

# The Percentiler - The Flagger: Mid- to long-term quality monitoring

Dec 9<sup>th</sup> 2015 Gent  
Kenneth Goossens (Ugent)

**EMPOWER** *IVD* ● **GLOBE**

**Dietmar Stöckl**  
dietmar@stt-consulting.com

**Linda Thienpont**  
linda.thienpont@ugent.be

**Thienpont & Stöckl**  
Wissenschaftliches Consulting GbR

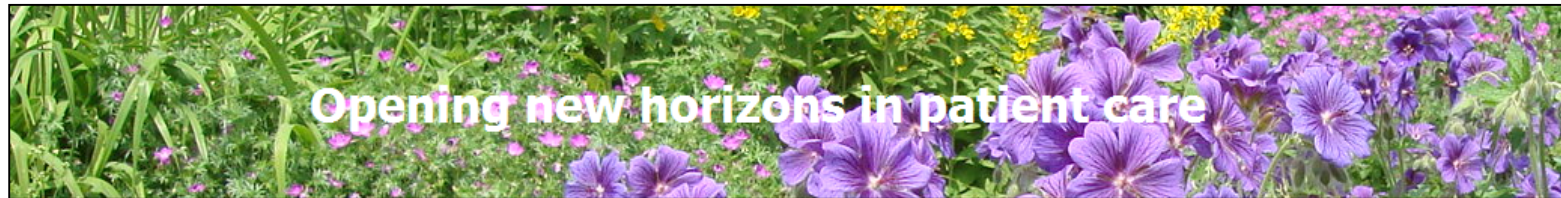


# Overview

## 1. Theoretical background

## 2. The Percentiler

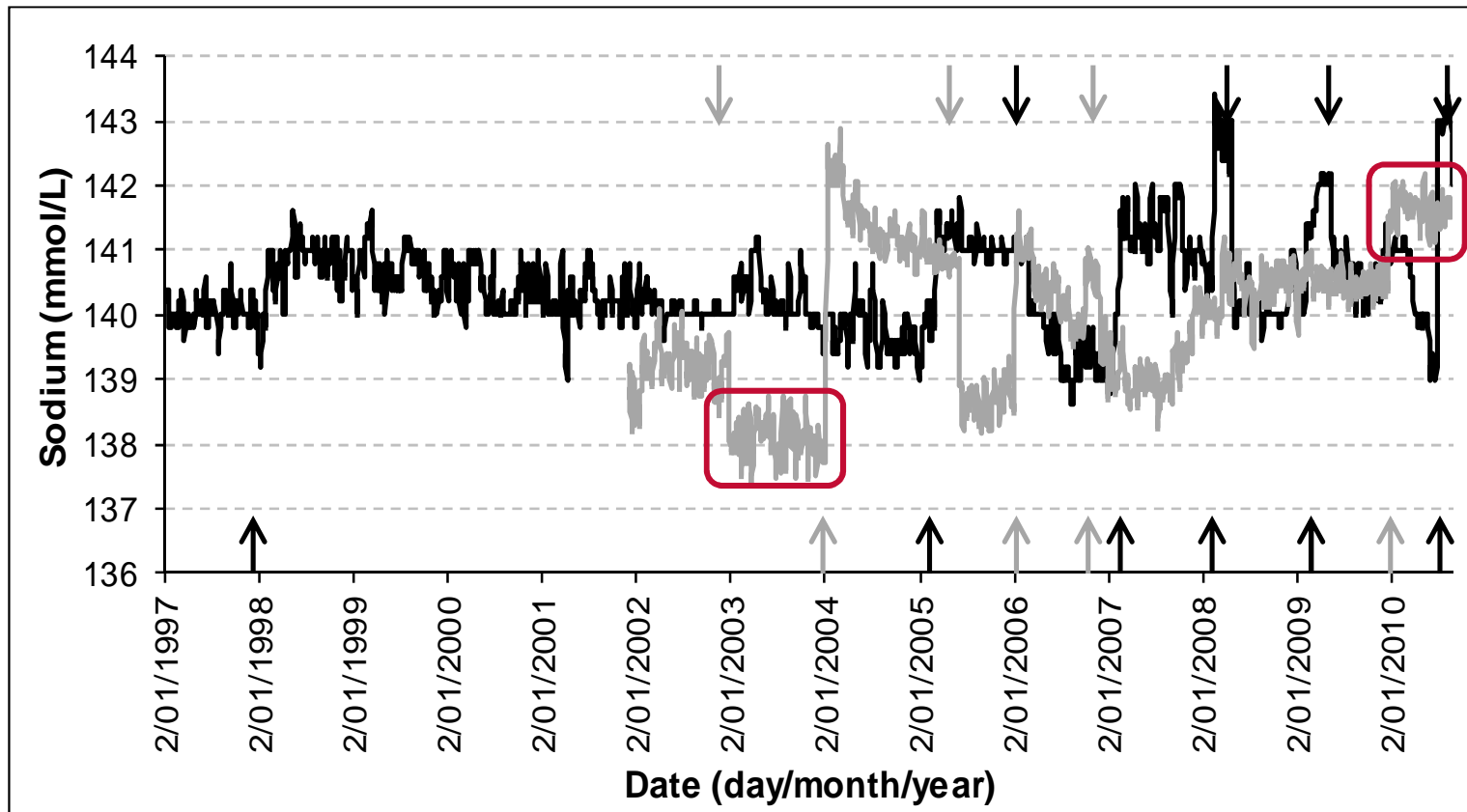
## 3. The Flagger



# Theoretical Background

“Surrogate” medical decision hyponatremia

- **Triplication** “low versus high” period ( $\pm 2$  mmol/L)!
- **Benchmark stability: 8 years  $\pm 1$  mmol/L**



# Concept

## Patient is **not** measured

- By a laboratory

## Patient **is** measured

- On **rotor 1** of instrument **x** in laboratory **y** with the assay of manufacturer **z**.

**Only The Percentiler and The Flagger deliver that depth of information! (by plotting the moving medians; grouped per 5, 8 or 16 days)**

- **The Percentiler:** monitoring of patient medians
- **The Flagger:** monitoring of hypo- and hyper-flagging rate

# The Percentiler

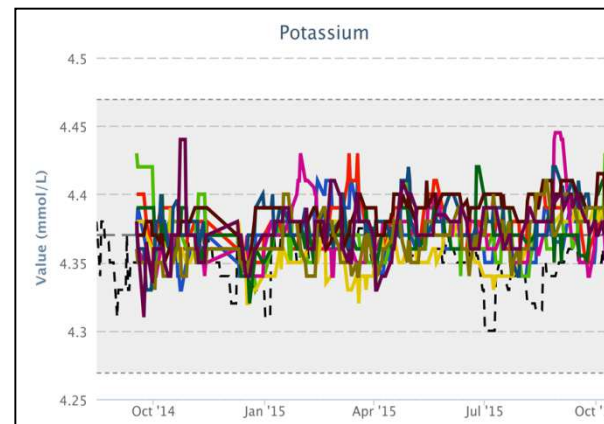
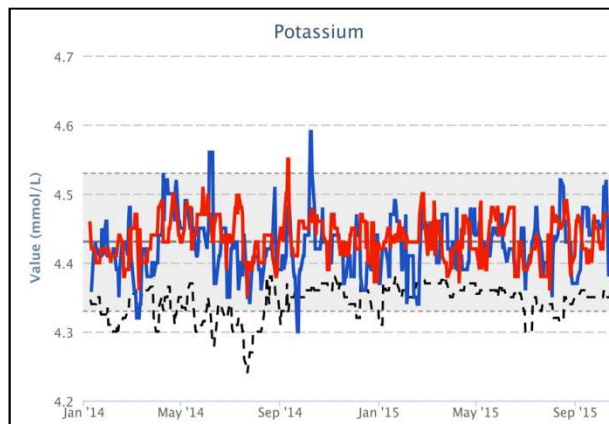
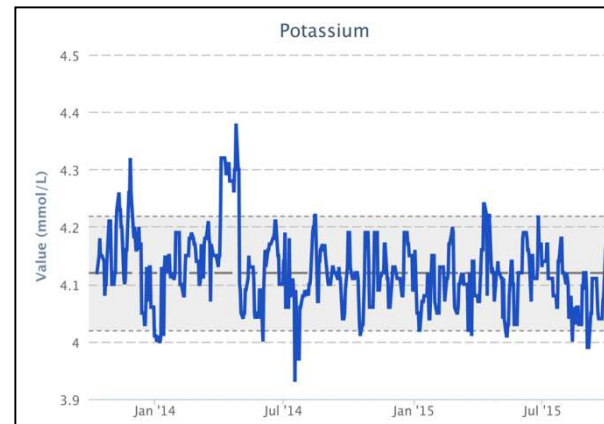
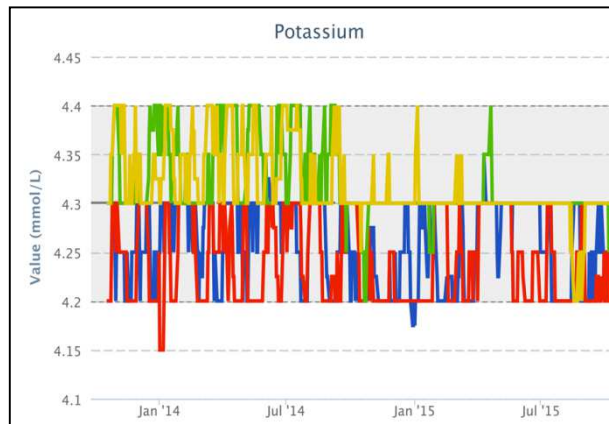
# Percentiler Limits

	Bias Biology (%)	Bias Empower (%)	Bias Biology (unit)	Bias Empower (unit)	Unit	Median "SI"
<b>ALB</b>	1.3	2.3	0.56	1	g/L	43.0
<b>ALKFOS</b>	6.4	7.0	4.6	5	U/L	71.9
<b>ALT</b>	11.4	11.0	2.1	2	U/L	18.1
<b>AST</b>	5.4	4.9	1.1	1	U/L	20.4
<b>BILTOT</b>	11.4	12.2	0.94	1	µmol/L	8.21
<b>CA</b>	0.8	2.1	0.019	0.05	mmol/L	2.38
<b>CHOL</b>	4	4.1	0.20	0.2	mmol/L	4.91
<b>CL</b>	0.5	1.0	0.51	1	mmol/L	102.0
<b>CRP</b>	21.8	11.0	0.40	0.2	mg/L	1.82
<b>GGT</b>	10.8	9.4	2.3	2	U/L	21.2
<b>GLUC</b>	2.2	3.8	0.12	0.2	mmol/L	5.24
<b>K</b>	1.8	2.3	0.08	0.1	mmol/L	4.44
<b>CREAT</b>	4	4.1	2.9	3	µmol/L	73.0
<b>LDH</b>	4.3	5.4	7.9	10	U/L	183.6
<b>MG</b>	1.8	3.5	0.015	0.03	mmol/L	0.85
<b>NA</b>	0.3	0.7	0.42	1	mmol/L	140.6
<b>P</b>	3.2	3.6	0.036	0.04	mmol/L	1.11
<b>PROT</b>	1.2	1.4	0.83	1	g/L	69.5
<b>UREA</b>	5.5	5.5	0.30	0.3	mmol/L	5.45
<b>URIC ACID</b>	4.9	4.7	15.5	15	µmol/L	317
<b>FT4</b>	3.3	3.4	0.5	0.5	pmol/L	14.9
<b>TSH</b>	7.8	7.3	0.13	0.12	mU/L	1.65

# Percentiler Limits

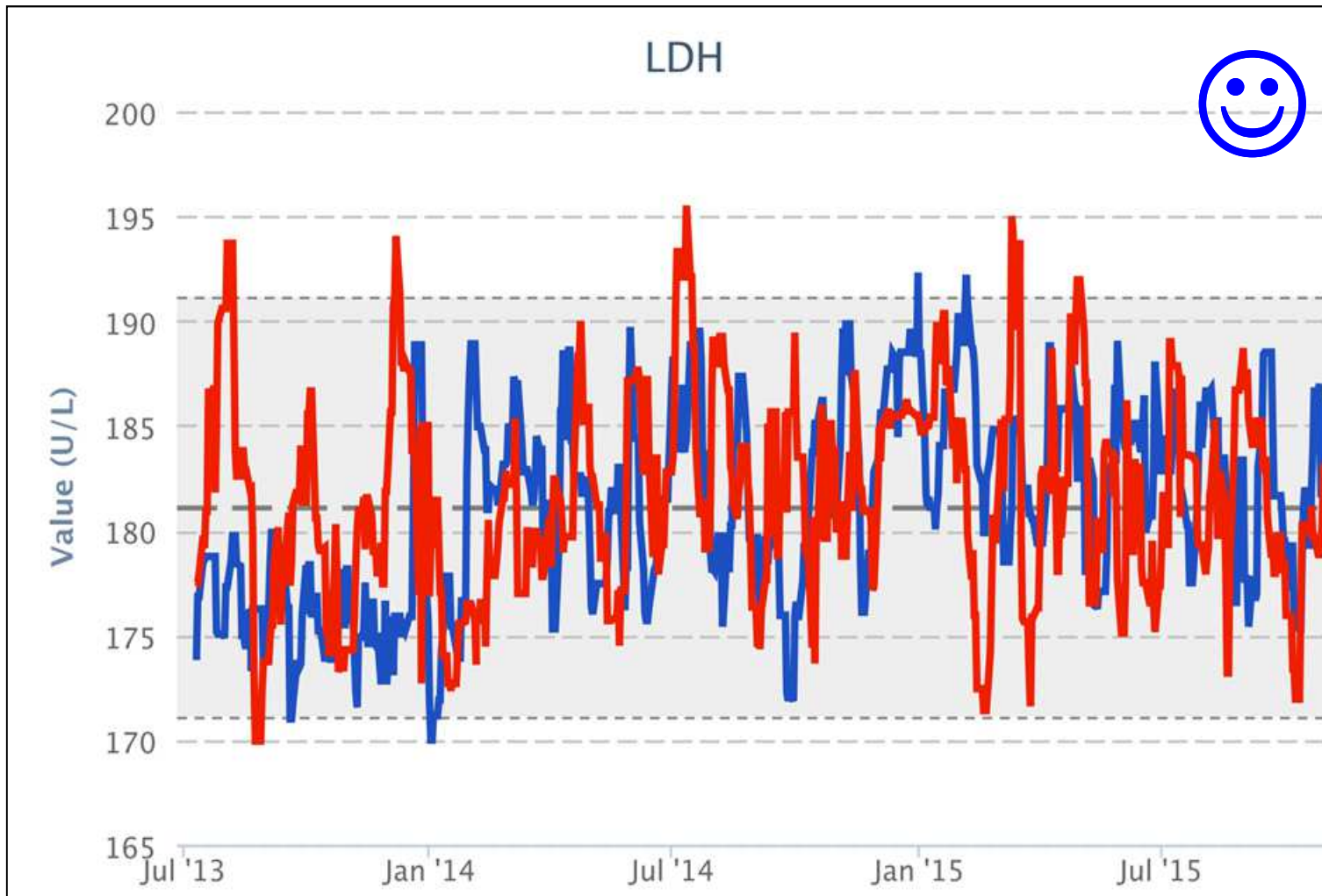
## Potassium

Limits lowered: 0.15 to 0.1 mmol/L  
(0.08 mmol/L ~ biological variation)



# Percentiler Applications

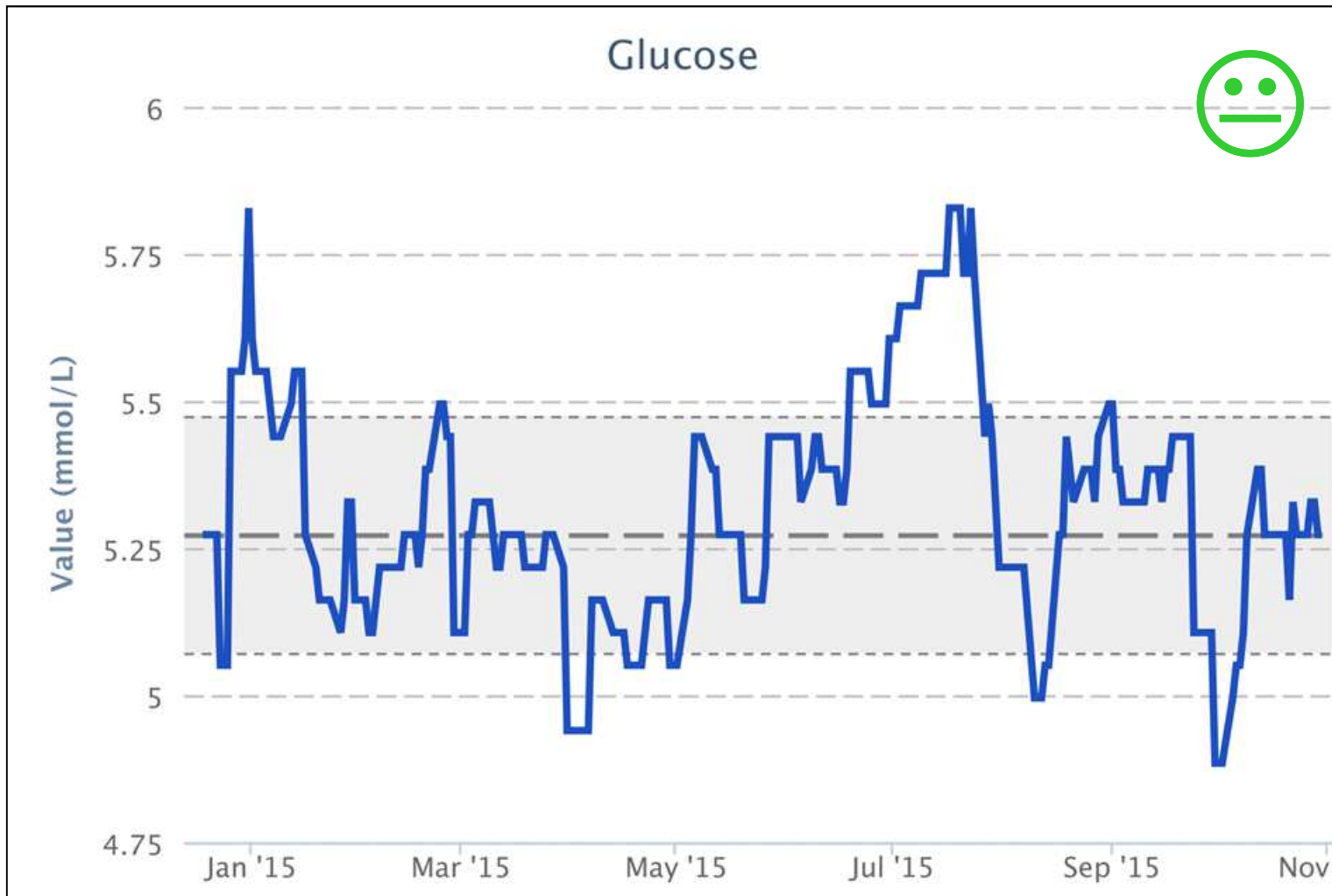
## Identifying problem analytes (lab-specific)





