SIEMENS

Urgent Field Safety Notice

3510

March 2013

IMMULITE® 2500

IMMULITE 2500 IGF-I Shift in Patient Medians

Our records indicate that you have received the following product:

Table 1.

Product	Catalog Number	Siemens Material Number (SMN)	Lot Number
IMMULITE 2500 IGF-I*	L5KGF2	10381367	189 – 227**

* IMMULITE 2500 system has been discontinued.
** See Appendix, Table 4 for full list of kit lot numbers. These kit lots have been determined from the alignment of release dates to the IMMULITE 2000/IMMULITE 2000 XPi platform.

All IMMULITE®/IMMULITE® 1000 IGF-I and IMMULITE® 2000/IMMULITE® 2000 XPi IGF-I customers previously received Urgent Field Safety Notice #4005 regarding this product issue. **Siemens Healthcare Diagnostics has now identified this issue as also applicable to the IMMULITE® 2500 IGF-I assay.**

There is **no new information** pertaining to the IMMULITE/IMMULITE 1000 IGF-I and IMMULITE 2000/IMMULITE 2000 XPi IGF-I in this Urgent Field Safety Notice.

Reason for Customer Notification

Siemens confirmed a negative bias in patient medians of approximately 5 to 20% using the IGF-I assay as compared to the reference range medians provided in the IGF-I Instructions For Use (IFU) with kit lots released August 2008 through July 2011.

After extensive review of Real Time Solutions (RTS) data, Siemens identified a negative bias of approximately 20% starting with IMMULITE 2000/IMMULITE 2000 XPi IGF-I kit lot 416 (released August 2008).

RTS data prior to 2008 is limited and insufficient for adequate statistical assessment. Since IMMULITE 2000/IMMULITE 2000 XPi IGF-I kit lot 416, two positive shifts in patient medians have occurred. An initial positive shift of approximately 15% was observed with IMMULITE 2000/IMMULITE 2000 XPi kit lot 441 (released December 2009),with an additional positive shift of approximately 5% observed with IMMULITE 2000/IMMULITE 2000 XPi kit lot 469 (released July 2011), leading to the total positive shift of approximately 20%.

Risk to Health

Two potential health risk scenarios exist.

If a laboratory used the initial reference range and medians from the IFU without in-house validation of the reference interval, low bias in patient results prior to 2009, relative to the reference ranges used in the laboratory, could mask uncontrolled acromegaly and thus adversely impact patient treatment. The low bias may also lead to over-diagnosis of growth hormone deficiency in short-statured children and thus growth hormone supplementation.

If a laboratory adjusted the median with in-house data, high bias in patient results after mid-2011, relative to the reference ranges established in the laboratory prior to 2011, could lead to under-estimation of hGH deficiency in children with borderline hGH deficiency and potentially result in missed or delayed opportunity to treat with hGH supplement. The high bias may also lead to an incorrect diagnosis of uncontrolled acromegaly and thus further patient evaluation and investigation.

Due to the difference in laboratory reference ranges, the laboratory should consider reviewing previously reported results at their discretion, based on the information on kit performance, and specific settings of their reference ranges.

Additional Information

Siemens compared IGF-I reference range median data, generated in two separate studies in 2009 and 2012, from a U.S. national referral laboratory to the IMMULITE Systems IGF-I IFU data. These comparisons are provided in Table 4 and Figure 2.

The U.S. national referral laboratory data was generated with patient populations for whom the IGF-I tests were ordered. Although the patient population is not characterized as “healthy”, the medians from January to June 2012 are in relatively good agreement with the medians from a healthy population, with the exception of certain age groups (< 7, 13 – 18 years old). In those age groups the U.S. national referral laboratory medians could be low biased due to the population of patients with underproduction of IGF-I.

Data from the U.S. national referral laboratory from 2009 confirms the negative bias of reference range medians in the RTS data observed with IMMULITE 2000/IMMULITE 2000 XPi IGF-I kit lots 416 – 468. Data from the U.S. national referral laboratory from 2012 confirms that IMMULITE 2000/IMMULITE 2000 XPi IGF-I kit lots 469 and above are in alignment with the IGF-I IFU reference range medians.

These positive shifts are based on aggregate populations of diseased and normal IGF-I patient data. See Table 2.

