To: Adam Rosendorff[arosendorff@theranos.com]; Mark Pandori[mpandori@theranos.com]; Daniel Young[dyoung@theranos.com]; Langly Gee[lgee@theranos.com]
Cc: Samartha Anekal[sanekal@theranos.com]; Elizabeth Holmes[eholmes@theranos.com]
From: Sunny Balwani
Sent: Tue 2/25/2014 7:34:59 PM
Importance: Normal
Subject: RE: proficiency testing for LDTs
Received: Tue 2/25/2014 7:35:02 PM

All.

I also want to reiterate this point. I am extremely irritated and frustrated by folks with no legal background taking legal positions and interpretations on these matters and junior CLIA and non-CLIA personnel challenging our CLIA SOPs. **This must stop**. If there are any legal interpretations questions, please send me or Elizabeth questions and we will forward to outside counsels. If needed, we have **EXTREMELY** strong and positive relationships with CMS and other regulatory bodies that we can reach out to if need be. However in this case, AAP is a well-established industry standard that we vetted and signed off on. If there are questions around this then call a meeting and the appropriate members including Daniel, myself and Elizabeth will participate. However, at this point, seems like this is not the case anymore based on Adam's email below.

These past few days, we have wasted so much time talking to people outside of CLIA who have come to us to share that our PT on Vitamin D on Edison has failed. These PT samples should have never run on Edisons to begin with. We should follow our current SOPs regarding PT. There is an SOP in place around PT that was signed off. This randomness makes us look like immatures and this needs to stop.

Adam/Mark. Once we have run the Vitamin D study inhouse that we discussed to generate internal data, we need to properly communicate to the CLIA team and others involved so people understand our assays are good and why we do PT the way we do and why we have a current AAP SOP. The 3 of us will work together on a explanation email that you can send out to CLIA.

It is critical that if ANYONE in CLIA or outside has any questions, they ask you (Mark and Adam) and they be referred to the SOPs. Please communicate this to the TS and GS and CLSes also. No Personal Opinions. Right now, every CLS or TS or GS considers themselves as regulatory expert and this culture must be nip in the bud. If there are things that you are unsure about, we will get clarify from counsel or regulatory bodies and then they become part of SOPs. We must run CLIA lab by SOPs only.

Thanks.

From: Elizabeth Holmes
Sent: Monday, February 24, 2014 11:07 PM
To: Adam Rosendorff
Cc: Sunny Balwani; Daniel Young; Langly Gee; Mark Pandori; Samartha Anekal
Subject: Re: proficiency testing for LDTs

We engaged top counsel on this some time ago. Sunny will debrief you tomorrow - it is critical that no one is guessing on matters like these. This is why we retained the best regulatory counsel in the country.
Elizabeth
On Feb 24, 2014, at 10:28 PM, "Adam Rosendorff" <arosendorff@theranos.com> wrote:

> All:
>
> Reading through the regulations more finely- if we did enroll in PT for Theranos methods, we would need to do an alternate assessment protocol (AAP) in any event, because the results would be ungraded (fewer than 10 participants). Ungraded events have to undergo an AAP according to CLIA regs.
>
> My question is what PT do we report to commercial PT providers (eg API, NYS, CAP), and hence to CMS?
> Adam
>
> ---
>
> **From:** Sunny Balwani
> **Sent:** Monday, February 24, 2014 10:20 PM

To: Daniel Young
Cc: Adam Rosendorff; Langly Gee; Mark Pandori; Samartha Anekal; Elizabeth Holmes
Subject: Re: proficiency testing for LDTs

Ccing clizabeth on this as we went thru these discussion over a year ago also.
On Feb 24, 2014, at 10:01 PM, "Daniel Young" <dyoung@theranos.com> wrote:

To add more details about my concerns related to using PT samples without extensive study with our LDTs and without a peer group, I wanted to highlight why the peer group methods were established for PT and other challenges related to matrix effects. These factors are why I had recommended last year the approach that we since captured in our CLIA SOPs last year (namely running PT on FDA-cleared predicates in our CLIA lab, and running internal Alternative Assessment Programs (AAP) (namely, using actual patient samples) to ensure that our LTDs (ELISA, cyto and GC) are accurate with respect to these predicates). (Note that CAP is developing some unmodified samples for PT, but this is still in development (something we should further engage CAP on).)

