section provides, as here relevant:

> After evaluating all available information, including any explanation presented by the investigator[9], if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50 or Part 56, . . . the Commissioner will notify the investigator and the sponsor[9] of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

8/An investigator is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject." 21 C.F.R. § 312.3.

9/A sponsor is "a person who takes responsibility for and initiates a clinical investigation." An individual who initiates and conducts a clinical investigation is referred to as a "sponsor-investigator." 21 C.F.R. § 312.3(b).

21 C.F.R. § 312.70(b).

V. ANALYSIS

In preparing my report, I have carefully reviewed the information in the administrative record and the information presented at the hearing.[10] I find that Dr. Aroonsakul repeatedly violated the regulations in Parts 312 and 50 and therefore, pursuant to 21 C.F.R. § 312.70(b), should be disqualified from receiving investigational drugs. I will discuss each charge and my findings separately below.

Charge #1: Dr. Aroonsakul violated 21 C.F.R. §312.42(a) by dosing subjects 33, 36, 37, 38, 39, 40, 41, and 42 with the investigational new drug in 1986 and 1987, after FDA imposed the "clinical hold" prohibiting her from administering the investigational new drug, human growth hormone, to study subjects.

Dr. Aroonsakul admitted that during 1986 and 1987, she administered human growth hormone to patients as a treatment for Alzheimer's disease. Trans. at 51-52. However, Dr.

10/I did not consider information submitted after the hearing except that information for which I specifically permitted additional time for submission pursuant to 21 C.F.R. § 16.80(b).

Aroonsakul maintained, contrary to the Center's charge, that she did not administer human growth hormone as an investigational drug, but that she administered the drug in the course of her private practice of medicine.

According to the regulations, a drug is an investigational drug if it is used in a clinical investigation in one or more human subjects. A clinical investigation is any use of a drug except for the use of a marketed drug in the course of a medical practice. See 21 C.F.R. § 312.3. If a person intends to use a drug in a clinical investigation, he or she makes this intent known to the agency by submitting an IND which describes the drug, dosage, route of administration, and indication(s) for use. See 21 C.F.R. § 312.20.

Once a sponsor-investigator submits an IND that expresses this intent, and then uses the drug in human subjects for the same indication specified in the protocols submitted to the IND, the agency properly concludes that the sponsor-investigator has used the drug as an investigational drug under the IND. This inference is appropriately based on the intent expressed by the submission of the IND and by the sponsor-investigator's actions after the IND is submitted. The agency, in such circumstances, has a basis for finding that the sponsor-investigator is administering an

investigational drug under the IND. The burden is on the sponsor-investigator to express his or her intention not to conduct a clinical investigation by withdrawing or inactivating the IND. Statements by the sponsor-investigator that he or she is not conducting a clinical investigation cannot be held to negate the effect of an IND submission under the regulations. Such statements do not relieve that individual of the responsibilities incurred under the IND regulations in the absence of actions by the sponsor-investigator that would support such statements (e.g. formal withdrawal of the IND).

There is no dispute that an IND was submitted by Dr. Aroonsakul as a sponsor and investigator of a clinical investigation of the use of human growth hormone on individuals with Alzheimer's disease.[11] Consistent with the

---

11/Dr. Aroonsakul has alleged that the sponsor of the IND was originally Dr. and that she was not responsible for the IND until October 31, 1986, at which time she received her first letter from FDA as the sponsor of the IND. The original IND was filed by an attorney for his clients, Drs. and Aroonsakul. Both Dr. and Dr. Aroonsakul signed the original submission. Within the IND submission the Foundation was listed as the sponsor in some places and Drs. and Aroonsakul as the sponsor in other places. CX 1. While FDA designated Dr. as the sponsor of the IND, since his name appeared first on the IND, Dr. Aroonsakul has maintained since October 14, 1985, that she along with Dr. was a sponsor of the IND. CX 49. Finally, in June 1986, Drs. and Aroonsakul requested, by letter, that FDA designate Dr. Aroonsakul as the sponsor. CX 10,11. Therefore, I find that Dr. Aroonsakul had sufficient connection to the original IND submission to be held

regulations in effect at that time,[12] the existence of the IND expressed Dr. Aroonsakul's intent to use human growth hormone for investigational purposes, that is, to test its effects on the clinical course of senile dementia, including diagnosed cases of Alzheimer's disease. CX 1.

