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May 13, 2008
By fax to 240-276-3943
and by mail

Daniel G. Schultz, M.D.
Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration
9200 Corporate Boulevard, Room 100
Rockville, MD 20850

Dear Dr. Schultz:

I am writing to confirm some comments made to me on the phone last week by Ms. Adrienne Burns, your Executive Assistant. On May 7 she said you and your associates were planning to respond to the letter of April 30 by Ms. Danielle Brian (Executive Director of POGO) and me. The subject of this letter is CDRH's apparent decision not to enforce 21 CFR Part 58, the Good Laboratory Practice (GLP) regulations.

I wish to confirm Ms. Burns's statement that you and your associates are preparing a reply that will probably be sent out late this week (around May 16) or, if not, then early next week.

In addition, further information that may help in the preparation of your reply is included below. The quoted passages confirm similar material in the POGO letter of April 30.

All the passages that follow are quoted from the preamble to the final rule, dated December 4, 1978, by Donald Kennedy, the FDA Commissioner of Food and Drugs, and published in the Federal Register, vol. 43, no. 247, December 22, 1978. The preamble indicates that before the GLP regulations were finalized, proposed regulations were published in the Federal Register of November 19, 1976. Interested persons were given 120 days to submit comments, and public hearings were held.

The long preamble to the final rule (a total of 253 numbered items) contains discussions by Commissioner Kennedy of the many comments received, about half of which came from manufacturers and private laboratories. Each published discussion first summarizes the comments by interested persons and then presents Commissioner Kennedy's decisions. In most cases the final regulations (final rule) are unchanged from the proposed regulations published previously (November 19, 1976). In a few cases, in response to the comments received, the final regulations differ from the proposed regulations.

666 Eleventh Street, NW
Suite 900
Washington, DC
20001-4542
Phone: 202-347-1122
Fax: 202-347-1116

www.POGO.org
pogo@pogo.org

The item numbers below follow the numbering of items in the preamble. *The passages following each item number are quoted verbatim from the preamble.* Ellipsis marks indicate passages that have been omitted. A few comments of mine are included in brackets.

Item 5

A number of comments challenged the general legal authority of FDA to issue good laboratory practice regulations. Other comments challenged the legal authority to require record retention or quality assurance units, or to specify the content of required records or location of storage.

The Commissioner finds that the authority cited in the preamble to the proposal (41 FR 51219; Nov. 19, 1976) provides a sound legal basis for the regulations. . . . [The legal basis for the regulations is then discussed at length, with citations of decisions by circuit courts and the Supreme Court.]

Item 8

A number of comments said the cost of implementing the proposed regulations would be prohibitive to smaller testing laboratories and would, at the least, result in a substantial increase in the cost of product testing.

The Commissioner agrees that implementation of these regulations will increase the cost of nonclinical laboratory testing. The Commissioner finds, however, that such costs are justified on the basis of the resultant increase in the assurance of the quality and integrity of the safety data submitted to the agency. . . .

Item 10

Products regulated by the agency, for which safety data may be required, cover a wide range of diverse items that pose quite different types of risk. Examples include implantable medical devices; . . . .

Item 12 [This item is the one quoted in POGO's letter of April 30.]

More than 20 comments sought the addition of specific language exempting various classes of FDA-regulated products, such as medical devices, from coverage by the regulations.

The Commissioner has generally elected not to permit exemptions based on broad categories of regulated products because no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another. Proper safety decisions are important for all these products; accordingly, the processes by which such safety data are collected should be subjected to identical standards of quality and integrity.

Item 26

Several comments objected to the inclusion of medical devices in § 58.3(e) (16), 17, and (18), stating that medical devices were not "test substances," that medical devices should not be included because the rules for data submission for such devices were as yet undefined, and that inclusion of medical devices would be unduly restrictive. These comments suggested either total or partial exclusion from coverage under the good laboratory practice regulations.

For reasons stated previously, the Commissioner does not agree that medical devices, as a category, should be excluded. Implantable devices may be composed of polymeric materials that contain components capable of leaching from the device into the body of the recipient or may themselves be adversely affected by body constituents. In either case, safety studies would be necessary to demonstrate that components of the device did not cause harm or that the body constituents did not promote breakdown or malfunction of the device.

Item 75 [under the subheading "Quality Assurance Unit"]

More than 100 comments objected to part or all of § 58.35 as proposed. Many comments questioned the need for a quality assurance unit as proposed. Some comments stated that the establishment of such a unit would increase the administrative burden and costs of performing nonclinical studies to the point of forcing small facilities out of business. Others stated that the provisions would interfere with management's prerogatives to organize the facility or with the informed scientific judgment of principal investigators or study directors.

The Commissioner has retained the requirement that each testing facility have a quality assurance unit (QAU) to monitor the conduct and reporting of nonclinical laboratory studies. In view of the potential gain to management, to sponsors, and to FDA, through the added assurance of well-conducted studies, increased costs, if any are justified. . . .

Item 130 [under the subheadings "Testing Facilities Operation: Standard Operating Procedures"]

Two comments suggested deleting § 58.81 in whole or in part. Several others said the requirements for standard operating procedures were unnecessary and burdensome.

The Commissioner does not agree. The use of standard operating procedures is necessary to ensure that all personnel associated with a nonclinical laboratory study will be familiar with and use the same procedures. These requirements will prevent the introduction of systematic error in the generation, collection, and reporting of data, and they will ensure the quality and integrity of test data that are submitted to FDA to become the basis for decisions made by the agency. The Commissioner recognizes that the requirements for standard operating procedures may place an additional burden on testing facilities, but finds that the resulting benefits should outweigh the burden. The requirements will benefit the public by producing better quality data and will benefit the testing facility by reducing the need to repeat nonclinical laboratory studies because of errors in the data.

This concludes the excerpts from the preamble to the final rule. Ms. Brian and I look forward to receiving your comments on the important subject of CDRH's enforcement of the GLP regulation.

Sincerely,

Ned Feder

Ned Feder. M.D.
Staff Scientist
Project On Government Oversight
666 11th Street, NW, Suite 900
Washington, DC 20001
Phone: 202-347-1122
Fax: 202-347-1116
nfeder@pogo.org

Copies:
Adrienne Burns, Executive Assistant, Office of the Director, CDRH (by email)
Danielle Brian, Executive Director, Project On Government Oversight