Urgent Field Safety Notice

AIMC 20-05.A-2.OUS

August 2020

ADVIA Centaur® XP
ADVIA Centaur® XPT
ADVIA Centaur® CP

ADVIA Centaur HER-2/*neu* (H2n) Positive Bias versus Internal Standardization

Our records indicate that your facility may have received the following product:

Table 1. ADVIA Centaur® Affected Product(s)

Product Name	Siemens Material Number (SMN)	Kit Lot Number	1st Distribution Date (YYYY-MM-DD)	Expiration Date (YYYY-MM-DD)
ADVIA Centaur HER-2/*neu* Assay 50 Test Kit	10308994	43157138 81653138 99728138 24043138 32477138	2019-10-28 2020-01-22 2020-03-09 2020-04-30 2020-06-26	2021-01-30
ADVIA Centaur HER-2/*neu* Calibrator (2 Pack)	10308993	64661A48 81211A48 91743A48	2019-12-07 2020-01-31 2020-03-02	2020-11-12
		22142A49	2020-05-08	2020-12-11

Reason for Urgent Field Safety Notice

The purpose of this communication is to inform you of an issue with the product indicated in Table 1 above and provide instructions on actions that your laboratory must take.

Siemens Healthcare Diagnostics has confirmed an average positive bias of 50.5% (ADVIA Centaur XP/XPT) and 22.2% (ADVIA Centaur CP) with current in date lots listed in Table 1 as compared to Siemens internal standardization. The bias is proportional across the assay range. In addition, Siemens confirmed that Upper Limit of Normal (ULN) as claimed in the Instructions for Use (IFU) was no longer achieved and ADVIA Centaur CP results are recovering lower than results generated on the ADVIA Centaur XP/XPT. See Additional Information section below for details of the observed bias.

Alignment to the internal standardization and alignment between the ADVIA Centaur CP and the ADVIA Centaur XP/XPT has been restored with ADVIA Centaur H2n reagent kit lots ending in 140 and higher, when calibrating with ADVIA Centaur H2n calibrator lots ending in 54 and higher (available in August 2020). Moving forward, this alignment will be maintained through enhancements to the control system.

Customers will observe a negative shift when transitioning from current to new ADVIA Centaur H2n reagent and calibrator lots. See Additional Information section below for details on the expected shift.

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The ADVIA Centaur H2n assay and associated materials are not “lot-locked”. However, the specified mandatory lot combinations must be used as noted in Table 2 below.

Table 2. Mandatory Lot Combinations

Component	Current Lot Combinations	New Lot Combinations
ADVIA Centaur H2n Assay 50 Test Kit (lots ending in)	138	140 and above
ADVIA Centaur H2n Calibrator (2 pack) (lots ending in)	48 and 49	54 and above
ADVIA Centaur H2n Quality Control (QC) lots	4226001/4226002, 4230601/4230602 and 4202311/4202312	4202011/4202012 and future lots
ADVIA Centaur H2n Master Curve Material (MCM) lots	62271 and 81621	46524 and future lots

Siemens is currently investigating the root cause of this issue.

Risk to Health

The issue described causes a positive proportional bias across the entire analytical measuring range. Erroneously elevated H2n results may lead to additional investigations that are clinically well tolerated. The slow rate of increase in bias across different reagent lots does not impact treatment decisions or the ability to monitor treatment efficacy. The test results are not used in isolation, rather in conjunction with the overall clinical picture and history and other results such as imaging. Siemens is not recommending a review of previously generated patient results.

Actions to be Taken by the Customer

- Please review this letter with your Medical Director.
- You may continue use of ADVIA Centaur H2n lots in Table 1 until you receive replacement product in your laboratory. Refer to Table 3, Figure 1, and Figure 2 for ADVIA Centaur H2n bias information.
- If you are currently using ADVIA Centaur H2n Assay kit lots and calibrator lots in Table 1, review your inventory of these products, as well as the associated ADVIA Centaur H2n QC and MCM, and order replacement products by completing the Field Correction Effectiveness Check Form attached to this letter.
- Upon acceptance of the replacement lots in Table 2 New Lot Combinations column, discontinue use of and discard the products listed in Table 2 Current Lot Combinations column. Refer to Figures 3 through 8 for expected results with replacement lots.
- Complete and return the Field Correction Effectiveness Check Form attached to this letter within 30 days.

Please retain this letter with your laboratory records and forward this letter to those who may have received this product.

