DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 18 2003

VIA OVERNIGHT MAIL

Frederick Coulston, Ph.D.
CEO, Chairman of the Board
Coulston Foundation
2512 Christina Place
Alamogordo, New Mexico 88310

NOTICE OF OPPORTUNITY FOR A HEARING

Dear Dr. Coulston:

This letter offers you an opportunity to request a regulatory hearing to determine whether Coulston Foundation (CF) should be disqualified as a testing facility for nonclinical laboratory studies. If no written response is received within ten (10) business days after receipt of this letter, you will be deemed to have waived any right to a regulatory hearing; and a decision in this matter will be made based on the facts available to the agency without a hearing.

The United States Food and Drug Administration (FDA) has information indicating that CF has violated federal regulations while operating in its capacity as a testing facility for the conduct of nonclinical laboratory studies governed by Title 21 Code of Federal Regulations (21 CFR), Part 58–Good Laboratory Practice for Nonclinical Laboratory Studies (the GLP regulations). CF's violations of the GLP regulations provide the basis for disqualification, which would result in excluding its studies from consideration in support of applications for research or marketing permits for products regulated by the FDA.

FDA is proceeding with disqualification of CF based on the findings from inspections of the testing facility between July 26 and August 19, 1999, and between November 27 and December 8, 2000; and on information from written and telephone communications with CF, including two warning letters and a consent agreement, from July 1999 to the present regarding lesser regulatory actions by FDA that have not resulted in compliance by CF.

As described below, FDA has information which establishes that the grounds for disqualification under 21 CFR 58.202 exist:

a) CF's noncompliance with the GLP regulations;
b) CF's noncompliance adversely affected the validity of studies; and,
c) Lesser regulatory actions, including two warning letters and a consent agreement have not resulted in compliance by CF.

CF is hereby offered an opportunity for a regulatory hearing pursuant to 21 CFR 58.204(b), on the matter of whether it should be disqualified as a testing facility for the conduct of nonclinical laboratory studies. CF has the right to be represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR Part 16, and the agency's guidelines on electronic media coverage of administrative proceedings, 21 CFR Part 10, Subpart C. Copies of these regulations are enclosed.

Noncompliance with the GLP regulations that adversely affects the validity of studies. [21 CFR 58.202(a) & (b)]

A listing of selected violations follows. These are matters that will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation.

I. Organization and Personnel

A. Test Facility Management

1. Testing facility management failed to assure that corrective actions were taken and documented for deviations from the GLP regulations. [21 CFR 58.31(g)] For study [redacted] nine quality assurance unit (QAU) reports to management were signed and returned to the QAU without documentation of the corrective action taken.
2. Testing facility management failed to assure that all personnel clearly understood the functions they were to perform. [21 CFR 58.31(f)] This violation was noted at both inspections.

a) The testing facility failed to maintain a current job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study. Specific examples include the Chief Executive Officer/Chairman, the President, the Executive Vice President, and the Director of Comparative Fertility and Sterility.

b) No job descriptions were found in the personnel/training files of three of the four Study Directors.
c) The facility failed to assure that employees clearly understood the functions they were to perform by not requiring employees to be familiar with Standard Operating Procedures (SOPs).

3. Testing facility management failed to assure that the QAU monitored each study for conformance with the GLP regulations. [21 CFR 58.31(c) and 58.35(a)] Studies [redacted] and [redacted] did not have any QAU oversight.

B. Study Directors

1. The study director(s) for studies [redacted], [redacted] and [redacted] failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. [21 CFR 58.33(f)] This violation was noted at both inspections.

a) For completed study [redacted] there were seven envelopes (each approximately 1 inch thick), of miscellaneous correspondence, records, and raw data located in the study director's possession that were not transferred to the archives.
b) For study [redacted], there were several types of raw data that were not archived.
c) For study [redacted], there were several types of raw data that were not archived.