In addition, the Center demonstrated that Dr. Aroonsakul did in fact administer human growth hormone to patients for the purpose of treating Alzheimer's disease. Dr. Aroonsakul's patient records obtained during the 1988 FDA inspection document her administration of human growth hormone to patients as a treatment for Alzheimer's disease. The record for subject 41, a 64 year old patient, documents the administration of human growth hormone to the patient on August 1, 1986, September 2, 1986, March 5, 1987, and April 2, 1987. CX 24. The record for subject 37, a 77 year old patient, documents the administration of human growth hormone several times during 1986 and 1987. CX 25. The Center also presented the records of subjects 33, 38, 36, 39, 42, and 40 that document Dr. Aroonsakul's administration of human growth

---

responsible for it.

12/See 21 C.F.R. § 312.1 (1985). The regulations were revised in 1987 to make this requirement more explicit. See 52 Fed. Reg. 8798 (1987).

hormone to these patients throughout 1986 and 1987 as a treatment for Alzheimer's disease. CX 26-31.

Moreover, Dr. Aroonsakul did not dispute that she administered human growth hormone to patients as a treatment for Alzheimer's disease during 1986 and 1987. She admitted this fact at the hearing. Trans. at 51-52.

In response to the Center's charges that she used human growth hormone under the IND Dr. Aroonsakul maintained that she administered the drug in her private practice of medicine, rather than in a clinical investigation under the IND. Much of the confusion in this matter is caused by the fact that Dr. Aroonsakul used a natural human growth hormone from cadavers to treat patients with Alzheimer's disease prior to the submission of the IND. Trans. at 258-264. According to Dr. Aroonsakul, she and Dr. submitted the IND to gain access to a synthetic human growth hormone made by which was not yet approved for marketing by FDA, because the natural human growth hormone from cadavers was voluntarily withdrawn from the market in May 1985 by its manufacturer due to viral contamination. CX 1, Trans. at 263, 280. Since no other growth hormone was approved by FDA for any indication at the time of the

original IND submission,[13] Dr. Aroonsakul admitted her use of the IND process to gain access to a then investigational drug to continue treatment of her patients. While this may have been Dr. Aroonsakul's original purpose in submitting the IND, the fact is that by doing so, she committed herself to fulfill all of the responsibilities and obligations of a sponsor-investigator who is using a drug for investigational purposes. 21 C.F.R. § 312.60.

It would have been a simple matter for Dr. Aroonsakul to make clear her intent to use the drug to treat Alzheimer's disease in her private medical practice by withdrawing the IND. That would have been another situation whose merits we need not reach here. However, Dr. Aroonsakul did not withdraw the IND even though she was presented with several opportunities to do so by FDA. CX 14, 55. Dr. Aroonsakul's assertions that she did not administer human growth hormone as an investigational drug for Alzheimer's disease, but used it in her practice of medicine, are insufficient to negate her obligations incurred by the existing IND submission, particularly since she did not withdraw the IND. Given Dr. Aroonsakul's allegations that she submitted the IND for the

---

13/The product listed in Dr. Aroonsakul's IND was approved by FDA for the treatment of dwarfism in the pediatric population on October 30, 1985.

sole purpose of gaining access to the drug to administer it to patients in her private practice, it is unclear why she continued to pursue the IND after the date of October 30, 1985, on which human growth hormone was approved for marketing by FDA. It has been shown that Dr. Aroonsakul came to the agency and expressed her intent on several occasions to use the drug for investigational purposes. CX 8, 10, 12, 49, 69. Therefore, it is appropriate to hold Dr. Aroonsakul to that expressed intent. To rule otherwise would be to create the possibility that any sponsor-investigator, when confronted with his or her failure to comply with the IND requirements, could claim that he or she was simply conducting the "practice of medicine." Such a potential loophole would render the IND regulations virtually meaningless.

