CORE
Center for Organ Recovery & Education
204 Sigma Drive
RIDC Park
Pittsburgh, PA 15238
1-800-DONORS-7
(1-800-366-6777)

October 1, 2001

Ruth Solomon
Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Subject: Genetic Systems Hepatitis B Surface Antigen Assay on Cadaver Blood Samples

Dear Ms. Solomon:

Enclosed is a copy of an October 2, 2001 letter sent to Linda Miller, (Technical Support Rep, Bio-Rad Laboratories distributor of Genetics Systems Hepatitis B Surface Antigen Assay). In addition to the letter data tape results were also enclosed for the two assays in question.

Two of the cadaver samples in question tested positive on initial screen and tested negative on duplicate repeat testing. This phenomenon occurs with frequency and Bio-Rad has not been able to explain why the problem is occurring. Such duplication of testing is causing an increased financial burden to our organization.

Recently, BioRad made several procedural suggestions in an attempt to solve the problem. In our most recent conference call several points were discussed regarding the Hepatitis B Surface Antigen assay and are listed as follows:

1. Peel off plate cover from the direction of row 12 to row 1 to avoid any potential for aerosol, which I stated the techs always pull in that direction because that is where the pull-tab is located on the cover.
2. When using an 8-channel pipette, dispense reagents in the direction from row 12 to row 1 to avoid potential for reagent carry-over or cross-contamination, which I implemented that day.
3. When washing the plate using the automated washer it was suggested the tech always observe the wash procedure and to listen for the aspiration/dispensing sound that should occur and to watch the solution being dispensed from the wash probes to ensure even distribution of all wells. I ensured all my techs were paying special attention to the automated washer with every wash step.
4. I suggested we try to position our patient/donor samples at the bottom of the second row across from the negative controls instead of across from the positive control wells since you stated our initial positives were always in well one or two of the second row. You will see that on the enclosed runs the position of the sample didn't eliminate the problem nor did the suggestions stated in items 1-3.

OOD-1393 C7

It doesn't seem to matter what is implemented or what tech in the lab performs the assays we continue to experience the same problem of positive screening results followed by negative repeats.

This is the eighth letter sent to BioRad (Genetics Systems Assays) and the seventh letter forwarded to the FDA regarding the same or similar issues when testing cadaveric samples.

I ask that you please review the continued problems that are being brought to the company's attention and continue to share our concern. Again, we want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to either false positive results or delays in testing.

Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory

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(1-800-366-6777)

October 1, 2001

Linda Miller
Bio-Rad Laboratories
6565 185th Avenue NE
Redmond, Washington 98502
425-881-8300

Dear Linda,

Enclosed are two data result reports for Hepatitis B Surface Antigen Assays that show positive absorbencies initially then repeated negative in duplicate.

In our most recent conference call several points were discussed regarding the Hepatitis B Surface Antigen assay. Your suggestions were as follows:

1. Peel off plate cover from the direction of row 12 to row 1 to avoid any potential for aerosol, which I stated the techs always pull in that direction because that is where the pull-tab is located on the cover.
2. When using an 8-channel pipette you said to pipette reagents in the direction from row 12 to row 1 to avoid any possibility of carry-over, which I implemented that day.
3. When washing the plate you suggested the tech always observe the wash procedure and to listen for the aspiration/dispensing sound that should occur and to watch the solution being dispensed from the wash probes to ensure even distribution of all wells. I implemented that check that day.
4. I suggested we try to position our patient/donor samples at the bottom of the second row across from the negative controls instead of across from the positive control wells since you stated our initial positives were always in well one or two of the second row. You will see that on the enclosed runs the position of the sample didn't eliminate the problem nor did the suggestions stated in items 1-3.

It doesn't seem to matter what we implement or what tech in the lab performs the assays we continue to experience the same problem of positive screening results followed by negative repeats.

I am still concerned with the number of initial positive results my laboratory has obtained in using the Genetics Systems Hepatitis B Surface Antigen assay.

I will continue to monitor the problem and make you aware of any further issues.