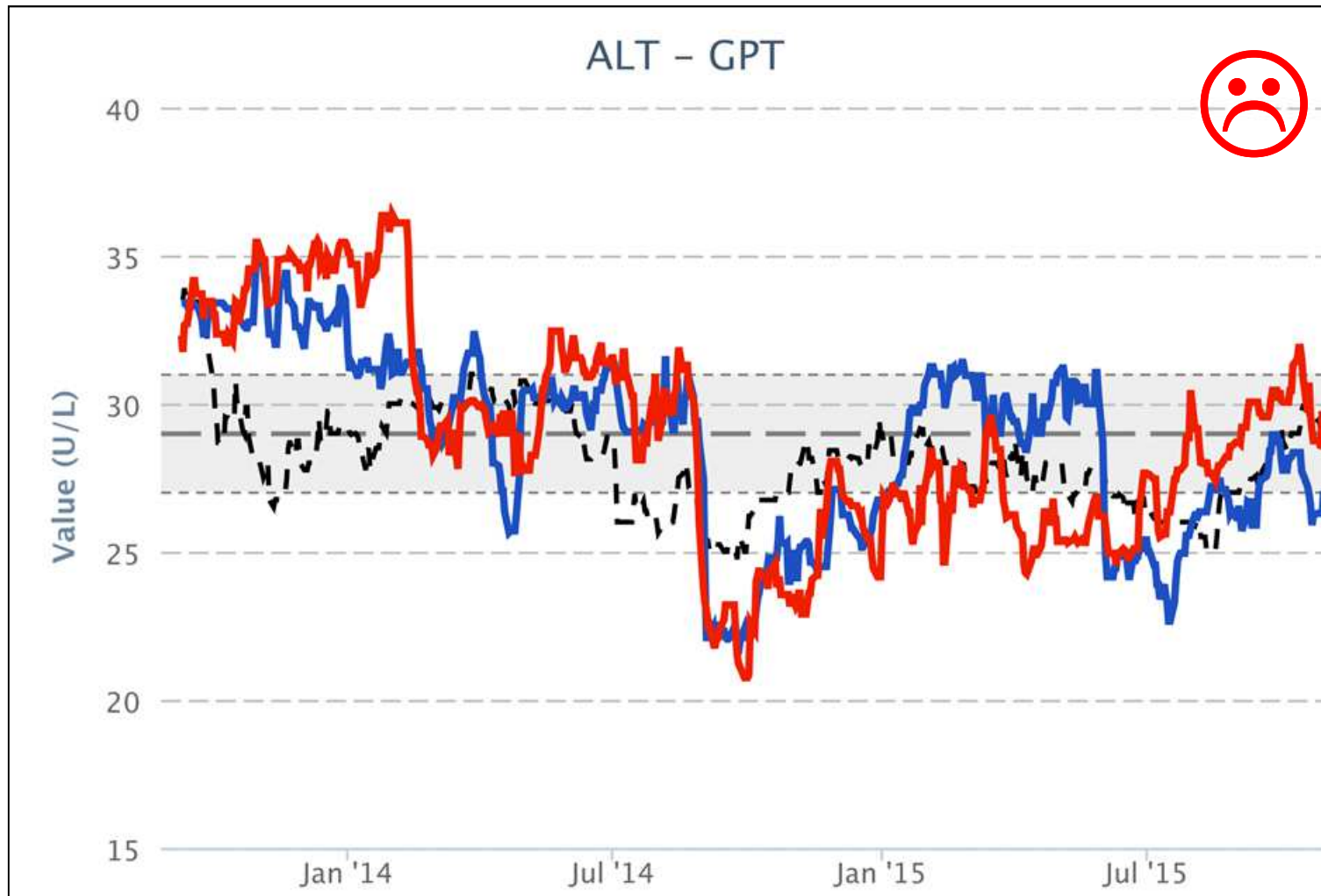
# Percentiler Applications

## Identifying problem analytes (lab-specific)



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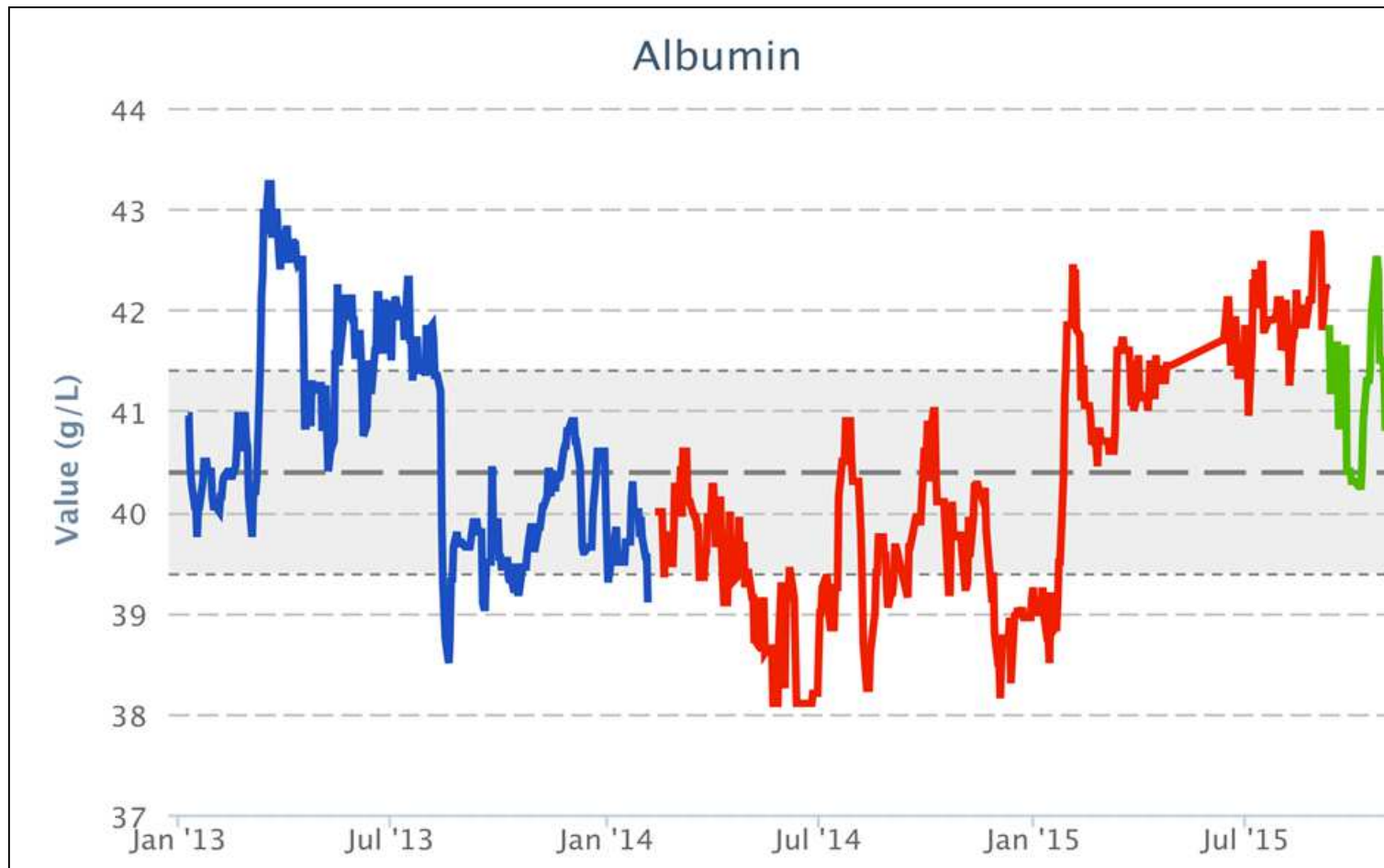
Identifying problem analytes (peer-specific)



# Percentiler Applications

Identifying problem analytes (peer-specific)

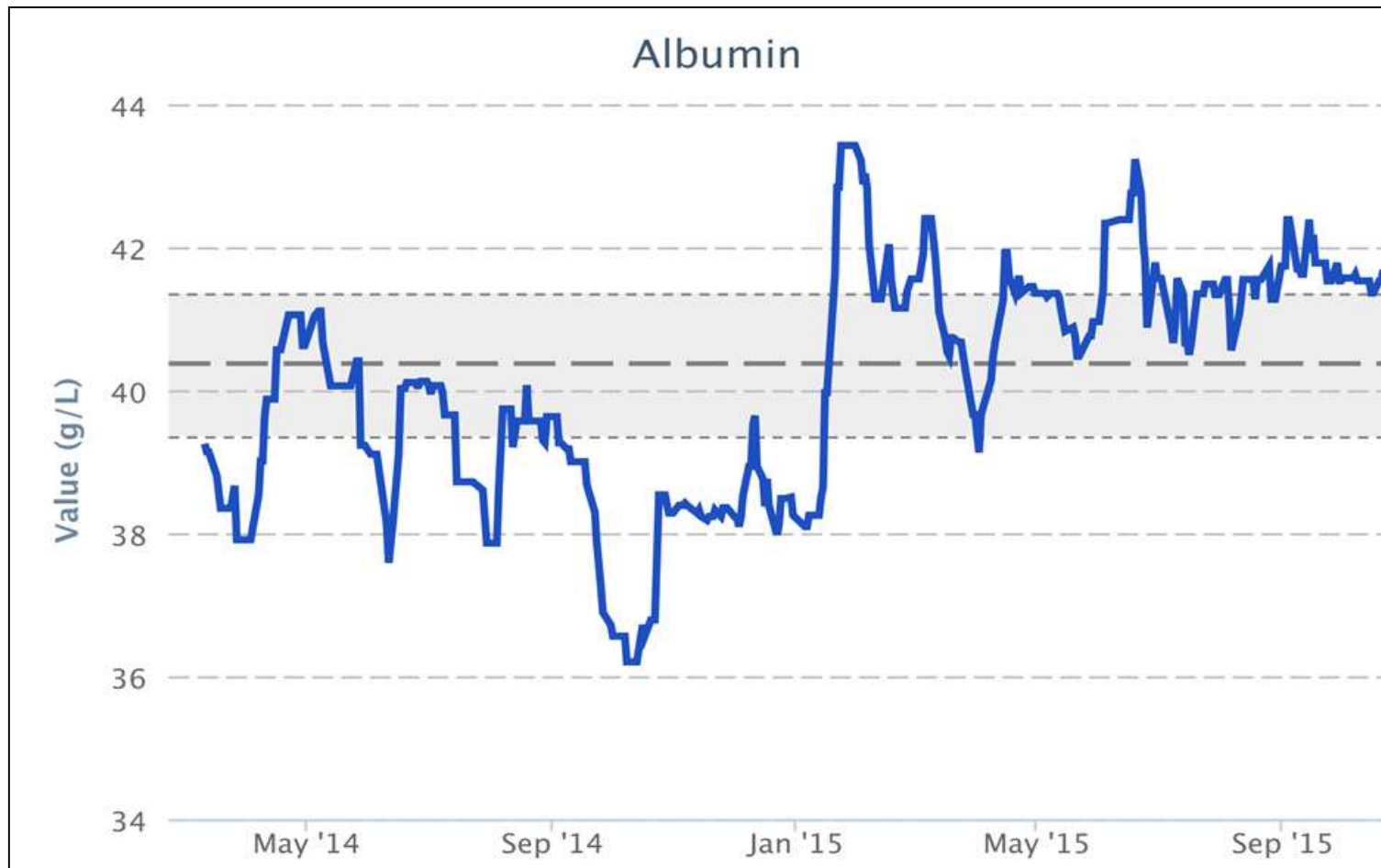
Albumin – Manufacturer A



# Percentiler Applications

Identifying problem analytes (peer-specific)

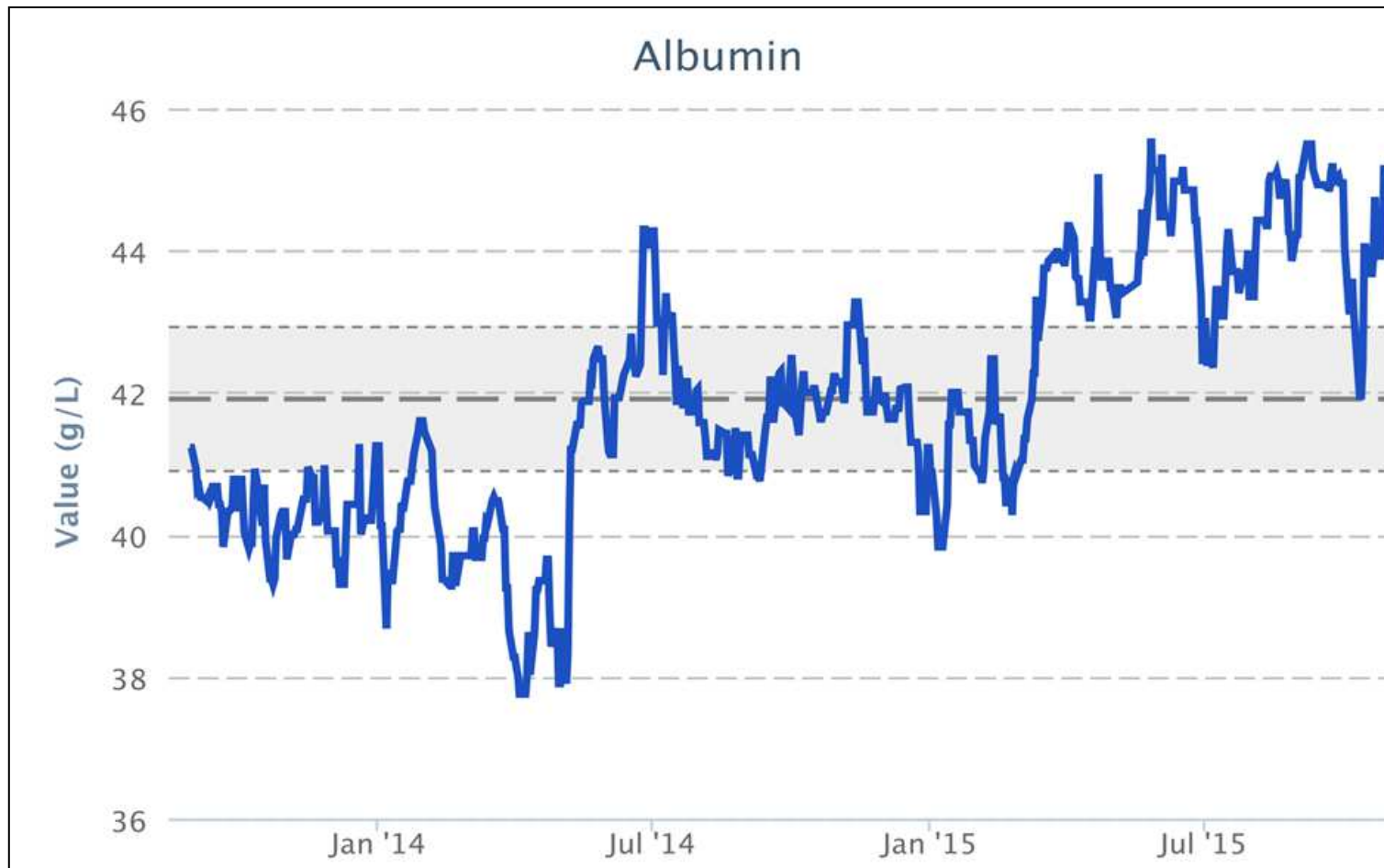
Albumin – Manufacturer A



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Identifying problem analytes (peer-specific)

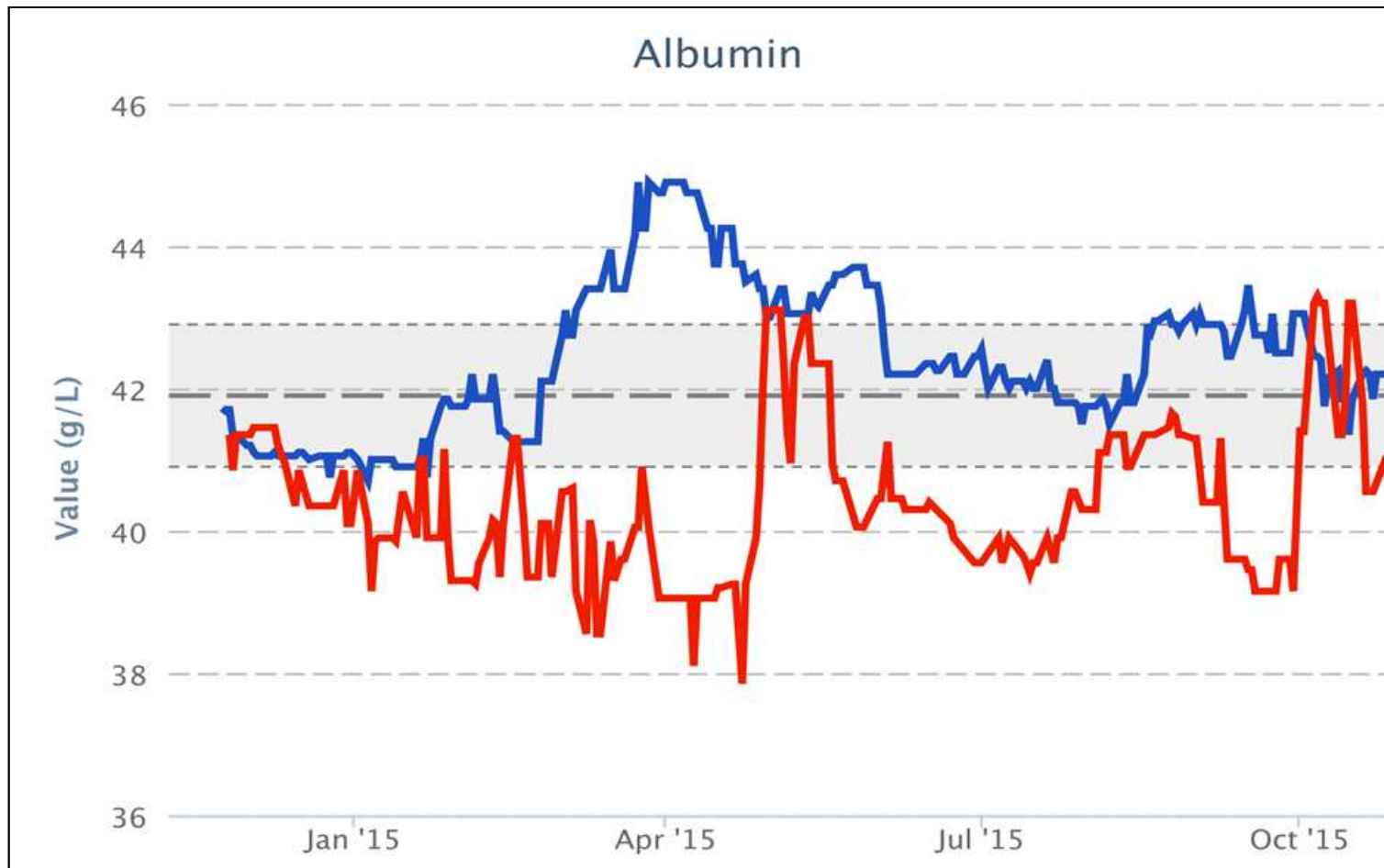
Albumin – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

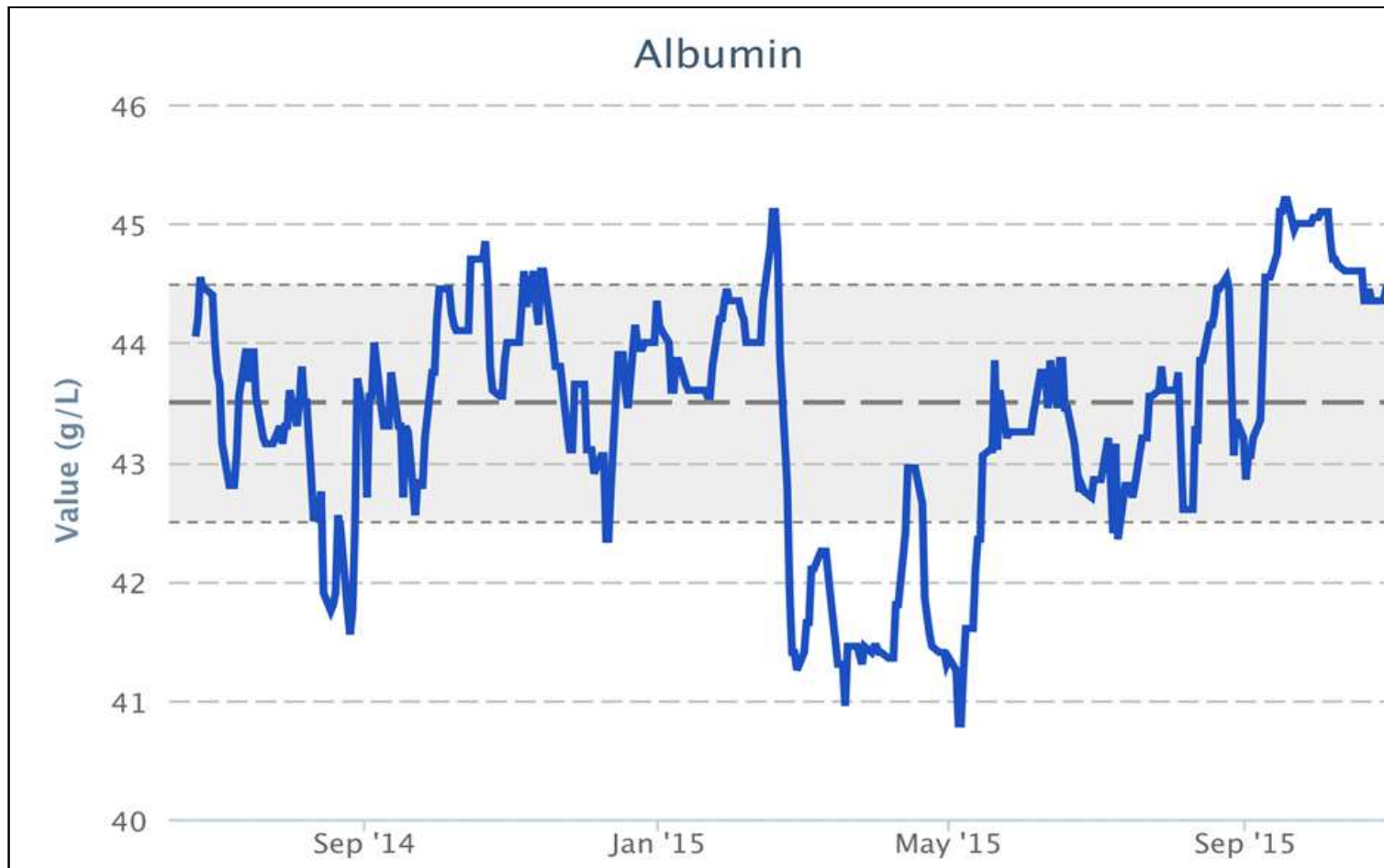
Albumin – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

