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Comments on FDA's draft guidance on In Vitro Diagnostic Multivariate Index Assays

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I am a research associate at the Department of Public Health and Primary Care at the University of Cambridge in the United Kingdom, where I work as part of a research team who have spent the last three years exploring the policy issues around the evaluation and regulation of genetic tests.

Our forthcoming report will explore two key questions:

What are the incentives test developers need to generate good evaluative data on new tests?

What are the appropriate regulatory mechanisms for evaluation of such data?

In the course of our research we have looked at the regulatory regimes in Europe, the US, Canada and Australia and we have spoken to 80 individuals from key stakeholder groups - policymakers, regulators, diagnostics companies, clinicians, patients groups. We have had the good fortune to enjoy active FDA involvement in our research; members of OIVD have participated in focus groups we have run in Washington and London and we received an FDA Leveraging/Collaboration award for our work.

This response draws on our research, but is a personal rather than a collective response to the draft guidance. It offers strong but qualified support for the IVDMA guidance, arguing that there is good reason to believe that FDA have correctly identified the category of laboratory-developed tests which are most urgently in need of the Agency's regulatory scrutiny, but concluding that this is only a partial answer to the broader problem of the lack of a level playing field between test kits and lab-developed tests.

Regulating laboratory-developed tests

Many of the stakeholders we have spoken to expressed the view that public confidence in genetic testing can only be maintained if there is a clear and coherent framework of regulation. There was general agreement that the status quo was not adequate; that new tests should be subject to some form of systematic independent pre-market evaluation. Many US participants expressed some frustration that despite the detailed policy work of successive task forces and advisory committees there was still no progress on these issues.

Much of this US concern centres on what some term the 'homebrew loophole', the lack of a level playing field between test kits and in-house developed tests, whereby the former are subject to FDA regulations but the latter are not. We found broad support for the CLIA certification process for laboratories as an important and necessary part of ensuring the safety and effectiveness of pathology tests but also widespread concern that it is insufficient; pre-market review of novel tests to assess their analytic and clinical validity is also required. In our research many stakeholders expressed concern that at the

moment the CLIA-certified lab status misleads consumers by giving the impression that tests have been subject to independent pre-market scrutiny.

If we look at the issue of laboratory-developed tests internationally we can see a clear trend in IVD regulation towards explicitly bringing laboratory-developed tests into device regulations, exemplified by the new regulatory system being developed in Australia and the IVD Directive in Europe. However, the regulatory gap in the United States is not as clear cut as is sometimes suggested – whilst FDA has hitherto only rarely exercised its regulatory authority over in-house tests, a significant proportion of them are subject to pre-market review by New York State Department of Health under their Clinical Laboratory Evaluation Program. We have been told that the New York state system of pre-market review is not dissimilar in its evidence requirements to a 510(k) review by FDA.

What can we learn from the New York State model? Clearly the new draft IVDMIA guidance has aroused concerns amongst some of the companies that may be affected who fear that FDA regulation of in-house tests may become a block on innovation. Yet companies like Quest, LabCorp and Genomic Health, who are all NY-licensed, are at the leading edge of diagnostic innovation. This would suggest that pre-market review of in-house tests need not be a major block on innovation.

IVD innovation

Innovation is important - the IVDMIA guidance is best understood in the context of a discussion of the changing models of innovation in the IVD industry. The IVD industry has traditionally held intellectual property (IP) in test platforms, not in biomarkers. This means it is a very competitive industry with low profit margins compared with the pharmaceutical sector. With little protection on investment, relatively low margins and little experience or infrastructure for clinical evaluation, the traditional sector is ill-equipped to undertake large-scale clinical studies. This model of weak IP in biomarkers has meant that no one party is responsible for developing the data on the clinical validity of a new test. Academic studies and professional advocates have filled the gap, often promoting tests on the back of ad hoc clinical experience.

