

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

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**Re: Docket No. 2001D-0044; Draft Guidance for Industry and Food and Drug Administration Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 Waiver Applications**

6 December 2005

Dear Sir or Madam:

Genzyme Corporation of Cambridge, MA is a large diversified biotechnology company providing therapeutic drugs, devices, and biologicals, as well as diagnostic products and genetic testing services. Genzyme Diagnostics Division develops, manufactures and distributes in vitro diagnostic medical devices that are used in clinical laboratories worldwide. Our devices are used in both centralized laboratories and in near patient testing facilities. Genzyme's products include rapid tests that detect hormones and infectious agents to aid in the diagnosis of conditions and diseases important to the health care community. Many of these tests have achieved CLIA-waived status, so our comments are offered with extensive experience in successfully demonstrating that these tests can be used safely in waived laboratories where users have had little or no formal training. Therefore, we support reasonable and logical guidance to assure that such tests can continue to have a positive impact on public health, especially in clinics, physician's offices and in emergency departments.

Genzyme appreciates the opportunity to comment on the FDA's Draft Guidance for Industry and Food and Drug Administration Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 Waiver Applications. We recognize the Agency's efforts in attempting to provide structure and guidance to a process that has been arduous and unpredictable for industry and the Department of Health and Human Services.

Genzyme agrees with the recommendations (some with noted qualification) that:

1. There should be flexibility in how a manufacturer can enable the user to demonstrate a device is working properly; examples included are an alert mechanism, use of external controls, use of internal controls. (page 9)
2. The use of hazard (risk) analysis/assessment to establish effective means to mitigate potential user error. Manufacturers should (and many do) conduct such assessments for these (and other) purposes. FDA has asked for this in recent waiver petitions and Genzyme supports its continued use. (page 9)

Qualification: Genzyme is concerned that the guidance indicates that "all" potential sources of error be identified. This is an unobtainable goal, and the guidance should be modified to read "foreseeable sources of error." In addition, the foreseeable risks to be included in a waiver petition should include only those that can be caused by user error, which should include operation, interpretation, clarity of instructions, storage, handling, etc.

3. Manufacturers should be responsible for providing clear explanations to the user what functions or steps the control mechanisms or procedures are designed to mitigate. (page 13)

Qualification: Genzyme does not agree with including alarming statements that lead the user to question the capability and quality of the waived device, for example "Obtaining the correct result on the built-in control indicates that sufficient sample was added, but does not necessarily mean that your patient result is correct, ..." (page 30) Millions of waived tests have been performed since the enactment of CLIA '88 and there are few, if any, reports of such serious failures that would warrant such warnings to appear in labeling.

4. Clearly marked instructions to the user that the Instruction for Use should be followed to obtain reliable results are appropriate for "self-trained" users. (page 29)
5. Genzyme applauds FDA in recommending that any alternative approaches that the manufacturer wants to consider for obtaining waiver can be discussed with the Agency.

Qualification: The number of devices and test conditions (or diseases) that would not fit within the structure that FDA suggests for qualitative devices is so numerous that the number of required conferences would increase significantly, rather than decrease, as the Draft Guidance would anticipate. The criteria of acceptance are so formidable that manufacturers would be hard pressed to offer alternative strategies that would meet such unrealistic goals.

Genzyme has great concern with this Draft Guidance, with regard to:

1. The fact that it goes well beyond the intent of Congress, as expressly stated in House Report 105-310, of the House Committee on Commerce (on H.R. 1411) when Congress amended the CLIA waiver section of the law in 1997 to direct reviewing agencies to consider *only* "likelihood" of error "*by the user*". [Emphasis added.] The report indicates: "Without the clarifying 'by the user,' interpretations of 'erroneous result' and 'accurate' could include the inherent clinical sensitivity/specificity of a test system, parameters that are properly reviewed by the FDA in its process of determining whether to approve or clear product for marketing."
2. The Agency's approach for obtaining waiver does not meet the objectives of "Least Burdensome." In addition to the fact that the Draft Guidance goes beyond the intent of Congress (mentioned above), the approach does not recognize the benefits of the Quality System Regulation (21 CFR 820) that provides assurance that safe and effective devices are designed and placed on the market. Nor does the Guidance recognize that the evaluation studies submitted to FDA in the device's premarket submission already have demonstrated the effectiveness of the device. The only outstanding issue for waiver is whether self-trained users can achieve comparable performance with the (candidate) waived device as professionally trained operators would when using the same or similar devices that are available to clinical laboratories.

