On June 1, 2011, the US Food and Drug Administration (FDA)2 Office of In Vitro Diagnostic Device Evaluation and Safety issued draft guidance for industry and FDA staff intended to provide guidance regarding the FDA’s thinking about in vitro diagnostic device (IVD) products labeled for “Research Use Only” (RUO) or “Investigational Use Only” (IUO) (1). Reagents may be marketed under either of these labels without FDA premarket review and are partially or totally exempt from compliance with the Quality Systems Regulation (21 CFR 820). Therefore, an IVD manufacturer might it very tempting to avoid the trouble and expense of a 510(k) or premarket-approval submission by labeling a product as RUO or IUO, despite knowing full well that the product is likely being used as an IVD under conditions in which there is no research protocol and no oversight by an institutional review board. There is no doubt that the FDA’s intent is to improve patient safety. Compliance with the Quality Systems Regulation provides assurance that an IVD meets manufacturing specifications and that lot-to-lot variations are minimized and well understood. FDA clearance provides further assurance that the performance characteristics of laboratory tests are sufficiently well understood as to enable their intelligent use. Furthermore, the use by clinical laboratories of FDA-cleared IVD products likely reduces interlaboratory variation in testing and increases the ease with which results can be “ported” from one healthcare facility to another, potentially reducing healthcare costs that arise from duplicate testing. Nevertheless, the laboratory community is right to be concerned about the guidance document statement that manufacturers should not sell RUO or IUO reagents “to laboratories that they know use the product for clinical diagnostics use.” This statement could have unintended consequences that adversely affect patient care. In particular, the molecular diagnostics community has expressed concern that such reagents as PCR primers and sequencing reagents and equipment could become unavailable and that this outcome could affect many aspects of medical care, including newborn screening, HLA testing, and human papilloma virus genotyping, among others.

When considering approaches by which the FDA and the laboratory community can improve patient care and safety, it is important to consider the overall medical and regulatory environment in which laboratory tests that currently use RUO and IOU IVDs are conducted. In the remainder of this Opinion, I consider potential deficits in laboratory testing that currently do not rely on FDA-cleared IVDs and discuss principles that the FDA and other agencies may wish to consider when determining whether a regulatory solution is the most appropriate way to address the perceived deficits in laboratory testing.

The design and implementation of regulations entail substantial costs on the part of both regulator and regulated, both of which must ultimately be borne by the public. Therefore, regulators should take a measured approach when deciding to implement a regulatory solution to a perceived problem. In my opinion, such decisions should be based on a careful and narrow definition of the public health problem to be addressed, a scientifically valid and quantitative assessment of the magnitude of this problem, and strong evidence that the overall cost of implementing the regulatory approach (including both the cost to the regulator and the cost to the regulated entities) is cost-effective. The regulatory reasoning and the cost–benefit analysis should be published together to facilitate public scrutiny and comment. Implementation of this approach would unquestionably be associated, at least initially, with an adverse financial impact on regulatory agencies, because the assessment of regulatory impact would undoubtedly be more costly than is currently the case. The overall cost to the public seems likely to be offset, at least in part, by avoidance and/or rescission of ineffective and costly regulatory interventions.
The recent FDA guidance document does not implement such an approach, so I consider some of the issues that the agency may have attempted to address.

Several potential problems are associated with the use of RUO and IUO reagents in clinical laboratory testing: (a) the creation of an uneven playing field for manufacturers; (b) the perception that manufacturers or laboratories are defying FDA regulatory authority; and (c) the reporting of inaccurate, misleading, or inconsistent results, either within a laboratory or among several laboratories. There is no question that the cost avoidance produced by ignoring regulatory requirements creates an economic environment that gives unfair advantage to commercial manufacturers, compared with institutions that play by the FDA interpretation of the law. Both the clinical investigations and the paperwork requirements associated with FDA submissions are costly. These costs may come at the expense of profit or at the expense of healthcare organizations and insurers (including the federal government).

Inaccurate or misleading results can occur when a clinical laboratory result does not mean what a clinician believes that it means. That situation could arise, for example, if an RUO or IUO reagent is not what the vendor says it is or performs in a manner that both is inconsistent with what the vendor states and is unexpected by the clinical laboratory. It is thus incumbent on laboratories to conduct their quality-assurance activities in a manner that ensures that reported results mean exactly what they purport to mean, whether or not a laboratory test has been cleared by the FDA. Under the framework proposed above, increased regulatory effort by the FDA might be appropriate if evidence of harm exists, although CLIA also provides a framework for achieving this objective.

Although the FDA has not officially elucidated the reason for issuing the guidance document, there have been a number of reports of inaccurate testing with laboratory-developed tests. Perhaps the most prominent is prescribing Herceptin® based on the results of immunohistochemical tests for HER2 (human epidermal growth factor receptor 2) overexpression. Some of these results have depended on the use of uncalibrated laboratory-developed tests; indeed, some authors have postulated that as much as 20% of immunohistochemical HER2 testing used for selecting patients for Herceptin therapy has not been correlated, either directly or indirectly, with response to the drug (2). If true, that finding demonstrates a clear failure of the CLIA framework alone to adequately protect public health, and it seems likely that the burden of regulatory compliance, if narrowly directed to this issue, is proportionate to the problem. Inaccurate or misleading results have also been associated with direct-to-consumer genetic testing (3), which is widespread. The magnitude of the harm associated with such testing is uncertain but may be considerable, and oversight under the CLIA mechanism has failed to address the issue.

The potential reach of the FDA guidance document is broader than necessary to deal with HER2 assessment and direct-to-consumer testing. There are substantial numbers of important laboratory-developed tests for which only RUO and IUO reagents are currently available. The FDA guidance document (which, I should note, is nonbinding) could lead to withdrawal of these tests from clinical practice. In my opinion, FDA officials should work to minimize the likelihood of such an occurrence. In addition, there is a risk that innovative new tests for which only RUO and IUO reagents are available will not be deployed in a timely way, further compromising patient well-being. There is clearly a role in medical practice for laboratory-developed and -validated tests that will, of necessity, use reagents that have not passed FDA muster. The failure of CLIA oversight mechanisms is not a reason for the FDA to act unilaterally. Enforcement of both the Food Drug and Cosmetics Act and the Public Health Service Act [which created the CLIA 88 (CLIA amendments of 1988) framework] falls to the Department of Health and Human Services. It is thus appropriate for the FDA and the Centers for Medicare and Medicaid Services to work cooperatively, not only with each other but also with industry and laboratory communities, to develop a robust framework for reducing inaccurate and unreliable laboratory testing while maintaining access to high-quality laboratory testing and minimizing its economic burden.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

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1 HER2 is used in this Opinion to refer to the protein encoded by the gene with HUGO-approved gene symbol ERBB2 [v-erb-b2 erythroblastoid leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)], as HER2 is the name commonly used in practice.
Employment or Leadership: T.J. O’Leary, Association for Molecular Pathology and *Journal of Molecular Diagnostics*.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: None declared.

Expert Testimony: None declared.

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