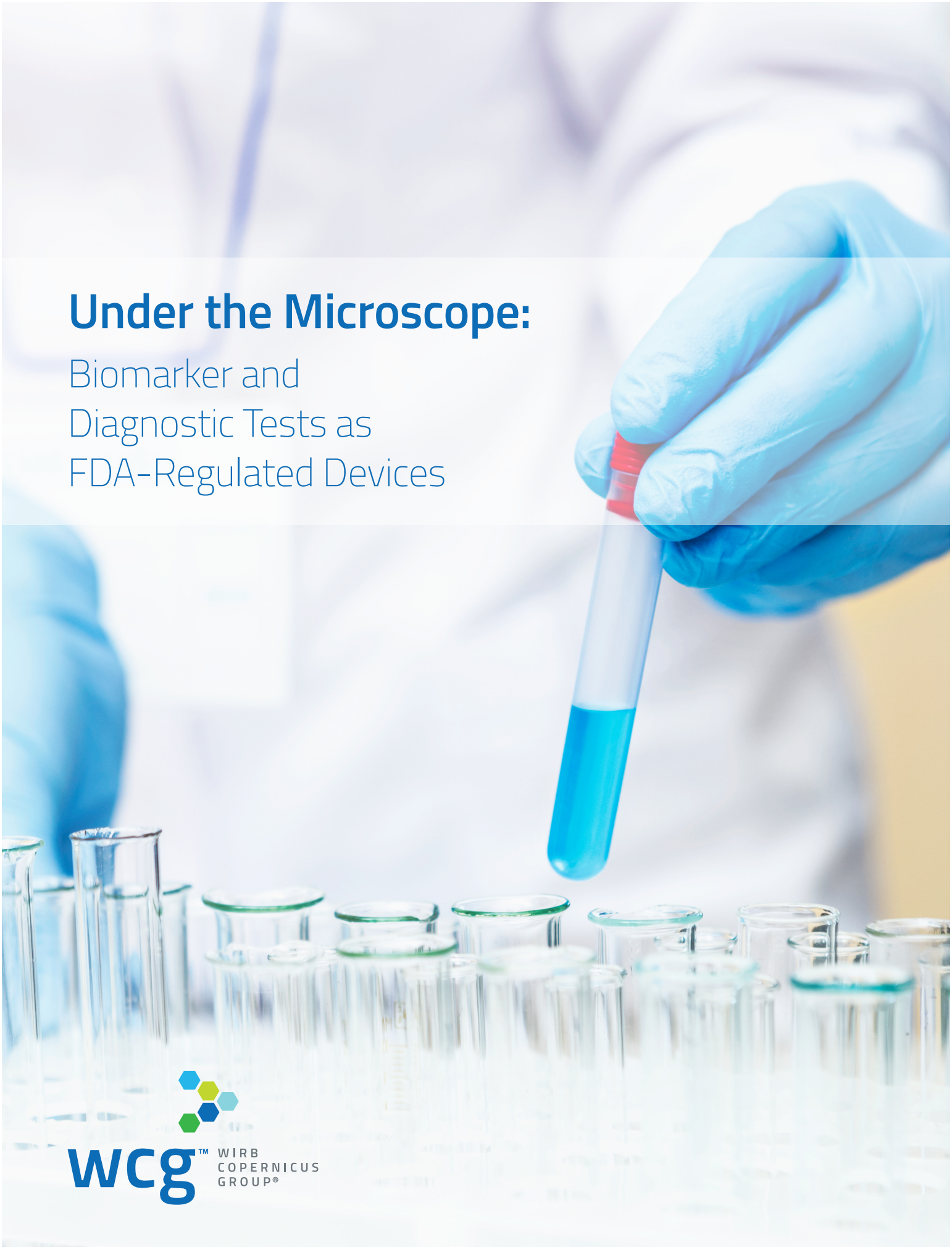

Under the Microscope:

Biomarker and Diagnostic Tests as FDA-Regulated Devices

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Introduction

The technological leap and informational explosion of biomarker and genetic mutation tests raises complex issues for the conduct of FDA-regulated clinical investigations.

