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

Docket No. 2006D-0347: Draft Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff on In Vitro Diagnostic Multivariate Index Assays

Cepheid develops, manufactures, and markets *in vitro* diagnostic (IVD) test systems that perform genetic analysis, including DNA and RNA analysis, for clinical genetic assessment and detection of infectious disease in humans, as well as for the assessment of biothreat agents in the environment, and reagents for life sciences research. As a manufacturer of both IVD test systems and Analyte Specific Reagents (ASRs), we have concerns about the scope and perspectives presented in the recent guidance document, ***In vitro Diagnostic Multivariate Index Assays (IVDMIA)***, published on September 7, 2006. Cepheid does not provide laboratory testing services, and thus will refrain from comment on whether particular services warrant FDA review. Instead, because our customers are high complexity clinical laboratories that use ASRs in developing their LDTs, we would like to offer suggestions to add clarity to the process and the policy. We are strongly committed to the Agency's mission to both protect and promote public health; assuring the safety and effectiveness of new devices while balancing assurance that patients are not denied access to beneficial medical technologies because of regulatory constraints.

Executive Summary: Recommendations

Cepheid respectfully requests that:

- **FDA convene a classification panel to discuss issues raised in the new guidance. Following consultation with experts in laboratory medicine, consumer groups, and industry, FDA then issue a notice of proposed rulemaking to clarify or refine the scope of the new regulations, to further define key concepts, and to identify the decision-making criteria by which a laboratory developed test (LDT) will be determined to be subject to pre- and/or post- market requirements. Classification should be determined based on the risk associated with use in a particular patient population for a particular condition (consistent with current statute), rather than on the technology or sponsor (i.e., manufacturer or laboratory).**

- **At minimum, in lieu of rulemaking or while rulemaking is being planned, FDA should release the next version of this guidance as second draft.**

- **If FDA is to regulate LDTs and IVDMIAs, FDA should clarify what regulations laboratories would be held to (i.e., register and list? Medical device reporting? Pre-market review? QSR? Labeling?), and which could potentially be waived if a lab is CLIA compliant.**

- **FDA should clarify to what extent LDTs that undergo the 510(k) process can serve as predicate devices for other LDTs or IVDs, given that reagents and test systems used in LDTs are usually not in commercial distribution. For example, would/how could the recently cleared MammaPrint assay by Agendia be used to make a determination of substantial equivalence for another laboratory's or company's microarray test to determine the risk of metastasis of an existing breast cancer?**

Background

Laboratory developed tests (LDTs), though often deemed by FDA to be medical devices under its regulatory authority, have not previously been required to undergo pre-market review by the Agency. In fact, regulatory authority for laboratory testing services was granted to the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). While the focus of ASR rule was ASRs that move in commerce, not tests developed in-house by clinical laboratories or ASRs created in-house and used exclusively by that laboratory for testing services, the ASR Rule did address some issues related to the use of LDTs. The preamble to the ASR Rule (62 FR 62249), indicates that "FDA believes that clinical laboratories that develop such [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act. However, FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health." .In Comment 27 (p 62252), FDA reserved its right to develop further regulatory measures for LDTs: "If future developments in laboratory technologies or marketing of in-house developed tests indicate that additional regulation is necessary to provide an appropriate level of consumer protection, FDA may reevaluate whether additional controls over in-house developed tests are warranted (see also comment 29)." Under the IVDMIA draft guidance, FDA is now concerned that IVDMIAs are not within the ordinary "expertise and ability of laboratories" and therefore must meet pre- and post- market review requirements for class II and III devices.

- **We request that FDA convene a classification panel, followed by formal rulemaking procedures to determine what, if any, laboratory services would be subject to FDA regulation.**

The Food, Drug and Cosmetic Act (Sec 321(h)) defines a medical device as:

> "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article that is (1) recognized in the official National Formulary, or the United states Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals…"

Most provisions in the FDC Act such as those requiring registration and listing, classification of devices and premarket submission, focus on devices that are intended for the "introduction or delivery for introduction into interstate commerce for commercial distribution." In contrast to manufactured ASRs and IVDs, components of LDTs are indicated for the sole use of an individual laboratory and are not sold to other laboratories or otherwise introduced into commerce. For this reason, we believe that while LDTs may be medical devices as defined by the FDA Act, FDA's change in position regarding the use of its enforcement discretion, warrants a public decision making process as defined by the Administrative Procedures Act.

According to Sect 513 (b) of the Food Drug and Cosmetic Act, classification panels are for the purposes of—

(A) determining which devices intended for human use should be subject to the requirements of general controls, performance standards, or premarket approval, and
(B) providing notice to the manufacturers and importers of such devices to enable them to prepare for the application of such requirements to devices manufactured or imported by them.

Such a classification panel would allow FDA to hear concerns of the varied stakeholders and make transparent decision-making criteria for determining which LDTs would be subject to more stringent review. Once decision-making criteria were established, the panel could provide recommendations to FDA on specific tests or on specific indications for use that raised new concerns of safety and effectiveness. Likewise, to balance increases in FDA's workload in calling for premarket submissions for new categories of tests, the panel could also identify previously unclassified molecular tests (de facto Class III devices, requiring a PMA or de novo petition) that could be Class II or I by order of regulation. Presumably, tests which are well-established with a significant literature base to mitigate the risks associated with their use, would qualify under this re-classification. Cepheid believes that in many cases, molecular tests for the same intended use as an older technology could be placed in the same class as their non-molecular counterparts. For example, see Cryptococcus neoformans

serological reagents (21 CFR 866.3165, Class II, exempt). Cepheid questions any rationale that places molecular diagnostics for the same intended use as an exempt device in a higher classification simply because of their technical nature.