2. Studies [redacted] and [redacted] were not conducted in accordance with the protocol. [21 CFR 58.130(a)] The study director for study [redacted] failed to assure that the protocol, including any changes, was approved as required by 21 CFR 58.120 and was followed. [21 CFR 58.33(a)] These violations were noted at both inspections.

a) The protocol for study [redacted] required that "treatment of animals will be in accordance with institutional standards." Per SOP [redacted], Food and Fluid Deprivation and restriction, [redacted] The animals were fasted the day prior to any study activity. There was study activity daily for the first 14 days of the study, and weekly thereafter. Animals experienced decreased appetite and diarrhea, and four of them lost 18%

or more of their body weight. No animals were taken off the study for health reasons.

b) Numerous requirements of the protocol for study [redacted] were not consistently met: unique test substance control number; records of sterilization of instruments; records of animal room temperature and humidity; records of physical or neurological examination; preoperative fluoroscopy; radiographs; antibiotic treatment records; records of autologous bone grafts; quantitative records of food consumption; records of blood samples; and records of resampling of contaminated samples of animal drinking water.

c) For protocol amendment #1 for the [redacted] study, [redacted] the study director sent a facsimile to the sponsor on the [redacted] day asking that the sponsor's personnel falsely backdate their signatures to the [redacted] day when the study started.

3. Study directors failed to have overall responsibility for the technical conduct of studies as well as for the interpretation, analysis, documentation and reporting of results, and did not represent the single point of study control. [21 CFR 58.33]

Study directors failed to consistently assure that:

a) All required personnel were available. Studies [redacted] and [redacted].

b) All applicable GLP regulations were followed. Study [redacted]

c) Protocols, including changes, were approved prior to starting study procedures. Studies [redacted] and [redacted]

d) All raw data, documentation, protocols, specimens, and final reports were transferred to the archive. Studies [redacted], [redacted], and [redacted]

e) Test systems were as specified in the protocol. Studies [redacted] and [redacted]

f) Study personnel were following SOPs. Studies [redacted], [redacted], and [redacted]

g) Study personnel were following the protocol and/or amendments to protocol. Studies [redacted], and [redacted]

h) All experimental data, including observations of unanticipated responses of the test system were accurately recorded and verified. Studies [redacted], [redacted], and [redacted].

i) All equipment utilized in the study was functioning as intended. Study [redacted].

C. Quality Assurance Unit

1. The QAU failed to maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of the study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director. [21 CFR 58.35(b)(1)]

   a) At the first inspection, there were twelve examples of such failures involving twenty studies, including various inaccuracies and omissions. These examples are listed in item nine of the Form FDA-483 that was given to CF at the conclusion of the first inspection.

   b) At the second inspection, there were thirteen examples of missing or contradictory elements in the master schedule databases. These deficiencies included six instances of missing or contradictory dates the studies were intitiated, and seven instances of missing or contradictory information about the current status of the studies. In addition, three studies were missing from the master schedule in their entirety.

2. The QAU failed to assure that the final study reports were an accurate reflection of the raw data. [21 CFR 58.35(b)(6)] This violation was noted in both inspections.

   a) At the first inspection, FDA noted that the final report for study [redacted] excluded certain assay data collected under the approved protocol. Thus the study report did not represent an accurate reflection of the raw data.

   b) At the second inspection, FDA noted that:

      (1) In the final report for study [redacted], the Summary of Validation data for dose analysis contained only the highest analytical results rather than all analytical results.

      (2) In the final report for study [redacted], Appendix G consisted of urinalysis results for female animals and did not include data for Urobilinogen, Occult Blood, Nitrite, and Leukocytes.

3. The QAU failed to assure management that the GLP regulations were being followed. [21 CFR 58.35(a)] Discrepancies in the SOP manuals used by the QAU impaired its ability to assure that the GLP regulations were being followed.

   a) SOP [redacted] was retired on 11/19/1999. The same SOP number was reassigned to a different procedure, effective 02/02/2000. When facility personnel discovered the problem, the second SOP was renumbered [redacted] however, the SOP erroneously numbered [redacted] remained in the QAU SOP Manual.
   b) The dating format on the SOPs was not standardized. For example, 10 SOPs in QAU SOP Manual [redacted] had a combination of day-month-year format and month-day-year format.
   c) SOP [redacted] had a division/department approval signature with the implausible date of 8/115/00.
   d) SOP [redacted] referred to a related form called [redacted] that was not located in the QAU Forms Manual.

