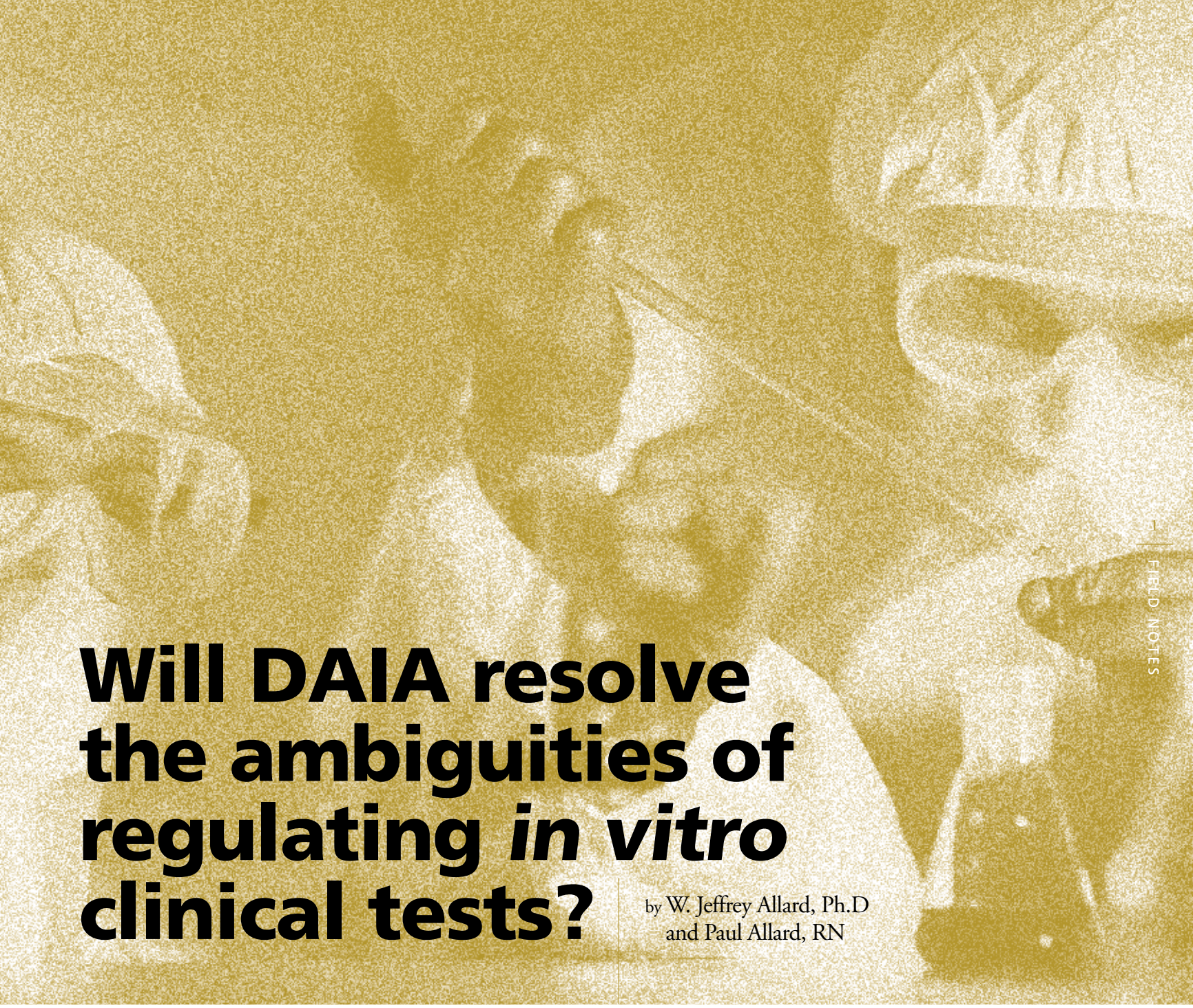

Will DAIA resolve the ambiguities of regulating *in vitro* clinical tests?