Since a buccal swab, tissue, or blood sample can provide data that determines a person's eligibility or assignment in a clinical trial, it is critical that the results of these tests be accurate. And sometimes, ensuring the accuracy of this crucial data requires research into the test that produces it. When biomarker or mutation testing is part of a clinical trial protocol, the sponsor and Institutional Review Board (IRB) must make a determination as to whether the testing (and testing device) itself is investigational, and sometimes the answer to this question comes as a surprise to sponsors. This paper discusses the roles of the FDA, sponsor and IRB in determining when biomarker testing, conducted as part of a clinical investigation, is considered FDA-regulated medical device research.

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Background: FDA's Authority

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act broadly define a device in a way that clearly covers diagnostic devices. In vitro diagnostic products (IVDs) are medical devices as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act. In addition, some IVDs are classified as biological products subject to section 351 of the Public Health Service Act. Like other FDA regulated medical products, IVDs are subject to premarket and post-market controls.

Laboratory developed tests (LDTs) are a subset of IVDs, created by a laboratory and then used on-site at that laboratory. They are not sold commercially as an IVD for other parties to use, but the laboratory that creates the LDT charges a fee for providing results. LDTs are also subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA), but that is a separate regulatory framework that does not limit FDA's oversight. While CLIA does require quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results, it does not require that an LDT meet the same safety and efficacy requirements that come from FDA oversight. As a result, an LDT created and used in a laboratory does not need data to support the validity of the test in clinical use.[1]

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Background: FDA's Authority

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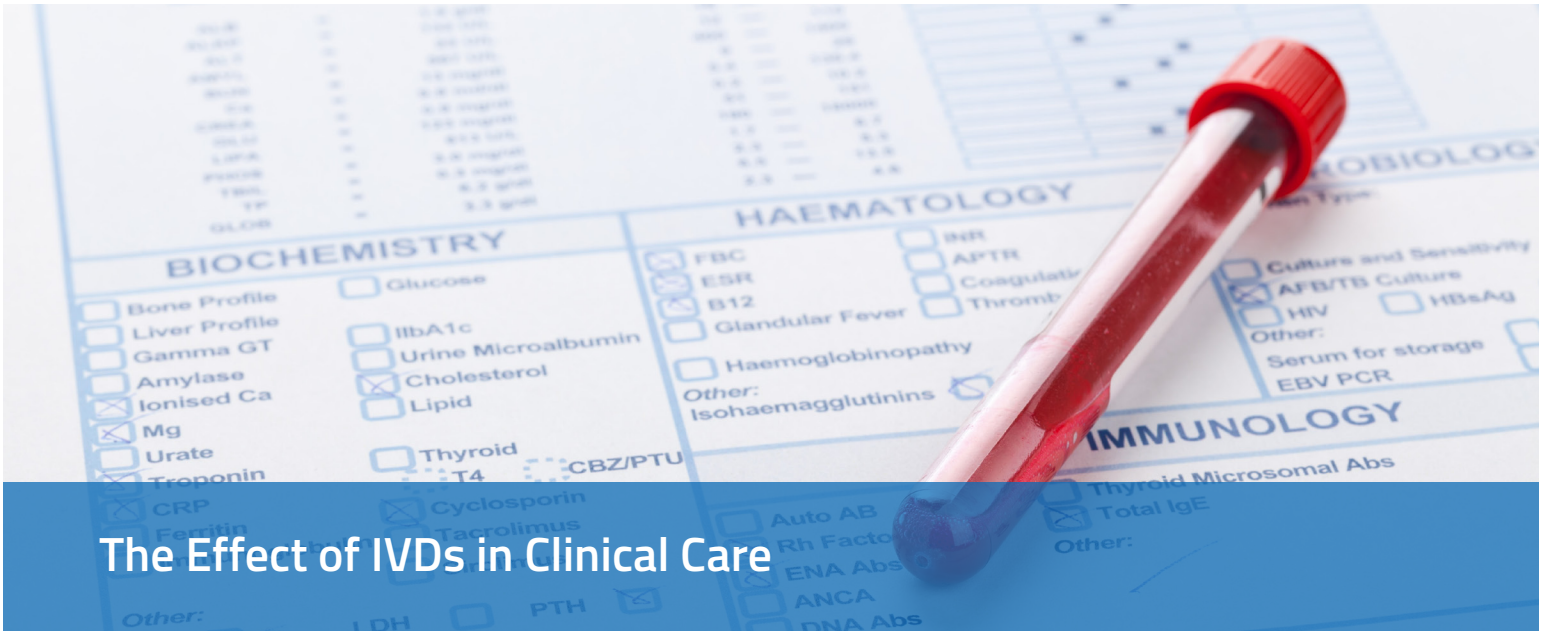
When the Medical Device Amendments were released in 1976, LDTs were simple lab tests and available on a limited basis. Although they technically fell under the regulations, FDA chose to apply enforcement discretion and did not require compliance with premarket review and other applicable FDA regulations. However, since that time, LDTs have evolved and expanded substantially. Increasingly complex, and often nationally available, these tests are now used to evaluate a host of serious health issues including the risks for breast cancer and Alzheimer's disease.[2] On July 31, 2014, FDA provided notice to Congress of its plan to issue draft guidance on the regulation of LDTs as required by the 2012 FDA Safety and Innovation Act.[3] Final guidance is still pending as of the writing of this paper. During this period of transition, some newer tests have undergone premarket review under the FDA device regulations where pre-existing tests did not. As a result, for certain diseases there are both FDA-approved and non-FDA-approved clinical tests commercially available.