Albumin – Manufacturer B

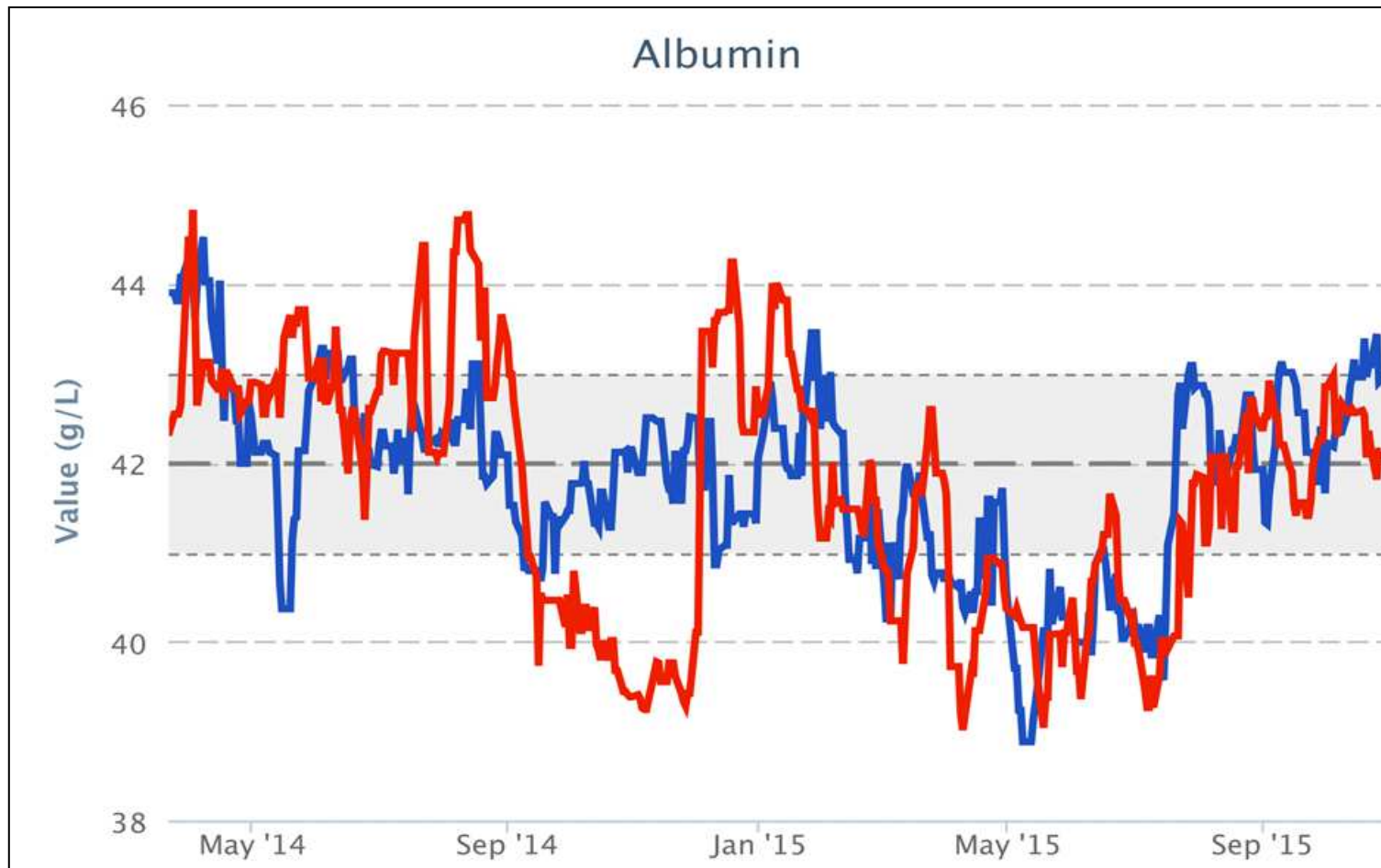




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Identifying problem analytes (peer-specific)

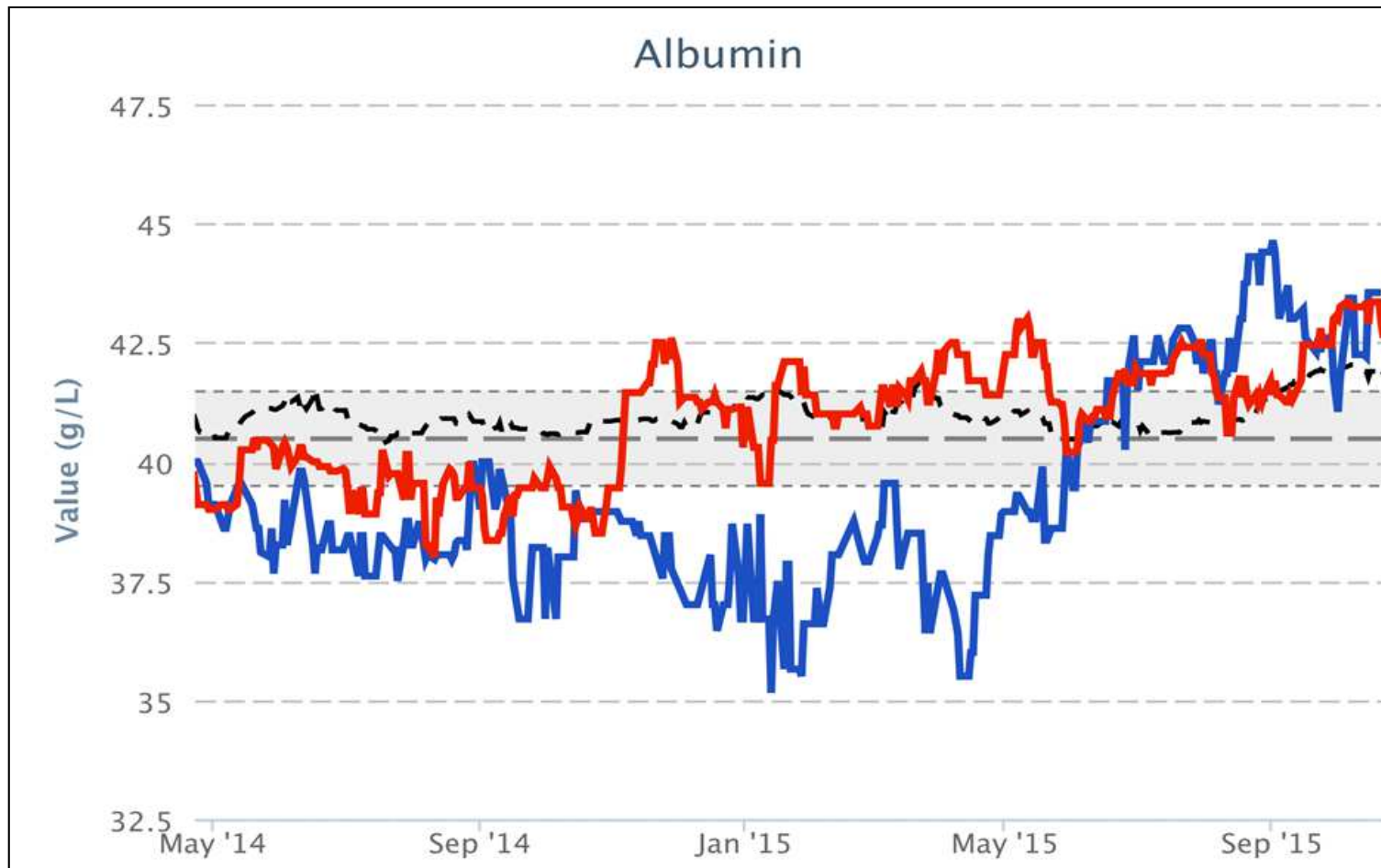
Albumin – Manufacturer C



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Identifying problem analytes (peer-specific)

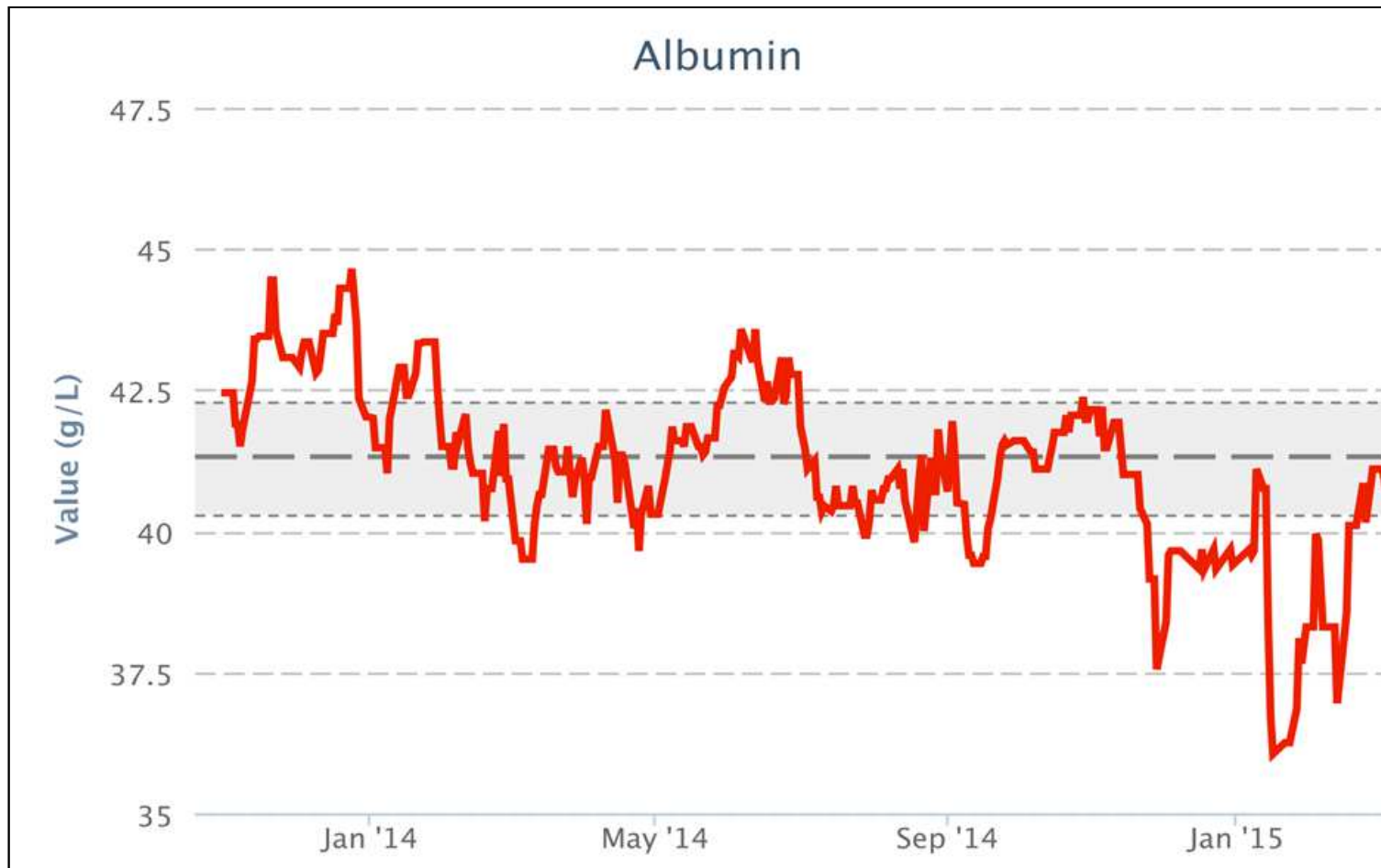
Albumin – Manufacturer C



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Identifying problem analytes (peer-specific)

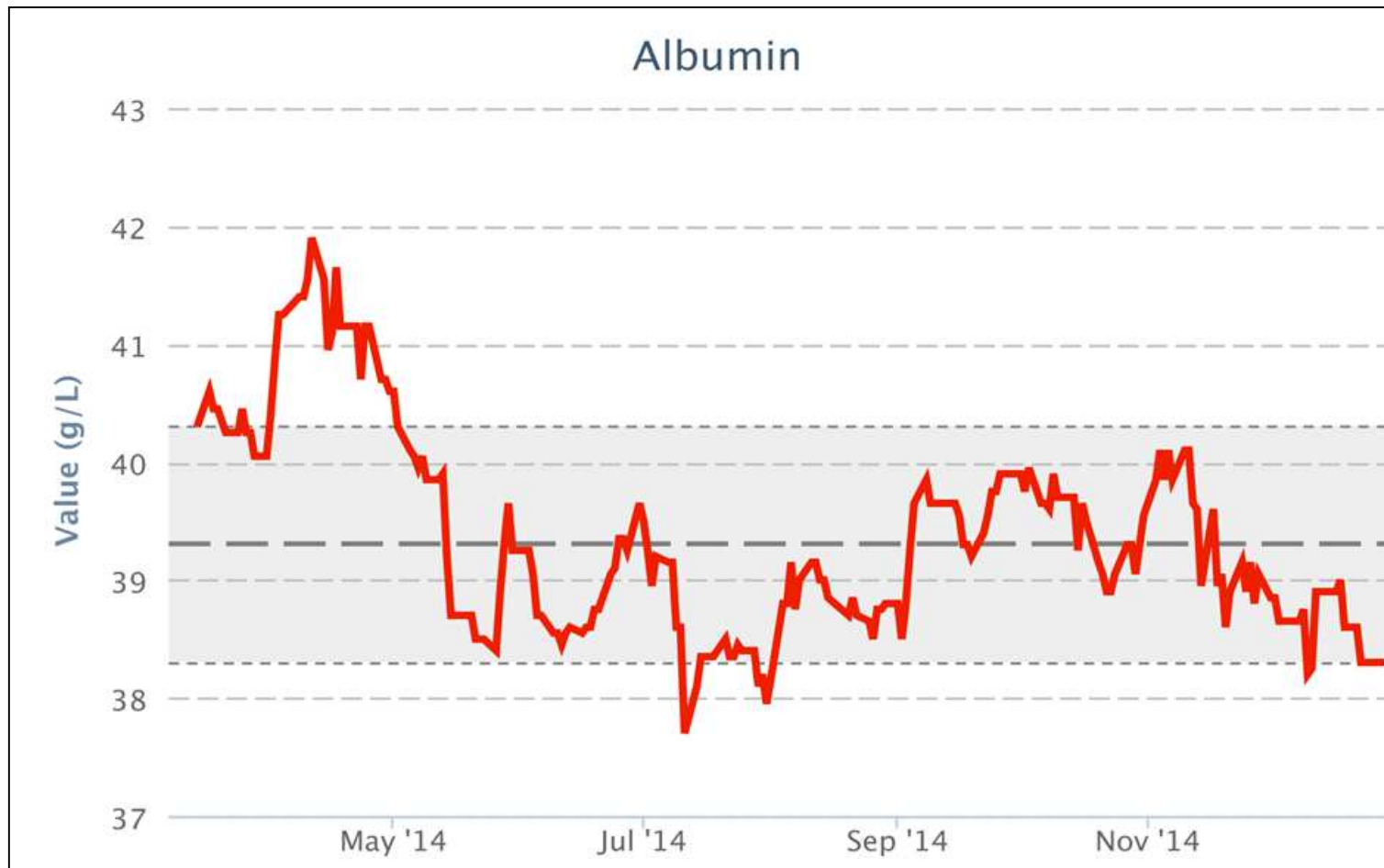
Albumin – Manufacturer C



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Identifying problem analytes (peer-specific)

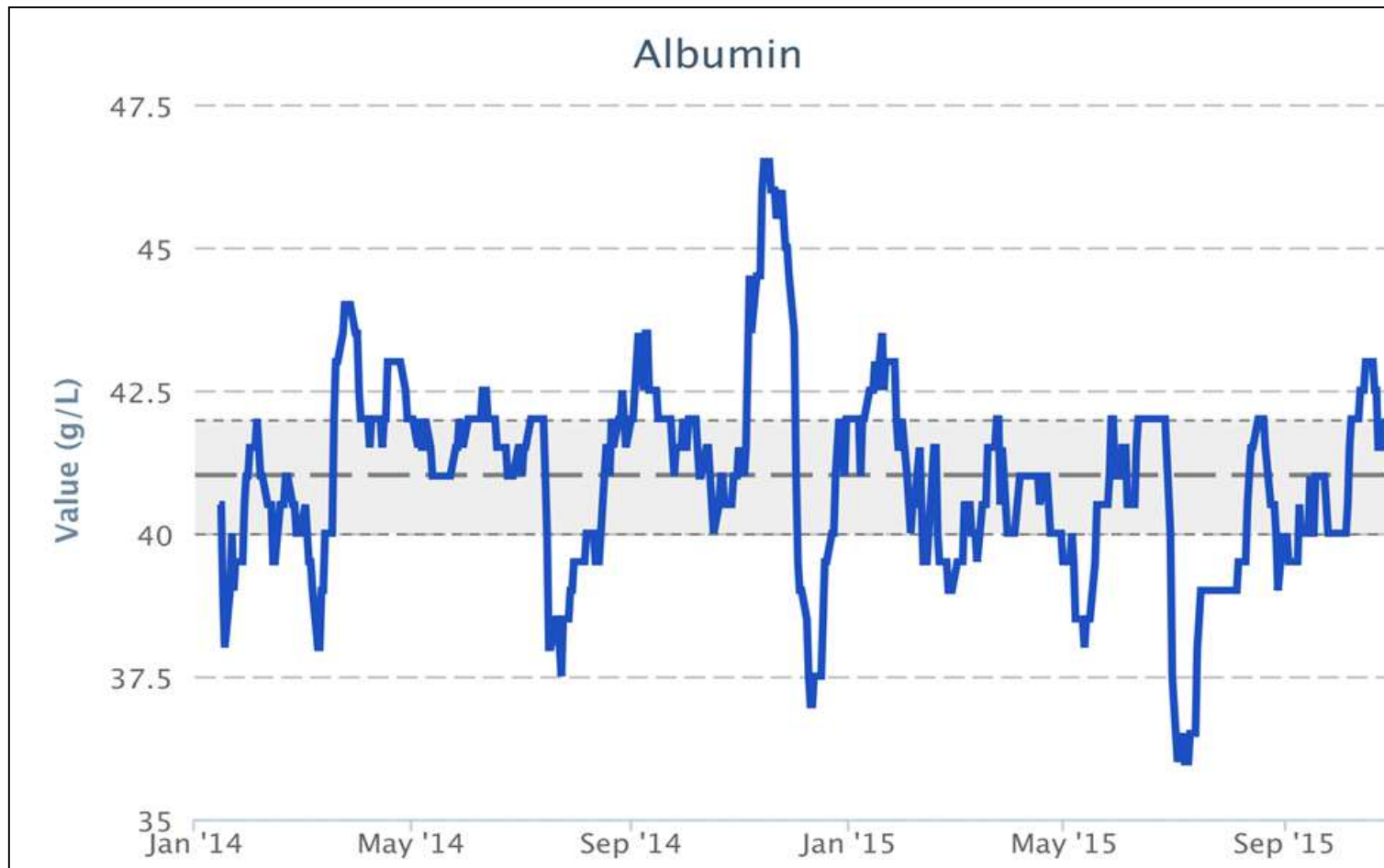
Albumin – Manufacturer D



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Identifying problem analytes (peer-specific)

