To: Elizabeth Holmes[eholmes@theranos.com]
From: Sunny Balwani
Sent: Mon 11/11/2013 1:28:30 AM
Importance: Normal
Subject: FW: Compliance with Federal Law CFR 493.1253
Received: Mon 11/11/2013 1:28:00 AM

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 5:28 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

I will do.

Thanks,

Adam

From: Sunny Balwani
Sent: Sunday, November 10, 2013 5:26 PM
To: Adam Rosendorff
Subject: RE: Compliance with Federal Law CFR 493.1253

I spoke with the teams today and they are all going to put long hours and do whatever it takes to get this done tomorrow. We already have all the data, they will complete the reports.

Please spnd time on this and highlight if there is anything missing. We don't want to go thru this again.

Thanks.

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 5:25 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

Sunny

No they are required. Very important in fact. For instance, if a person has a triglyceride level of 150 mg/dL (very easy after a meal), then it is essential to prove this doesn't interfere with the modified assay- otherwise it's a fasting assay which we don't want.

Adam

From: Sunny Balwani
Sent: Sunday, November 10, 2013 4:34 PM
To: Adam Rosendorff
Subject: RE: Compliance with Federal Law CFR 493.1253

If the specificity studies are not required (and hence were to be done as revisions) then that's what we should do and not have them hold back what we are doing.

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 3:13 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

Sunny

My apologies for the late feedback regarding our readiness. It sometime takes me a little time to see the whole picture. The specificity studies were added to some validation documents after my signature, whereas they should have been done as revisions. It was not highest on our list of priorities as we were expediting to get these studies done.

I do feel that it was very difficult to get answers from Daniel's team- while I respect Daniel's intelligence and inventiveness, he is not as responsive as I would like to my queries, and we were only able to get answers on the ISE protocols from Rose on Friday, in a telegraphic SOP- this despite a meeting at least twice with detailed outlines regarding SOP structure, etc.. to outline CLIA requirements for SOPs. I still have not seen any ISE validation work, despite numerous requests.

Thanks for listening.

Adam

From: Sunny Balwani
Sent: Sunday, November 10, 2013 3:04 PM
To: Adam Rosendorff
Subject: RE: Compliance with Federal Law CFR 493.1253

Adam.

As you know, we take these issues with seriousness. Why didn't you raise these before to me when I was asking for any issues for months? It was only a month+ ago when you signed off on these assays. Same thing around ULOQ. This is what we meet every week for and I have proactively seeking out any concerns for every member throughout the company.

I will circle back with other team members and get their responses.

Thanks.

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 2:51 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

Hi Sunny

Thanks for your comments.

In terms of specificity, the following have not been done:

ALT

Albumin

Alk Phos

Bicarb

BUN

Calcium

Chloride

CK

Potassium

Sodium

The specificity for the ISE analytes is also going to be different depending on the dilution protocol.

The following have been done:

Creat

Direct Bili

Glucose

HDL

LDL

Amylase

Trig

TP

Tchol

TBil

EtoH

Lipas

GGT

Lithium

iPhos

Mg

Iron

Salicylates

Uric Acid

For the other issues- please see my comments below…

Regards,

Adam

From: Sunny Balwani
Sent: Sunday, November 10, 2013 2:42 PM
To: Adam Rosendorff
Subject: RE: Compliance with Federal Law CFR 493.1253

Please my comments below. I consulted with other team leads in the office today on this so this is authoritative:

(v) While we have established the low end of the reportable range (LLOQ), we have not established the upper end (ULOQ). Therefore as of today, we are in violation of this standard.

As noted in the assay validation reports, the analytic measurement range of the assays was addressed in two ways:

1) The limit of blank, limit of detection, and limit of quantification were determined for each assay, establishing the lower limit of the range.

2) For linearity (and the upper end of the range), the validation reports refer to the Siemens product information. This was determined to be a conservative approach given that in some of the modified protocols, the samples are being diluted further compared to the baseline Siemens protocol. ULOQ may have changed if the concentration of R1 and R2 reagents has changed in the assay, or if the total reaction volume has changed in the assay. Therefore we cannot assume that the predicate ULOQ would apply.

- (viii) 3 we have not established control procedures for ISEs (diluted protocols) or Edisons.

For ISE, the assay developers have been running GC procedures on a regular basis (at least every 8 hours). Everyone is following this process religiously. If this is not in the SOPs then I will make sure this gets there tomorrow. Regarding Edison, the QC procedures were worked out and communicated to the CLIA team- I am still working with the ELISA team to establish the acceptable QC for the Edisons….

.The next step was to document these procedures in SOPs in CLIA approved and released protocols, train the CLIA staff, and have them implement these procedures independently moving forwards. This is what we had spoken to Kerry about 2 weeks if you recall. I will followup with the team to make sure this is in place tomorrow also.

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 2:10 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

I am going through them now- I know that Paul has done some Specificity studies, but so far there is no info for ALT, Albumin, Alk Phos, AST, bicarb, BUN, Calcium, Chloride- I am going through the rest of the list.

From: Sunny Balwani
Sent: Sunday, November 10, 2013 2:04 PM
To: Adam Rosendorff
Cc: Daniel Young; Elizabeth Holmes
Subject: RE: Compliance with Federal Law CFR 493.1253

What GC assays?

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 2:02 PM
To: Sunny Balwani
Subject: RE: Compliance with Federal Law CFR 493.1253

Sunny

Sorry I also forgot to mention, that specificity studies are missing for a number of GC analytes.

Adam

From: Adam Rosendorff
Sent: Sunday, November 10, 2013 1:47 PM
To: Sunny Balwani
Subject: Compliance with Federal Law CFR 493.1253

Hi Sunny

Please see highlighted below, areas in which we are currently not compliant in terms of CLIA law.

CLIA addresses test performance in standard 493.1253: Establishment and verification of performance specifications:

§ 493.1253

Standard: Establishment and verification of performance specifications.

(a) Applicability. Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.

(b) (1) Verification of performance specifications. Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results:

(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:

(A) Accuracy.

(B) Precision.

(C) Reportable range of test results for the test system.

(ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population.

(2) Establishment of performance specifications. Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:

(i) Accuracy.

(ii) Precision.

(iii) Analytical sensitivity.

(iv) Analytical specificity to include interfering substances.

(v) Reportable range of test results for the test system.

(vi) Reference intervals (normal values).

(vii) Any other performance characteristic required for test performance.

(3) Determination of calibration and control procedures. The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section.

(c) Documentation. The laboratory must document all activities specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

My conclusions and interpretations of the above:

- (v) While we have established the low end of the reportable range (LLOQ), we have not established the upper end (ULOQ). Therefore as of today, we are in violation of this standard.

- (viii) 3 we have not established control procedures for ISEs (diluted protocols) or Edisons.

Thanks,

Adam

Adam Rosendorff, MD, FASCP

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