by W. Jeffrey Allard, Ph.D
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In 2015, the diagnostic industry and clinical laboratory groups formed the Diagnostic Test Working Group to envision more efficient regulation of in vitro diagnostic tests and to incorporate the thorny issue of Laboratory Developed Tests (LDTs) that has plagued the laboratory testing industry for over a decade. The Working Group's recommendations were passed along to members of the Energy and Commerce Committee of the US House of Representatives, who formulated draft legislation. In March 2017, Representatives Larry Bucshon, M.D. (R-IN) and Diana DeGette (D-CO) released a discussion draft of the Diagnostic Accuracy and Innovation Act (DAIA), intended to provide a predictable and timely path to market for innovative diagnostic tests.

The draft DAIA contains provisions to create a new Center within FDA – The Center for In Vitro Clinical Testing (IVCT) – and proposed that all tests, including LDTs, be regulated through the new center under low-, medium-, and high-risk categories. Response within industry was mixed, with laboratory groups continuing to claim that FDA lacks statutory authority to regulate laboratories, but others saw the move as a step toward much needed revision to FDA regulation of the laboratory testing industry.

In August of 2018, FDA released a Technical Assessment of the proposed DAIA legislation. FDA's approach was to rewrite the legislation in Congressional legalese. FDA redefined IVCTs as a laboratory test, a laboratory test protocol or a finished kit including software and instrument platforms. FDA rejected the need for a separate Center finding that costly and unnecessary. Rather, they proposed regulations for IVCTs that would be different than either the current process or that proposed by the DAIA including two principle regulatory pathways: premarket review and a precertification pathway. Provisional status was also included as an on-ramp for breakthrough technologies or tests meeting unmet needs. Such tests would not be required to demonstrate clinical validity and would do so as a post-marketing requirement.

The precertification pathway was floated by FDA previously. Manufacturers or laboratories could apply for such status for a laboratory test group defined by the technology used, the disease state addressed, and other characteristics such as the analyte, the sample type, the intended use population, and where the test is intended to be used(Hospital Clinical Laboratories, Point of Care Testing done at home, Reference Laboratories, Primary care offices, etc...). Following precertification, the test developer could then launch additional tests in the group through the listing process and follow their approved quality system. While this pathway seems to offer many advantages, a submission is still required; the test developer must achieve an approval prior to commercialization; and the approval will cover a specific set of tests based on the characteristics listed above.

The proposed path for pre-market review reads very much like current Class III PMA requirements, with the apparent exception of a pre-approval manufacturing audit. Premarket review will apply to all first-of-a-kind tests; tests for screening; and what FDA labeled as "cross-referenced tests" to encompass CDx and other tests that reference other products in their labeling.

Provisional status is a potentially intriguing pathway that could lessen the burden for clinical validation studies (particularly for small start-up test developers), though the required level of analytical and clinical data is unclear. A possibility is the standard currently used for Humanitarian Use Devices which is "probable benefit" as opposed to the higher bar of "Safety and Effectiveness" required for Class III devices.

So, what does all of this proposing and posturing mean for developers of companion diagnostic tests? Well, the first conclusion is that no one knows what the final legislation will look like; nor can we predict the timing for introduction of a draft bill to the full House and Senate; or if the draft bill will be introduced at all! Will this require a change in administrations or can new legislation to increase the efficiency of the FDA move forward under an administration and Senate controlled by the Republican Party? We have no answers to these questions (let alone the "unknown unknowns").

There is much to applaud in FDA's proposed language. The two principle regulatory pathways would simplify the approval process – somewhat. The Provisional pathway could provide an incentive to start-up test developers and manage their costs while shortening time to market for novel tests. Dropping the requirement for pre-approval manufacturing and quality audits – if indeed that is the intent which is not entirely clear to us – would improve turnaround times for pre-market review.