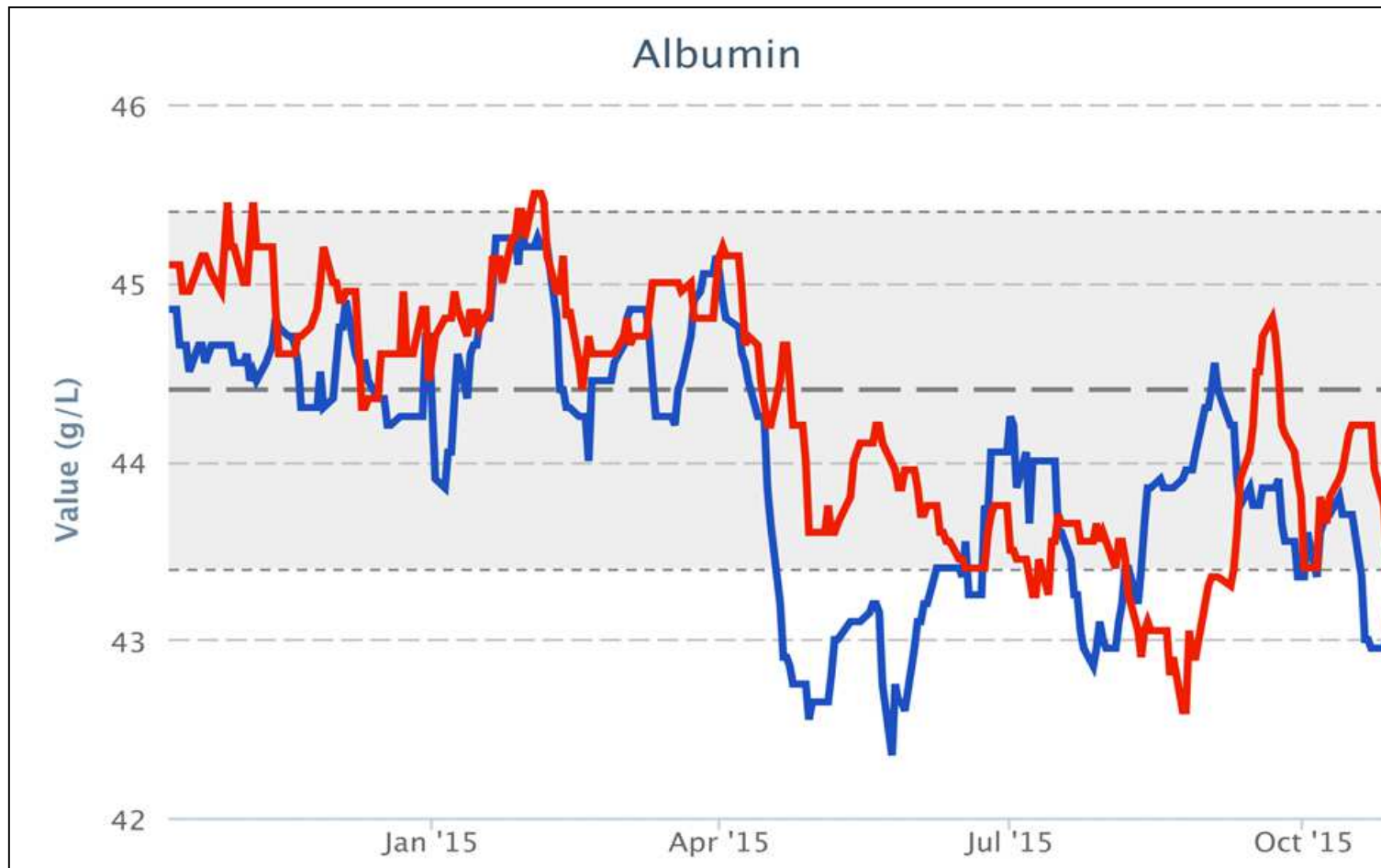
Albumin – Manufacturer E



# Percentiler Applications

Identifying problem analytes (peer-specific)

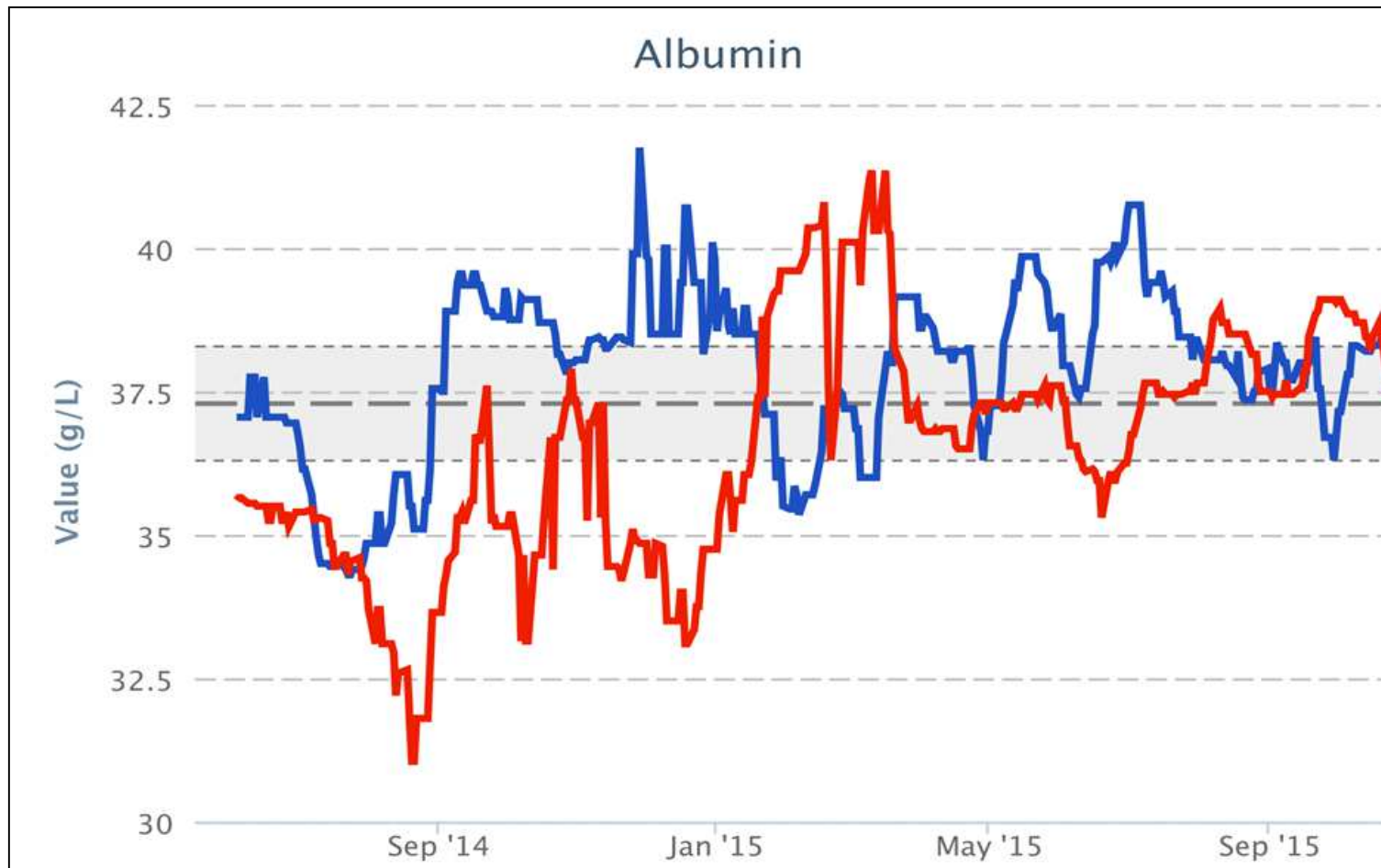
Albumin – Manufacturer F



# Percentiler Applications

Identifying problem analytes (peer-specific)

Albumin – Manufacturer G

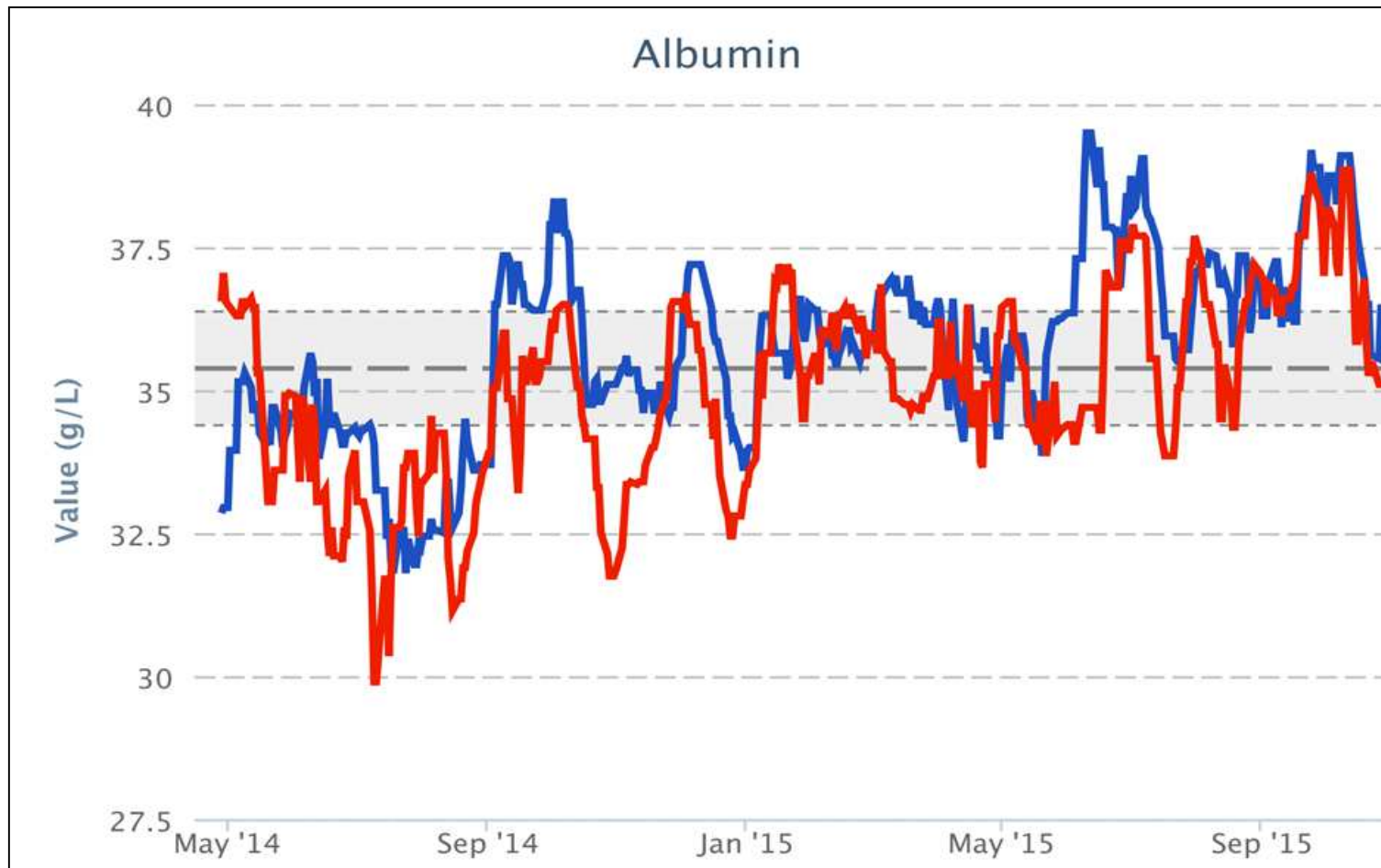




# Percentiler Applications

Identifying problem analytes (peer-specific)

Albumin – Manufacturer G

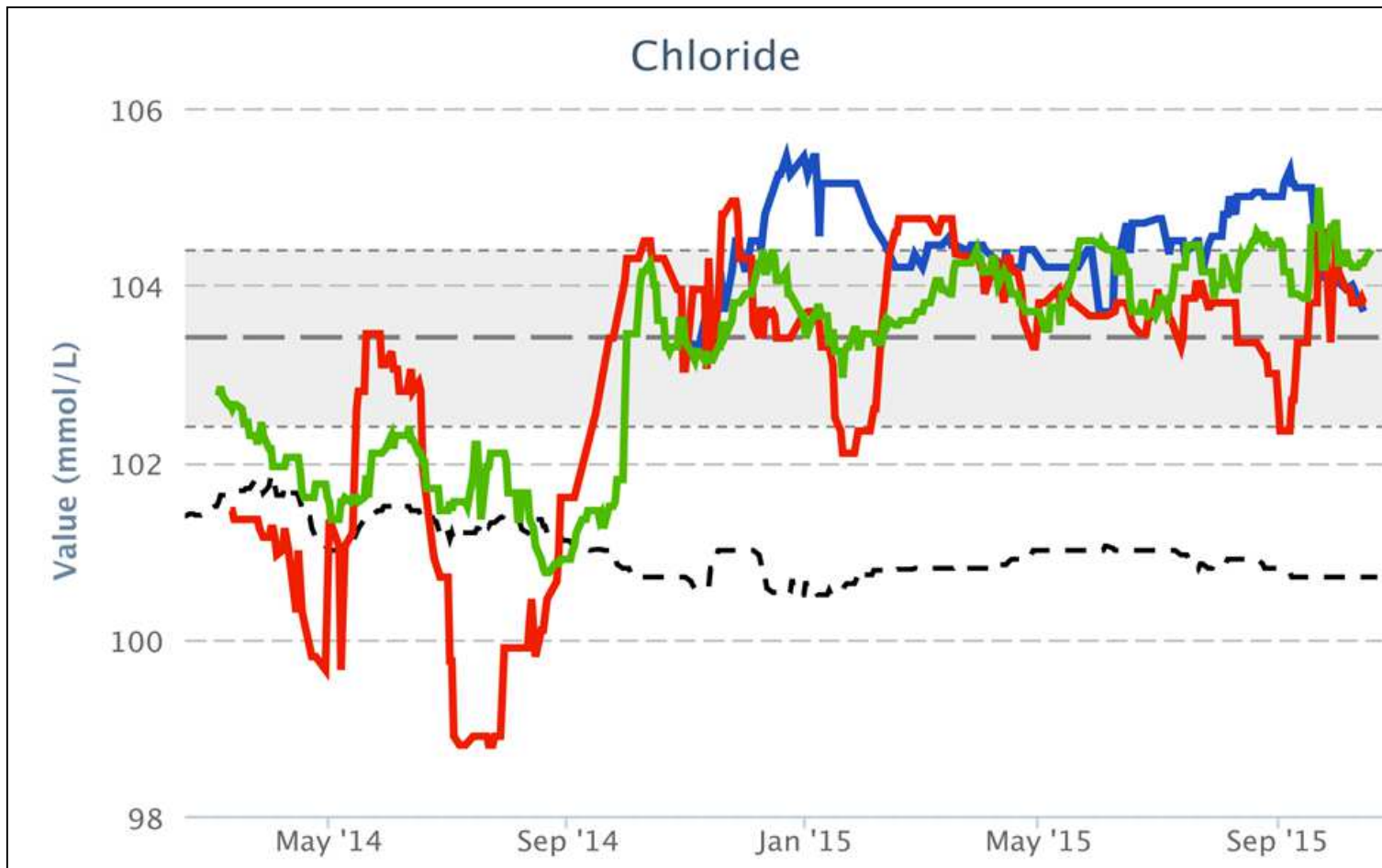




# Percentiler Applications

Identifying problem analytes (peer-specific)

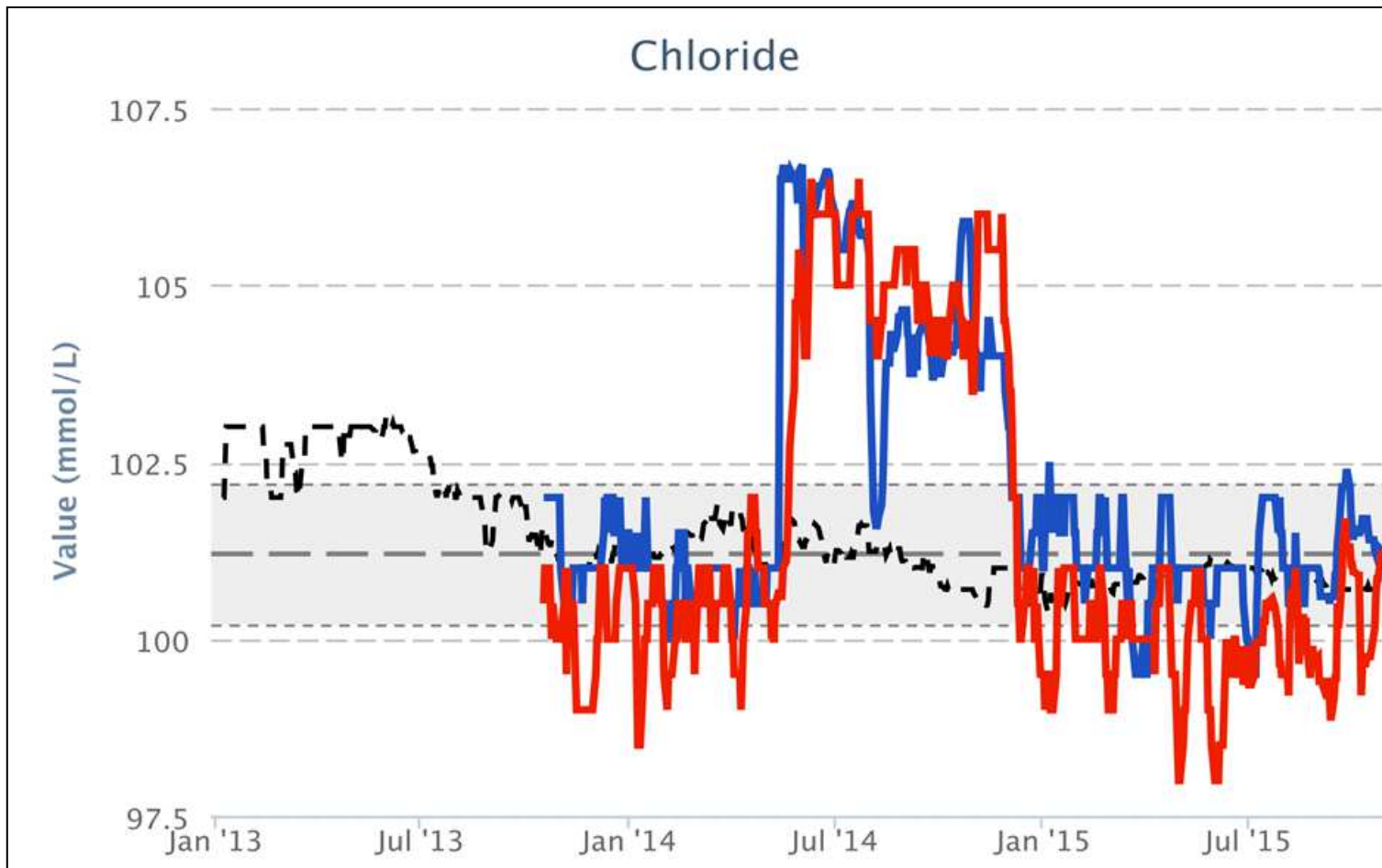
Chloride – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