Sincerely,

Karen A Brown, B.A.,MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

SDP Microplate Assay Testing System V4.82 AVD V4.83 PRD V4.81 - Complete Results

Run # 1 Assay: User(HBsAg) Plate ID: 01U2-29SEP-1912 Master lot number: 131UM1 Exp. date: 26-MAR-02

Cutoff calculation: $NC\bar{X}$ + 0.070 = 0.170 $NC\bar{X}$ = 0.100 $PC\bar{X}$ = 1.676 $PC1\bar{X}$ = 0.429
Cutoff relationship: (Reactive is greater than or equal to cutoff) Validation protocol: GSC HBsAg EIA 2.0, Ver 1.00

Reader type: (SDP PR2100 V1.00) Dual wavelength reading: (Sample filter: 450 nm, Reference filter: 630 nm)
Load direction: A->H Loading method: MANUAL Curve fit method: NONE

Function	Tech Name	Start Time	End Time	Elapsed Time
enter info	JL			
load plate	JL			
inc 1	JL	00:07	01:08	1:00
inc 2	JL	01:14	02:15	1:01
inc 3		02:21	02:52	0:31

(Assay date & time: 30-SEP-01 02:53)
(Read date & time: 30-SEP-01 02:53)
(Print date & time: 30-SEP-01 02:53)
(Total assay time: 2:45)

Key: - .. Non-reactive	R+ .. Reactive	-- .. 2 of 3 tests Non-Reactive	* .. Value Over Range
G- .. Non-reactive Gray Zone	R2- .. Retest Non-reactive	+++ .. (2 or 3) of 3 tests Reactive	(.. Value Under Range
G+ .. Reactive Gray Zone	R2+ .. Retest Reactive	??? .. Error	INV .. Assay Invalid

Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result
A1	POS CTRL	1.720	R+ ok	G1	NEG CTRL	0.100	- ok	D2	xxxx	0.004	-
B1	POS CTRL	1.631	R+ ok	H1	01092803	0.027	- [redacted]	E2	xxxxx	0.004	-
C1	POS CTRL1	0.437	R+ ok	A2	x	0.004	-	F2	01092804	0.368	R+ [redacted]
D1	POS CTRL1	0.421	R+ ok	B2	xx	0.003	-	G2	01092805	0.240	R+ [redacted]
E1	NEG CTRL	0.103	- High	C2	xxx	0.003	-	H2	01092901	0.064	- [redacted]
F1	NEG CTRL	0.100	- ok								

Testing center: CORE
204 Sigma Drive
Pittsburgh, PA 15238

END OF REPORT

SDP Microplate Assay Testing System V4.82 AVD V4.83 PRD V4.81 - Complete Results

9-30-01
TC

Run # 2 (Assay: User(HBsAg)) Plate ID: 02U2-30SEP-0253 Master lot number: 131UM1 Exp. date: 26-MAR-02

Cutoff calculation: $\overline{NCX}$ + 0.070 = 0.107 $\overline{NCX}$ = 0.037 $\overline{PCX}$ = 1.626 $\overline{PC1X}$ = 0.386
Cutoff relationship: (Reactive is greater than or equal to cutoff) Validation protocol: GSC HBsAg EIA 2.0, Ver 1.00

Reader type: (SDP PR2100 V1.00) Dual wavelength reading: (Sample filter: 450 nm, Reference filter: 630 nm)
Load direction: A->H Loading method: MANUAL Curve fit method: NONE

Function	Tech Name	Start Time	End Time	Elapsed Time
enter info	JL			
load plate	JL			
inc 1	JL	03:28	04:28	1:00
inc 2	JL	04:34	05:34	1:00
inc 3		05:40	06:10	0:30

(Assay date & time: 30-SEP-01 06:11)
(Read date & time: 30-SEP-01 06:11)
(Print date & time: 30-SEP-01 06:11)
(Total assay time: 2:43)

Key: - .. Non-reactive	R+ .. Reactive	— .. 2 of 3 tests Non-Reactive	* .. Value Over Range
G- .. Non-reactive Gray Zone	R2- .. Retest Non-reactive	+++ .. (2 or 3) of 3 tests Reactive	(.. Value Under Range
G+ .. Reactive Gray Zone	R2+ .. Retest Reactive	??? .. Error	INV .. Assay Invalid

Well	Sample ID	O.D.	Result
A1	POS CTRL	1.686	R+ ok
B1	POS CTRL	1.565	R+ ok
C1	POS CTRL1	0.392	R+ ok
D1	POS CTRL1	0.379	R+ ok
E1	NEG CTRL	0.031	- ok
F1	NEG CTRL	0.051	- ok
G1	NEG CTRL	0.028	- ok
H1	01092804	0.016	- [redacted]
A2	x	0.004	-
B2	xx	0.004	-
C2	xxx	0.003	-
D2	xxxx	0.005	-
E2	xxxxx	0.004	-
F2	01092804	0.063	- [redacted]
G2	01092805	0.026	- [redacted]
H2	01092805	0.035	- [redacted]

