Comments to the FDA on the draft IVD-MIA rules

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Overview:

1. **What will be the likely consequences of this new proposed regulation to healthcare innovation?**
2. **How is this new class of tests distinct from traditional IVDs so as to justify a different regulatory framework?**
3. **What alternative path(s) should the FDA take?**

1. Consequences of Proposed Guidelines

If implemented these guidelines would likely have significant unintended consequences with respect to the development and delivery of innovative, medically needed diagnostics. Investment in this field would be dramatically curtailed and life saving tests would be delayed from reaching patients by many years. Moreover, it is by no means clear that these new regulations would yield better quality products; to the contrary, resulting product might be more static than those being developed under the existing "home brew" regulatory framework.

The following describes some of these likely consequences.

- ***The proposed regulation will dampen investment interest resulting in fewer new diagnostic companies and products***

A key anticipated consequence of these proposed changes would be a dramatic halt in investment dollars flowing to emerging diagnostics companies thereby significantly reducing the number of novel and effective diagnostics reaching the marketplace over the next few years.

Despite the enormous clinical significance of molecular diagnostics, there has historically been very little venture capital activity in this space. According to *BioCentury*, only about 3 percent of all healthcare VC dollars went to diagnostics companies in 2004.[1] The reasons for this lack of Dx investment activity include historically low margins, commoditization, poor reimbursement, and generally smaller markets compared to pharmaceuticals.

[1] Kurtzman, "A Business Model for a New Generation of Diagnostics Companies", *Biotechnology Healthcare*, Oct. 2005 page 52.

Fortunately, investment interest in molecular diagnostics seems to be picking up. One of the key drivers of this renewed interest, according to several recent commentaries, is the less burdensome regulatory path of diagnostics as compared to drugs.

> [A]s an institutional investor in diagnostics, why am I bullish? … Importantly, products can be brought to the point of revenue generation without extensive FDA oversight as "in-house developed" or "home brew" tests in a CLIA certified reference laboratory to perform tests of "high complexity." As a result, revenue can be generated by running these tests while additional clinical data are being collected. Depending on the particular test, full FDA review then can proceed under the less rigorous 510(k) process or through a more extensive premarket approval application.[2]

In other words, under the present FDA framework companies can use the revenues and data generated from their ASRs or CLIA lab to support later regulatory filings. This has become a very popular business model among diagnostics start-ups.
The advantages of the status quo regulatory system for diagnostics was underscored in a recent commentary titled "A change in the market—investing in diagnostics" that appeared in August in *Nature Biotechnology*:

> Although the potential returns for diagnostics are clearly less inviting to investors, this sector does offer several advantages… [M]anufacturers can forgo FDA regulatory oversight completely by building their own laboratory—or working with an existing laboratory that is compliant with the Clinical Laboratory Improvements Amendments of 1988 (CLIA)—to market their diagnostics as a so-called 'homebrew.' Yet another route is to sell one or more of their components of their diagnostics to testing laboratories as analyte-specific reagents (ASRs), thus enabling early market penetration and enhancing early adoption of their technology.[3]

In sum, the ASR and CLIA paths to market are among the few attractive features to historically reluctant investors in diagnostics that would become eliminated if the FDA implements its draft guidelines. This would significantly curtail the number of innovative products that are developed and enter the marketplace in the years to come.

- ***The proposed regulation will encourage "me too" products and discourage innovation***

High regulatory hurdles combined with historically low reimbursement will drive companies away from innovative product development towards more generic, commodity type products that have historically dominated the diagnostics industry. Rather than invest time and money on riskier Class III submissions companies will focus on safer Class II products for which there is already an approved predicate device. Since there

[2] Id. page 54
[3] Nature Biotechnology, Volume 24 Number 8, August 2006, at pages 922-923.

are now very few approved multiplex or "companion" diagnostics to function as a predicate, such products would not likely advance for many years.

- ***The proposed regulation will encourage static tests of lower quality and poorer diagnostic accuracy***

Multiplex biomarker tests appear to be at the forefront of effective new screening tools for cancer and other diseases. Over the past two years a number of studies have been published in leading medical journals showing the power of various arrays to identify lung, ovarian, and prostate cancers much earlier and with far superior diagnostic accuracy than exiting technologies. Most of these tests would likely fall under the FDA's definition of IVDMIA since they typically use algorithms and weights to derive results using a computer program.

Traditionally, assays must be "locked down" in static form before being approved by the FDA as an IVD kit. Even slight changes to reagents, instrumentation, or test methodology can have severe repercussions to regulatory status often requiring entirely new clinical trials and approvals. This traditional approach is entirely incompatible with emerging array based testing where new biomarkers are routinely being discovered and validated, thereby permitting test accuracies to be re-evaluated and improved on an ongoing basis.

<u>Requiring all gene, protein, and antibody arrays to have FDA approval before being used to screen patient samples will delay the launch of life saving tests for the early detection of many cancers by at least 5-10 years. Moreover this will result in static tests with lower diagnostic accuracies than those that would be developed and routinely improved under the present ASR / CLIA framework</u>.

- ***The proposed regulation will discourage development of assays for personalized medicine and orphan diseases***

Requiring algorithm based assays to undergo costly FDA pre-market approval will mean that only products that address the largest diseases will make it to market. Tests for orphan diseases as well as "companion" diagnostics for targeted patient populations will typically lack the market size to justify the exorbitant costs of obtaining FDA approval. This problem was pointed out by one recent commentator:

> A rough rule of thumb is that a market opportunity of $10-50 million is required to generate a positive return on investment and to justify pursuing approval of FDA-cleared (class II) or approved (class III) diagnostic kits. As the market for many molecular diagnostics—with the exception of tests for large patient populations, such as factor V Leiden or cystic fibrosis—is likely to be smaller than this, ASRs and homebrews have become an increasingly popular route for companies such as the suppliers Promega and Third Wave Technologies.[4]

[4] Id. at 923

Thus, the new FDA rules would significant curtail development of tests for genetic and orphan diseases as well as companion diagnostics which are usually administered to narrowly defined disease groups being considered for particular therapies.

2. Why not apply the traditional IVD regulatory framework?

Laboratory developed assays (LDAs) differ significantly from traditional in-vitro diagnostics (IVD) kits and warrant a lower regulatory threshold. LDAs, unlike IVDs, are typically run by the same personnel at the same location using the same instruments, equipment, and reagents. Thus there are far fewer variables and "moving parts" with LDAs and QA/QC procedures are easier to implement. Furthermore, the GMP procedures needed for IVDs are inapplicable for LDAs.

Also, as stated, traditional IVD kits must be "locked down" in static form before being approved by the FDA. The paradigm is entirely incompatible with newer genomics and proteomics based tests that are rapidly evolving as new markers are discovered and validated.

3. What should the FDA do?

The FDA and HHS should take a two pronged strategy for helping to increase the quantity and quality of diagnostics in our healthcare system. First, FDA and HHS should ask Congress for an array of new incentives—including those in the Orphan Drug program--to accelerate the pace at which new and effective tests reach the healthcare marketplace. Most importantly a new Diagnostics Advanced Research to Products Agency (DxARPA) (along the lines of the newly created BARDA) should be established. DxARPA would provide matching funds to companies seeking to bridge the "valley of death" between NIH grant funding and substantial investment by VCs and large companies.

Second, the FDA should establish and maintain a publicly accessible database to which labs providing tests commercially would be required to provide standardized information about the diagnostic accuracy and validity of their tests. Beyond that, FDA approval should not be required before laboratory developed tests can be marketed nor should such tests be classified as medical devices.

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