We apologize for the inconvenience this situation may cause. If you have any questions, please contact your Siemens Healthineers Customer Care Center or your local Siemens Healthineers technical support representative.

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Additional Information

Note: Data and plots below that reference ADVIA Centaur H2n calibrator lot ending in 49 are representative of performance seen on ADVIA Centaur H2n calibrator lots ending in 48 and 49.

Current Lot Combination Performance Compared to Internal Standardization

Current lot performance compared to internal standardization was evaluated with 46 serum samples covering the assay range (0.5 – 350 ng/mL). Table 3 summarizes the biases observed when comparing ADVIA Centaur H2n reagent kit lot ending in 138 with H2n calibrator lot ending in 49, to the internal standardization.

Table 3. ADVIA Centaur XP/XPT and ADVIA Centaur CP H2n Reagent Lot 138 Bias vs. Internal Standardization

H2n Dose	ADVIA Centaur XP/XPT		ADVIA Centaur CP	
	Average Bias	Range of Bias	Average Bias	Range of Bias
<15.0 ng/mL	59.2%	49.4% to 91.7%	27.2%	17.3% to 63.7%
15.0 ng/mL to 50.0 ng/mL	46.3%	45.5% to 49.4%	16.9%	16.3% to 18.1%
>50.0 ng/mL	47.0%	45.5% to 48.9%	22.8%	18.2% to 28.7%
Overall Bias Across Assay Range	50.5%		22.2%	

In addition, Siemens' investigation included a review of historical H2n assay performance and determined the current bias versus the internal standard developed slowly over multiple lots (~4%/year (~2 lots/year)).

Current Lot Combination Upper Limit of Normal

Testing was performed following CLSI Guidance EP28-A3c "Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory" using 132 patient samples (premenopausal and postmenopausal, without a history of cancer) to evaluate the Upper Limit of Normal (ULN) stated in the IFU (15.2 ng/mL, defined as the 95th percentile of the observed results). The results in Table 4 demonstrate the reference interval was not achieved with ADVIA Centaur H2n reagent lot ending in 138 with ADVIA Centaur H2n calibrator lot ending in 49.

Table 4. Evaluation of Upper Limit of Normal (ULN)

Reagent Kit Lot ending in 138 (Current)	
ADVIA Centaur XP/XPT % <15.2 ng/mL (n < 15.2 ng/mL)	30% (39)
ADVIA Centaur CP % <15.2 ng/mL (n < 15.2 ng/mL)	83% (110)

Current Lot Combination Bias between ADVIA Centaur CP and ADVIA Centaur XP/XPT

Note: Data and plots below that reference ADVIA Centaur XP/XPT are representative of performance seen on both the ADVIA Centaur XP and ADVIA Centaur XPT systems.

Method comparison studies included n=100 samples across the assay range (0.5 – 350 ng/mL) with ADVIA Centaur H2n reagent lot ending in 138 and ADVIA Centaur H2n calibrator lot ending in 49 for comparison of ADVIA Centaur CP H2n result recovery versus ADVIA Centaur XP/XPT utilizing Ordinary Least Square and Passing-Bablok analysis.

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Figures 1 and 2 display the observed biases on the ADVIA Centaur CP system compared to the ADVIA Centaur XP and ADVIA Centaur XPT systems.