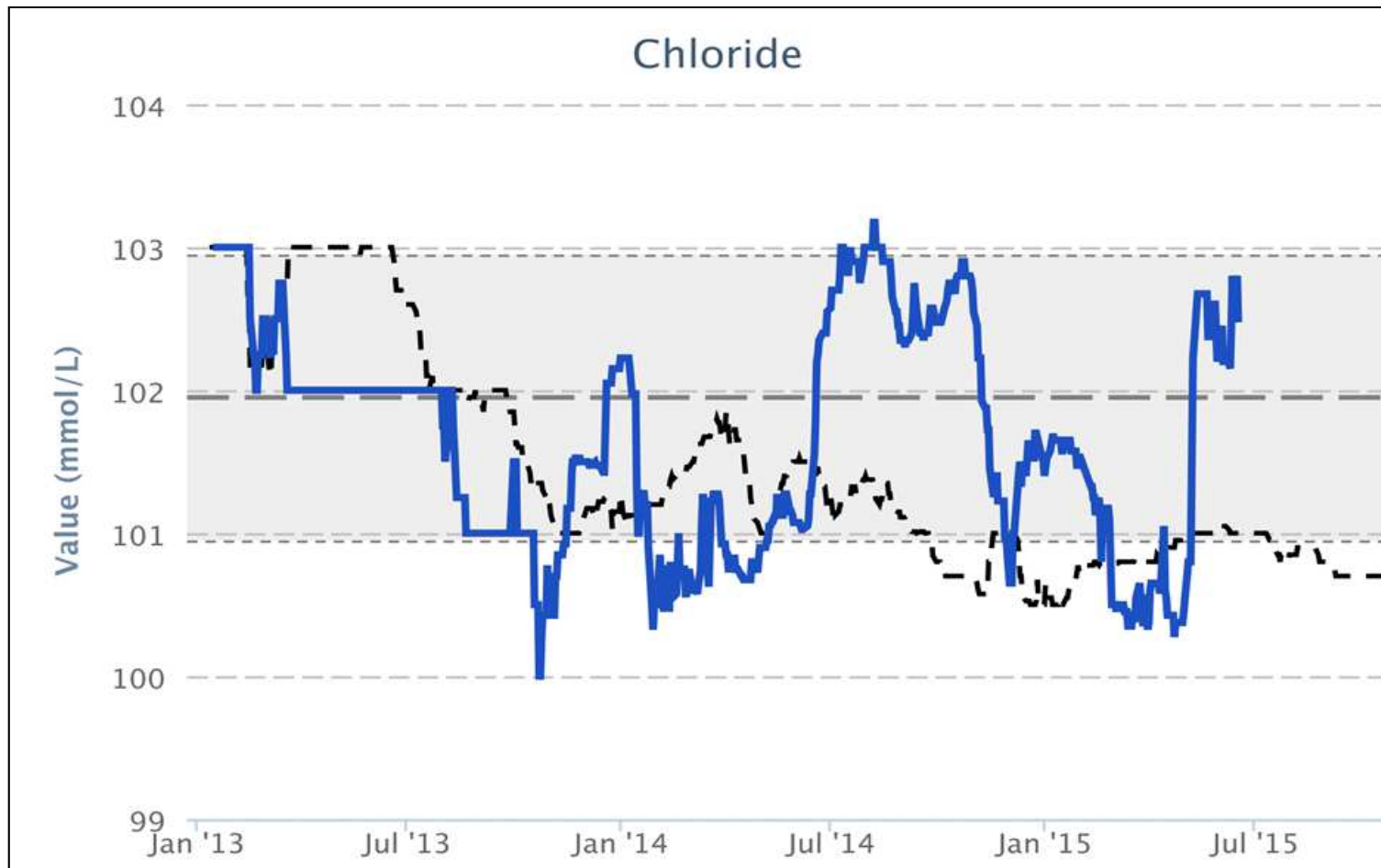
Chloride – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

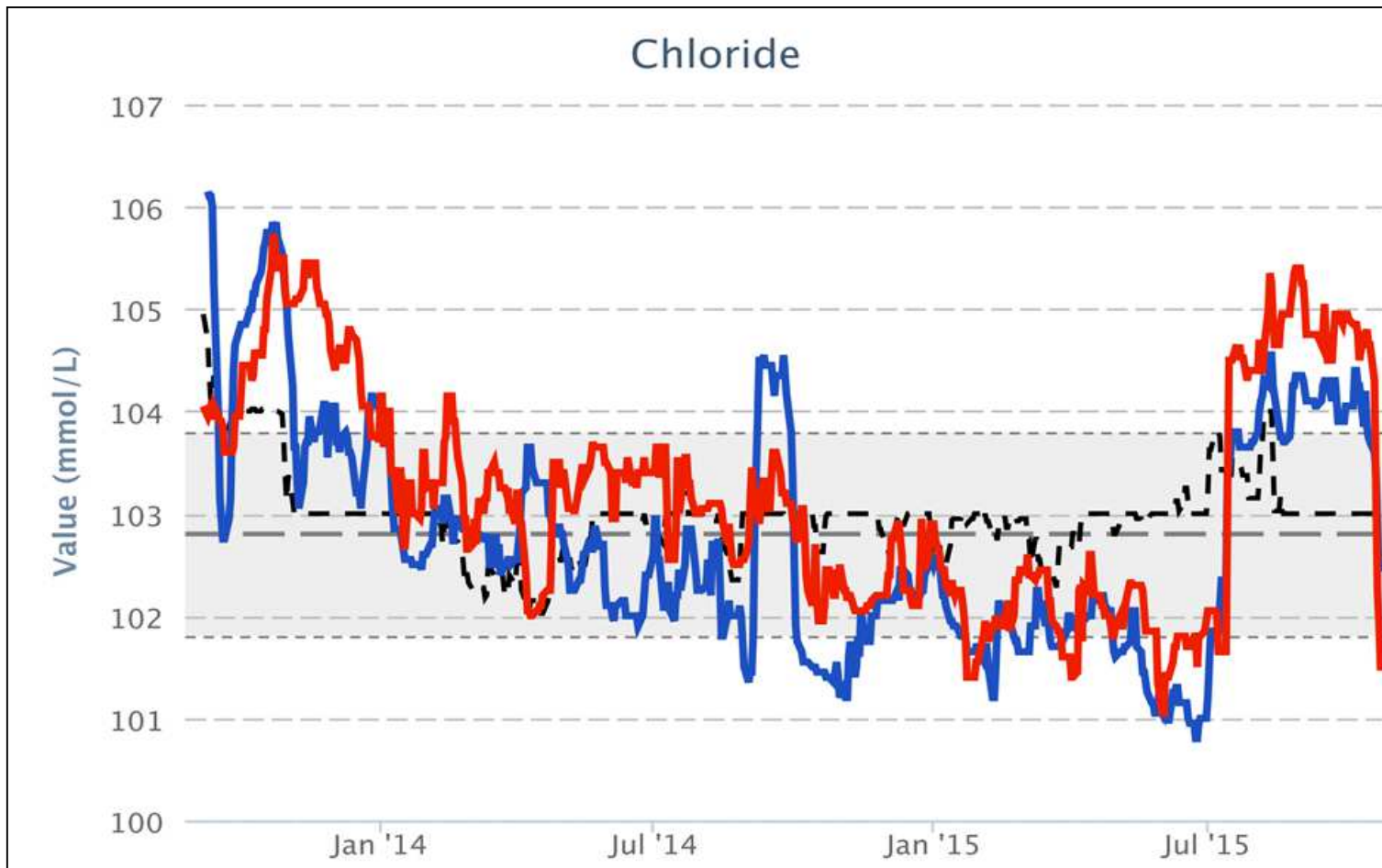
Chloride – Manufacturer B



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Identifying problem analytes (peer-specific)

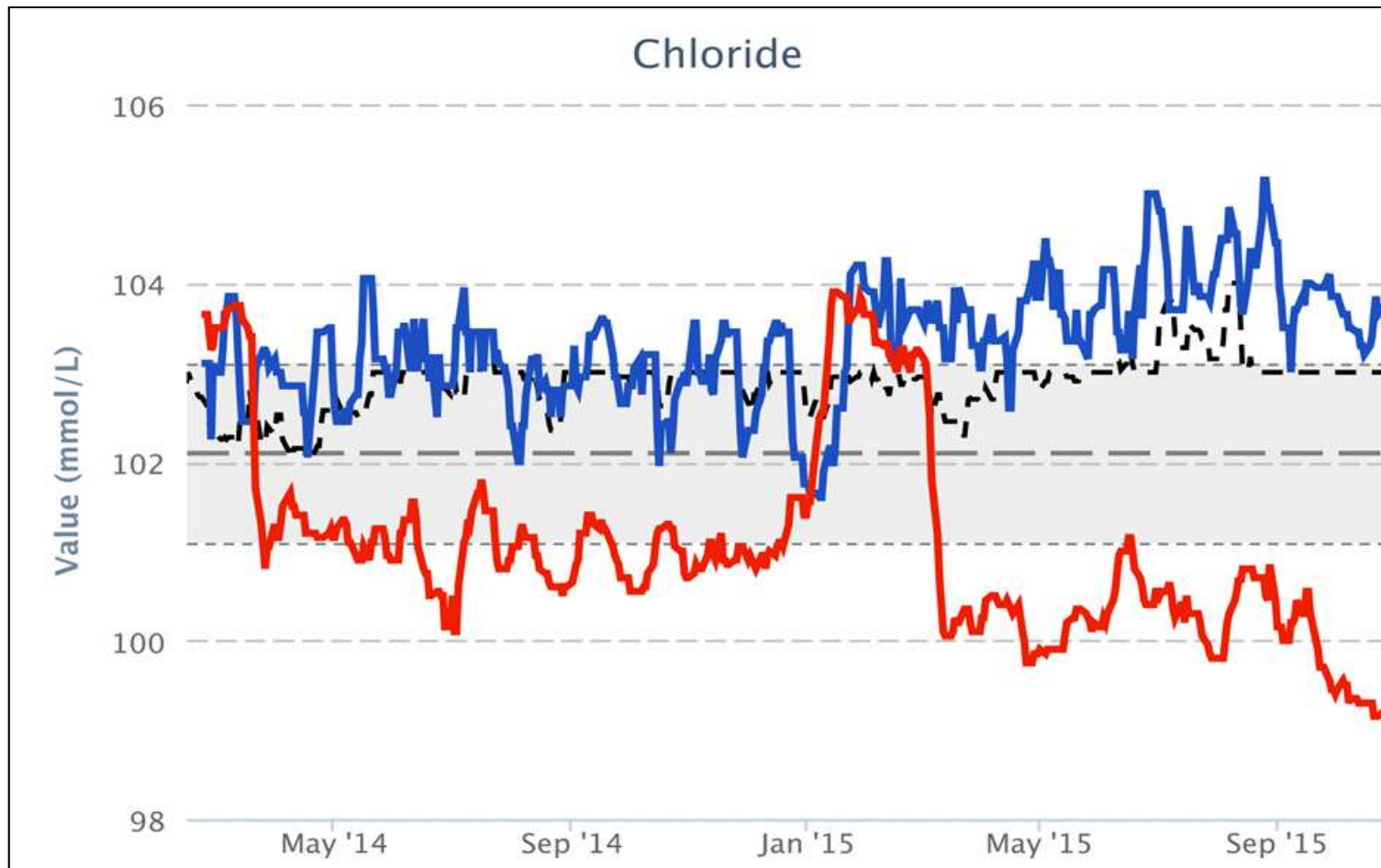
Chloride – Manufacturer C



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Identifying problem analytes (peer-specific)

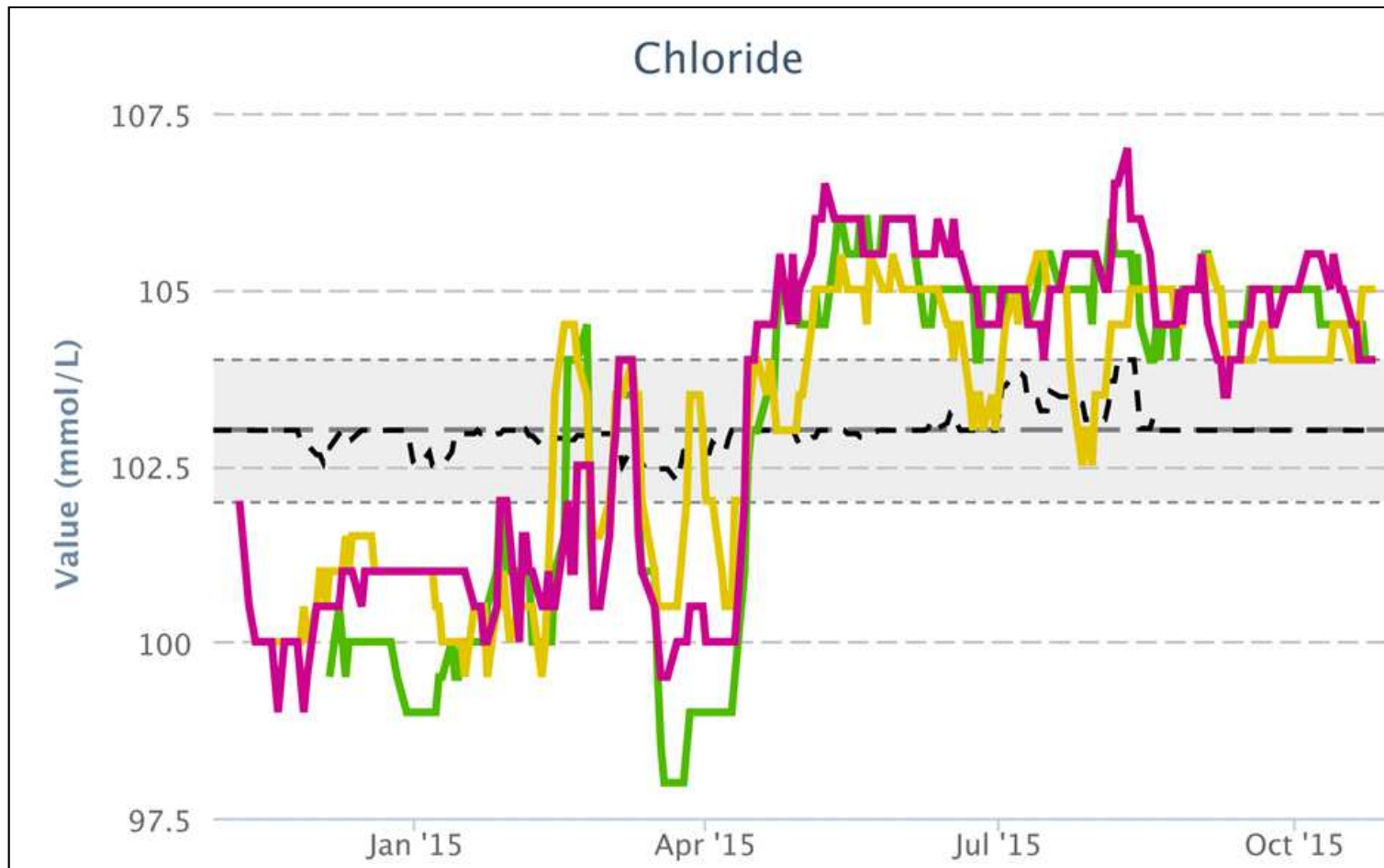
Chloride – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Chloride – Manufacturer C

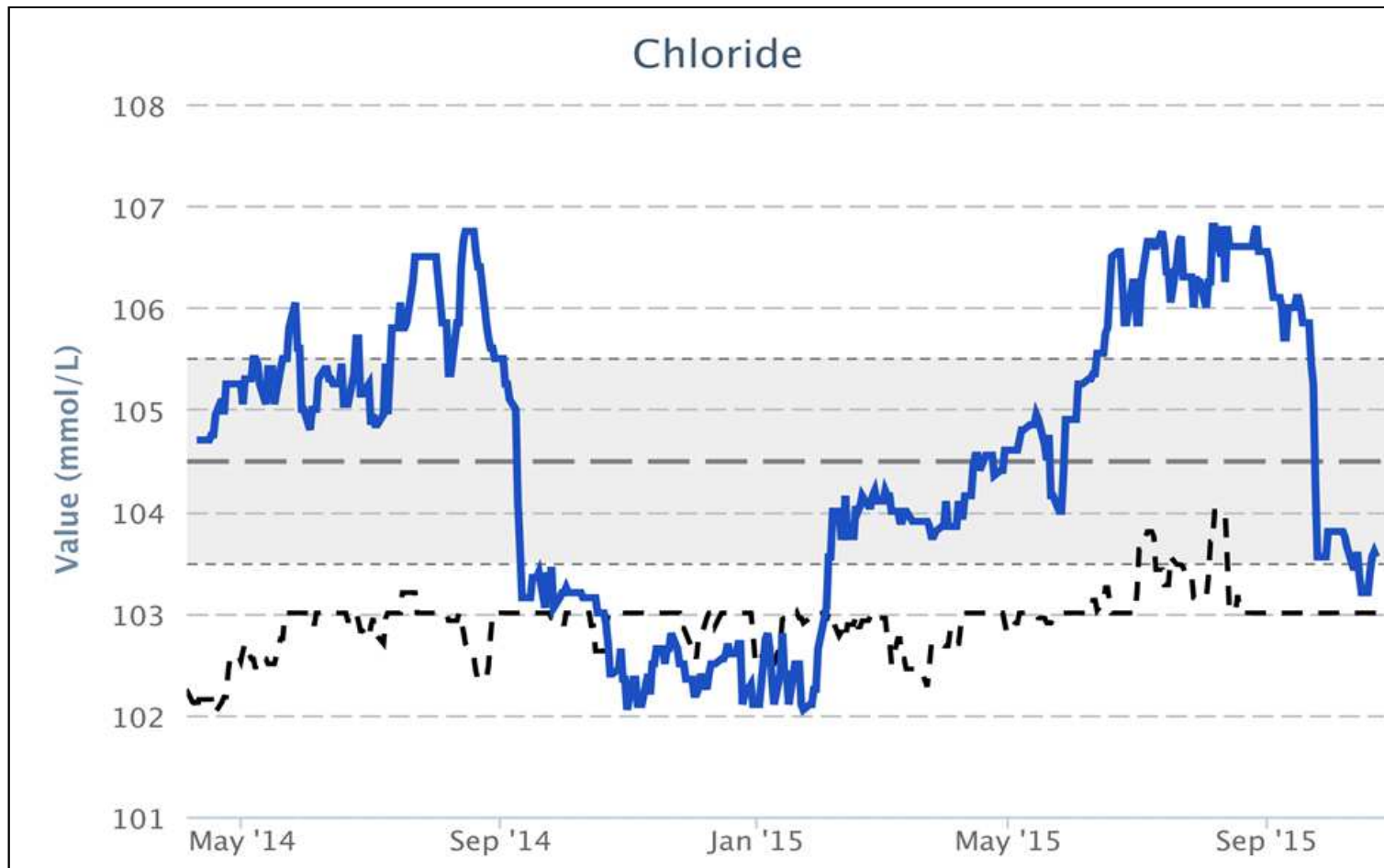




# Percentiler Applications

Identifying problem analytes (peer-specific)