There is some evidence that the emerging field of molecular diagnostics has disrupted the traditional model in a number of ways. A number of companies developing genetic tests based on patent protection of the gene and its association with disease have emerged, with products near or on the market. deCODE, InterGenetics and Celera are devoting some, or all, of their R&D activity to heritable risk predictors and are close to tests to market, often with IP on the biomarkers and/or the interpretative algorithm which creates a clinical result from the analysis of multiple analytes. Companies such as Cepheid and Tm Bioscience, whose core business has been founded on molecular tests for well-established markers, are also looking to exploit stronger IP by developing novel biomarkers. The emerging market for gene expression and proteomic tests is based on similar strong IP rights.

Strong IP in biomarkers allows companies to charge higher prices for their tests because it gives them longer on the market before the arrival of competing products. IP gives small companies the leverage to access the money needed for clinical studies – they can raise money from venture capitalists or find a bigger partner, either a major diagnostics manufacturer, or a major reference laboratory. So IP has become an important incentive for funding clinical studies for new molecular diagnostics and thus it is not just the technology which is changing, it is the business model and the innovation process.

Regulating IP-protected tests

Do IP-protected tests, such as IVMDIAs, present special regulatory problems? IP in biomarkers can lead to monopolistic provision of tests. And the homebrew loophole has made it more attractive for companies to develop their tests as in-house tests which are carried out on a monopolistic basis by the test developer, or two or three exclusive licensees. Many clinicians and laboratory directors have opposed this, arguing that monopolistic provision circumvents the traditional (informal) methods of test evaluation, whereby in-house tests are subject to peer-review in the field. They are concerned that it creates a situation where the only people who can perform a new test are those with a vested interest in its promotion and this creates anxiety that in order to recoup their R&D investment, companies may make strong clinical claims for their tests at a stage when the evidence base is still developing. Controversy over emergent IP-protected tests has been seen repeatedly in recent years with little agreement about when tests are ready for routine clinical use. The novelty and complexity of many of the tests involved only heightens concerns.

The point is **not** that all companies producing IVDMIAAs are bad players making dangerous tests. The point is that without independent evaluation by FDA, there is no way for doctors and patients to distinguish good from bad.

Responding to concerns

Over the last few years the FDA has written letters to several companies about the regulatory status of their in-house tests. Many industry people we spoke to thought there was a clear pattern emerging about when FDA might intervene – algorithm-based tests with high-risk applications and strong clinical claims. Last year we wrote a report on pharmacogenomics for the Canadian government. We noted this trend and suggested that it was likely to increase in pace and would eventually have to be resolved by a formal guidance document or even a rule akin to the ASR rule.

Our research has indicated the importance which companies place on regulatory guidance documents. Guidance can aid test developers by providing clarity on both the review processes and standards of evidence required - vital information for those taking strategic business decisions about product development. This was clearly an area where clarification was needed. Whilst there are concerns about the ambiguities in the document the draft guidance has provided a rationale for FDA's recent activities in this field. It represents a major step forward. Yet it raises as many questions as it answers.

The new guidance does not cover all monopolistic providers, let alone all laboratory-developed tests, so the playing field remains uneven, with device manufacturers still competing with in-house tests which do not need to go through FDA review. Yet, having asserted its authority over in-house tests, FDA must accept it may be called upon to exercise that authority. What will the Agency do if it receives complaints about a test which falls outside the IVDMA guidance? It cannot state that the matter is outside its jurisdiction, and there is no other authority to whom the problem can be referred. Yet for the FDA to respond by investigating other tests on an ad-hoc basis would simply add to the confusion about its position. This is not a hypothetical situation – witness the current controversy surrounding DTC genetic tests, which are generally laboratory-developed tests but not all of which may fall under the new IVDMA guidance.

The only solution is for a comprehensive approach to in-house tests. One which leaves test developers in no doubt about the regulatory pathway they must follow and which gives doctors and patients greater confidence that the tests on which they rely are both safe and effective.