Here are some excerpts from a 2013 article that I think are highly relevant (I can provide references if people want them):

> "Peer grouping was determined to be necessary for many analytes because the modified constituents of PT samples can sometimes affect test results (matrix effects), and these inaccuracies cannot be corrected. The causes of matrix effects can include lyophilization (freeze-drying), addition of stabilizers and preservatives, and other manipulations that cause PT materials to behave differently than unmodified patient specimens.
>
> "In addition to differences in the matrix that can alter test results between test systems, inherent differences in the measured entity can differentially affect test results depending upon the test system used. For example, when the measured entity is an enzyme, in order to get sufficiently elevated concentrations of that enzyme in PT samples it may be necessary to add concentrated enzyme materials that behave differently than unmodified patient specimens. These materials can work well to assess relative accuracy within a peer group, but they may not be useful to assess absolute accuracy if they are not commutable with patient specimens. The term "commutability" means that PT specimens behave like patient specimens when tested on different test systems. Commutability of PT specimens cannot be assumed unless unaltered patient specimens are used in PT, and this has not been possible for large scale PT programs, except in a few cases. Miller et al showed the viability of using patient materials for PT."

There are additional points we can discuss about the "primary" test method, and treating PT samples in the same manner as patient specimens. But overall, the lack of a peer group for our LDTs and the nature of these PT samples make them inadequate on their own and make them problematic for the intended goal of assessing accuracy of our test method. The proposed internal AAP approach was devised to overcome these limitations of our LDTs. Looking forward to discussing these matters further.

Thanks,
Daniel

From: Sunny Balwani
Sent: Monday, February 24, 2014 8:39 PM
To: Adam Rosendorff; Daniel Young; Langly Gee
Cc: Mark Pandori; Samartha Anekal
Subject: RE: proficiency testing for LDTs

And our validation against immulite has been excellent in the past. It is these PT samples that are off.

This is a great place to start is what Mark, you and I discussed today – to run internal PTs here and compare with samples we draw here. lets run few studies on these 4-8 assays. I think our answers will become very clear that what Daniel is suggesting is accurate.

Thanks.

From: Adam Rosendorff

Sent: Monday, February 24, 2014 8:37 PM
To: Sunny Balwani; Daniel Young; Langly Gee
Cc: Mark Pandori; Samartha Anekal
Subject: RE: proficiency testing for LDTs

Yes

They were validated on the Imulite for the most part

Adam

Sent from my Windows Phone

From: Sunny Balwani
Sent: 2/24/2014 8:36 PM
To: Adam Rosendorff; Daniel Young; Langly Gee
Cc: Mark Pandori; Samartha Anekal
Subject: RE: proficiency testing for LDTs

I don't think the ELISA assays in question here are validated with siemens instruments.

From: Adam Rosendorff
Sent: Monday, February 24, 2014 8:34 PM
To: Daniel Young; Sunny Balwani; Langly Gee
Cc: Mark Pandori; Samartha Anekal
Subject: RE: proficiency testing for LDTs

Our Theranos assays are validated with the Siemens instruments, therefore PT should be comparable with regards to matrix...

Sent from my Windows Phone

From: Daniel Young
Sent: 2/24/2014 8:28 PM
To: Sunny Balwani; Langly Gee
Cc: Mark Pandori; Adam Rosendorff; Samartha Anekal
Subject: RE: proficiency testing for LDTs

We also need information about the PT samples, such as what matrix where they, did they have anticoagulant in them, etc. These PT samples are usually formulated with certain test systems in mind, which is one of the reasons I am not comfortable using them without a peer group. Otherwise, we have to do extensive study to understand our these PT samples may perform differently on our system vs one of the so called clunkers.

-Daniel

From: Sunny Balwani
Sent: 2/24/2014 8:25 PM
To: Langly Gee
Cc: Mark Pandori; Adam Rosendorff; Daniel Young; Samartha Anekal
Subject: RE: proficiency testing for LDTs

Where and who pulled the results for Edisons runs?

I would like to see the raw data for these and make sure the calibrations etc were properly applied.

From: Langly Gee
Sent: Monday, February 24, 2014 8:17 PM
To: Sunny Balwani

Subject: FW: proficiency testing for LDTs

Sunny:

See attached.

Langly

From: Langly Gee
Sent: Monday, February 24, 2014 6:22 PM
To: Adam Rosendorff; Daniel Young; Mark Pandori
Subject: RE: proficiency testing for LDTs

All:

Attached is data I have collected on our past API and NY proficiencies that compares predicate versus Edison on Vitamin D, TSH, FT4 and PSA. David Ramos will be providing me with more assay data to compare this week.

I should be receiving NY's and API's acceptable range within 2 weeks which I will share with all.

Also, I have attached NY proficiencies results for IgA, IgG and IgM which showed very good correlations.