II. Testing Facility Operations

A. The testing facility did not have written SOPs setting forth nonclinical laboratory study methods adequate to insure the quality and integrity of the data generated in the course of a study. [21 CFR 58.81]

1. At the first inspection, FDA noted that the SOPs did not set forth *adequate study methods for:*

   a) Function of a study coordinator.
   b) Use of a study box.
   c) Testing strips used to monitor temperature of cage washing machines.
   d) Defining certain fields in the master schedule.
   e) Use of a form in recording receipt of test articles.
   f) Treatment of study animals when the study director is unavailable.
   g) Monitoring whether temperature limits are exceeded in refrigerators, freezers, and food storage areas.
   h) Responding to fires in the archives.

i) Entering operator and other information when using a flow cytometer.

In addition, certain SOPs were not current in both a laboratory and in a breeding unit building. Of the nineteen such outdated SOPs, two examples are [redacted] and [redacted]

2. At the second inspection, FDA noted that:

a) There was no SOP defining the methods for use and maintenance of the "study box."
b) There was no SOP describing a method for testing temperature sensitive strips used in the Cage washing system.
c) SOP [redacted] titled the Quality Assurance Master Schedule, describes the contents of the Master Schedule. The Master Schedule contains the following fields that are not defined in the SOP; (1) Start Date, (2) Entered, (3) Updated, (4) Archived.

B. SOPs were not followed, and deviations were not authorized and documented. [21 CFR 58.35(b)(5) and 58.81(a)]

1. For study [redacted], there were eight instances of failures to follow SOP [redacted] (titled, "In-Life Study Inspections").
2. There were multiple instances of failures to review SOPs annually, as required by SOP [redacted]. The first inspection found 6 SOPs that had not undergone annual review. The second inspection found that QAU SOP Manual number [redacted] contained 22 SOPs that had not undergone annual review and that QAU SOP Manual number [redacted] contained 10 SOPs that had not undergone annual review.
3. There was no validation documentation for the following equipment as required by SOP [redacted]

a) [redacted] Flow Cytometer. This violation was noted at both inspections. After the first inspection, the facility promised to produce such documentation, but failed to do so.
b) Other computer controlled equipment that was not validated as required by SOP [redacted] were a [redacted] Automatic Analyzer and a [redacted] Hematology System.

III. Conduct of Nonclinical Laboratory Studies

A. Changes in automated data entries were made without an indication of the reason for change. [21 CFR 58.130(e)]

1. For flow cytometry data from study [redacted], there were unexplained date changes, missing sequence numbers, and duplicate animal numbers.
2. For electrocardiograph data from study [redacted] a hand written date differs from the automatically generated date.

B. The individual responsible for direct data input was not always identified at the time of data input into the automated data collection system [21 CFR 58.130(e)] This violation was noted at both inspections. In the first inspection, FDA found that the documentation did not always reflect the individual identified as responsible for data input. In addition, during the second inspection FDA found that the identification of the individual was not always correct. Five flow cytometer reports, one dated 03/10/2000 and four dated 09/28/2000, contained the operator identification of an ex-employee who died 03/20/2000.

IV. Records and Reports

A. Raw data and documentation generated as a result of a nonclinical laboratory study were not retained [21 CFR 58.190(a)] for the following:

1. Study [redacted] stability data.
2. Study [redacted], radiographs and fluoroscopy records.
3. Study [redacted] chemistry records.
4. Study [redacted], cytometry records.

B. A final report was not prepared for each completed or closed nonclinical laboratory study. [21 CFR 58.185(a)]

FDA identified 30 studies that lacked final reports. Although the GLP regulations do not specify a time limit for the completion of final reports, eight studies that were started in 1993 did not have final reports at the time of the December 2000 inspection. Since this inspection, CF has not notified FDA of the completion of final reports for any of the eight studies started in 1993. CF notified FDA of completion of final reports for two of the other 22 studies, but did not furnish FDA the final reports themselves.

The above descriptions of violations are not intended to be an all-inclusive list of deficiencies at CF.

