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April 30, 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:

We are writing about the apparent decision by the Center for Devices and Radiological Health not to enforce 21 CFR Part 58, the Good Laboratory Practice (GLP) regulations. This is a matter of concern to our organization, Project On Government Oversight, which has been looking into GLP enforcement by CDRH. We are planning to publish a report on our findings and to provide this report to interested parties. POGO is an independent nonprofit organization that examines government operations with the goal of improving their effectiveness and achieving a more accountable government.

We ask that you provide us with answers to the questions below.

The apparent decision by CDRH to abandon enforcement of the GLP regulations was described last year on the "What's New" page of the website for Immel Resources LLC at http://immelresources.com. (See http://immelresources.com/OldWhats_New.html.)

In a short article entitled, "FDA No Longer Enforcing GLPs for Devices," Immel Resources stated that the FDA "announced the policy change in May 2007 at the Annual Meeting for the Society for Quality Assurance. An agency representative said that FDA does not intend to take enforcement action if a nonclinical laboratory is not following GLPs." The article quoted other comments made by the agency representative, including: "Historically, CDRH review divisions have not required animal safety studies to follow GLP" and "Many marketed devices did not follow GLP."

We have spoken with attendees at the SQA meeting who have confirmed this description of events and have told us about their great surprise when the change in enforcement strategy was announced on May 3, 2007. The announced change – from a requirement by CDRH for obligatory compliance with the GLP regulations to optional compliance (including noncompliance) – raises several questions.

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Legal issues

Question 1. What is the legal basis for CDRH's abolition or marked weakening, within CDRH, of the FDA's enforcement of the GLP regulations?

There appears to be a solid legal basis for the principle that sponsors' compliance with the GLP regulations is required, i.e., that compliance is not optional. In 1978, before the issuance of the final rule, the FDA had received comments on the draft rule from persons who favored the exemption of medical devices: "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." (This quotation comes from the preamble to the final rule, General Provisions, Scope, item 12, 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.)

But the FDA, in the passage immediately following the sentence quoted above, rejected the requests for such exceptions. Commissioner Kennedy dealt with the issue clearly and explicitly: "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*." (Emphasis added.)

We have sought but not found any legal opinion published on the FDA website that invalidates or reverses Dr. Kennedy's conclusion that the required standard for nonclinical testing of medical devices is the GLP regulation.

We are aware of published announcements on related subjects, for example, on FDA's use of a risk-based approach and "enforcement discretion" during the auditing of systems for compliance with 21 CFR Part 11 (related to electronic records). We are also aware of CDRH's statement that, because of its limited resources, it is using a risk-based strategy for field inspections in the post-marketing period. However, we are not aware of any published CDRH statements corresponding to the statements by CDRH's representative at the SQA meeting on May 3, 2007 to the effect that

- o CDRH has not required animal safety studies to follow GLP
- o Many marketed devices did not follow GLP
- o It is not feasible to require manufacturers to follow GLP

Question 2. Have any statements been published by CDRH on the FDA website about the change in CDRH policy, such as the three bulleted statements just above? If there are such statements overriding the previous GLP policy, we ask that you identify them.

The change in policy – from obligatory compliance to optional compliance or noncompliance with the GLP regulations – is a radical one. Question 3. If this change has been made without public notice and without the opportunity for public comment, what procedure was followed within CDRH in order to make the change, and what is the legal justification for such a procedure conducted without public notice in the Federal Register or elsewhere?

Ethical issues related to patient protection

The next question is based not on any legal requirement for GLP compliance, but solely on well-established ethical principles for patient protection requiring that devices should be as safe as is reasonably possible when they are implanted in patients.

Question 4. What is the *evidence* showing that the CDRH's current policy for the monitoring of safety for devices is at least as effective as strict enforcement by CDRH of the 21 CFR Part 58 regulations requiring GLP compliance?

If, as seems very likely, CDRH's current monitoring and enforcement practice is less effective than the past practice of enforcing GLP compliance, then patients are being put at increased risk due to the discontinuation of GLP enforcement. It is clearly unethical to increase the risk to patients in this fashion *without their informed consent.* We are unaware of any effort to inform patients or their physicians about the lowered standards for nonclinical laboratory testing. We ask that you let us know if CDRH is planning such an effort. If no such effort is planned, we ask that you explain the justification for the failure to obtain informed consent.

Years ago, when it was still customary for CDRH to enforce GLP, there were instances of GLP noncompliance discovered at the time of an inspection. These inspections had a salutory effect not only on the companies discovered to be GLP noncompliant, but presumably on all companies, since all were aware that inspections would continue. Indeed this was one of the main reasons that Congress enacted the GLP regulation: all companies would be motivated to comply with the GLP regulation by the FDA's inspection and occasional disciplining of a few companies.

But now there are far fewer inspections, and inspectors of nonclinical laboratories are not authorized by CDRH to look routinely for evidence of GLP noncompliance. Thus greater reliance is being placed on the judgment of CDRH personnel in deciding, in the absence of standards set by the GLP regulations, that devices are safe enough for human testing and subsequent widespread use. CDRH personnel are now responsible for making these difficult judgments – not only in the absence of standards set by the GLP regulations, but usually (and perhaps almost always) without any inspections whatsoever.

Question 5. Is there any *evidence* that manufacturers and their contract laboratories are *voluntarily* (i.e., without a requirement for GLP compliance and in the absence of inspections) *imposing sufficiently high standards on themselves*, namely, standards that are at least as high as those required by the GLP regulations?

Finally, we ask that you provide us with a very brief preliminary response to this letter. Please let us know promptly by email or fax if you are planning to reply more fully and if so, the estimated date of your full reply. If you decide to send us a reply, you should plan to do so within three weeks if possible and within 30 days at the latest.

The readers of our report will undoubtedly want to know whether there is or is not a sound legal and ethical basis for CDRH's policy on enforcement of the GLP regulations.

Thank you for looking into the matters discussed here. All of us – those inside CDRH, elsewhere in the FDA, and in nonprofit organizations such as Project On Government Oversight – are seeking the same goal: the best use of limited resources in a time of rising FDA responsibility for safe and effective medical devices.

Sincerely,

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