Langly

From: Mark Pandori
Sent: Monday, February 24, 2014 5:20 PM
To: Langly Gee
Subject: FW: proficiency testing for LDTs

Langly,

Please share with Daniel Young the comparison of predicate and Edison for the PT specimens we tested.

Thanks.

Mark Pandori

From: Daniel Young
Sent: Monday, February 24, 2014 5:19 PM
To: Mark Pandori
Subject: RE: proficiency testing for LDTs

Mark, can you also send me the Vit D PT data that you were referring to? Thanks.

From: Daniel Young
Sent: Monday, February 24, 2014 1:42 PM
To: Mark Pandori
Subject: FW: proficiency testing for LDTs

FYI: as background.

From: Adam Rosendorff
Sent: Tuesday, November 26, 2013 5:31 PM
To: Daniel Young
Cc: Elizabeth Holmes; Sunny Balwani
Subject: RE: proficiency testing for LDTs

Daniel

Thanks-

I'll write up the SOP and incorporate what we have discussed.
Adam

From: Daniel Young
Sent: Tuesday, November 26, 2013 5:03 PM
To: Adam Rosendorff
Cc: Elizabeth Holmes; Sunny Balwani
Subject: proficiency testing for LDTs

Here are my suggestions that I discussed with Adam. I'm providing some extra background info for reference.

Background:
There are 91 tests that are CLIA regulated and require proficiency testing (PT). For all other 'non-regulated' analytes, CLIA requires that labs have a quality assurance plan that establishes the accuracy and reliability of the testing at least twice per year. For example, the CAP Surveys and EXCEL proficiency testing programs offer products to assist labs in fulfilling this requirement. States and other accrediting agencies may also mandate additional requirements.

For our LDTs, all of which are CLIA regulated at the moment, we need SOPs for PT. However, there are several factors that prevent us from enrolling in the traditional PT programs. Most significantly is that performance in PT surveys is based on an evaluation against a peer group. A peer group is composed of different labs all running the same method/device. The goals of such PT is to compare the performance of an individual laboratory to their peer group and sometimes to target values established by reference methods or reference laboratories. The goals of PT differ from regular QC procedures which each lab also performs each day/shift that tests are performed. Namely, QC procedures ensure that performance within a given lab does not change over time and essentially assesses test precision. In contrast, PT assesses system accuracy.

Proposal:
Where traditional PT options are not available, we must initiate Alternative Assessment Procedures (AAP). Namely, for non-CMS-regulated tests, for those tests which lack FDA clearance or for tests that lack a suitable peer group, commercial or external PT programs are not available and AAP are used to help assess the quality/accuracy of laboratory test system performance. In essence, AAP are laboratory procedures by which Theranos defines an internal procedure to ensure quality/accuracy of our devices/methods. There are several methods that one can implemented for AAP, such as:

A. split sample analysis with reference or other laboratories;
B. split samples with an established in-house methods;
C. assayed material;
D. regional pools;
E. clinical validation by chart review; or
F. other suitable and documented means.

It is the responsibility of our CLIA lab to define such alternative assessment procedures, as applicable, in accordance with good clinical, scientific laboratory practice, and our business objectives.

I've recommended that we pursue options B, namely splitting samples where we take a venous sample and run it on the predicate and our LDT. The advantage of this approach is that we can use the predicate method for which PT is available to establish comparability for the Theranos LDT. It keeps the entire AAP process in-house for our LDTs.

Details to include in the SOP for AAP for each LDT:

- Frequency of AAP (2x per year; suggest scheduling it 1 month after predicate PT occurs)
- Predicate method for each LDT
- Sample type (suggest venous samples are used by default)
- Sample source (suggest in-house draws)
- Sample number: 10 different samples per AAP event per LDT (sample can be shared across multiple LDTs)

- Analytic range per LDT: if random samples do not cover the desired range based on an annual review, spike in or other specially collected samples may be used to supplement the data
- Acceptance criteria:
    - Each sample will be tested 3 times on the predicate method and the mean value considered the "truth"
    - Out of 10 samples tested, at least 8 LDT results must fall within the CLIA total error allowance compared to the predicate mean result
    - If <8 samples fall within the range, corrective actions need to be taken (follow typical SOP for PT)
- If a predicate method is not available, samples should be split with a reference lab

Please let me know if you have any questions.

-Daniel

Daniel Young, PhD
Vice President, Theranos Systems
Theranos, Inc
1601 S. California Ave
Palo Alto, CA 94304
650-470-6119 (office)
650-804-8185 (mobile)