A flexible approach to regulation

When the idea has been mooted in the past FDA officials have regularly expressed anxiety about the scale of the task presented by the wholesale extension of its activities to in-house tests. Many of those who would become subject to FDA regulation have also expressed concern at the thought of additional regulatory burdens. Part of the solution is more generous funding for the Agency, but just as important is a willingness to contemplate new regulatory approaches. This is not the place for a detailed discussion of how FDA could develop its approach to the regulation of in-house tests. However, it is worth noting that the Agency has at its disposal a range of flexible regulatory tools which might be applied to ensure that FDA review is not unduly burdensome on either the Agency or the regulated industry:

- Third-party review - in Australia the TGA have adopted third-party review – authorising the professional pathology bodies as reviewers but with TGA retaining ultimate authority and a standard-setting role. There may be some categories of lab-developed tests for which this approach may be most suitable.
- Orphan disease status – orphan status can be given to rare disease tests to address the unique challenges faced in this area.
- Focus on truth-in-labelling - the Secretary's Advisory Committee on Genetic Testing identified an approach to pre-market review which focuses on ensuring truth-in-labelling, as one which may be of assistance. This may be consistent with use of the 510(k) review process, indeed FDA have asserted they took this approach in their reviews of both the Roche Amplichip and the UGT1A1 test from Third Wave.
- Conditional licensing – where a test is considered higher risk because of its intended clinical use or the novelty of the technology, and has only very limited

data to support its use, FDA may wish to take a more rigorous approach to pre-market review, delaying market approval pending further studies. However, even here there may be ways to minimize the regulatory burden. One option is to allow a more controlled entry to the market by using conditional approval or mandated Phase IV studies.

- Postmarketing controls – the use of conditional licensing could be extended beyond Class III PMAs, to Class II devices as part of a refocusing of regulatory activity on postmarket controls. Our research found strong support for the view that improving postmarketing surveillance should be considered a prerequisite for a least burdensome system based on more rapid entry to the market.
- Multiple gatekeepers and the scope of review - Consideration of postmarket controls, understood more broadly as all those oversight mechanisms which exist beyond premarket review, brings to the fore the role of gatekeepers other than FDA. Premarket review can be minimised where there is confidence that reimbursers will use processes such as formal HTA reviews to evaluate new tests and control clinical uptake through evidence-based practice guidelines. Our research found strong support for the idea that pre-market review should focus on evaluating evidence on the analytic and clinical validity of new tests and evaluation of clinical utility should be left to reimbursers and professional bodies.
- Responsive regulation - a move towards PMS could also be seen as a shift in favour of responsive regulation – that is companies which clearly play by the rules are given relative freedom but those who transgress come under greater regulatory scrutiny.
- NY State model - the US has, in the NY State model, an alternative pre-market review process which is already applied successfully to in-house tests and it may be that FDA can learn from this model.

Whilst FDA could achieve much by creative use of its existing regulatory toolkit, it needs to engage in a detailed, formal consultation with all stakeholders if it is to achieve a more comprehensive approach to the regulation of lab-developed tests.

Conclusion

There are good reasons for FDA to bring IVDMIAs under its regulatory scrutiny. The new guidance promises to bring greater clarity and consistency to the Agency's previous piecemeal approach to this class of tests. Furthermore, FDA's decision to assert its authority over lab-developed tests begins to bring it in line with the regulatory approach of both Europe and Australia, creating greater consistency across the international market for IVDs. However, a more comprehensive approach to in-house tests is required if FDA are to fulfil their mission to assure the safety and effectiveness of novel diagnostics. This in turn will require a thorough review of OIVD's regulatory processes to ensure that least burdensome approaches to regulation. The IVDMIA guidance is not the end of the

process, it can only be the beginning. FDA are to be applauded for taking the initiative, they deserve the active support of other stakeholders in completing the task.

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