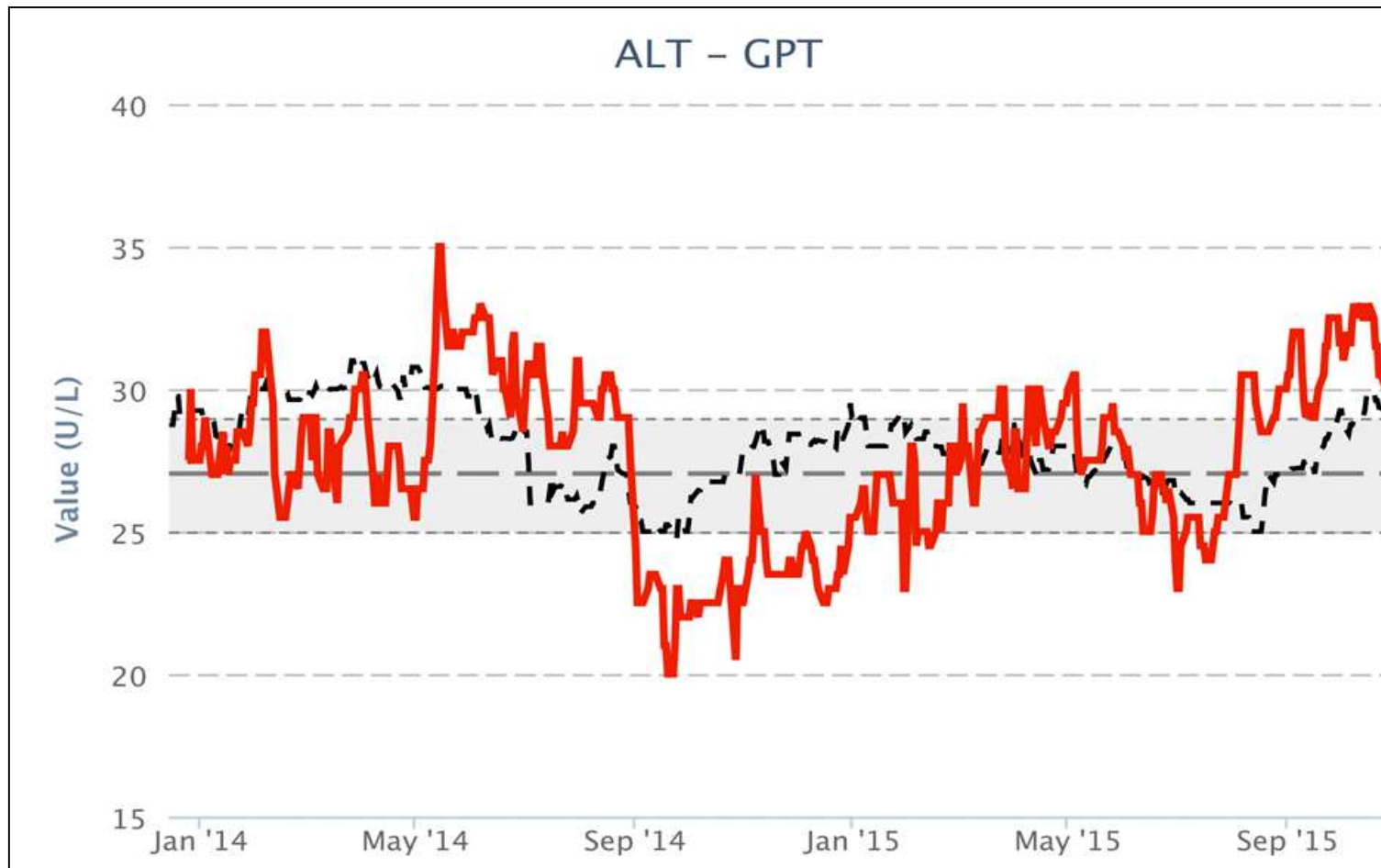
Chloride – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

ALT – Manufacturer C

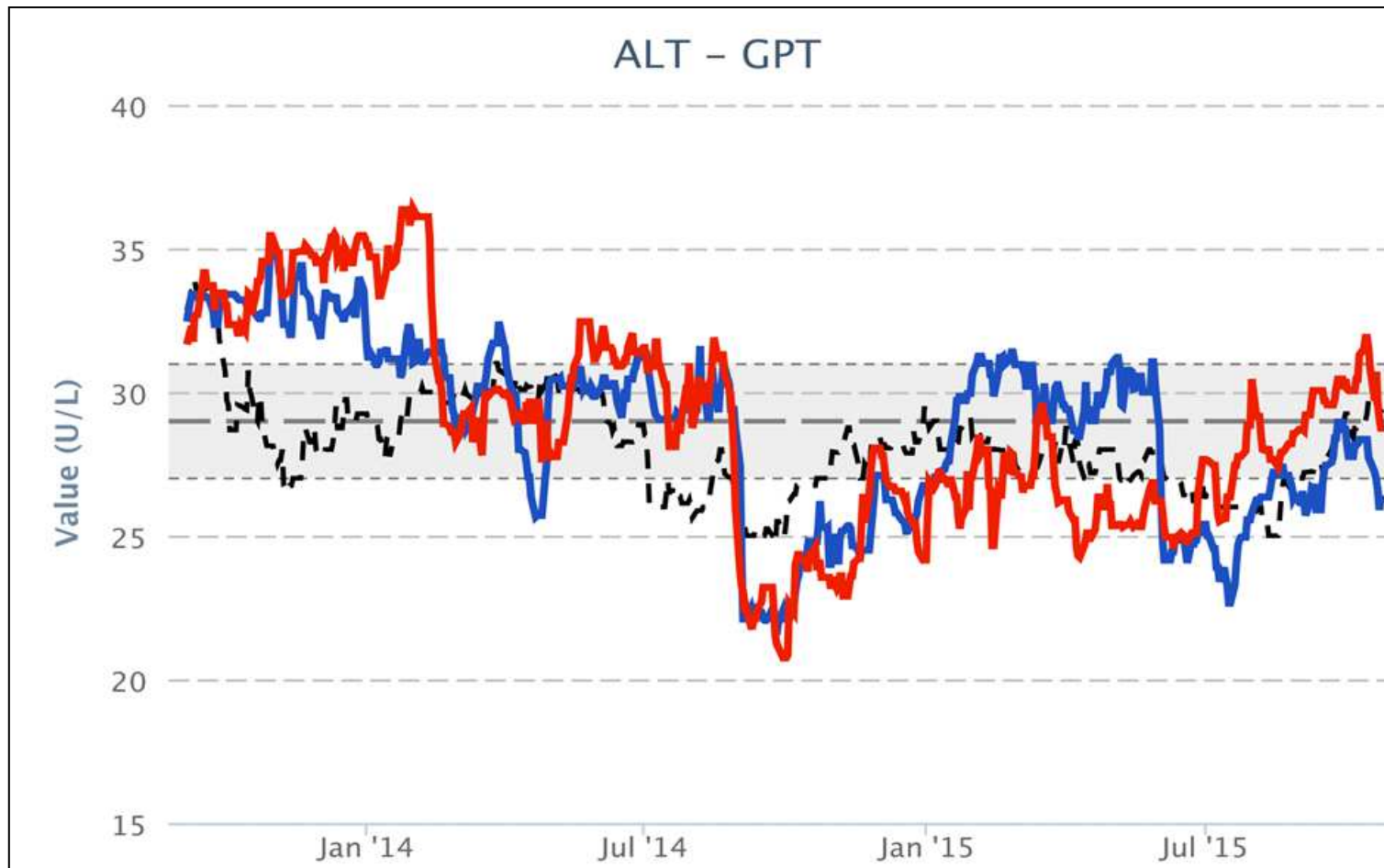




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Identifying problem analytes (peer-specific)

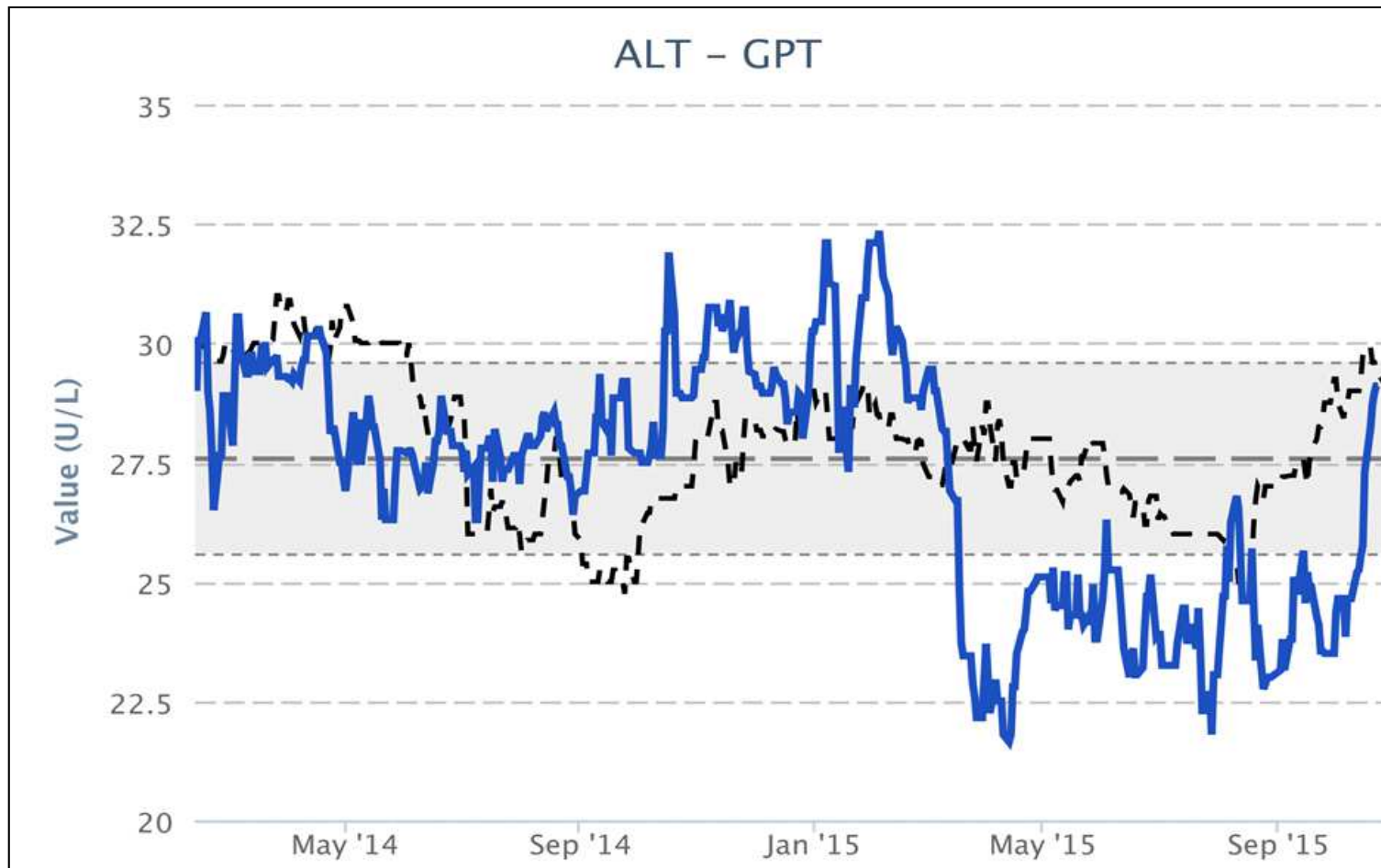
ALT – Manufacturer C



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Identifying problem analytes (peer-specific)

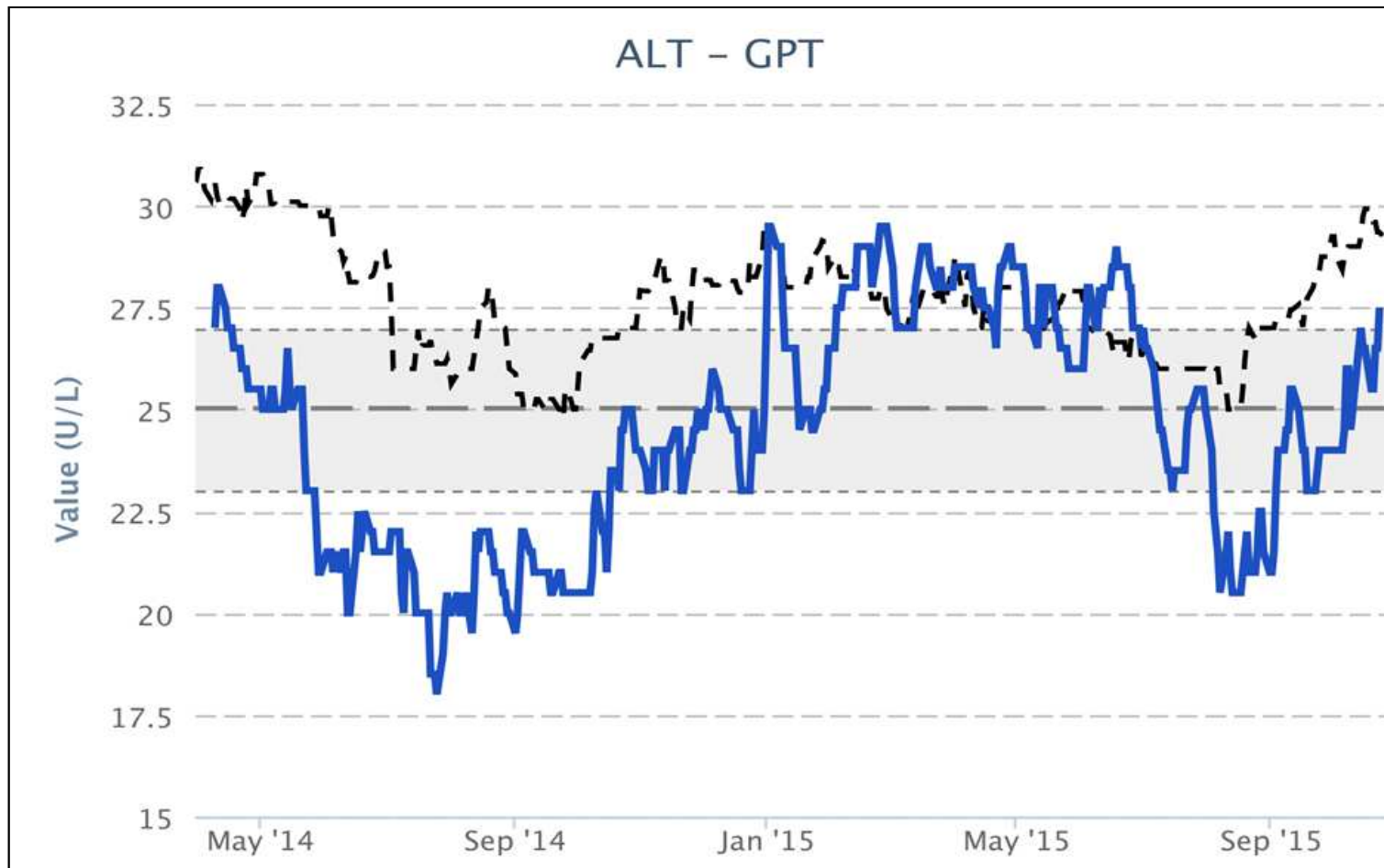
ALT – Manufacturer C



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Identifying problem analytes (peer-specific)

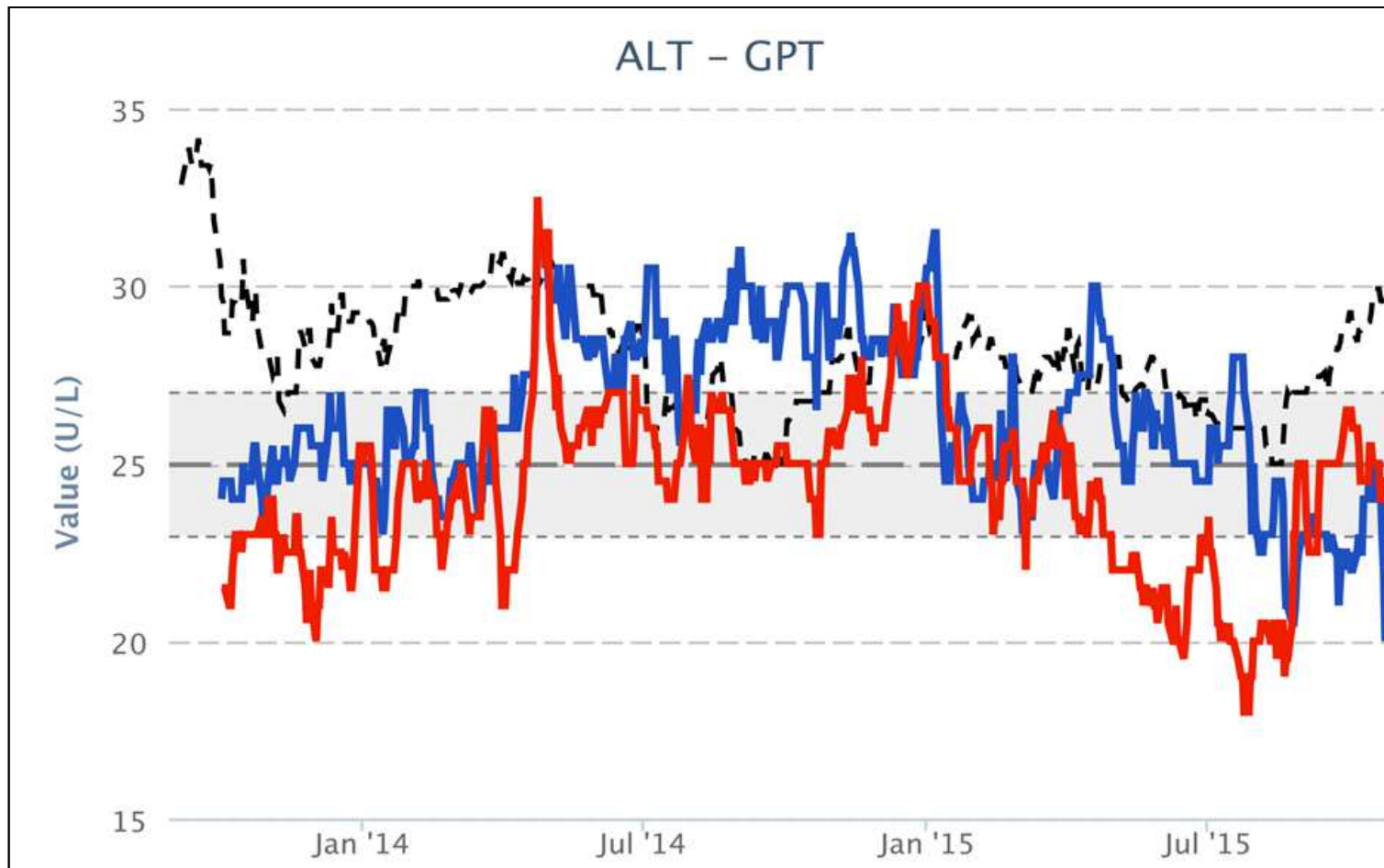
ALT – Manufacturer C



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Identifying problem analytes (peer-specific)