Figure 1. ADVIA Centaur CP H2n Recovery vs. ADVIA Centaur XP/XPT Graph

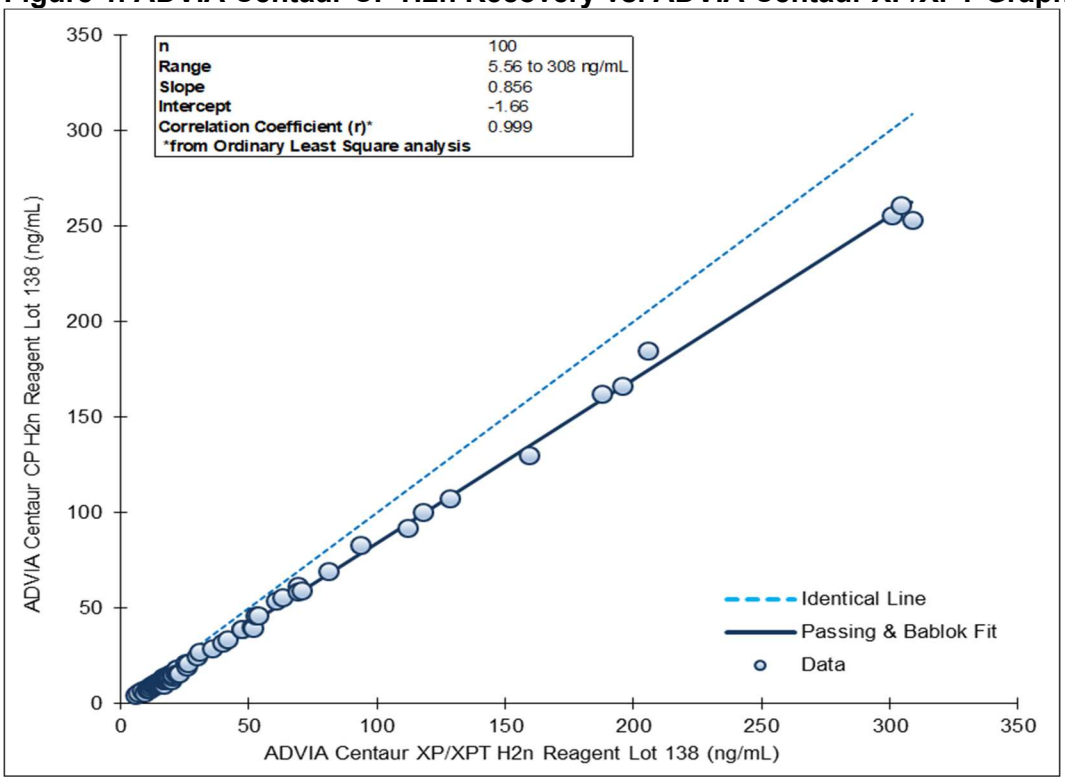
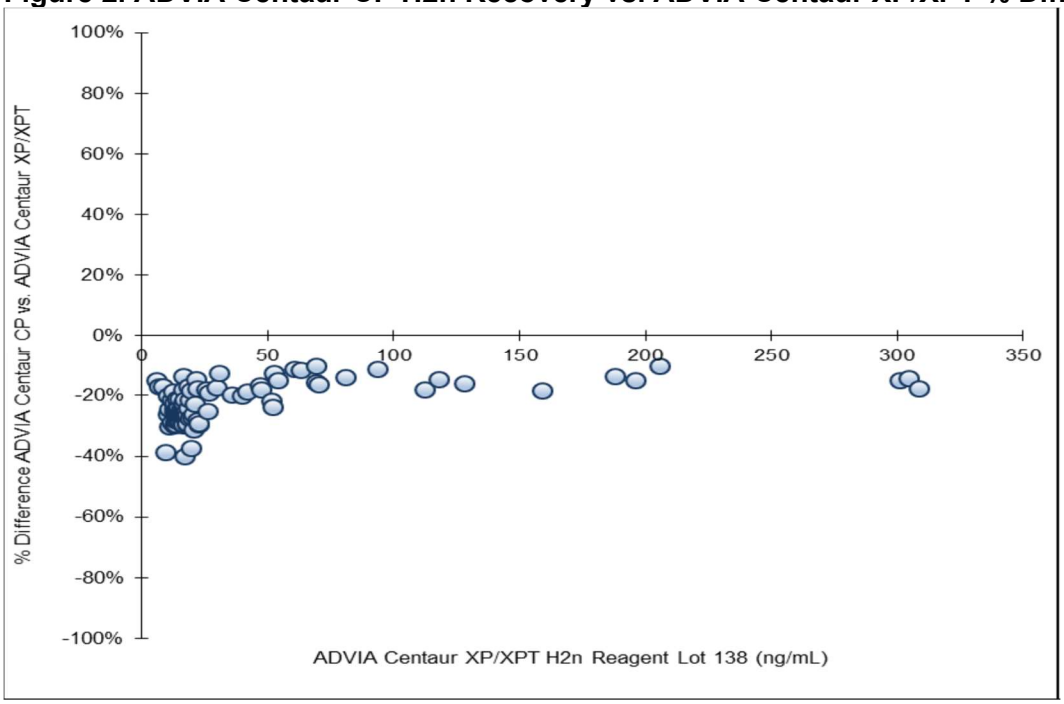


Figure 2. ADVIA Centaur CP H2n Recovery vs. ADVIA Centaur XP/XPT % Difference Plot



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Restoration with New Lot Combination

The reference interval in the IFU was restored and the bias throughout the assay range was eliminated. In addition, Siemens Commercial Controls and Master Curve Material targets were reset starting with the new lot combinations in Table 2 to ensure acceptable performance. IFU performance claims were verified including the ADVIA Centaur CP H2n result alignment compared to ADVIA Centaur XP/XPT and Upper Limit of Normal.

