GEN-PROBE

2656 '03 MAY 22 P3:16

May 20, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: Docket Number 03N-0134

Dear Dr. Goodman and Mr. Taylor:

This letter is in regard to the referenced docket concerning the agency's measurement of the effectiveness of the Team Biologics Inspection Program. Gen-Probe Incorporated is a manufacturer of licensed In Vitro Diagnostic Devices (IVDs) as well as IVDs regulated by the Center for Devices and Radiological Health (CDRH). I will comment only on Team Biologics inspection effectiveness of licensed IVDs. This includes manufacturers who do not collect or transfuse blood or plasma and also at establishments that do collect and transfuse blood and plasma. For the purpose of this letter, I will refer to manufacturers who do not collect or transfuse blood as "licensed IVD manufacturers" and locations that are also licensed IVD manufacturers, e.g., blood banks, that do collect or transfuse blood as blood and plasma establishments.

Although these comments are being provided on behalf of Gen-Probe, I am also providing comments based on my experience as a former FDA Investigator, who, as part of my routine activities, was an active participant in the inspection of blood and plasma establishments and as a trainer of other Investigators on these inspections. My experience at the FDA included a variety of compliance actions, including FDA's first mass seizure, halting clinical evaluations as well as initiating a great variety of Official Action Indicated (OAI) and Voluntary Action Indicated (VAI) compliance actions. I also had the ability to get in and out of a firm quickly after compliance was established. This latter accomplishment seems to be less evident in today's Team Biologics cadre.

The next section of this letter details the specific information requested in your letter

03N-0134 C1

Gen-Probe Incorporated • 10210 Genetic Center Drive • San Diego, California 92121-4362
(858) 410-8000 • FAX: (858) 410-8625

Topics for Discussions

1. Assessing industry compliance with applicable laws and regulations:
   a. Discuss how industry compliance can be measured and what tools should be used to evaluate the information.
   b. What criteria should be used in assessing the effectiveness of core team biologics in achieving industry compliance?

Comments: A reproducible inspection program can best measure Industry compliance. While all FDA Investigators need flexibility to pursue issues affecting reproducibility of manufacturing and product safety, an advanced system has been adopted by CDRH, the Quality System Inspection Technique or QSIT, which should be fully applicable to licensed IVD manufacturers. The QSIT system should be used for licensed IVD manufacturers because it is faster, more efficient, effective and consistent. More importantly, the use of the Team Biologics skills for licensed IVD manufacturers is likely inappropriately applied considering the much lower incidence of biological product deviations and compliance issues for IVD manufacturers than for blood and plasma establishments. Therefore, CBER should reconsider using headquarters managed Team Biologics Investigators as the inspection force for licensed IVD manufacturers in favor of the QSIT system and district managed field Investigators. Since virtually all of these licensed IVD manufacturers also provide products that are regulated by CDRH, the QSIT inspection system would provide consistency in assessing compliance. Adopting this approach would also reduce FDA cost as many of the Team Biologics cadres must travel to conduct their inspections. QSIT inspections by the field Investigator group do not involve as much travel expense.

In conclusion, overall industry compliance cannot be measured when the inspection program is a bottom up approach that looks at individual items rather than a top down approach looking at effective systems. FDA should establish that effective systems are in place using the top down QSIT system and allow Investigators the freedom to look into individual areas as evidence that systems are effective or not. The bottom up approach currently used is simply a list of deviations that does not speak to system adequacy and rarely changes how products are designed, manufactured or released. The existing field force, under FDA field management should implement this system, QSIT. When FDA documents deviations from the QSIT system, the approach more readily allows improvement in how products are designed, manufactured and released.

2. Determining the consistency of our inspection and compliance activities.
   a. What criteria should be considered in assessing the consistency of Team Biologics' Inspectional approach? You may include factors that relate to the scope and depths of systems/products covered, scientific and regulatory knowledge, and skills of inspectional personnel, length and frequency of inspections, etc.
   b. Discuss your views on and or experience with post-inspection outcomes based on core team biologics inspections. Elaborate on the best way to determine if these outcomes (such as post-inspectional correspondence, administrative and legal actions, regulatory meetings, teleconferences, etc.) are consistently and fairly applied throughout the biologics industry.

Comments: Team Biologics inspections of licensed IVD manufacturers are not consistent. While there is a certain amount of formatting that is historically necessary, such as history of business, responsibility, etc., Team Biologics primarily inspect areas of interest to greater or lesser depths based on their general guidance, history of business, personal interests, and experience. All Investigators should have the option to pursue areas within the inspectional venues of interest when there is evidence that product safety and reproducibility may be in question. However, the more traditional Team Biologics "bottom up" approach of reviewing individual complaints, investigations and rejected/returned goods first, is an outdated method to establish state-of-control. As described in question one, a more consistent approach for Investigators would be use of the QSIT system. The QSIT process determines if it is worthwhile to invest time in review of large numbers of individual complaints, investigations and rejected/returned goods documentation.