At the end of the classification process, the notice of proposed rulemaking and subsequent final rule will ensure transparency and public participation in the process. While it may take longer, we believe such discussion is important to truly understand the impact of increasing regulations for LDTs on laboratories, manufacturers, patients, healthcare providers in terms of access, innovation, quality and safety. Of particular concern, we believe that FDA must consider the potential market disruption for LDTs, particularly for products that are for rare or emerging diseases, and should address the boundaries between regulation of the tests themselves and guidelines and regulations concerning the provision of laboratory services under practice of medicine. Further, FDA, in consultation with the public, should consider whether nucleic acid tests are being regulated differently than other laboratory tests, and whether LDTs are being subject to more stringent or duplicative requirements than other medical devices (i.e., ASRs or IVDs).

- **At minimum, in lieu of rulemaking or while rulemaking is being planned, FDA should release the next version of this guidance as second draft.**

Cepheid further believes that it would be inappropriate for FDA to initiate compliance or enforcement activities on the basis of these draft guidance documents, which by its own language are not legally binding on industry or FDA. A classification panel, followed by promulgation of a formal rule could create legally binding requirements and prohibitions that are clearly communicated to the industry, that can be anticipated as products are developed, and that maintain a level playing field between manufacturers and laboratories.

- **FDA should clarify in a public forum, conditions under which software and/or a medical algorithm(s) for interpretating laboratory with or without other patient data appropriately considered a medical device under the law.**

FDA defines an IVDMIA as "a test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition, or is used in the cure, mitigation, treatment, or prevention of disease." FDA claims that developers of the IVDMIA use a specific algorithm to calculate patient specific data that cannot be independently derived or confirmed by a different laboratory, and to report a result which cannot be interpreted by a well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding clinical performance and effectiveness. FDA believes that the IVDMIAs have other elements (i.e., software and algorithms) that are not among the primary ingredients of in-house tests that FDA already regulates and therefore they raise safety and effectiveness concerns. Some of these interpretations are and have been longstanding standards in the practice of medicine (e.g., triple screen; imaging technologies). Other algorithms using patient information (tumor size,

extent of malignancy, node involvement, etc) have long been used to determine risk of recurrence of cancer, and of classification of particular cancers. In fact, many laboratory tests cannot be properly interpreted unless patient data is collected (e.g., risk of having a certain mutation without knowledge of disease in family members). Reference ranges (one element a laboratory has to validate for an in-house test regardless of whether a commercial ASR is used in the development) are often laboratory measurements that are normalized to specific patient parameters derived by the population in the laboratory's testing jurisdiction. Cepheid believes FDA should develop a clear rationale behind the new concerns over the safety and effectiveness of these devices, as well as their jurisdiction over medical testing algorithms. Discussions should be transparent and encourage public participation in the effort to determine which, if any, laboratory testing services should be subject to FDA regulation.

- **FDA should clarify what FDA regulations laboratories be held to (i.e., register and list? Medical device reporting? Pre-market review? QSR? Labeling?) and which could be waived if a lab is CLIA compliant.**

Laboratories are already held to requirements concerning quality assurance of the testing process. In fact, with the possible exception of design control requirements, and requirements on identification and traceability, many of the rules are similar (to a degree) for manufacturers and laboratories. While not required to register and list, laboratories must be certified by CMS to perform certain levels of testing (waived or non-waived (high or moderate complexity)). Laboratories are required to maintain document (and personnel) controls, verify and validate procedures using formal criteria, maintain process controls, be able to identify nonconforming product and establish corrective and preventive action plans. Laboratories are held to standards of truth in advertising by the Federal Trade Commission (FTC), but are not required to report LDT failures or laboratory errors to any federal agency.

- **FDA should clarify the relationship between Class II LDTs and their potential role as predicate devices.**

Since IVDMIA is a laboratory testing service and the reagents are not in commercial distribution, clarification is needed regarding when or if, after receiving clearance for an 510(k) application, an IVDMIA would be available as 'predicate' device for another IVDMIA performed by another laboratory and/or an IVD developed and commercialized by a manufacturer. How would another laboratory and/or manufacturer gain access to the test for substantial equivalence comparisons if the LDT reagents are not in commercial distribution? For example, would/how could the recently cleared MammaPrint assay by Agendia be used to make a determination of substantial equivalence for another laboratory or company's microarray test to determine the risk of metastasis of an existing breast cancer? The second test would likely evaluate different genes in much the same manner as immunological tests will use different antibodies for detection of the same clinical state or condition.

Cepheid would like to thank FDA for the opportunity to participate in discussions about these very important and timely issues, and looks forward to continuing to work with the Agency to develop clear, consistent, and equitable policies that balance important patient protections with fostering innovation and access.

Respectfully submitted,

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