

Legal Division
Pfizer Inc
235 East 42nd Street MS 235/21/07
New York, NY 10017
Tel 212 733 5325 Fax 212 309 4420
Email emily.marden@pfizer.com



0995 7 MAR -9 10:30

Emily Marden
Corporate Counsel

March 8, 2007

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

Re: Comments on Docket No. 2006D-0347

To Whom It May Concern:

Pfizer Inc ("Pfizer") submits the following comments in response to FDA's "Draft Guidance for Industry, Clinical Laboratories, and FDA Staff – In Vitro Diagnostic Multivariate Index Assays," Docket No. 2006D-0347, issued on September 7, 2006 ("IVDMIA Draft Guidance").

Pfizer is the world's largest research-based pharmaceutical company with over 200 active drug research programs, many of which include or may include multivariate index assays.

Pfizer acknowledges FDA's efforts to clarify the standards for compliance of new, in vitro diagnostic multivariate index assays ("IVDMIAs"), and FDA's application of a risk-based approach to regulation of these tests. At the same time, Pfizer believes that the breadth of FDA's intended oversight needs to be better characterized and we hope that FDA will develop its technical capabilities in this area to meet regulatory needs.

2006D-0347

e13

I. **FDA Exercise of Jurisdiction Is Appropriate for Complex Test Systems, but not all IVDMIAs**

Pfizer agrees that the agency's legal jurisdiction over medical devices, as defined in 21 USC § 321(h), extends to test systems such as IVDMIAs because such test systems are "intended for use in the diagnosis of disease or other conditions."

We understand that FDA has previously exercised enforcement discretion toward most laboratory-developed (also known as "homebrew") tests in recognition of the fact that laboratories certified under the Clinical Laboratory Improvement Amendments ("CLIA") had the necessary competence to interpret tests developed with analyte specific reagents ("ASRs").¹ Even in the preamble to the final rule on ASRs, however, FDA made clear that there could be instances where CLIA certification of the laboratories alone would not suffice to ensure the safety and efficacy of diagnostic tests using ASRs. Specifically, FDA identified predictive genetic diagnosis tests as posing "unique risks to the public health because of the substantial clinical impact of the information generated using these devices," 62 Fed. Reg. 62245. In the ASR rule, FDA concluded that "there are special issues related to genetic testing or predictive genetic testing and that these issues may affect the degree of regulatory control needed to establish the safety and effectiveness of these tests or the ASR's used in their development." *Id.* at 62247.

It appears that with the IVDMIA Draft Guidance, FDA is attempting to identify criteria for subjecting *certain* laboratory-developed genetic tests to more stringent regulatory controls. We agree with FDA that the performance of mathematical algorithms that form part of multivariate diagnostic tests does represent a new risk of technical failure which could result in harm to the public, *even when* such tests are developed and performed by high complexity in-house laboratories. The public health risk posed by technical failure of IVDMIA tests used to diagnose and treat serious medical conditions is highly significant. And while it is true that the laboratories developing and using these tests may be certified under CLIA, that statute does not require any review of individual diagnostic tests by a qualified standard-setting entity like FDA. 42 USC § 263a.

We therefore agree that the safety and efficacy of IVDMIAs needs to be managed and that FDA is an appropriate forum for that work.

¹ FDA's enforcement discretion rationale was articulated in the preamble to the final rule on ASRs, "Medical Devices: Analyte Specific Reagents; Classification/reclassification as restricted devices," 62 Fed. Reg. 62243 (1997). FDA stated therein that CLIA certified laboratories "have demonstrated the expertise and ability to use ASRs in test procedures and analyses," *Id.* at 62249, and that therefore minimal FDA oversight (application of general controls and a requirement that laboratories using ASRs be CLIA certified) for most ASRs would adequately ensure patient safety.

II. FDA's Definition of IVDMIAs Needs to be Revised

While some regulation of IVDMIAs is appropriate, the current Draft Guidance needs to be revised to adequately describe when FDA regulation will apply. As written, the definition of IVDMIA² is overly broad and the parameters of FDA's intended oversight are not clear.