Testing center: CORE
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Pittsburgh,PA 15238

END OF REPORT

SDP Microplate Assay Testing System V4.82 AVD V4.83 PRD V4.81 - Complete Results

Run # 1 Assay: User(HBsAg) Plate ID: 01U2-01OCT-0040 Master lot number: 131UM1 Exp. date: 26-MAR-02

Cutoff calculation: $\overline{NCX}$ + 0.070 = 0.113 $\overline{NCX}$ = 0.043 $\overline{PCX}$ = 1.710 $\overline{PC1X}$ = 0.404
Cutoff relationship: (Reactive is greater than or equal to cutoff) Validation protocol: GSC HBsAg EIA 2.0, Ver 1.00

Reader type: (SDP PR2100 V1.00) Dual wavelength reading: (Sample filter: 450 nm, Reference filter: 630 nm)
Load direction: A->H Loading method: MANUAL Curve fit method: NONE

Function	Tech Name	Start Time	End Time	Elapsed Time
enter info	MH			
load plate	JL			
inc 1	MH	00:48	01:49	1:01
inc 2	MH	01:56	02:57	1:01
inc 3		03:03	03:33	0:31

(Assay date & time: 01-OCT-01 03:34)
(Read date & time: 01-OCT-01 03:34)
(Print date & time: 01-OCT-01 03:34)
(Total assay time: 2:46)

Key: - .. Non-reactive	R+ .. Reactive	-- .. 2 of 3 tests Non-Reactive	* .. Value Over Range
G- .. Non-reactive Gray Zone	R2- .. Retest Non-reactive	+++ .. (2 or 3) of 3 tests Reactive	(.. Value Under Range
G+ .. Reactive Gray Zone	R2+ .. Retest Reactive	??? .. Error	INV .. Assay Invalid

Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result
A1	POS CTRL	1.739	R+ ok	D1	POS CTRL1	0.399	R+ ok	G1	NEG CTRL	0.041	- ok
B1	POS CTRL	1.680	R+ ok	E1	NEG CTRL	0.044	- ok	H1	01092903	0.113	R+ [redacted]
C1	POS CTRL1	0.409	R+ ok	F1	NEG CTRL	0.045	- ok				

Testing center: CORE
204 Sigma Drive
Pittsburgh,PA 15238

END OF REPORT

)P Microplate Assay Testing System V4.82 AVD V4.83 PRD V4.81 - Complete Results

un # 4 Assay: User(HBsAg) Plate ID: 04U2-01OCT-0612 Master lot number: 131UM1 Exp. date: 26-MAR-02

utoff calculation: $\overline{NCX}$ + 0.070 = 0.124 $\overline{NCX}$ = 0.054 $\overline{PCX}$ = 1.548 $\overline{PC1X}$ = 0.407
utoff relationship: (Reactive is greater than or equal to cutoff) Validation protocol: GSC HBsAg EIA 2.0, Ver 1.00

Reader type: (SDP PR2100 V1.00) Dual wavelength reading: (Sample filter: 450 nm, Reference filter: 630 nm)
Load direction: A->H Loading method: MANUAL Curve fit method: NONE

Function	Tech Name	Start Time	End Time	Elapsed Time
enter info	MH			
load plate	MH			
inc 1	MH	**:**	**:**	OVERRIDE
inc 2	MH	**:**	**:**	OVERRIDE
inc 3	MH	**:**	**:**	OVERRIDE

(Assay date & time: 01-OCT-01 06:13)
(Read date & time: 01-OCT-01 06:13)
(Print date & time: 01-OCT-01 06:13)
(Total assay time: OVERRIDE)

Key: - .. Non-reactive
G- .. Non-reactive Gray Zone
G+ .. Reactive Gray Zone
R+ .. Reactive
R2- .. Retest Non-reactive
R2+ .. Retest Reactive
— .. 2 of 3 tests Non-Reactive
+++ .. (2 or 3) of 3 tests Reactive
??? .. Error
* .. Value Over Range
(.. Value Under Range
INV .. Assay Invalid

Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result	Well	Sample ID	O.D.	Result
A1	POS CTRL	1.507	R+ ok	G1	NEG CTRL	0.051	- ok	D2	x	0.008	-
B1	POS CTRL	1.589	R+ ok	H1	01092903	0.035	- Kusturas	E2	x	0.006	-
C1	POS CTRL1	0.407	R+ ok	A2	x	0.005	-	F2	x	0.006	-
D1	POS CTRL1	0.407	R+ ok	B2	x	0.011	-	G2	x	0.005	-
E1	NEG CTRL	0.055	- ok	C2	x	0.007	-	H2	01092903	0.058	- [redacted]
F1	NEG CTRL	0.055	- ok								