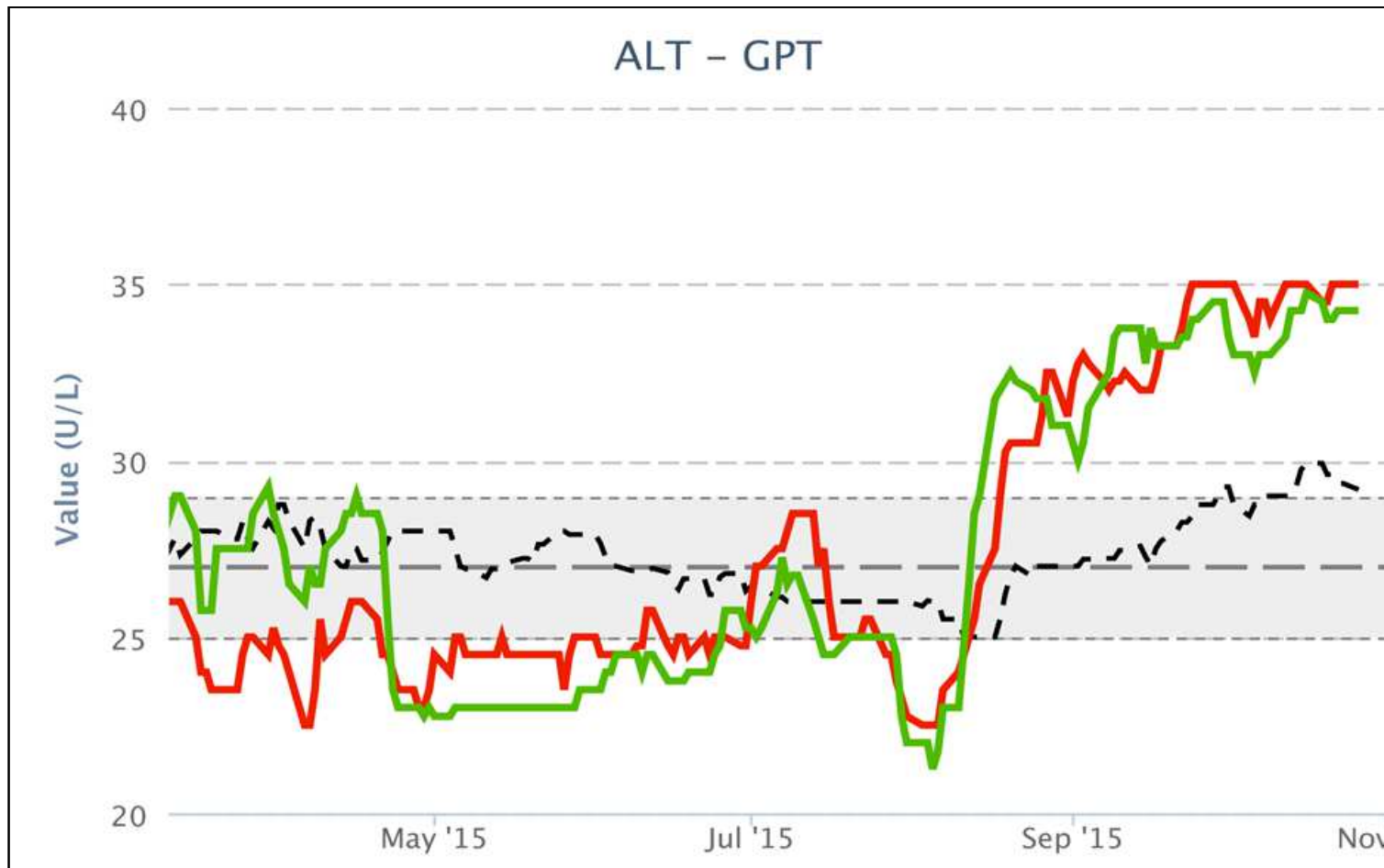
ALT – Manufacturer C



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Identifying problem analytes (peer-specific)

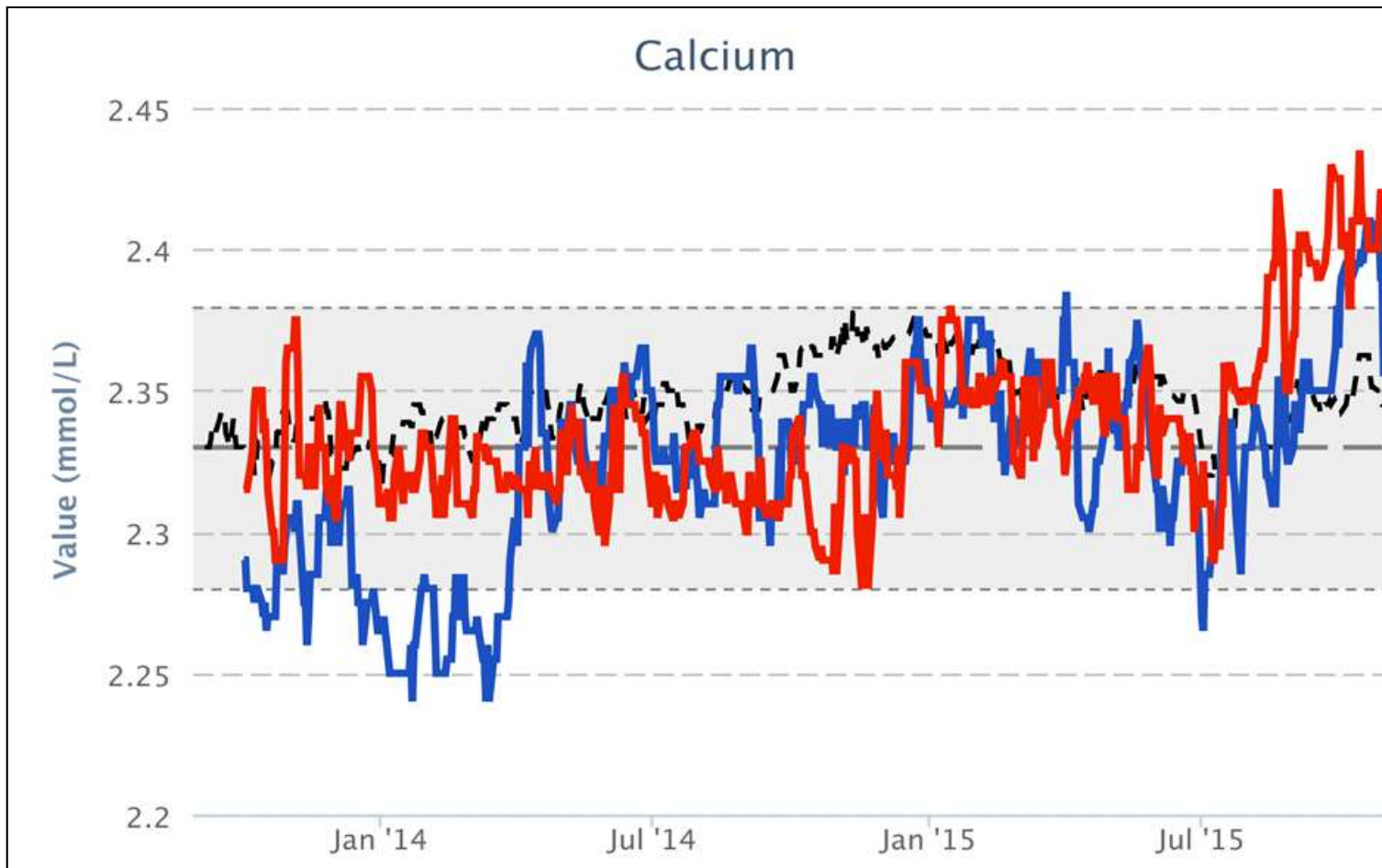
ALT – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Calcium – Manufacturer C

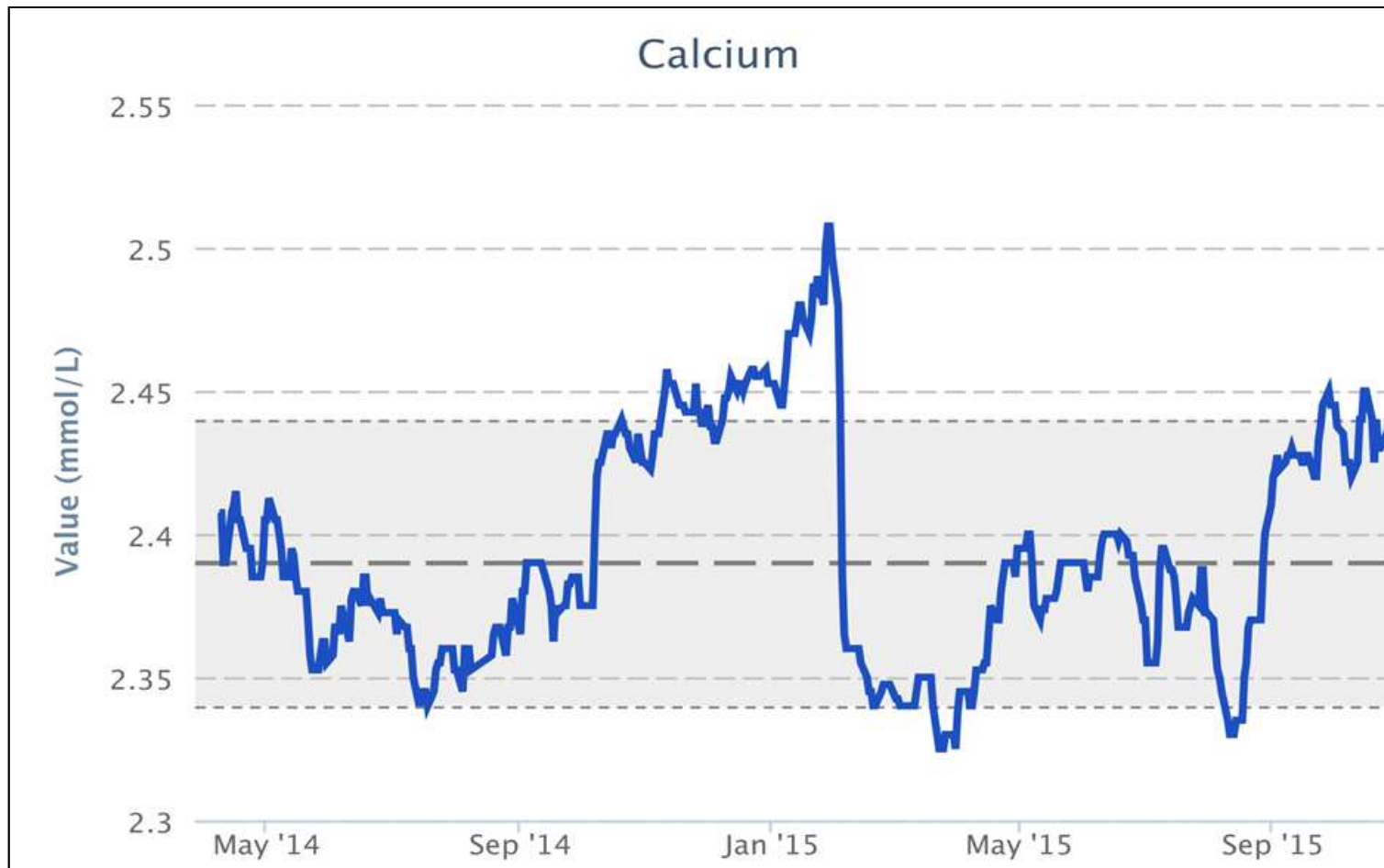




# Percentiler Applications

Identifying problem analytes (peer-specific)

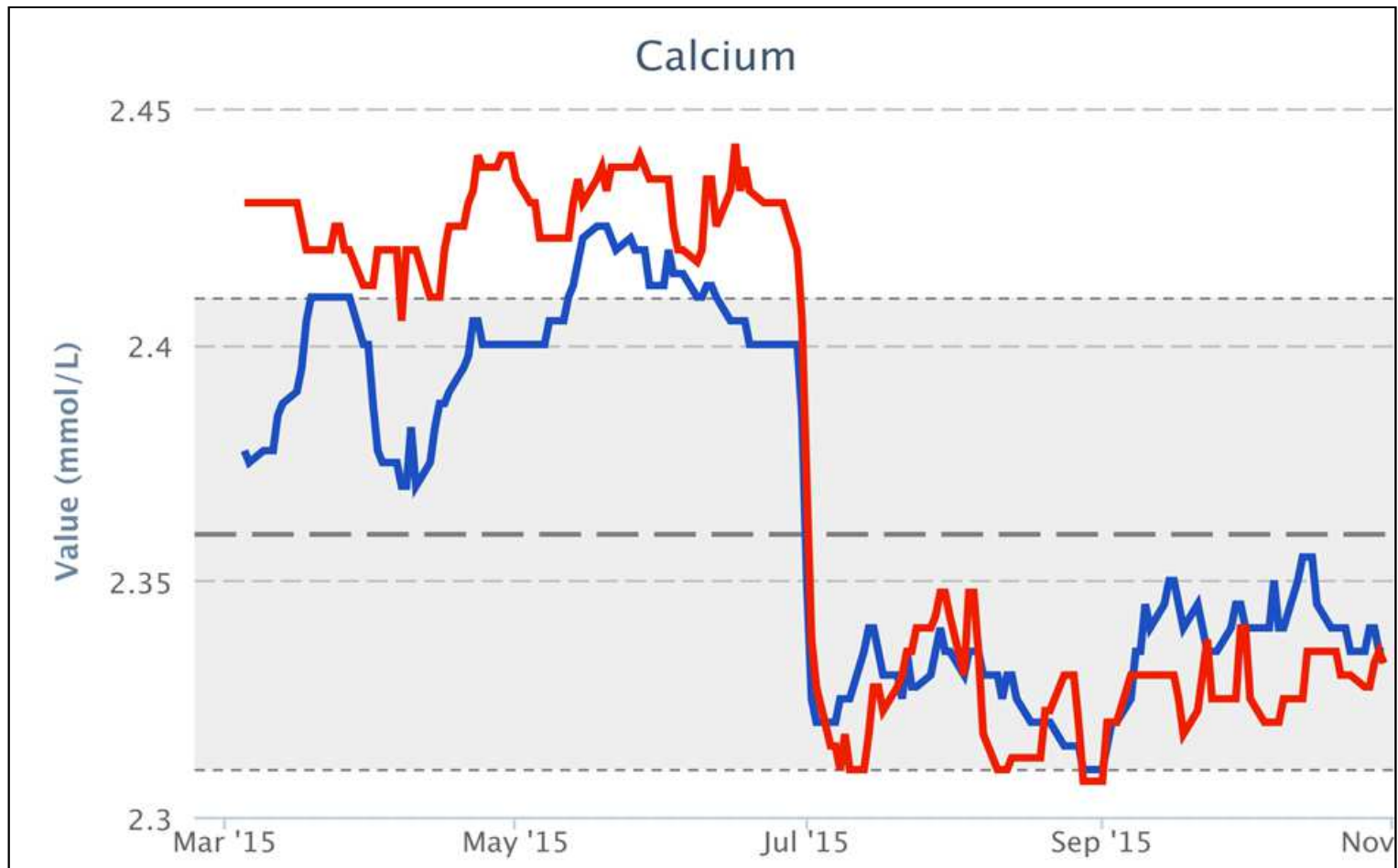
Calcium – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Calcium – Manufacturer C

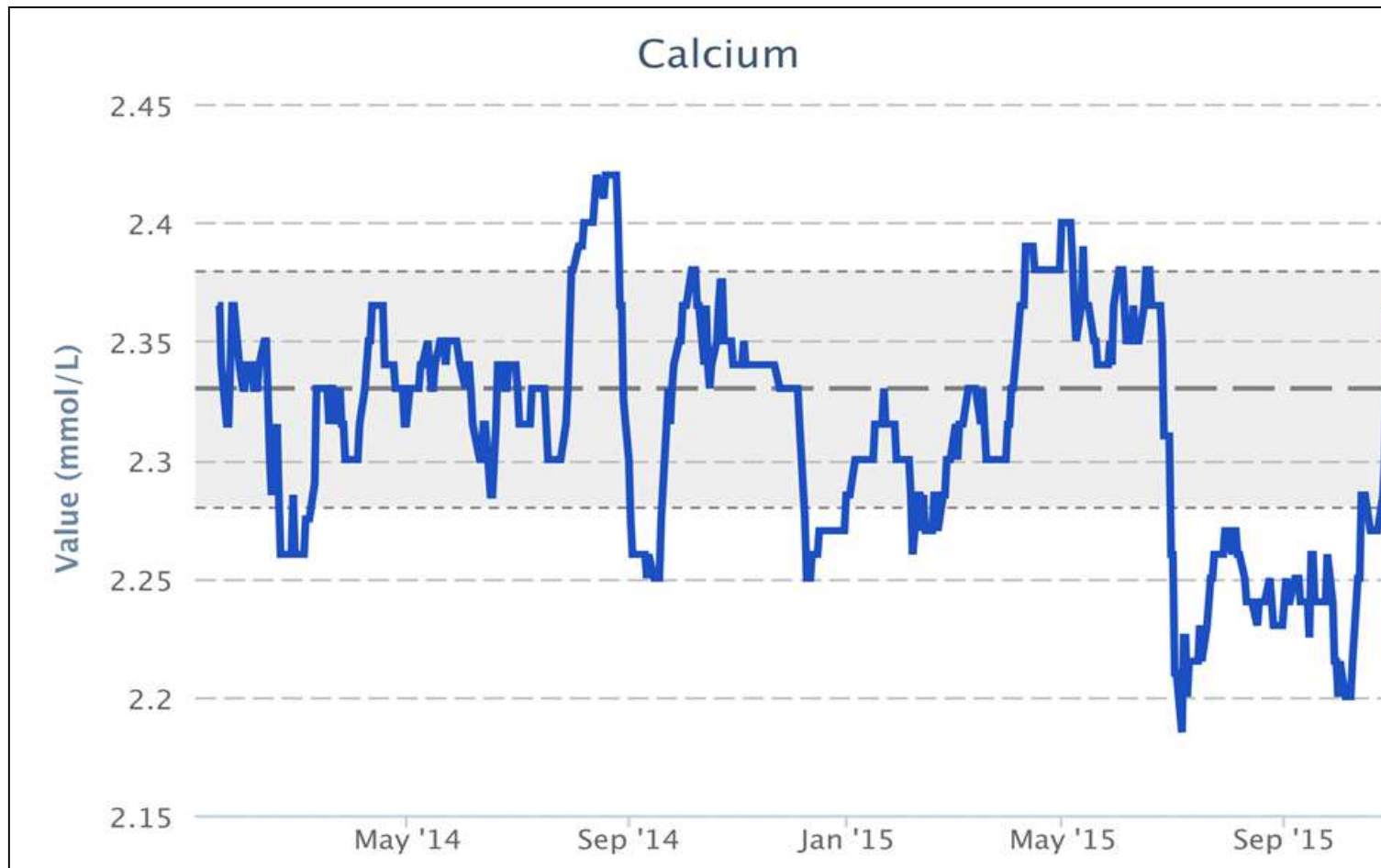




# Percentiler Applications

Identifying problem analytes (peer-specific)

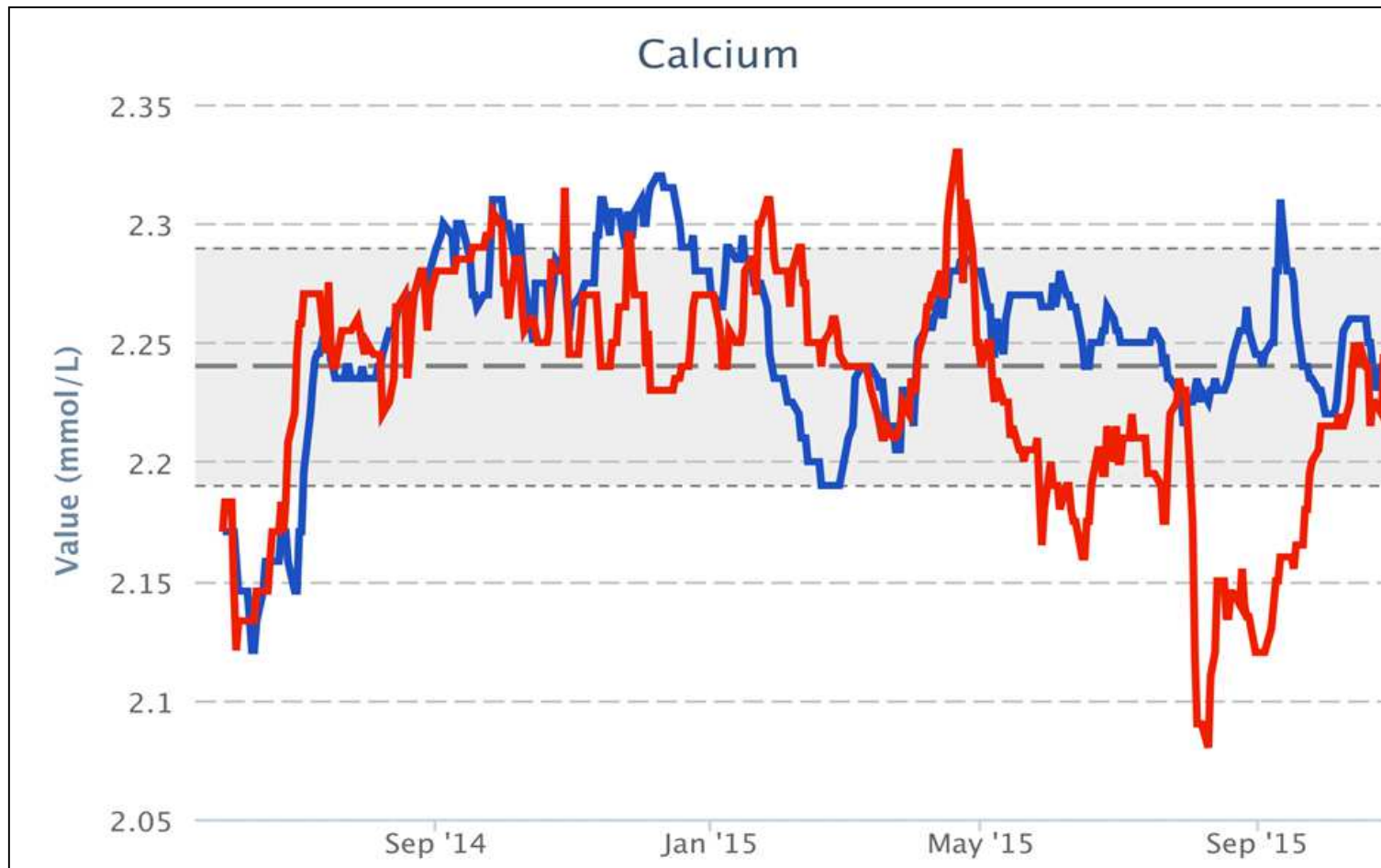
Calcium – Manufacturer G



# Percentiler Applications

Identifying problem analytes (peer-specific)