FDA DEFINITION OF A DEVICE:
"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure of any function of the body and which does not achieve its primary intended purpose through chemical action and which is not depended upon being metabolized for the achievement of its primary intended purposes."



The Effect of IVDs in Clinical Care

In vitro testing has real-life consequences in clinical research and medical care. FDA has identified serious problems with numerous high-risk LDTs including claims that are not adequately supported with evidence, lack of appropriate controls yielding erroneous results, and falsification of data.[4] On the basis of these erroneous, inappropriate or false results, people could initiate unnecessary treatment or forego treatment for a condition which could result in serious illness or death. Possible consequences of faulty LDTs include: patients potentially being over- or undertreated for heart disease[5]; cancer patients being exposed to inappropriate therapies or not receiving effective therapies[6]; incorrect diagnoses of autism[7]; unnecessary antibiotic treatments[8]; and exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease.[9] Significant differences in results have been noted between FDA-approved tests and those that did not receive FDA approval: one paper's analysis of HER2 testing (a gene associated with breast cancer, which can direct treatment options) showed a false negative rate of 11% for an FDA-approved test and 25% for an unapproved test, with false positive rates of 0% for the FDA-approved test and 5% for the unapproved test.[10]

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The Impact of New FDA Enforcement on Clinical Trials

The decision of the FDA to end enforcement discretion and to enforce the applicable regulations going forward applies not just to the use of these tests in clinical practice, but extends into their use in clinical trials as well.

Very early biomarker research to collect basic physiologic information using a test, but not evaluating the safety and efficacy of that test, is unlikely to be considered a clinical investigation of a device.[11] For example, sequencing genes for general research purposes would not be considered a clinical investigation, while similar sequencing to study the safety and efficacy of the diagnostic test would.[12] The practice of medicine, including the use of IVDs and LDTs purely for clinical care, is outside of the scope of FDA oversight of clinical investigations: individual physicians must make treatment decisions with their patients using what information is available. However, conducting research to determine the safety and efficacy of an IVD (including LDTs that could be used for care) would be a clinical investigation under FDA oversight.[13]

Currently, the FDA position is that if an IVD (including LDTs) is used in a clinical investigation, and that IVD is not cleared or approved by FDA,

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The Impact of New FDA Enforcement on Clinical Trials

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then the IVD is investigational and must be treated as an investigational device (as stated in the Congressional communication).[2] This is true even if the IVD (LDT) is used in a CLIA-certified laboratory. Therefore, it is necessary to assess the use of the IVD in the study as an investigational device, and the IRB overseeing the study must confirm that the appropriate regulatory designation has been made by the sponsor. This may be unexpected by sponsors, because the primary purpose of the clinical investigation may not be to confirm the safety and efficacy of the IVD. In many cases, the safety and efficacy of the IVD is included in a clinical trial of a drug in which potential subjects are selected on the basis of certain biomarkers for which the drug is considered more efficacious. These IVDs may become "companion" diagnostic devices and derive their approval from the efficacy of the drug on the pre-selected population. Since the device manufacturer and the pharmaceutical sponsor are often different entities, pharmaceutical protocols only rarely address the investigational status of the device itself.