In promulgating the GLP regulations, FDA explained "that the purpose of the ...[GLP] regulations is to ensure, as far as possible, the quality and integrity of nonclinical laboratory data submitted to FDA ..." 41 Fed. Reg. 51209. Further, "quality data accrue as a result of proper utilization of and control over the facilities, personnel, and procedures involved in the study." Id. In addition, FDA stated that "the regulatory standards focus on the process by which scientific data are generated; that is, the regulatory requirements are designed so that, if good faith compliance occurs and the protocol is scientifically sound, there is reasonable assurance that the data generated are scientifically valid." Id. at 51216. The above descriptions of the numerous violations serve as evidence that CF's noncompliance adversely affected the validity of the nonclinical laboratory studies conducted at CF.

Regarding disqualification, FDA stated that "[t]he primary function of the agency's regulation of nonclinical laboratory testing is to assure the quality and integrity of data used in making judgments about the safety of products regulated by the agency. The grounds for disqualification are based on those types of noncompliance that significantly impair achievement of those objectives." 43 Fed. Reg. 60010. FDA also stated that disqualification "would be utilized when the deficiencies found at a facility are of such a widespread or fundamental nature that the quality and integrity of every study being conducted by the facility has probably been compromised, or when the facility has failed to comply with the [GLP] regulations after previous warning from FDA." 41 Fed. Reg. 51216. As indicated by the numerous violations, FDA believes the deficiencies at CF are so widespread that the quality and integrity of studies conducted at CF have been compromised.

Lesser regulatory actions including warning letters and a consent agreement have not been adequate to achieve compliance. [21 CFR 58.202(c)]

1. FDA issued a warning letter to CF on December 22, 1999. This warning letter requested CF to immediately take action to correct and prevent violations of GLP regulations, and to refrain from initiating additional nonclinical laboratory studies prior to completion of the actions to achieve compliance.

2. FDA issued a second warning letter on October 11, 2001, after a follow-up inspection revealed that serious GLP violations continued, and that

CF had initiated five additional nonclinical laboratory studies contrary to the previous warning.

3. FDA met with CF on November 5, 2001, to discuss the seriousness of the noncompliance and to reiterate the agency's concern that immediate corrections are required to achieve compliance.

4. FDA and CF entered into a consent agreement effective on May 14, 2002, establishing an agreed-upon framework for CF's corrective actions. (copy enclosed)

5. FDA sent CF letters and made several phone calls to CF after the agency discovered provisions of the consent agreement were violated (e.g., provisions 6 and 16).

6. FDA extended deadlines for achieving compliance under the agreement, and offered CF the option to sign a consent agreement of voluntary disqualification. CF failed to meet extended deadlines for achieving compliance, and did not sign the second consent agreement. Although FDA received various materials from CF in late September 2002, including a summary of calibration records and a master schedule, no corrective action plan was included, and the materials were incomplete and unsatisfactory to achieve compliance.

A final decision by the agency on the matter of disqualification of CF has not been made at this time. CF is hereby advised that if disqualified under 21 CFR 58.206, the following conditions that are found under 21 CFR 58.210 will apply:

1. Any nonclinical laboratory study conducted by CF that is determined to be essential and is submitted to FDA in an application for a research or marketing permit before or after disqualification may be presumed to be unacceptable; and
2. Persons relying on a nonclinical laboratory study by CF may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information.

Your request for a hearing must be made, in writing, within ten (10) business days after receipt of this letter and directed to Dr. James F. McCormack, Coordinator, Bioresearch Monitoring Program, Office of Enforcement, Division of Compliance Policy (HFC-230), 5600 Fishers Lane, Rockville, Maryland 20857, Telephone (301) 827-0425, FAX (301) 827-0482. If no response to this letter is received by that time, CF will be deemed to have waived any right to a regulatory hearing, and a decision in this

matter will be made without a hearing based on the facts available to the agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that the material submitted had raised no genuine and substantial issue of fact. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing CF's reply. The letter should state that CF waives its right to a hearing and that it wants a decision on the matter to be based on its written response and other information available to the agency.

The agency's offer to enter into a consent agreement of voluntary disqualification (attached to the agency's September 10, 2002, letter) remains available. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding.

Please inform Dr. McCormack within ten (10) business days of whether you wish to request a hearing or to have this matter resolved by information available to the agency.

Sincerely yours,

John M. Taylor, III
Associate Commissioner for
Regulatory Affairs

Enclosures:
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 58.200-215
Consent Agreement

cc:
F. Randolph Burroughs, Counsel to Coulston Foundation