We agree that where the number of variables in the multivariate test is high, the failure of the mathematical component of the test under "real world" conditions would represent a new risk that is not managed by conventional technical validation methods for diagnostic tests. However, it is hard to believe that all IVDMIA tests would require complex interpretations and present a relatively high risk to public health without independent review and approval of the algorithms by FDA.

Perhaps a better approach would be that FDA regulation would apply where the complexity or number of dimensions involved in the test algorithm is sufficiently high such that a person reasonably skilled in the field would be unable to interpret the pattern of results without using an algorithm – and this would represent the boundary for triggering regulatory review by FDA. Such a definition would place the focus on the interpretation of the assay, rather than on the mere use of an algorithm. The net result would be to limit FDA regulation to those tests where a person reasonably skilled in the field could not act as an external check on the efficacy of results offered by a new test system.

III. FDA's Risk Based Approach to Regulation Is Appropriate

We applaud the tolerability of risk approach to regulation outlined in the IVDMIA Draft Guidance, whereby regulatory stringency (Class 1 versus Class II devices) is related to the purpose, risk, and potential harm of an incorrect result.

However, as written in the IVDMIA Draft Guidance, it is unclear how FDA will apply this approach. The agency needs either a larger number of examples, or some specific definition of harm from the failure of the test, such as 'likely to result in death or significant harm to individuals' (e.g. those tests requiring Class III submission versus any benign adverse outcome).

Pfizer would recommend that a new IVDMIA test be allowed on the market without FDA review, or with a lesser submission as a Class II device, prior to the accumulation of large volumes of data, *provided that* such test is intended to be used and labeled for use as a *supplement* to physician's judgment or other tests (equivalent to labeled for second or third line therapy for pharmaceutical

² IVDMIA is defined to mean "test systems that employ 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."

products). Once the test's performance as a "second line" or supplementary information source was established, and as performance data accumulates postmarket for that labeled use, a new submission as a Class II or III device might enable the test to be approved as a "first line" diagnostic with decision-making ability. Such a strategy would not restrict innovation or the ability to accumulate large volumes of data at low cost such as could be needed for qualification of highly dimensional tests.

We would also welcome a method for regulators to quickly review and approve improvements to previously approved IVDMA mathematical algorithms as data accumulates. Such mathematical "classifiers" must be allowed to improve with a minimum of obstacles, as it is highly likely that the first generation algorithm will be imperfect.

IV. FDA Expertise For Evaluation and Regulation of IVDMIAs

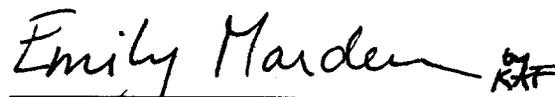
Although we agree with the need for review of the performance of such tests, FDA would need to develop additional expertise in this area. In the workshop on genomic biomarker qualification in 2006, the presentation by Gordon Lan (Johnson & Johnson) showed that the FDA's hitherto favored strategy of suggesting development of a mathematical algorithm during early drug development and then confirming it during the second half of phase III was unlikely to work in practice. Specific competence in multidimensional mathematics (and its data requirements) is needed.

V. FDA Must Continue Developing Qualification Criteria in Other Areas

Qualification of algorithms for use in IVDMIAs is not in-principle different to the qualification of biomarkers and laboratory and medical tests. The development of qualification criteria was a declared need in FDA's Critical Path opportunities list. Yet there is yet little progress in developing such criteria. In their absence, the acceptance or rejection of multidimensional algorithms will remain subjective and be open to bias and external pressures. We recommend that FDA work with the PhRMA biomarker working group and other entities as appropriate to develop

such criteria. We would be happy to make our in-house experts available to FDA and other members of the biomarker consortium.

Sincerely,



Emily Marden
Pfizer Inc
235 East 42nd Street
New York, NY 10017