The FDA determines if the study is one of safety or effectiveness of a device and "is not bound by the manufacturer's or distributor's subjective claims of intent but rather can present objective evidence." [14]

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The Impact of New FDA Enforcement on Clinical Trials

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Basically, FDA can determine on its own what the intended use is. Essentially, this means that whether or not the research is actually testing the device, or merely using it as part of a study, the review is the same.

The FDA can be queried through the pre-submission process for an initial determination of the regulatory status of the device. FDA expects the IRB to make this decision if the FDA has not been consulted prior to the point of IRB submission. To assist the IRB in an efficient review, the sponsor should provide their device status assessment to the IRB for consideration as part of the initial review. This information will provide the basis on which the IRB can then determine the extent of review required.

Complex and Multi-Factor Components

Experience in this review is crucial, of course. Investigational device studies can be exempt from the Investigational Device Exemption (IDE) requirements, be determined to meet the abbreviated IDE requirements, or require a submission to FDA for an IDE. Studies using IVDs are exempt if they meet certain requirements under the regulations or if they are an FDA-approved or cleared device being used according to its labeling.[15, 16, 17] For example, a study requiring testing so that only people with certain genotypes of the Hepatitis C virus can be included would not be exempt as the results from that test are determining study inclusion without another confirmatory test or procedure. Therefore, to be exempt, the testing would need to come from an FDA-approved test, even if a similar test had data to support its reliability.

If the device is not exempt, the sponsor must make a determination whether the use of the device in the study makes it a non-significant risk device study (NSR) which qualifies for the abbreviated IDE requirements. If not, the sponsor should request that the FDA determine if it is a significant risk device study that requires an IDE. When making this determination, as IVD tests that are not currently banned, are not intended as implants, and are not supporting or sustaining life, the sponsor can focus on whether the device's use is substantially important in diagnosing, curing or treating disease and therefore presents a potential for serious risk to the health, safety, or welfare of the subject.

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Complex and Multi-Factor Components

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When determining the risk of the device's use, a sponsor should include all factors that impact an in vitro companion device's risk. As the use of the test requires tissue, the sampling or biopsy required also affects risk. Low risk samples include a blood sample or use of archival tissue. Biopsies can be higher risk. Describing the specifics around the biopsy can be a significant factor in risk assessment when fresh biopsies are required. Another factor affecting the risk determination is that the more specific the test results are to the decision-making, the greater the risk. For example, if the test is for a biomarker for which a targeted drug is being tested, the impact of the results —and therefore the risk — is increased by exposing patients with false positive results to a treatment that is unlikely to be effective, and by denying those with a false negative result a potentially useful treatment. Additional risk assessments based on the reasonably available alternatives and the clinical situation may be considered, including if the test results will be used to:

- Determine eligibility for enrollment, i.e., if a positive test is required for inclusion
- Decide study drug assignment or stratification, e.g., arm, dose, or timing
- Monitor for a safety signal[18]

This full risk assessment should then be provided to the IRB for review. Although the sponsor and the IRB must make preliminary findings on a device's regulatory status, ultimately FDA is the final arbiter. Understanding the FDA's perspectives and previous interpretations for this review can require significant experience. Even if FDA has already reviewed the submission, ensuring that the IRB is aware of that review requires disclosure by the sponsor.

Appropriate Outcomes From Clear Communication

Given the regulatory complexity of medical device review, the importance of the validity of the data from research that includes the use of medical devices, and the clear safety and welfare implications for research participants, the IRB and sponsor must cooperate in the sharing of critical information in order to provide the study sponsor with an appropriate review of the research protocol. Sponsor awareness of the information needed for completion of the necessary elements of review will enhance clear communication with the IRB and regulatory agencies, which can greatly improve the efficiency of the review process. That review, and the communications that go into it, result in improved research protections for subjects, and in the potential for important knowledge to benefit society.

"Sponsor awareness of the information needed for completion of the necessary elements of review will enhance clear communication with the IRB and regulatory agencies, which can greatly improve the efficiency of the review process."

Authors

Currien MacDonald, MD, CIP is the Medical Lead IRB Chair for Western IRB, a WIRB-Copernicus Group Company.

David Forster, JD, MA, CIP is the Chief Compliance Officer at the WIRB-Copernicus Group.

Glenn Veit, JD, CIP is the IRB Advisor and Executive IRB Chair at the WIRB-Copernicus Group.

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