3. The historical experiences of waived tests have not been considered to “test” the validity of requirements in the Draft Guidance. Dozens of tests have been approved for waiver in the last 17 years (although the process has often been arduous and arbitrary). Genzyme questions whether these devices could obtain waiver under the conditions outlined here. Excluding similar devices in the future would, in Genzyme’s opinion, have a negative impact on public health due to restricted access to important testing.
4. The emphasis on the use of real patient samples as the primary (best) means of demonstrating that a device is simple to use and free from error is misguided for many devices – especially for many single use rapid test devices, for which Genzyme has extensive expertise. In the evaluation and demonstration of ease of use, Genzyme has successfully used contrived samples effectively. They provide several advantages:
  - a. Many of these devices require sample collection by swab, which would entail more discomfort for patients if the type of comparisons outlined in the Draft Guidance were conducted. Often times, to meet the objectives of waiver testing, i.e., to show performance between untrained and professional users are comparable, the use of fresh samples are not required. Genzyme has demonstrated in this approach in previously submitted waiver petitions.
  - b. Many microorganisms are labile and do not lend themselves to demonstrating exact equivalence unless extraordinary care is taken for transport and handling. Contrived samples are often more stable and easier to handle, while adequately mimicking fresh samples.
  - c. Many microorganisms are infectious and additional handling might not be warranted or justified to demonstrate that a device is worthy of CLIA waiver.
  - d. Demonstrating performance over a range of levels for testing is more easily controlled when contrived samples are used. (Genzyme has concerns over the specific requirements for qualitative testing that are not included in these comments. We hope to continue to work with the Agency on the specifics and details of a more useable Guidance).
  - e. Genzyme has analyzed the cost of conducting a CLIA-waiver study that involves a clinical trial for a device that is intended to be used as an aid in the diagnosis of a seasonal infection (such as flu) that has a prevalence of approximately 20% in the tested population and where the sponsor could not predict where the outbreak would occur during a short, perhaps 10 week season. We estimate that 15 to 20 sites would need to be enrolled (taking approximately four to five months of preparation time for contact, contracts IRB approvals, etc.), based on experience with similar 510(k) submissions. Our estimate is that this would cost approximately \$1.25 million. Additionally, such studies would need to be conducted over two flu seasons, because of the initial efforts needed to demonstrate the safety and effectiveness of these devices while using trained operators. The financial risks of conducting simultaneous testing are too great for most firms to tolerate.
5. The reporting requirements for MedWatch are inconsistent with the goal of having users perform these tests correctly. The manufacturer should be responsible for providing support to users, with contact information included in the labeling. If the user is asked or required to provide a MedWatch report, we believe he or she will also expect help in the use of the device from the recipient of the MedWatch form. This will lead to delays or non-response (from the Agency) for corrective actions. Additionally, to add this requirement would overburden FDA’s vigilance monitoring

system, which is already overwhelmed with MDR submissions. The responsibility to report malfunctions that could lead to death or serious injury is left to the manufacturer. Finally, there are few waived tests that have the potential to cause such harm, so a general requirement is neither prudent nor will it be effective, in Genzyme's opinion. Complaint handling and any needed corrective actions (internal and field corrections) are already adequately regulated in various chapters of 21 CFR.

In conclusion, Genzyme strongly recommends that FDA withdraw this guidance because of the significant inconsistencies, duplications of effort and enormous burden it would impose. Genzyme reiterates that our comments are based on our experience in developing products that have achieved waived status and our success in supporting their use in order to provide access to important testing in near patient environments.

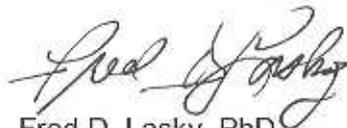
Genzyme looks forward to continuing to work with FDA on developing a reasonable and effective guidance that can increase access to safe and effective diagnostics that will benefit public health.

Genzyme appreciates the opportunity to comment on this notice. Please contact either (any?) of us should you have any questions regarding this letter.

Sincerely,

*for*

Gene Goorchenko  
Director



Fred D. Lasky, PhD  
Director

*for*

Robert E. Yocher  
Vice-President, Regulatory Affairs