Table 2. Patient Median Bias Compared to the IGF-I IFU Reference Range Medians

IMMULITE 2000/2000 XPi IGF-I Kit Lots	Median Performance Compared to IGF-I IFU Reference Range Medians
469 and above	In alignment with medians in the IGF-I IFU
441 – 468	Approximately 5% average negative bias relative to the medians in the IGF-I IFU
416 – 440	Approximately 20% average negative bias relative to the medians in the IGF-I IFU

IMMULITE 2500
RTS data is limited for the IMMULITE 2500 IGF-I assay and insufficient for adequate statistical assessment. However, the IMMULITE 2500 IGF-I assay and the IMMULITE 2000/IMMULITE 2000 XPi IGF-I assay used the same components. Therefore, their performance is expected to be equivalent. Shifts observed on the IMMULITE 2000/IMMULITE 2000 XPi IGF-I are likely to be applicable to the IMMULITE 2500 IGF-I kit lots released December 2009 – July 2011. Refer to Table 4 for a full list of IMMULITE 2500 IGF-I kit lots and their matching IMMULITE 2000/IMMULITE 2000 XPi kit lots.

The root cause of the shifts in patient medians is still under investigation.

Actions to be Taken by the Customer

Please review this letter with your medical director.

In addition, please perform the following:

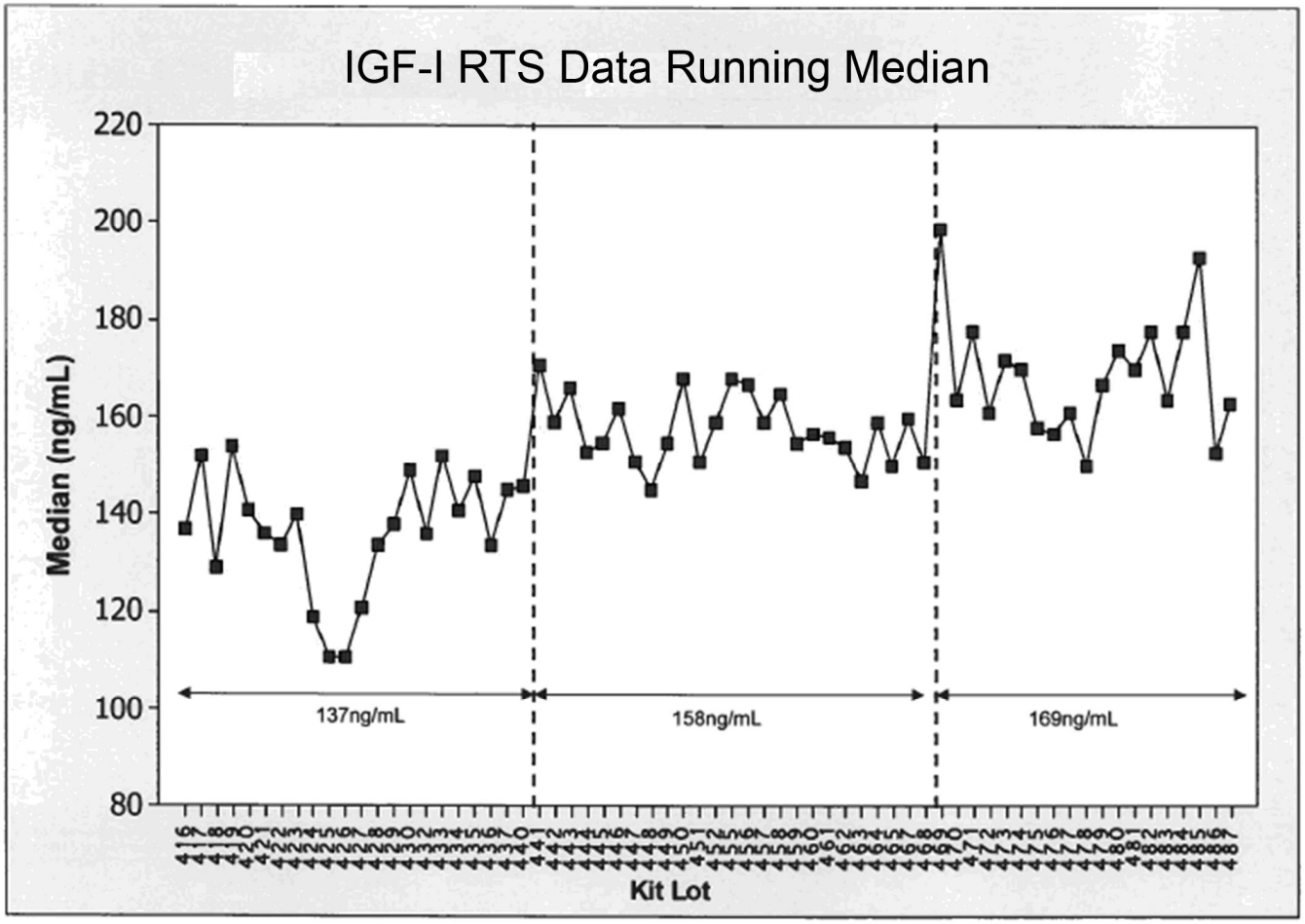
- Complete and return the Field Correction Effectiveness Check form attached to this letter within seven (7) days.
- Keep this letter with your laboratory records.
- Forward this letter to whomever you may have distributed these products.