Dr. Aroonsakul was a sponsor of the IND submitted for the purpose of investigating the use of human growth hormone in the treatment of Alzheimer's disease and administered the drug specified in the IND for the indication specified in the IND. I, therefore, find that Dr. Aroonsakul violated 21 C.F.R. § 312.42(a) by dosing study subjects 33, 36, 37, 38, 39, 40, 41, and 42 with the investigational new drug, human growth hormone, after the IND was placed on clinical hold.

Charge #2: Dr. Aroonsakul failed to obtain approval from an institutional review board as required by 21 C.F.R. § 312.66.

The Center charges that Dr. Aroonsakul administered the investigational new drug, human growth hormone, to study subjects throughout 1986 and 1987 without institutional review board review or approval as required by section 312.66 of the regulations. That section provides that "[a]n investigator shall assure that an institutional review board that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study." Dr. Aroonsakul, as the investigator for the human growth hormone study, had this responsibility. Dr. Aroonsakul did not present any evidence that she had obtained review or approval of the IND study by an institutional review board. Therefore, I find that Dr. Aroonsakul failed to obtain review and approval of the proposed IND study from an institutional review board as required by the IND regulations.

Charge #3: Dr. Aroonsakul failed to obtain informed consent from study subjects as required by 21 C.F.R. § 50.20.

The Center alleges that the consent form used by Dr. Aroonsakul did not conform to the regulatory requirements

because it did not inform study subjects that they would be dosed with the investigational new drug, human growth hormone, or identify the potential risks associated with the use of the drug, and, therefore, that she did not obtain informed consent from the patients treated with the drug. Section 50.20 of the regulations provides that "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject. . . ." Section 50.25 requires that informed consent include certain basic elements, such as a statement that the study involves research, an explanation of the purpose of the research, the expected duration of the treatment, a description of the procedures to be followed, a description of any foreseeable risks, a description of the benefits, disclosure of alternative procedures, and a statement that FDA may inspect the subjects' records. Section 50.20 provides that informed consent may not include any exculpatory language through which the "subject or the representative is made to waive any legal rights."

The Center presented the consent forms signed by patients who received human growth hormone from Dr. Aroonsakul as a

treatment for Alzheimer's disease.[14] CX 24, 25, 28. The consent form included the individual's authorization for Dr. Aroonsakul's treatment. The consent form stated that the nature and purpose of the treatment, the possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained. The consent form stated that the individual understands what the treatment consists of and lists certain side effects. The consent form released Dr. Aroonsakul from all claims, damages and causes of action that may arise from the treatment.

The consent form did not, however, advise individuals of the investigational nature of the treatment, specify that the investigational drug, human growth hormone, would be administered or specify other information that is required by section 50.25 of the regulations. In particular, the consent form included exculpatory language intended to release Dr. Aroonsakul from any liability arising from the treatment in violation of section 50.25 of the regulations. Therefore, I find that Dr. Aroonsakul failed to obtain informed consent

---

14/Dr. Aroonsakul presented another consent form in her post-hearing submissions that she alleged is the consent form for the IND study. However, she did not present any evidence that the form was signed by any patients who received human growth hormone as a treatment for Alzheimer's disease.

from the subjects of the human growth hormone study as required by the regulations.

Charge #4: Dr. Aroonsakul failed to maintain adequate records showing the receipt of the investigational new drug as required by 21 C.F.R. § 312.57.

The Center alleges that Dr. Aroonsakul did not show the dates and the quantities of human growth hormone that she received from the manufacturer or identify the actual source and name of the investigational drug given to study subjects. Section 312.57 of the IND regulations requires that a sponsor maintain "adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment."