New Lot Combination Comparison to Current Lot Combination

After restoring alignment to the internal standardization as claimed in the IFU with the new lot combinations in Table 2, Siemens completed internal testing to evaluate the performance of ADVIA Centaur H2n reagent kit lot ending in 140 (new) compared to ADVIA Centaur H2n reagent kit lot ending in 138 (current). Siemens completed method comparison studies utilizing the same method comparison samples and study format as noted above for Figures 1 and 2 to evaluate the performance of ADVIA Centaur H2n reagent kit lot ending in 140 (new) with ADVIA Centaur H2n calibrator lot ending in 54 (new) compared to ADVIA Centaur H2n reagent kit lot ending in 138 (current) with ADVIA Centaur H2n calibrator lot ending in 49 (current).

Figures 3 through 6 show the approximate negative 43% (ADVIA Centaur XP/XPT) and negative 29% (ADVIA Centaur CP) shift that is expected when transitioning to the new reagent and calibrator lots. Data demonstrates that ADVIA Centaur CP H2n required additional correction to achieve alignment to the internal standardization and the ADVIA Centaur XP/XPT systems.

Figure 3. ADVIA Centaur XP H2n Reagent Lot 140 (new) vs. Reagent Lot 138 (current) Graph

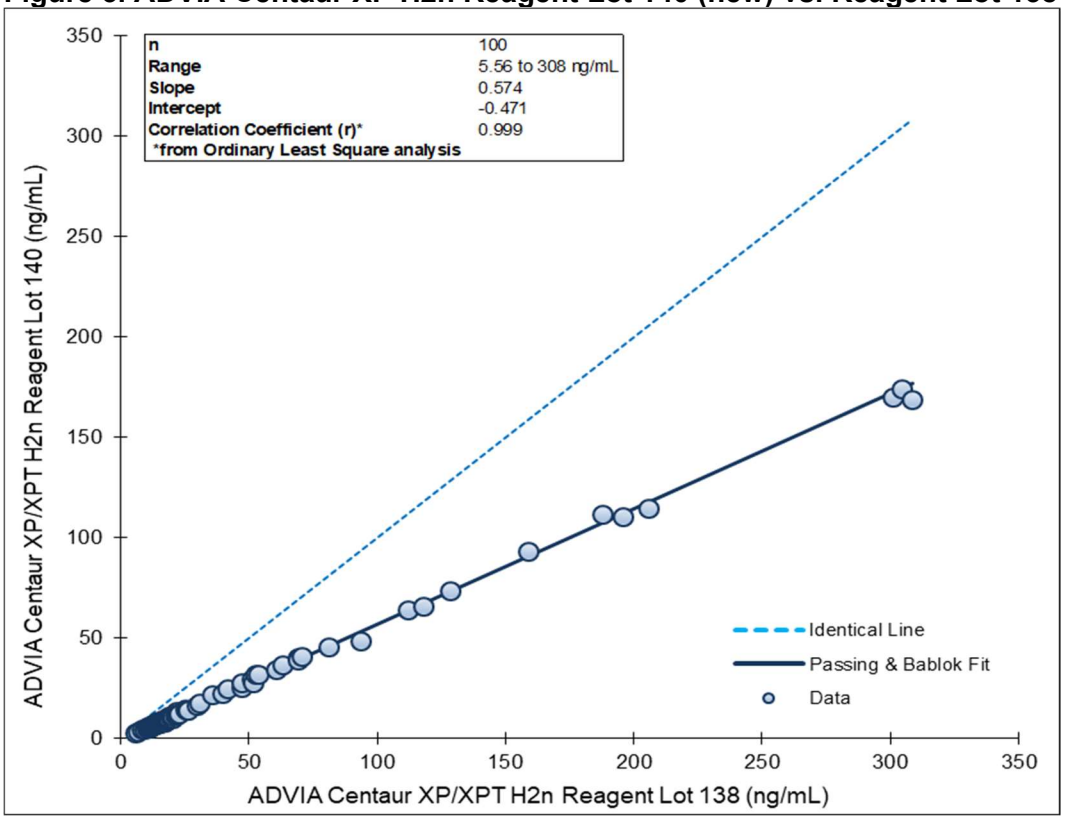

Figure 4. ADVIA Centaur XP H2n Reagent Lot 140 (new) vs. Reagent Lot 138 (current) % Difference Plot