Testing center: CORE
204 Sigma Drive
Pittsburgh, PA 15238

END OF REPORT

March 8, 2001

Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Dear Sir/Madam:

Enclosed is a copy of the letter sent to Dr. Ruth Solomon on August 1, 2000 expressing my concern with using the Genetics Systems assays for Hepatitis B Surface Antigen and HIV I-II. As you are well aware, on January 31, 2001 the FDA mandated the use of the cadaveric blood approved Genetics Systems kits on all cadaveric blood samples collected on tissue and/or cornea donors.

Since the January 31, 2001 implementation date our laboratory experienced numerous problems with the assays, in particular, the Hepatitis B Surface Antigen assay. Enclosed are copies of letters sent to BioRad (distributor of Genetics Systems assays) technical support staff. In addition, copies of assay data tapes were submitted for their review. To date there is no viable resolution to the problems brought forth by CORE to their technical support staff other than the suggestions outlined in the copy of the enclosed letters to BioRad.

I ask that you please review the problems that are being brought to the company's attention and share our concern. We want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to false positive results and delays in testing. I would only ask that the FDA prioritize approval of any other companies seeking the cadaveric sample claim on their test kits.

Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory

March 12, 2001

Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Dear Sir/Madam:

Enclosed is a copy of a March 12, 2001 letter and data tape results for a positive Hepatitis B Surface Antigen Assay sent to Linda Miller, (Technical Support Rep, Bio-Rad Laboratories) for review. Letters and data tapes were also sent to Bio-Rad on March 1 and March 8, 2001 regarding numerous problem Hepatitis B Surface Antigen and/or HIV I-II assays when running cadaver blood specimens. All of the previous letters and data tape examples were forwarded to the FDA for review. It is our concern that when hemolyzed blood samples are tested the assay picks many of these up as false positives either on initial screen and/or on duplicate repeat testing.

I ask that you please review the continued problems that are being brought to the company's attention and continue to share our concern. We want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to false positive results and delays in testing. I would only ask that the FDA prioritize approval of any other companies seeking the cadaveric sample claim on their test kits.

Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory

March 13, 2001

Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Dear Sir/Madam:

Enclosed is a copy of a March 13, 2001 letter and data tape results for a positive HIV I- Assay sent to Linda Miller, (Technical Support Rep, Bio-Rad Laboratories) for review. Letters and data tapes were also sent to Bio-Rad on March 1, March 8, and March 12 respectively regarding numerous problems with Hepatitis B Surface Antigen and/or HIV I-II assays when running cadaver blood specimens. All of the previous letters and data tape examples were also forwarded to the FDA for review.

Bio-Rad has been in contact with me regarding these issues and has requested the samples in question to be shipped to their technical branch for investigation. Bio-Rad is also requesting additional information on these and other cadaver samples such as, sample quality, date/time of sample collection, date/time of assay performed and date/time of donor death. I have cooperated with Bio-Rad in providing this information and samples in order to help resolve the problem.

I ask that you please review the continued problems that are being brought to the company's attention and continue to share our concern. We want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to false positive results and delays in testing. I would only ask that the FDA prioritize approval of any other companies seeking the cadaveric sample claim on their test kits.

Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory

March 30, 2001

Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Subject: Genetic Systems Hepatitis B Surface Antigen Assay on Cadaver Blood Samples

Dear Sir/Madam:

Enclosed is a copy of a March 30, 2001 letter and data tape results for two Hepatitis B surface antigen assays sent to Linda Miller, (Technical Support Rep, Bio-Rad Laboratories) for her review.

One of the samples in question, a cadaver specimen, tested positive on initial screen however, tests negative on duplicate repeat testing.

The other sample, a pre-mortem specimen, demonstrates an absorbance value very close to the positive cutoff value even though the screen is interpretated as negative. Samples testing so close to the positive cutoff concern me.

All of the previous correspondance and data tape examples were submitted to the FDA for review. With the exception of the two samples mentioned above, Cindy Jenniman from Bio-Rad has been in contact with me regarding these issues and has requested samples and additional information for her to review.

I ask that you please review the continued problems that are being brought to the company's attention and continue to share our concern. Again, we want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to false positive results and delays in testing. I would only ask that the FDA prioritize approval of any other companies seeking the cadaveric sample claim on their test kits.

Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory

May 23, 2001

Center for Biologics Evaluation & Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Final Rule 21 CFR 1270.21 (d)

Subject: Genetic Systems Hepatitis B Surface Antigen Assay on Cadaver Blood Samples

Dear Sir/Madam:

Enclosed is a copy of a May 23, 2001 letter and data tape results for two Hepatitis B surface antigen assays sent to Linda Miller, (Technical Support Rep, Bio-Rad Laboratories).

Two of the cadaver samples in question tested positive on initial screen and tested negative on duplicate repeat testing. This phenomenon occurs with frequency and Bio-Rad has not been able to explain why we are experiencing the problem. User technique has been ruled out as a potential cause of the problem. It has been suggested by Bio-Rad technical support staff to delay testing to allow the serum to age, thus avoiding what they are calling a "fresh serum effect". I cannot delay testing due to placement constraints of the corneal tissue. There is nothing stated in the manufacturers package insert regarding a 'fresh serum effect".

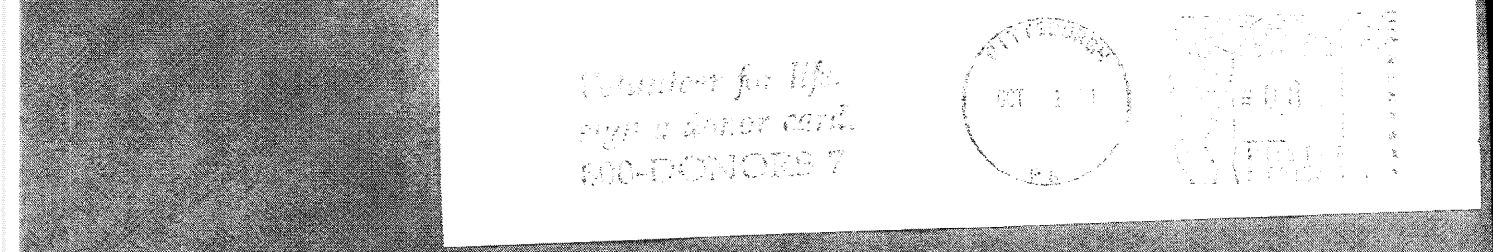
I ask that you please review the continued problems that are being brought to the company's attention and continue to share our concern. Again, we want to provide the safest possible tissue and corneas to the recipients of these gifts; however, our deepest concern is the loss of these tissues due to either false positive results or delays in testing.

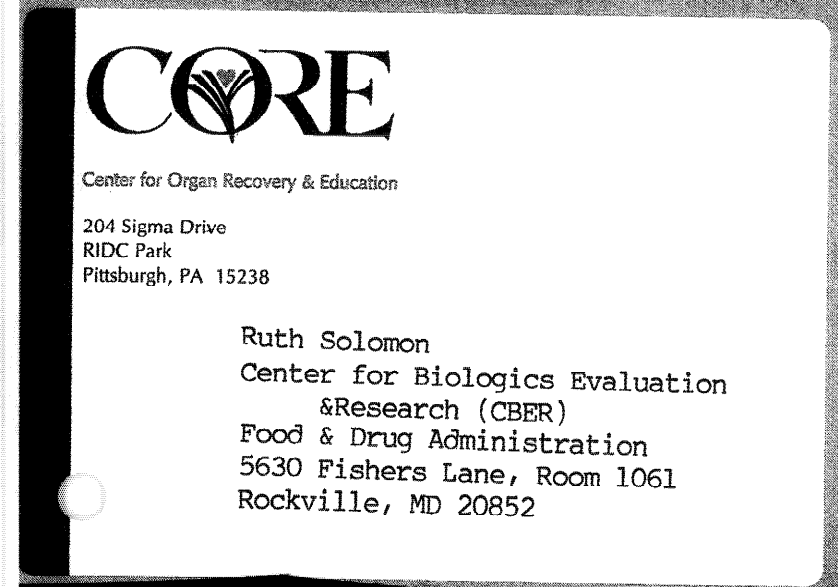
Thank you again for allowing me to share my concerns. I look forward to hearing from you.

Sincerely,

Karen A Brown, BA, MT(ASCP)
Director of Regulatory Affairs & Laboratory Services

Cc: Anthony Gialamas, MD
Medical Director, Laboratory





CORE

Center for Organ Recovery & Education

204 Sigma Drive
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Pittsburgh, PA 15238

Ruth Solomon
Center for Biologics Evaluation
&Research (CBER)
Food & Drug Administration
5630 Fishers Lane, Room 1061
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