From:	Aleksandr Rabodzey
To:	Brian Grossman; Vivek Khanna
CC:	Alex Virgilio; Sriram Balasuryan
Sent:	1/28/2014 8:31:07 PM
Subject:	Theranos Technical and Regulatory Assessment
Attachments:	Vitamin D assay.pdf; LH Vitamin D.pdf

Hi Team,
Following our discussions of the level of due diligence done by Theranos partners, and the level of disclosure that we get from Theranos, I spent more time on understanding the risks we have to account for here. I also had another call with someone from the industry who developed tests and had experience personally preparing 501k submissions and running clinical trials for MDx tests. We will have one more call tomorrow with another scientist.
Please consider my assessment below in the context of my skepticism to everything and my Russian negativity

Here is the summary of my research and the call:

- Every LDT is considered a device and thus falls under the FDA's jurisdiction, but the FDA usually turns a blind eye on the LDT within certain limitations: as we saw with NIPT market where SQNM marketed w/o FDA approval, but then Verinata chose to get it
- Thus, the FDA can intervene at any point in time and send a cease and desist order like they did with 23&Me. This decision would be primarily driven by importance of the test, complexity, volume, etc. There is no assurance that the FDA will not come out and demand FDA 501k filing for every test done by Theranos (all testing may be suspended in the interim), but I would expect the FDA to not do that for a year or two
- Important distinction between CLIA and FDA: "CMS' CLIA program does not address the clinical validity of any test – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not." http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf Thus, the FDA standards are higher AND require clinical validity, while CLIA does not. This is in contrast to what Theranos claimed today by saying that the requirements are essentially the same and getting CLIA is essentially the same as getting FDA approval.
- In fact, the FDA has a specific set of standards for validity: 40 samples is the absolute minimum (where 40 tests are done with reference method and the new method), R2 should be in general in line with other methods and generally >.9, 0.95 even better. Many manufacturers do 3 cites with 40 patients each for a total of 120 samples per test. http://isoforlab.com/phocadownload/csli/EP09-A2.pdf At this point many of Theranos tests would not qualify under one or the two or both requirements.
- To validate that test manufacturers follow these guidelines, I went through a list of tests, including Vitamin D, and most of these tests used >200 patients with multiple sites for their 501k. Thus, specifically, for the Vitamin D assay that they mentioned today I found an FDA approval for another test with 155 samples used to establish correlation with the reference method. In comparison to that, Theranos used 32 samples to validate their Vitamin B12 panel with R2 or 0.96 vs 0.99 for the FDA approved tests (both are good numbers)
- I then went ahead to check whether LH had a 501k for their Vitamin D test and while LH did not get a 501k clearance themselves, they are using FDA-cleared DiaSorin instrument (data for which I included below). See LH document and DiaSorin attached. This is contrary to Theranos' suggestions that LH does not get FDA approval for their tests

Let me digest this in a simple way:

1. The FDA could choose to send cease and desist order to Theranos any time because their tests are not FDA cleared. Historically, the FDA did not do this, so Theranos is correct that such an aggressive scenario is unlikely in the near future
2. CLIA does not guarantee the company that the FDA will not go after them, but there are examples of large CLIA labs operating w/o FDA approval: SQNM, MYGN, Ambry, etc
3. LH and DGX are using many (I am not sure if all) FDA approved tests and they are using FDA approved machines, while Theranos is not, hence Theranos position is weaker. That does not mean

the FDA will require a device approval right away, but probably within a some period of time

4. Based on the data I have seen so far I do not believe Theranos has adequate data for FDA approval for many of its tests today (they are clearly working on that). The key limitation is small sample size, which is easy to resolve, but for some tests the problem may be deeper (see below two examples where it is just unclear whether increasing the N would actually lead to tighter R2)

Conclusion: My take is that we do not have enough information to answer the question of whether the FDA will decide to regulate Theranos and when. We also do not know whether Theranos will have enough data on 99% of the testing volume to satisfy the FDA requirements. Since we cannot get access to their FDA communication on this topic and do not have a comprehensive access to data underlying the charts they presented, I think there is risk here. Thus, my conclusion is that we have to account for risk that the FDA will decide to regulate Theranos much earlier than they think, which may slow down or derail the launch. We also have to assume that there is a possibility that they will never be able to get certain tests approved by the FDA and they will remain venous blood draw tests (which they mentioned).

Action: I think there is a low, but unquantifiable, possibility that either the FDA will be more aggressive than Theranos thinks and/or that some of their tests will not clear the FDA review. It is not unusual to see risks like these in early stage investments, so this is not a problem per se, but is something we need to be mindful of and something we need to account for in our valuation of the company. Basically, I would assume 10-25% chance of a major delay or problems with getting all tests on the market through the FDA. Obviously, if everything goes well, this will be a huge success, so I don't want us to be too conservative here, but want to make sure we understand the risks involved since this may affect sizing decisions.