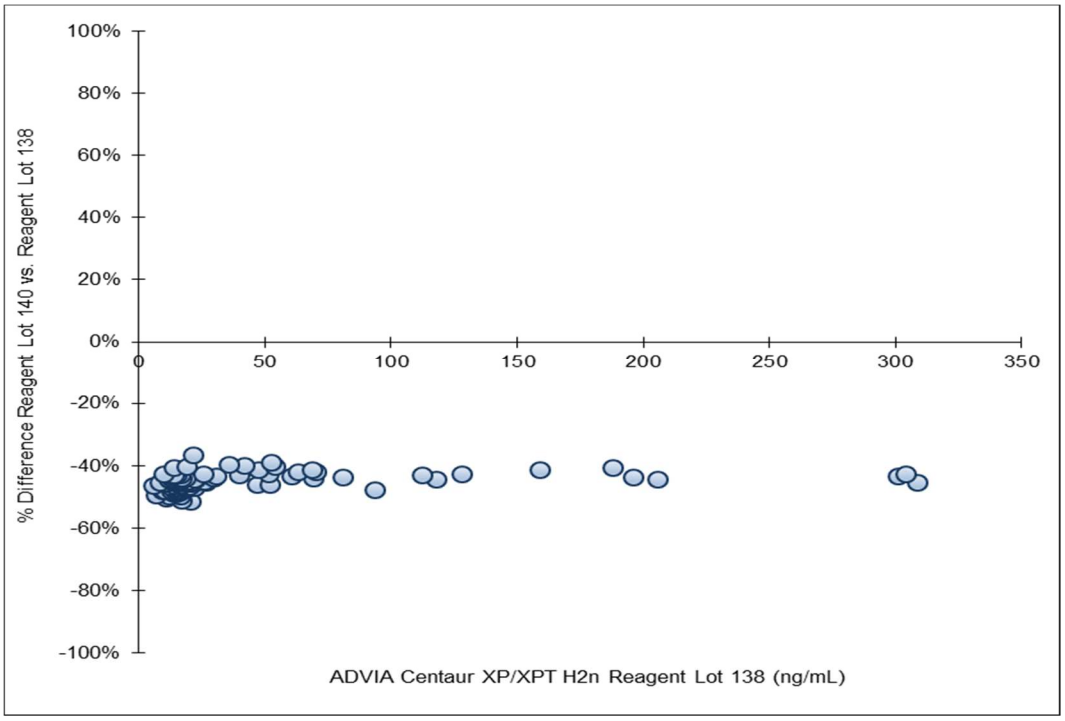

Figure 5. ADVIA Centaur CP H2n Reagent Lot 140 (new) vs. Reagent Lot 138 (current) Graph