It is clear from the evidence presented by the Center that Dr. Aroonsakul did not receive human growth hormone from the product's manufacturer, but rather she received the drug from other sources. According to the Center, Dr. Aroonsakul received the investigational drug from a Dr.
Dr. used her hospital privileges at the I.
Medical Center to buy the investigational drug

through the hospital pharmacy. Trans. at 53. Dr. Aroonsakul also obtained the investigational drug from a pharmacist, Trans. at 53.

The only records given to FDA documenting Dr. Aroonsakul's receipt of the investigational drug are a receipt, a cancelled check and checkbook stubs. Trans. at 53, CX 20. The records did not include the date of receipt, the quantity or the batch and code number. Therefore, these records are not adequate under section 312.57 of the regulations. Accordingly, I find that Dr. Aroonsakul failed to maintain the necessary records.

Charge #5: Dr. Aroonsakul failed to maintain adequate records to show the quantity and identity of the investigational new drug dispensed to study subjects as required by 21 C.F.R. § 312.62(a).

The Center alleges that Dr. Aroonsakul did not identify the study subjects who actually received the investigational drug or document the amount of human growth hormone dispensed to study subjects. Section 312.62(a) of the regulations provides that "[a]n investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects."

The patient records obtained during the 1988 inspection clearly specify the dates and quantity of the investigational new drug administered to study subjects. CX 24-31. Although the drug was not named in the patient records but rather was referred to by a code devised by Dr. Aroonsakul, she explained the code to FDA investigators so that they could determine that the investigational new drug was administered. Trans. at 106. Therefore, I find that Dr. Aroonsakul did not violate section 312.62(a) of the regulations.

Charge #6: Dr. Aroonsakul failed to maintain adequate and accurate case histories as required by 21 C.F.R. § 312.62(b).

The Center alleges that the evidence that it obtained reveals that Dr. Aroonsakul falsified certain subjects' actual laboratory values and mislabeled "somatomedin-C" to read "cholineacethylesterase." Trans. at 112-124. Section 312.62(b) of the regulations provides that "[a]n investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational drug. . . ."

Several case histories were obtained during the 1988 inspection. CX 24-31. However, only one case history shows an alteration of data. The changes made by Dr. Aroonsakul related to the results of blood draws for the provocative test. Dr. Aroonsakul graphed the values in a different order than that reported by the laboratory. CX 25. However, examination of that record indicates that, based upon the laboratory's accession numbers of the blood samples, the timed samples had to be in an obviously incorrect order. Therefore, the test results reported by the laboratory had to be incorrect. For example, the laboratory results showed the presence of a response to the provocative test prior to the time of administration of any drug, and then showed a decrease in the values to zero after the drug was administered. Knowing that these result could not be physiologically possible, and, therefore, were incorrect, Dr. Aroonsakul adjusted the order of the results and re-graphed the results accordingly. The graph, then, represented a pattern consistent with those reflected in the other case histories.

Because the Center did not offer any additional documentation of changes to the records, in this instance I do not believe that Dr. Aroonsakul's change in the order of the results altered the accuracy of the case history. Indeed, the change

corrected an apparent mistake made by the laboratory. Therefore, I find that Dr. Aroonsakul did not violate section 312.62(b) of the regulations.

Charge #7: Dr. Aroonsakul promoted the investigational new drug, human growth hormone, as an effective treatment for Alzheimer's disease in violation of 21 C.F.R. § 312.7.

Section 312.7 of the regulations provides that "[a] sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug." The regulation states that it "is not intended to restrict the full exchange of scientific information about the investigational new drug. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation."

The Center presented several pieces of evidence to establish that Dr. Aroonsakul promoted human growth hormone as an effective treatment for Alzheimer's disease. Dr. Aroonsakul's brochure entitled "Alzheimer's Disease-Now There Is Hope," implies that she has researched and developed an

effective treatment for Alzheimer's disease. CX 15, 21, 37. A copy of the brochure was sent to FDA by Professor of and additional copies were obtained during the 1986 and 1988 FDA inspections of Dr. Aroonsakul. While the brochure does not specify what the treatment is, there is no evidence that Dr. Aroonsakul has used or advocated any other treatment except the treatment involving human growth hormone.

