FDA regulations and novel molecular diagnostic tests

A recent draft guidance from the FDA appears to be setting new precedents for diagnostic laboratories. This article discusses these proposed regulations, particularly in relation to in vitro diagnostic multivariate index assays (IVDMIA).

by Dr. S. Little

For many years there has been something of a set of double standards in the way in which in vitro diagnostic tests are regulated in the USA. On the one hand in vitro diagnostic products - kits that are on sale to laboratories - have, in general, been very strictly regulated by the FDA. Extensive testing and validation has been required before approval for sale could be obtained. In contrast diagnostic assays that laboratories develop themselves - the so called "home brew" assays - have effectively by-passed FDA IVD regulation and fallen under an alternative system known by the acronym CLIA, which stand for the clinical laboratory improvements amendment. Home brew tests are subject to very light regulation, where it is essentially down to the laboratory developing the assay to show that it performs appropriately.

From the doctor’s or patient’s perspective this does not appear to be a satisfactory state of affairs. The customers seeking diagnostic information do not normally discriminate between the reliability of homebrew assays and FDA approved assays, and they make important medical decisions without regard to the regulatory system under which the data was generated. Why shouldn’t all assays enjoy the highest regulatory standards?

There are, of course, good reasons why this system has evolved, and these are primarily because of the need for the regulatory framework to reflect the real-world economics and practicalities of diagnostic testing. For very high throughput assays, for example HIV or blood glucose tests, it is readily straightforward to justify the cost of regulation (which can run into millions of dollars) in terms of the potential return on the product. However in the case of DNA based test for a rare genetic disease, although for the families with the syndrome the availability of a reliable diagnostic is essential to allow early diagnosis and reproductive decision making, it would be simply impractical to regulate such a diagnostic test to the same level as a high throughput routine diagnostic test. The cost of test validation required would become prohibitive, the test would not be developed and this would benefit no-one. It is because of the need to balance the cost of regulation against the benefit of the assay that the current system has evolved.

Based on this compromise, the assumption that most diagnostic service providers have made is that any homebrew tests would effectively bypass the FDA. This is despite the fact that the agency has reminded the industry on many occasions that it has the authority to regulate homebrew assays if it chooses, but prefers to "exercise enforcement discretion over laboratory developed tests”. This situation changed somewhat dramatically in September 2006, when the FDA released a draft guidance on "in vitro diagnostic multivariate index assays” [1]. According to the FDA these assays, known as IVDMIA, represent a new class of diagnostic, and a change is required in the regulatory system to encompass them.

In vitro diagnostic multivariate index assays

IVDMIA are one of the fruits of the human genome project. Now that most human genes are effectively known and tools for analysing them are available it has become increasingly straightforward to screen literally thousands of potential markers to find the subset of biomarkers which can predict a disease state, the likelihood of disease progression, the probability of responding to a therapy or other important medical information. An IVDMIA typically consists of three elements. A patient sample is tested for a number of different markers, each with a previously determined algorithm giving different weights or importance to the different markers, the results are processed and a diagnosis or prognosis is obtained. It is the need for the use of an algorithm which is currently exciting the FDA. They state in their draft guidance that "a physician could not use the variables derived... for the intended use of the test
absent the algorithm that integrates them to calculate the patient specific result”. In light of this they propose to apply the IVD product standards to home brew assays which fall under the IVD MIA classification.

This announcement has come as something of a surprise to the diagnostics industry and is likely to have a particularly significant impact on small innovative businesses such as Genomic Health which has developed an IVD MIA test known as Oncotype Dx. This test predicts the likelihood of breast cancer recurrence by measuring the expression levels of 21 separate genes and then uses an algorithm to compute a recurrence score. Genomic Health is a CLIA registered laboratory and would not have expected to be subject to such overseeing - the appearance of this new regulation can hardly have helped their business prospects. There are also many unanswered questions; the guidance doesn’t give any indication of timelines. Will there be a grace period? Where do companies stand that are performing such testing now? Will the guidance have any impact on patients and doctors? At present the document is a draft marked “not for implementation - contains non-binding recommendations” so there is no need for immediate action but change is on the way.

In vitro diagnostic regulation in the USA has always made compromises between the use of the thorough and extensive guidance and the practicalities of bringing rare and novel tests to market. With the release of the IVD MIA regulations the FDA has shifted the balance towards greater regulatory overseeing. Whether this is a wise move which will ensure that new tests are suitable for their intended use or whether it will stifle innovative new diagnostics by preventing a rapid route to market remains to be seen. What is clear is that the FDA are flexing their regulatory muscle when it comes to homebrew testing and now the industry must wait to see if the agency intends to extend its influence further, not only over IVD MIs but also over other assays traditionally provided as homebrews.

Reference

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Foodborne Parasites
by Ynes R. Ortega, ed • Published by Springer (2006), 197pp, €109.95

Microbiologists are being challenged as foodborne outbreaks are increasingly being observed worldwide. Most of these outbreaks are associated with viral and bacterial pathogens such as Campylobacter, Salmonella, and lately Escherichia coli 0157:H7, which emerged in the 1990s. Although parasites have been evolving with man since antiquity, the control and eradication of diseases caused by parasites are still far from being achieved. Parasites are more and more often being reported in the literature as causative agents of food and waterborne illnesses. This book examines the two major parasites groups that are transmitted via water or foods: the protozoa, which are single-celled organisms, and the helminths. These latter are classified into three groups, namely the cestodes (tapeworms), nematodes (round worms) and trematodes (flukes). To better understand their significance, each chapter covers the biology, the mechanisms of pathogenesis, epidemiology, treatment and inactivation of these parasites. This important new text is crucial to a better understanding of the biology and control of parasitic infections necessary to reduce and eliminate future outbreaks throughout the world.

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