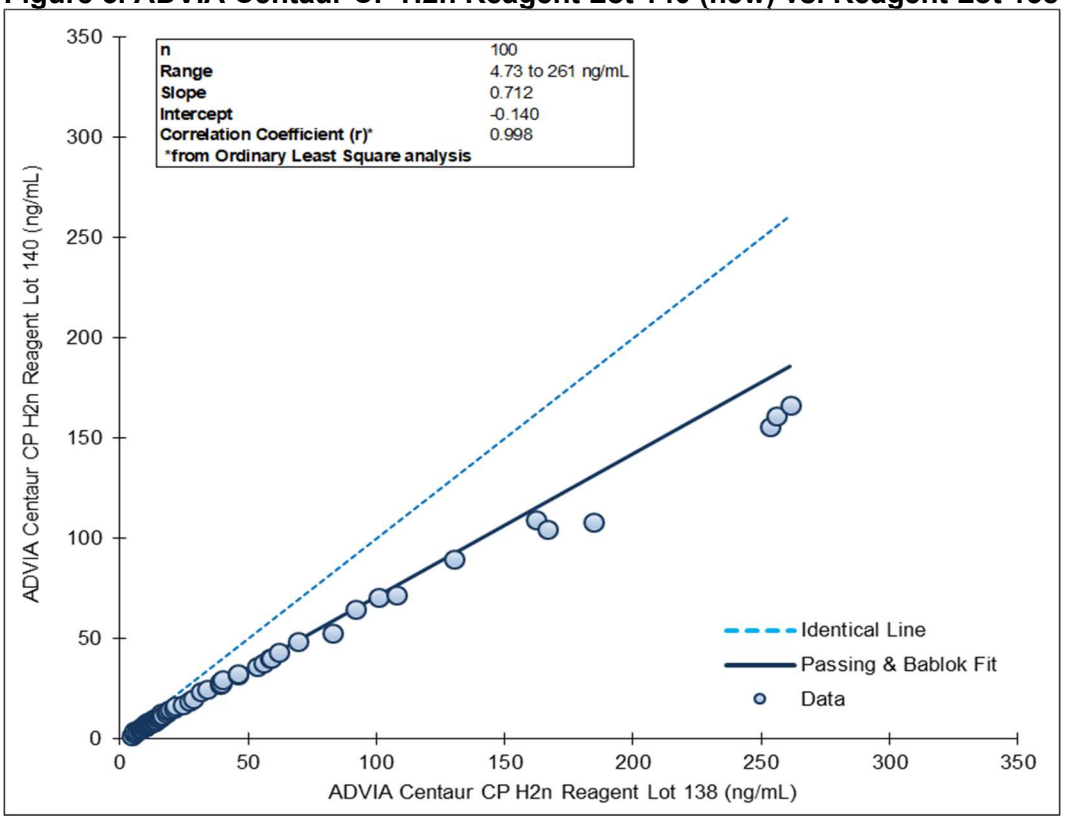

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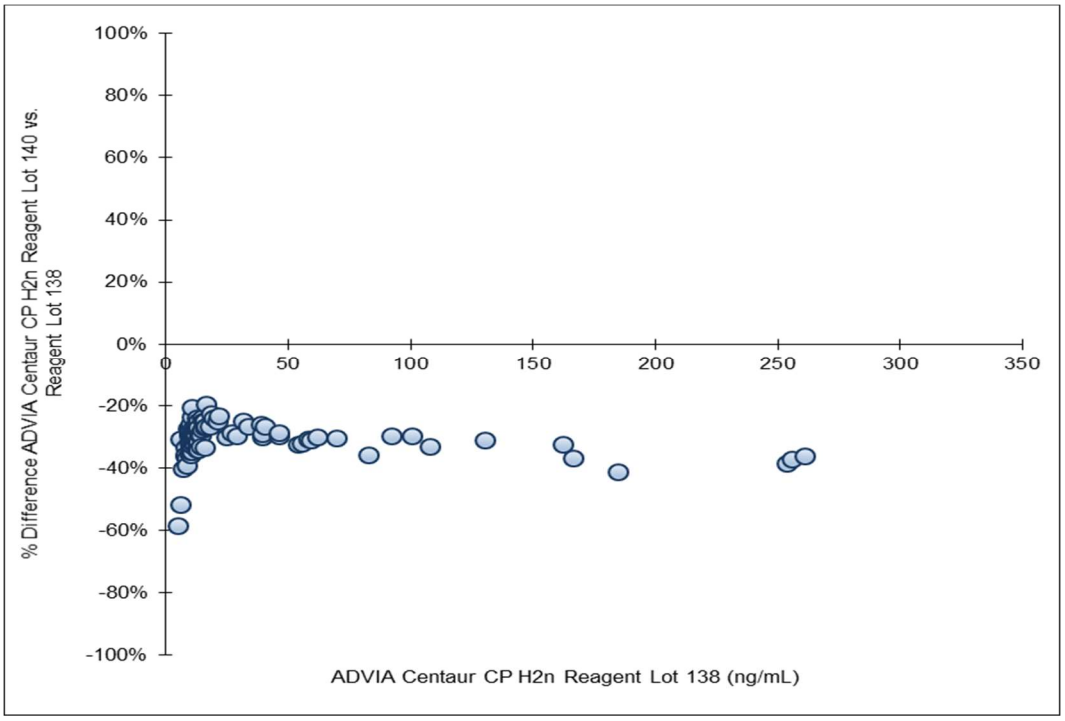
Figure 6. ADVIA Centaur CP H2n Reagent Lot 140 (new) vs. Reagent Lot 138 (current) % Difference Plot



New Lot Combination Upper Limit of Normal

The same testing protocol using the same patient samples noted above was completed with ADVIA Centaur H2n reagent kit lot ending in 140 (new). The results in Table 5 demonstrate the Upper Limit of Normal has been restored with ADVIA Centaur H2n reagent kit lot ending in 140.