To reiterate, QSIT is a top-down inspection process that can more rapidly and effectively establish state-of-control, as well as risks of reproducibility errors in product manufacturing. The current Team Biologics approach is less effective than field inspections using QSIT for licensed IVD manufacturers and should, therefore, be eliminated from this class of firm.

Regarding post-inspection activities, it still takes FDA headquarters too long to close an establishment inspection. Inspected firms should receive completed inspection reports within two months of the close of the inspection. It currently takes much longer.

3. Determining the effects of our inspection and compliance activities on product quality: Define product quality. Discuss the approaches you feel would be useful in assessing the impact of inspections on overall product quality. Consider the scope of deviations from GMPs that would trigger an assessment of product quality.

Comments: There is very little evidence that the current Team Biologics approach for licensed IVDs has any impact whatsoever on product quality. In addition to the IVD manufacturers' own very thorough quality control and release processes, CBER continues to independently test licensed IVDs as part of their lot release program. Therefore, to define product quality, there are two components. The actual quality control test results are one parameter, and manufacturing reproducibility is the second factor. As stated in the items above, the QSIT approach establishes a reproducible system to design, manufacture and release licensed IVDs. There is very little value in a Team Biologics inspection approach, for example of a licensed IVD manufacturer's lots of rejected raw materials. Similarly, review of individual complaints and investigations should be inspected for thoroughness against a system, not just as stand alone documents. Therefore, system state-of-control should be the first consideration in establishing a firm's ability to manufacture reproducible product and manage customer experience. The QSIT based inspection allows inspectional confirmation of reproducible product quality; the traditional bottom-up approach only provides data, and is not state-of –the-art to establish control conclusions.

Another comment is that Team Biologics uses a drug GMP approach for well characterized materials/processes. While FDA may claim the Team is following part 820 and relevant Biologic regulations, the experience is different. For example, it is not possible to strictly apply all principles from the manufacture of defined chemical substances to biological materials. A specific observation would be related to failure to utilize a "stability indicating assay" for biological products. One assay or performance test will not fully describe the activity of a biological. Instead the science dictates the use of a series of carefully selected tests to provide analysis of the potency, activity, conformation, etc. Team Biologics should not look at our "science," they should look at our state-of-control and that we achieve GMP compliance objectives.

4. Assessing the impact of our approach on public health:

What criteria should be considered when assessing core team biologics impact on product safety and availability?

Comments: The primary criteria should be the use of the talent of Team Biologics where the problems lie. For blood and plasma establishments, the biological product deviation records show that problems are chronic and continuing. In fact, many of these sites have been under consent decrees for many years. Alternatively, other than one recent example that has been documented as "a corporate culture problem" IVD field Investigators, who already visit IVD manufacturers to conduct QSIT inspections, could quite adequately conduct licensed product inspections. Therefore, the criteria for assessing a core Team Biologics impact on product safety and availability would be reduction in problems at inspected facilities over time. Therefore, there is no evidence of impact for licensed IVD manufacturers and the Team Biologics approach appears to have made the issue worse at blood and plasma establishments. A QSIT approach at blood and plasma establishments may have helped those sites to look at the forest rather than the individual trees. Additionally, FDA should consider whether or not the inspection programs and official actions taken at blood and plasma establishments really do impact product quality and state-of-control, or whether FDA is simply contributing, in some areas, to a paperwork burden that is unrelated to product quality.

In summary, where there haven't been documented chronic problems in licensed IVD facilities, it makes more sense to have the field conduct inspections under QSIT for their CBER and CDRH regulated IVD product lines. These IVD manufacturers should also be considered for alternative ("third party") inspection under the recent User Fee Act. Where chronic problems have been in evidence, such as at blood and plasma establishments, it would make more sense to have Team Biologics spend more time at those sites, but they should use a system approach such as the one documented by FDA's QSIT program.

Finally, please note that licensed IVD manufacturers are regulated under part 820 device GMPs. All of the other manufacturers listed in the April 15, 2003 "Dear Colleague" letter are regulated under the more extensive part 211 drug GMPs. Lately, we have heard that the device GMPs, especially design control requirements, and QSIT, are being considered for application to these other types of manufacturers. This would be a good idea.

Sincerely,

Glen Paul Freiberg

Glen Paul Freiberg, RAC
Vice President
Regulatory, Quality & Government Affairs
Gen-Probe Incorporated

Copy: Dr. E. Jacobson, AdvaMed