We apologize for the inconvenience this situation has caused. If you have any questions or need additional information, please contact your Siemens Technical Solutions Center or your local technical support representative.

IMMULITE is a trademark of Siemens Healthcare Diagnostics.

Appendix

Figure 1. IMMULITE 2000/IMMULITE 2000 XPi (L2KGF2) IGF-I RTS Data Running Medians



Note: The concentration values printed on the graph are averages of the medians. The root cause of the low medians in kit lots 424 through 427 was associated with a specific lot of IMMULITE 2000 IGF-I Sample Diluent (L2GFZ lot 312).

The following data was generated by a large national referral laboratory. The patient medians in this data were determined to be comparable to the patient medians in the reference range data published in the IFU.

Table 3. Observed Patient Medians

IMMULITE Systems IFU Medians		National Referral Lab Medians			
Age (Years)	IFU Medians	N	January – June 2009	N	January – June 2012
1	134	437	46	435	41
2	125	308	59	300	55
3	119	252	69	300	63
4	118	239	84	286	80
5	119	254	88	264	93
6	124	269	96	300	117
7	134	339	120	381	128
8	148	373	129	456	152
9	169	358	149	467	184
10	200	386	168	485	202
11	247	424	170	546	230
12	315	549	240	627	296
13	395	563	265	662	339
14	462	502	325	564	374
15	486	403	349	442	397
16	452	276	336	332	386
17	376	227	288	221	358
18	308	225	273	181	304
19	261	133	224	151	275
20	232	105	221	135	284
21-25	203	667	190	727	244
26-30	196	867	170	963	211
31-35	188	927	159	1265	191
36-40	176	1217	150	1456	179
41-45	164	917	136	1417	172
46-50	154	1696	127	2107	158
51-55	144	1579	118	1819	146
56-60	135	1268	112	1567	139
61-65	126	1039	110	1256	135
66-70	118	779	105	968	121
71-75	110	512	99	646	116
76-80	102	337	87	372	111
81-85	95	186	81	246	91

Note: The referral lab data was generated with patient populations for whom the IGF-I tests were ordered. Although the patient population is not characterized as "healthy", the medians are expected to be in relatively good agreement with the medians from a healthy population, with the exception of certain age groups (< 7, 13 – 18 years). In those age groups the national referral laboratory medians could be low biased due to the population of patients with underproduction of IGF-I.

