



Immunohistochemical Manufacturers

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Docket Number 99D-2723  
Dockets Management Branch  
Division of Management Systems and Policy  
Office of Human Resources and Management Services  
Food and Drug Administration  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, MD 20852

Dear Sirs:

In order to provide constructive comments on the draft guidance document, "Guidance on Labeling for Laboratory Tests," it would be beneficial to understand FDA's reasons for changing the required information in the product labeling that is stipulated by statute in the section 21 CFR 809.10. This statutory requirement has been met by industry and accepted for use by laboratories since 1983, with the only change being the addition of ASR labeling text.

Application of Operational Truth appears to be more important for a new product/technology requiring PMA submission, for which there is no predicate. However, the classification status relative to the Operational Truth requirement is not addressed. The Operational Truth product may become the predicate for a future product. Newer products/technology often improve the sensitivity/specificity of the test in question. How can FDA determine whether the predicate or the new product reflects Operational Truth more accurately?

FDA's definition of Operational Truth is itself flawed in that it implies that "true" diagnostic state (patient clinical status or outcome) can be determined independently from the results of a single diagnostic tests. In reality, simple outcome measures such as survival vs. death, or presence/absence of symptoms, are of limited use in evaluating the test performance of many if not most *in vitro* diagnostics, due to the overwhelming influence of "relevant confounding medical conditions". The specific conditions FDA cites (myocardial infarction, lupus, H. pylori) exemplify this dilemma. The reality is that Laboratory Equivalence at some level is the only possible comparison for the vast majority of IVDs.

Additionally for older tests such as hematoxylin, labeling regarding Operational Truth may not be possible. Which hematoxylin is the correct or true diagnostic then for determining laboratory equivalence? Products such as these serve more as an aid to diagnosis rather than a test in itself, in that diagnostic outcomes for products such as these depend almost entirely on user skill and microscopic interpretation unrelated to actual product performance.

Another critical point refers to the test that was initially characterized to a gold standard predicate but has not been compared to "true" diagnostic states. Often, the product originally considered the gold standard is no longer available, having already been supplanted in the market by the very test that was compared to it. Must the manufacturer then compare the test results to Operational Truth, which is extremely burdensome for an already cleared product, or to some other product which may in fact be inferior? It appears that the expertise to determine

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the appropriate predicate test product will reside with FDA. Therefore, manufacturers will require FDA to identify the predicate test product for each test. If this predicate is different from that used in the original product submission, is this test suddenly considered misbranded until testing is repeated with the FDA-mandated predicate?

Also, the "true" diagnostic state may change with time. How is the potential change in true diagnostic state to be managed? Will FDA change the "true" diagnostic state when the different manufacturers' product submissions provide sufficient data to justify a change, or will industry be required to petition to change the "true" diagnostic state?

Overall, this proposed guidance document has the potential to change the labeling requirements for a standard that has been applied by manufacturers and utilized by laboratories for a number of years. Current labeling practice states the testing procedure by which a product has been qualified for use and the expected outcome. There does not appear to be concern on the part of the laboratories over the information currently provided in labeling.

The paragraph in the draft guidance document which requests information

"in cases where a candidate device is being compared to a predicate, the predicate and conditions under which it is performed should be defined. Conditions of use include operator experience, clinical laboratory facility or other test setting, controls applied, specimen acceptance criteria, etc." appears to address the FDA requirement to handle the CLIA complexity determination which has previously been determined by CDC. One would expect that FDA has the expertise within DCLD to review the product submission as well as to determine, from the instructions for use, to which level of complexity a test should be assigned. Additional requirements by FDA for manufacturers to perform FDA's assigned task places doubt on the competency of the reviewers.

These are only highlights of the comments presented by JCIM members. There are additional potential flaws in this guidance document that should be further discussed if FDA proceeds with the comment and review period.

Overall, JCIM is concerned that FDA is changing the labeling requirements via a guidance document rather than by rule-making activity. Further requirements placed on manufacturers using the guidance document practice rather than via the rule-making pathway is violative of the FDAMA intention.

JCIM respectfully requests that FDA not implement this draft guidance document. Rather, JCIM would request that FDA develop a guidance document for FDA's use to perform the complexity classification function if that was the intent of this guidance, that will be its responsibility in the near future.

Sincerely,

Joint Council of Immunochemical Manufacturers

*Helene Paxton by H. M. M. M.*

Helene Paxton, Chair

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