Table 5. Verification of Upper Limit of Normal (ULN)

Reagent Kit Lot ending in 140 (New)	
ADVIA Centaur XP % <15.2 ng/mL (n < 15.2 ng/mL)	98% (129)
ADVIA Centaur CP % <15.2 ng/mL (n < 15.2 ng/mL)	98% (129)

New Lot Combination Bias between ADVIA Centaur CP and ADVIA Centaur XP/XPT

Evaluation of ADVIA Centaur CP H2n result recovery compared to ADVIA Centaur XP/XPT utilized the same method comparison samples and study format as noted above for Figures 1 through 6, with ADVIA Centaur H2n reagent lot ending in 140 with ADVIA Centaur H2n calibrator lot ending in 54.

Figures 7 and 8 demonstrate H2n result alignment between the ADVIA Centaur CP and ADVIA Centaur XP and ADVIA Centaur XPT systems has been restored

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Figure 7. ADVIA Centaur CP H2n Recovery vs. ADVIA Centaur XP/XPT Graph

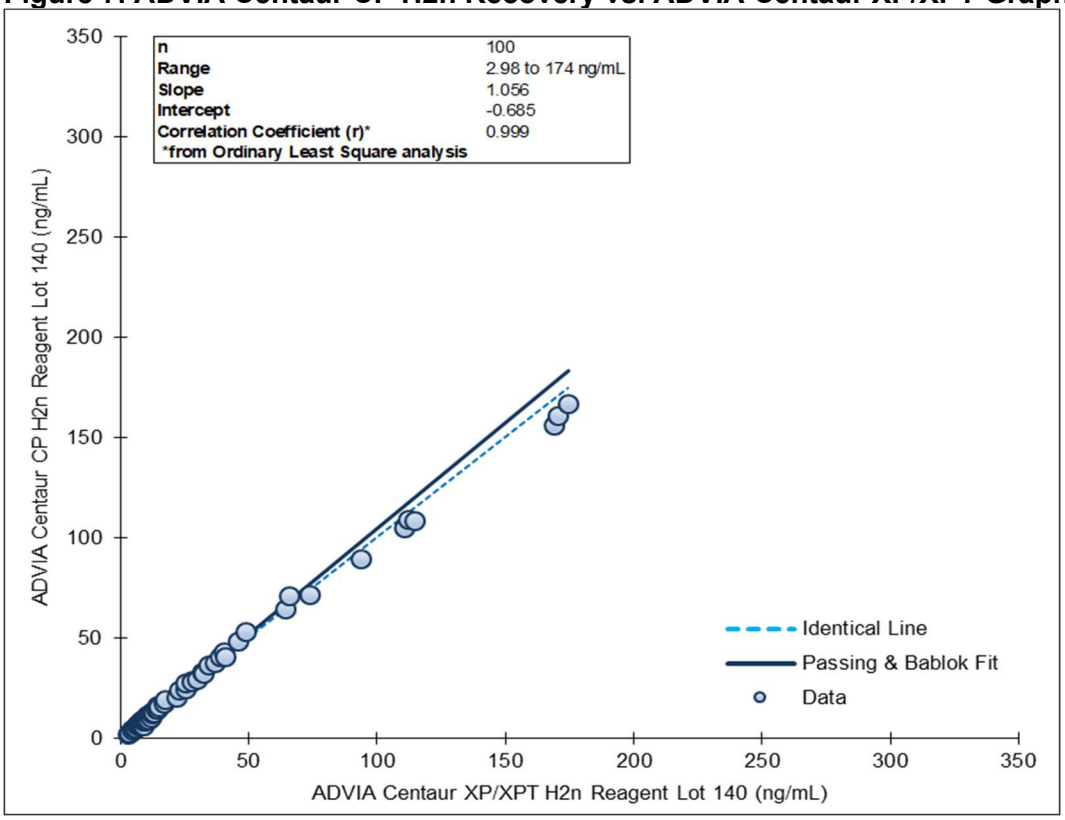
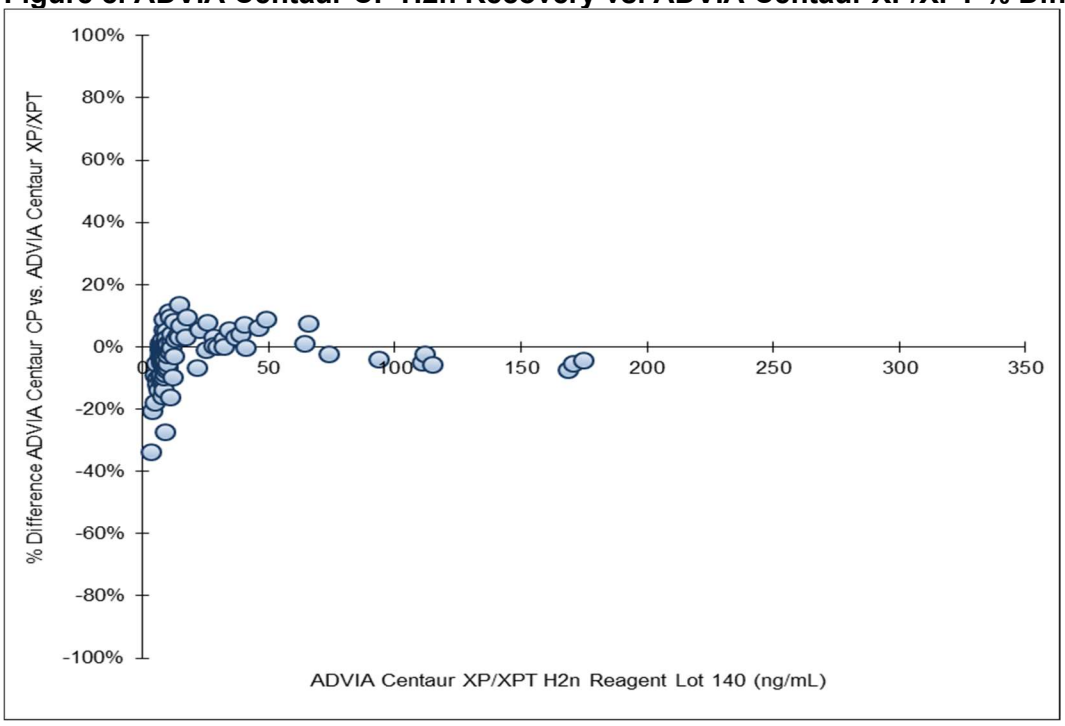