Figure 2. IFU Medians vs. Referral Laboratory Medians for January – June 2012

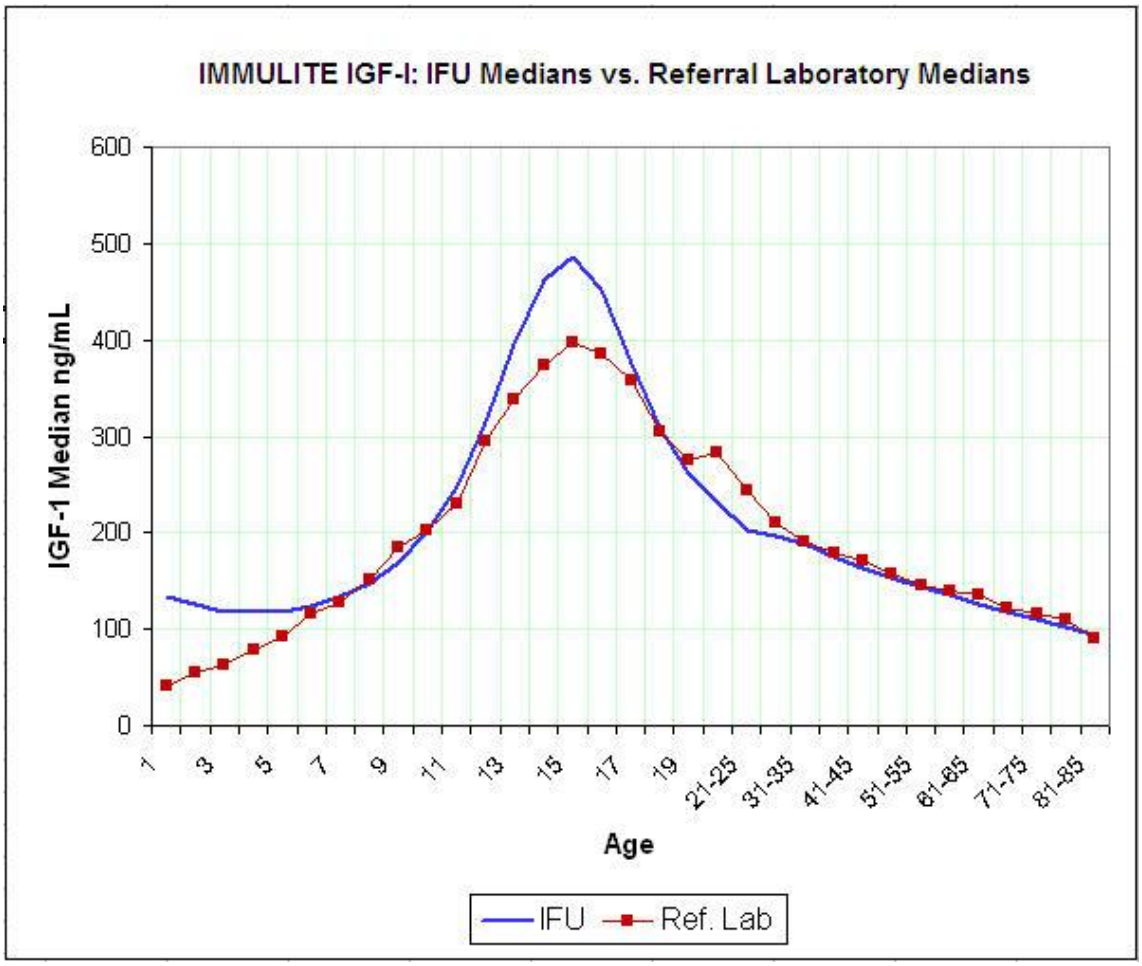


Table 4. IMMULITE 2500 IGF-I (L5KGF2) Kit Lots (Expired and Discontinued)

IMMULITE 2500 IGF-I (L5KGF2) Kit Lots			
Kit Lot	**Release Date**	**Expiration**	**Matching IMMULITE 2000/IMMULITE 2000 XPi IGF-I Kit Lot**
189	02/19/10	08/31/10	442
191	03/25/10	08/31/10	444
192	04/12/10	10/31/10	445
194	05/11/10	10/31/10	447
195	06/03/10	11/30/10	448
196	06/15/10	11/30/10	449
197	08/05/10	12/31/10	450
198	09/22/10	01/31/11	451
204	10/26/10	04/30/11	455
205	11/09/10	05/31/11	457
206	12/06/10	06/30/11	458
208	02/11/11	07/31/11	460
210	03/16/11	08/31/11	462
212	04/04/11	10/31/11	464
213	05/04/11	10/31/11	465
216	06/11/11	11/30/11	468
217	07/13/11	12/31/11	469
220	09/02/11	02/29/12	473
221	09/15/11	03/31/12	474
222	10/20/11	04/30/12	476
224	01/03/12	06/30/12	479
225	02/03/12	08/31/12	480
227	05/08/12	09/30/12	484

Note: No IMMULITE 2500 IGF-I kit lot was released which shared the same components as IMMULITE 2000/IMMULITE 2000 XPi kit lot 441.

FIELD CORRECTION EFFECTIVENESS CHECK

IMMULITE 2500 IGF-I Shift in Patient Medians

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice #3510 dated March 2013 regarding IMMULITE 2500 IGF-I Shift in Patient Medians. Please read the question and indicate the appropriate answer. Fax this completed form to Siemens Healthcare Diagnostics at the fax number indicated at the bottom of this page.

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

Name of person completing questionnaire:

Title: Ship To Account:

Institution: Instrument Serial Number:

Street: Date:

City: State: Phone:

PLEASE FAX THIS COMPLETED FORM TO THE TECHNICAL SOLUTIONS CENTER AT (###) ###-####.