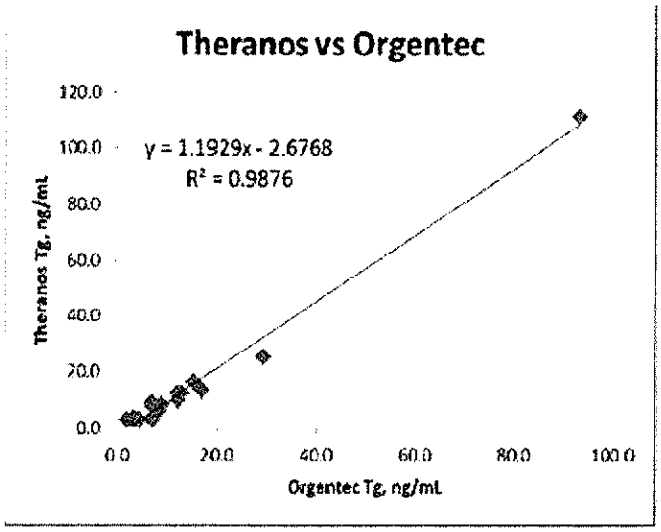
FDA-approved Vitamin D assay from LH/DiaSorin

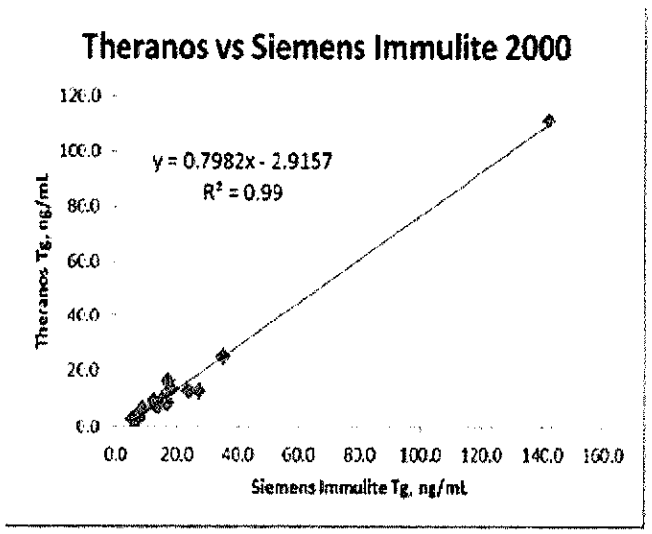
Assay Range (ng/mL)	Number of Samples
0-10	12
10-20	39
20-40	44
40-100	51
100-150	9

The study results showed correlation between the two methods as follows:
$y = 0.99x + 2.4$, $R = 0.97$

Theranos Tests with Insufficient N or possibility for non-linear trend

Thyroglobulin (antigen)





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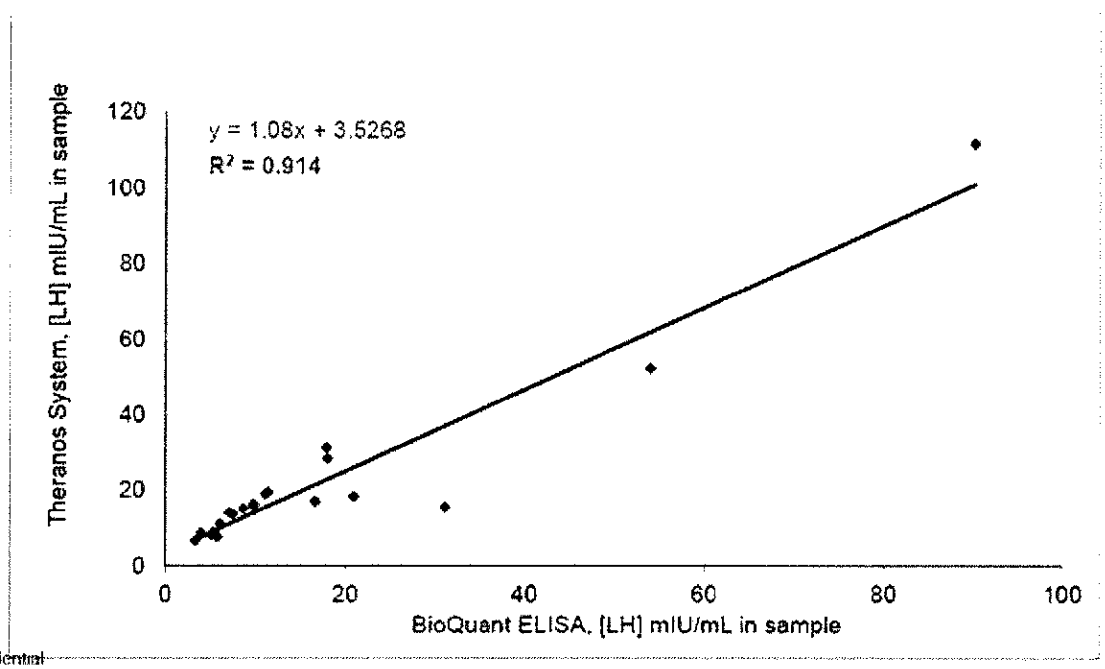
Luteinizing Hormone (LH)



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