Despite the ambiguities in the various proposals, we offer several conclusions. First, after many decades of laboring in the shadow of the pharmaceutical industry, laboratory testing is making its way into the sunlight of the consciousness of Congress and the American consumer. In addition, Congressional revision of the regulations governing clinical laboratory testing is likely, and it is clear that both FDA and Congress wish to regulate laboratory developed tests. There remain challenges to that contention – legal and otherwise – and the ultimate role that FDA will play relative to CMS remains unknown. Keep in mind that legislation that

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authorizes FDA to regulate LDTs may end the legal controversy.

One consequence of this legislation – unintended or intended – is that small start-up biotech companies will no longer have the LDT route available and will be forced to submit to FDA for either a pre-market approval or for a provisional application. Either approach may be onerous and may further frighten the investment community who have rarely shown excitement about the IVD field in general. Small start-ups are the engine driving innovation in the IVD industry. Larger companies seldom innovate, choosing instead to purchase novel technology at a later stage with lower risk. We suspect that the loss of the LDT option will benefit larger companies. Small start-ups may flounder and, if they do, they will become available for pennies on the dollar. In addition, it has been known for decades within our industry that FDA regulation can pose a barrier to competition for those sufficiently well-heeled to bear the burden in cost and time, as well as user fees. Whether the Provisional pathway will provide sufficient relief for start-up biotech companies remains to be seen.

Another consequence of FDA regulation of LDTs is the looming complexity of novel assays. Newer tests frequently use multiple molecular targets and mathematical algorithms. Some expect tests in the future will be agnostic to the biochemical structure of the target molecules and proteins, carbohydrates, lipids and nucleic acids may all be combined into single tests interpreted using complex algorithms such as machine learning and random forest. These kinds of innovative technologies with their accompanying complexity may prove difficult to regulate effectively, especially in the post-government shutdown world where attracting the best and brightest scientists into government positions may prove increasingly difficult.

For now, the LDT pathway remains a legal, ethical and moral approach that is available to test developers as a legitimate option to bring tests to market more rapidly and avoid the high cost and lengthy timeline of FDA approval or clearance. However, LDT providers would be wise to bear in mind that FDA regulation is a distinct possibility that will have to be dealt with sooner or later.

And whether developers commercialize their test as an LDT or choose the FDA route, regulatory changes seem imminent. One pragmatic approach in this age of uncertainty is to launch a test as an LDT and implement a post-market clinical trial such that some customers provide clinical and outcome data that can be used to validate the test for its intended use. In that way, developers can launch as soon as the test is ready, begin collecting revenue, and use that revenue stream to attract further investment and to pay for at least some of the cost of a clinical study. This results in a shorter time to market while still planning for an eventual submission to FDA.

We found shortcomings in all proposals to reform FDA regulation of IVDs, particularly from the standpoint of CDx developers. While the pre-certification program seems attractive, the exact definition of a laboratory test group is unclear and could be restrictive. This could lead to a requirement for pre-certification for every disease state, for each technology such as chemistry, immunoassays, and the various molecular technologies to measure or sequence RNA and DNA. Would FDA define a test group as an immunoassay to measure thyroid hormones? If so, then what about cancer biomarkers, fertility hormones, and the plethora of other tests that run on immunoanalyzers?

And make no mistake, precertification sounds a lot like a current de novo submission with all the usual analytical, clinical, labeling and other requirements. While precertification seems to provide a more rapid path to market, what will be considered breakthrough technology or, even more importantly, what is an unmet medical need? And whatever the precertification process provides, it will likely not apply to CDx.

Our reading of the various proposals leads us full circle for CDx testing: Manufacturers will continue to be subject to requirements for analytical validation, clinical validity, labeling and quality requirements. We see no signs that this will go away anytime soon for CDx or cross-referenced testing.

So, while the LDT window of opportunity remains open, test developers would be wise to be informed on FDA requirements and plan to meet them. Sooner or later, you will probably have to. ■

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