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Docket No. 2005D-0434: Draft Guidance for Industry and FDA Staff: Nucleic Acid Based In Vitro Diagnostic Devices for Detection of Microbial Pathogens

Dear Sir or Madam:

Attached please find our comment regarding the exclusion of amplification technologies from the replacement reagent policy. With respect to the remaining content of the guidance and with all due respect to the agency and the author(s), we question the scientific basis for differential treatment of multiplex assays. We do not believe multiplex testing adds more risk to patients than single target testing simply because multiple genetic sequences or multiple organisms are detected. Like other technologies and methods, the risk of using the test is associated with the intended use. For novel methods and/or markers, we agree that the manufacturer should provide enough data to establish safety and effectiveness. However, for established organisms and/or genetic targets, issues associated with multiplex testing are primarily concerned with development and optimization both of which are addressed by design controls and other aspects of QSR, particularly when the technology or method has been widely vetted in clinical literature. Along that line, we believe that both FDA and industry would benefit from public discussion around criteria by which a technology or method can be determined to be sufficiently established to warrant use of the literature in place of additional clinical studies, even for multiplex assays.

As always, thank you for the opportunity to comment on this important issue.

Best Regards,

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March 7, 2006

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Docket No. 2005D-0434: Draft Guidance for Industry and FDA Staff: Nucleic Acid Based In Vitro Diagnostic Devices for Detection of Microbial Pathogens

Dear Sir or Madam:

We are writing to comment on the exclusion of nucleic acid amplification technologies and multiplex testing systems from the Replacement Reagent (RR) Policy as stated in the guidances, *Nucleic Acid Based in vitro Diagnostic Devices for Detection of Microbial Pathogens* and Class *II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems*. We question the scientific or technical rationale behind the exclusion, and do not agree that these technologies should be broadly excluded for several reasons:

First, the replacement reagent (RR) policy is very clear in that it only applies to *reagents that have been previously cleared* by the Agency. The RR policy allows a manufacturer to use previously cleared reagents either with a different or new *previously cleared instrument* OR with a new member (i.e., model) of a *previously cleared instrument family*, without submitting a new 510(k). The concern that manufacturers would be combining different reagents with different instruments should be mitigated by the fact that the replacement reagent policy is *specifically limited to previously cleared systems*, though the components of which may not have been cleared together[1]. The policy does not apply to any reagents or instrument(s) family(ies) that have not been previously cleared, such as those which may be exempt[2]. Once cleared, any significant assay, instrument or software design changes, any modifications to the validation protocol, or failure of the new combination to meet pre-designed criteria may warrant the submission of a special 510(k). Similarly, any changes to the intended use of a reagent and/or instrument must be cleared through the traditional 510(k) process. In order to

[1]New instrument family members are often different 'generations' of a cleared instrument. New members must be similar in their basic design and function as previously cleared family members in order to invoke the replacement reagent policy.

[2] The replacement reagent policy would not apply to ASRs because ASRs should not be co-marketed with a specific instrument in the first place. For other combinations that may be exempt, classification rules state that the final classification of the combination is representative of the highest of an individual member. Currently, no nucleic acid-based assays are exempt according to the limitations on exemptions in 21 CFR 866.9. Therefore, all assays would have to be cleared before the replacement reagent policy could potentially apply.

mitigate the potential risk of using a "new" combination, before marketing the combination, the manufacturer must:

- Develop a validation protocol by which the new combination will be assessed to determine functional similarity with the previously cleared components (this protocol may be filed at the time of clearance of the first reagent-instrument combination and must be kept in-house for reference);
- Develop acceptance criteria and specifications for making a determination of functional similarity;
- Maintain appropriate documentation in-house.

Second, although FDA no longer requires manufacturers to file "add-to-file" letters, they do require that the "new" combination seek CLIA categorization for complexity. In requesting CLIA categorization, the manufacturer needs to submit the labeling for the system to FDA, along with instructions for use for any new family members. In the process of reviewing these documents for CLIA categorization, FDA has the opportunity to contact manufacturers if they have questions or concerns regarding the differences between the "new" combination and the cleared products on file, and the potential impact the changes may have on safety and effectiveness.

Third, there are many relatively simple commercial systems currently on the market. Many devices are simply labeled nucleic acid primers or probes and the associated general purpose reagents for conducting a hybridization or amplification reaction. The signals from these can often be detected with general purpose instruments that read specific colorimetric changes, wavelengths associated with the excitation-emission spectra of different fluorescent dyes, or that can detect radioactivity. Alternatively, a manufacturer may develop a closed system, which over time, different models (or family members) may evolve as a natural product of the device innovation process. These types of systems are not dramatically different than many chemistry analyzers or instruments that read immunoassays, which are used with primary (i.e., analyte specific) antibodies and secondary (i.e., detection) antibodies. In fact, in these types of capture and detection systems, nucleic acid binding to target properties are generally analytically sensitive and specific, and are often less subjective in their interpretation than antibody binding properties.

Fourth, the risks to health described in the document are no less relevant for nucleic acid-based assays than for other test systems of similar intended use, that are currently covered by the RR Policy. If the Agency feels that the risks associated with the use of cleared chemistry or immunoassay reagents on either a different cleared instrument system or a new member of a cleared instrument family can be mitigated by proper validation and testing, it should follow that the risks would likewise be mitigated if the analyte is nucleic acid.

Thank you for the opportunity to comment on this very important issue. We applaud FDA's efforts to keep up with the rapidly changing pace of technology, and support the agency's efforts to "facilitate progress in the field of pharmacogenomics and genetics … [and to] facilitate rapid transfer of new technology from the research bench to the clinical diagnostic laboratory," as stated in the draft guidance, *Pharmacogenetic Tests and Genetic Tests for Heritable Markers*. Please contact us if you have any questions regarding our comments.

Respectfully submitted,

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