Figure 8. ADVIA Centaur CP H2n Recovery vs. ADVIA Centaur XP/XPT % Difference Plot



ADVIA Centaur is a trademark of Siemens Healthcare Diagnostics Inc.

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FIELD CORRECTION EFFECTIVENESS CHECK

ADVIA Centaur HER-2/*neu* (H2n) Positive Bias versus Internal Standardization

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice AIMC 20-05.A-2.OUS dated August 2020 regarding ADVIA Centaur HER-2/*neu* (H2n) Positive Bias versus Internal Standardization. Please read each question and indicate the appropriate answer.

Return this completed form to Siemens Healthcare Diagnostics as per the instructions provided at the bottom of this page.

1. I have read and understood the Urgent Field Safety notice instructions provided in this letter. Yes ☐ No ☐

2. Do you now have any of the noted product(s) on hand? Please check inventories before answering. Yes ☐ No ☐

   If the answer to the question above is yes, please complete the table below to indicate the quantity of affected product in your laboratory and replacement product required.

Product Description **SMN and Lot #**	**Quantity Discarded/ Replacement Quantity Required**
ADVIA Centaur H2n Assay (50 test kit) SMN:10308994 Kit Lots ending in 138	
ADVIA Centaur H2n Calibrator (2 pack) SMN: 10308993 Kit Lot ending in 48 and 49	
ADVIA Centaur H2n QC SMN: 10308992 (Lots 4226001/4226002, 4230601/4230602 and 4202311/4202312)	
ADVIA Centaur H2n Master Curve Material SMN: 10324496 (Lots 62271 and 81621)	

Name of person completing questionnaire: _____

Title: _____

Institution: _____ Instrument Serial Number: _____

Street: _____

City: _____ State: _____

Phone: _____ Country: _____

Customer Sold To #: _____ Customer Ship To #: _____

Please send a scanned copy of the completed form via email to XXXX@XXXX

Or to fax this completed form to the Customer Care Center at xxxxxx
If you have any questions, contact your local Siemens technical support representative.

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