In addition, the Center presented a letter from the Foundation to the governors of North Dakota and Georgia that clearly characterizes Dr. Aroonsakul's treatment as the "first effective treatment of Alzheimer's disease" and states that she has successfully treated 35 patients. CX 17, 44. The Center also presented a copy of Dr. Aroonsakul's business plan for the "First Alzheimer's & Dementia Treatment Center" which includes claims regarding the effectiveness of Dr. Aroonsakul's treatment for Alzheimer's disease. CX 23. A copy of this business plan was forwarded to FDA from the Drug Enforcement Administration. That agency received it from who indicated that she received the plan from Dr. Aroonsakul. CX 68.

Additionally, the Center presented a letter dated May 22, 1987 on Foundation letterhead to an employee at the University regarding Dr. Aroonsakul's treatment. This letter clearly describes the treatment as "effective." CX 36. Trans. at 142. This letter was obtained from the University files. Trans. at 142-143.

Other evidence presented by the Center included Dr. Aroonsakul's coupon for a free evaluation for a "scientifically proven treatment that stops and reverses the deterioration process." CX 38. Trans. at 148-149. Copies of the coupon were obtained from the Alzheimer's Disease and Related Disorders Association, a national support group for patients with Alzheimer's disease. Trans. at 146, 148. The Association obtained these copies of the coupon from patients who received the coupon. Trans. at 148.

The Center has also submitted as evidence a document entitled "The Alzheimer's Disease Diagnostic and Treatment Project." CX 39. This document was obtained from the Hospital from its file of Dr. Aroonsakul's materials. Hospital officials told FDA inspector Doralee Segal that the document accompanied some of the materials that were sent to patients. Trans. at 156. The document refers to Dr.

Aroonsakul's treatment as "effectively" reversing the symptoms in all patients treated to date and states that her treatment is "effective" not only in the reversal of Alzheimer's symptoms, but also in those with senile dementia, Parkinson's disease, multiple sclerosis, stroke and other related diseases of the central nervous system. CX 39.

A letter from Dr. Aroonsakul's treatment center, dated November 7, 1988, to an individual referred to only as "Joyce," who was the daughter of a patient with Alzheimer's disease, states that Dr. Aroonsakul is "the leader in the development of the effective treatment of Senile Dementia, Alzheimer's Disease, Parkinson's Disease, and other chronic degenerative diseases of the aging." CX 42. This letter was obtained from Hospital. Trans. at 163.

In response to the Center's charges, Dr. Aroonsakul stated that the documents were not distributed to the public, but only to a few colleagues for review. However, in her testimony at the hearing, Dr. Aroonsakul admitted sending out the coupons. Trans. at 289. In addition, it is clear from the sources from which the Center obtained the documents that the documents had wide dissemination.

The large number of brochures and similar materials presented by the Center evidences an intent on Dr. Aroonsakul's part to use the materials to attract patients into her treatment program long before the completion of any required clinical protocol studies supporting this clinical indication for human growth hormone. The materials also anticipate effectiveness findings before such findings had been proven to the agency's satisfaction by submission, review and approval of a new drug application for the use of human growth hormone as a treatment for Alzheimer's disease. Therefore, I find that Dr. Aroonsakul did violate section 312.7 of the regulations by promoting the unlabeled use of the investigational new drug, human growth hormone, as an effective treatment for Alzheimer's disease.

VI. CONCLUSION

I conclude that Dr. Aroonsakul administered the investigational new drug, human growth hormone, in violation of 21 C.F.R. § 312.42(a). I also conclude that Dr. Aroonsakul violated 21 C.F.R. §§ 312.66, 50.20, 312.57, 312.62(a), and 312.7. Since Dr. Aroonsakul repeatedly violated the regulations in Parts 50 and 312, I conclude that Dr. Aroonsakul should be disqualified from receiving investigational drugs.

VII. RECOMMENDATION

I recommend that the Commissioner disqualify Dr. Aroonsakul from receiving investigational drugs.

Freddie Ann Hoffman, M.D.