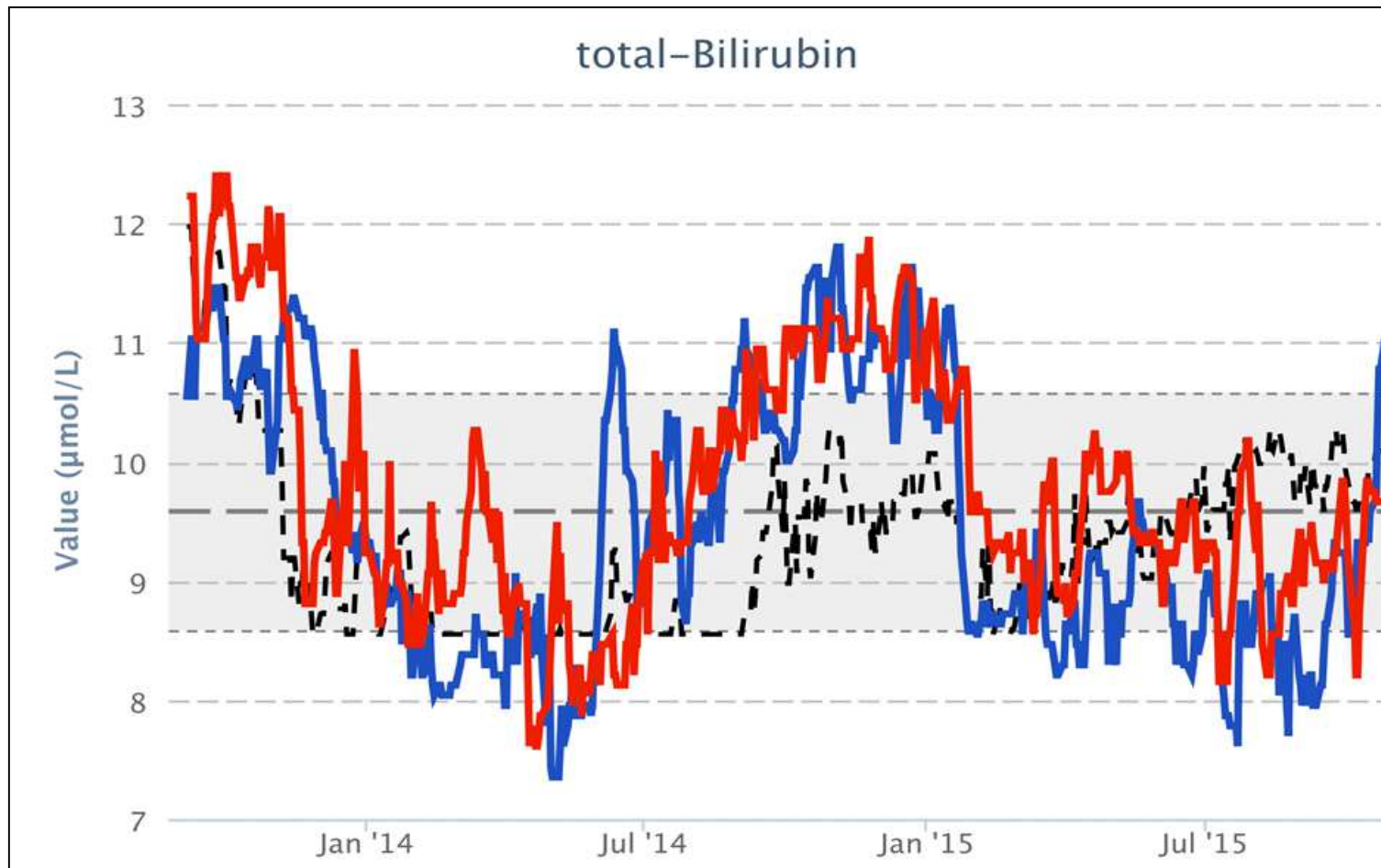
Calcium – Manufacturer G



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Identifying problem analytes (peer-specific)

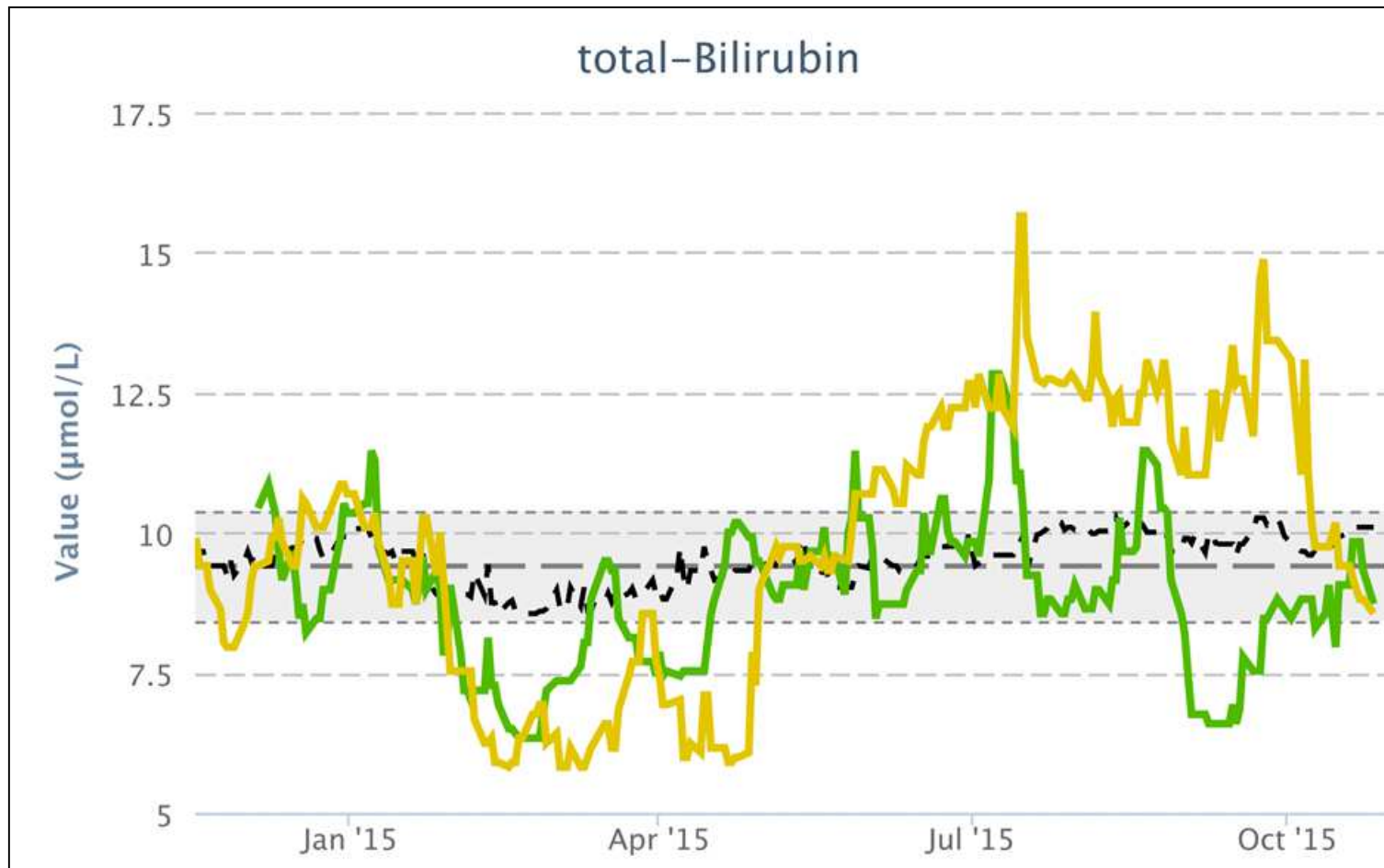
Total-Bilirubin – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

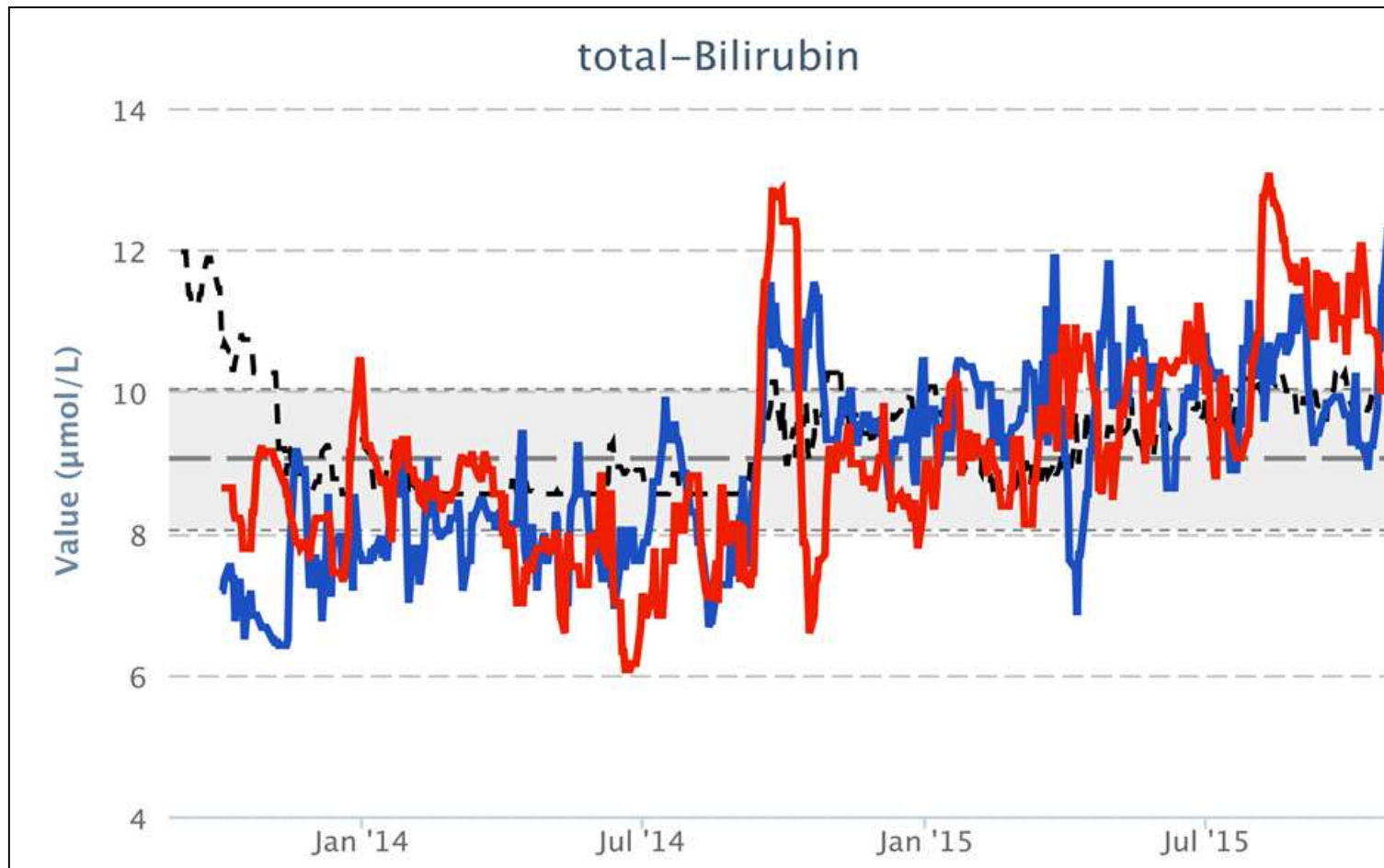
Total-Bilirubin – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

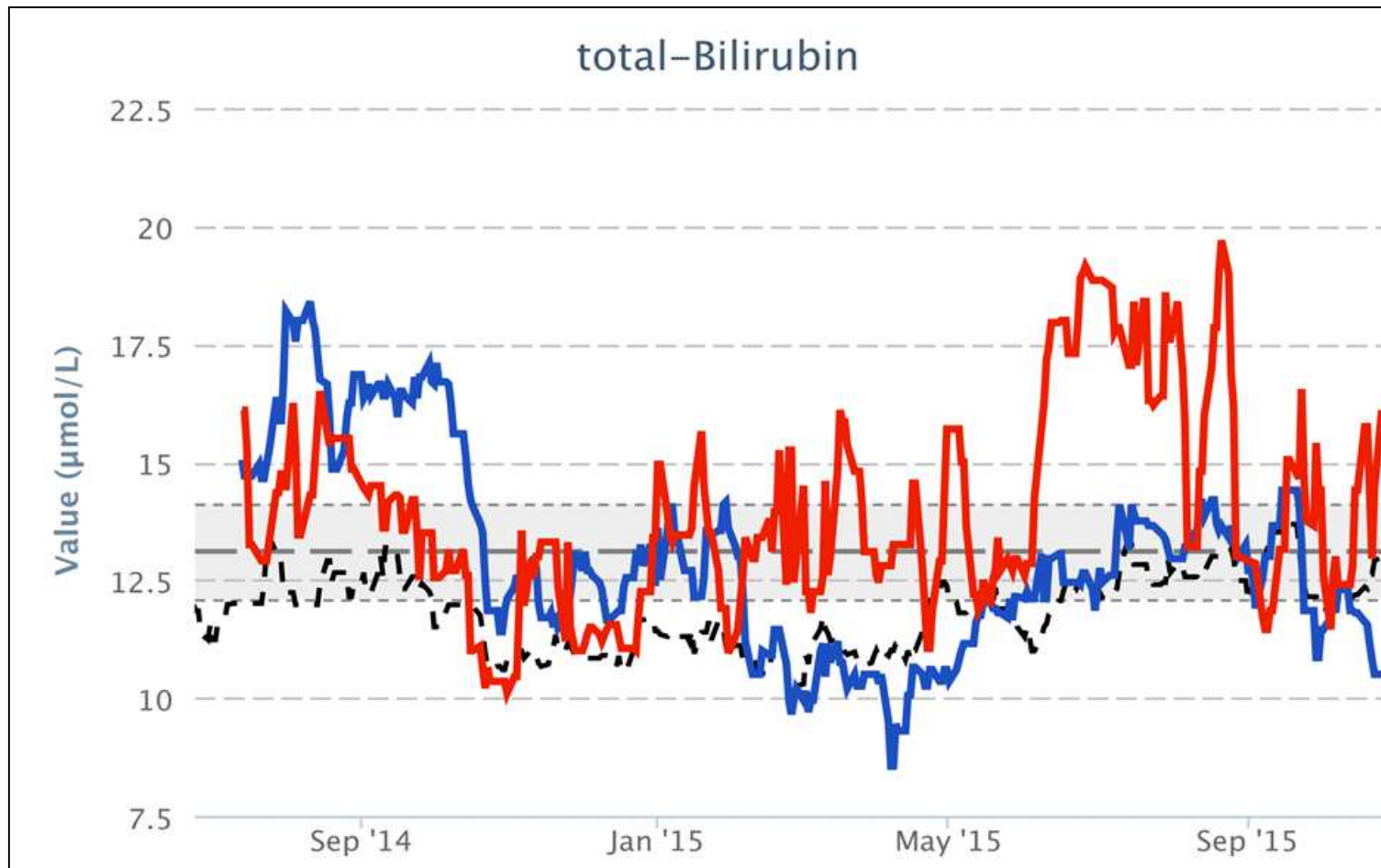
Total-Bilirubin – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Total-Bilirubin – Manufacturer D

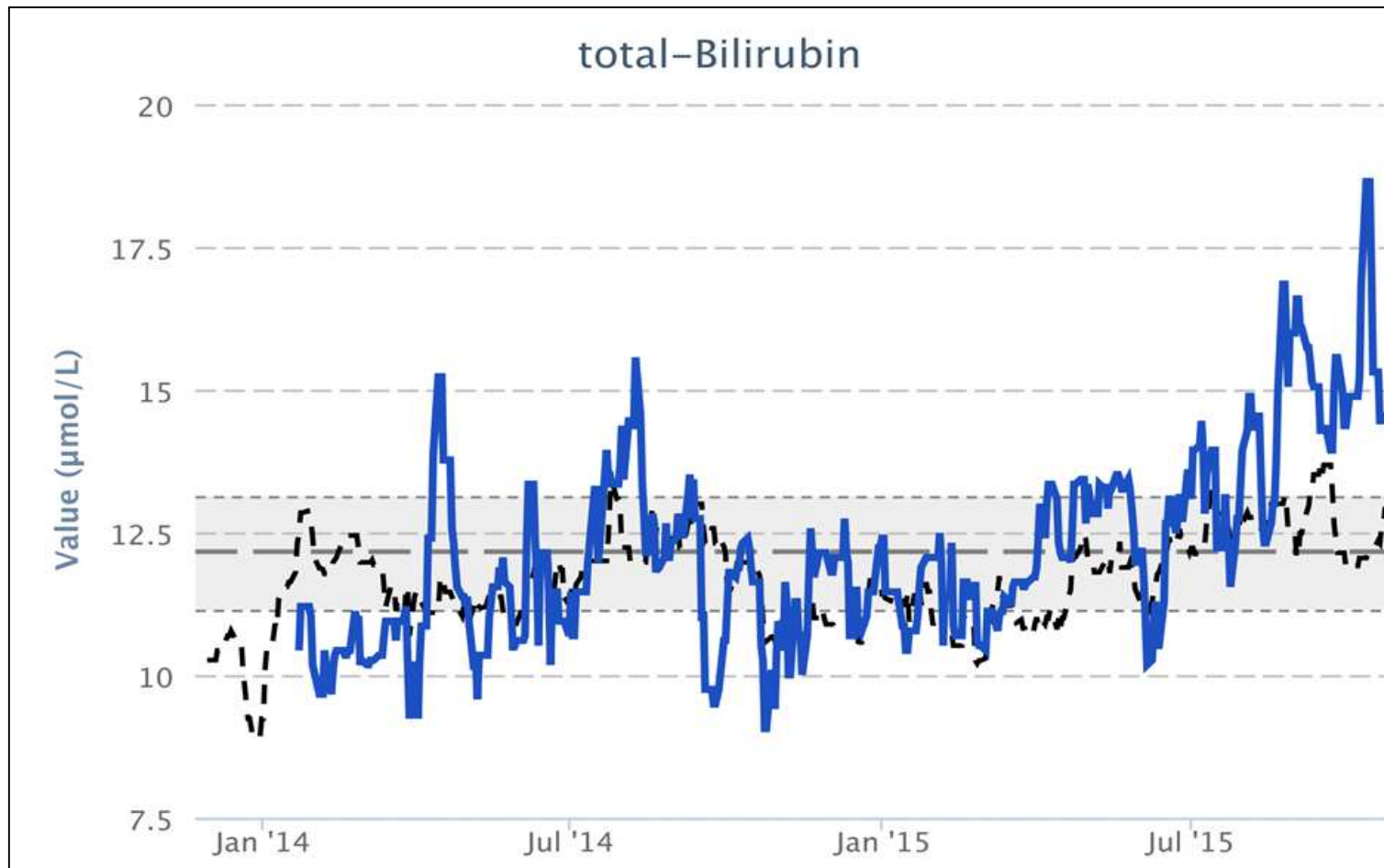




# Percentiler Applications

Identifying problem analytes (peer-specific)

Total-Bilirubin – Manufacturer D

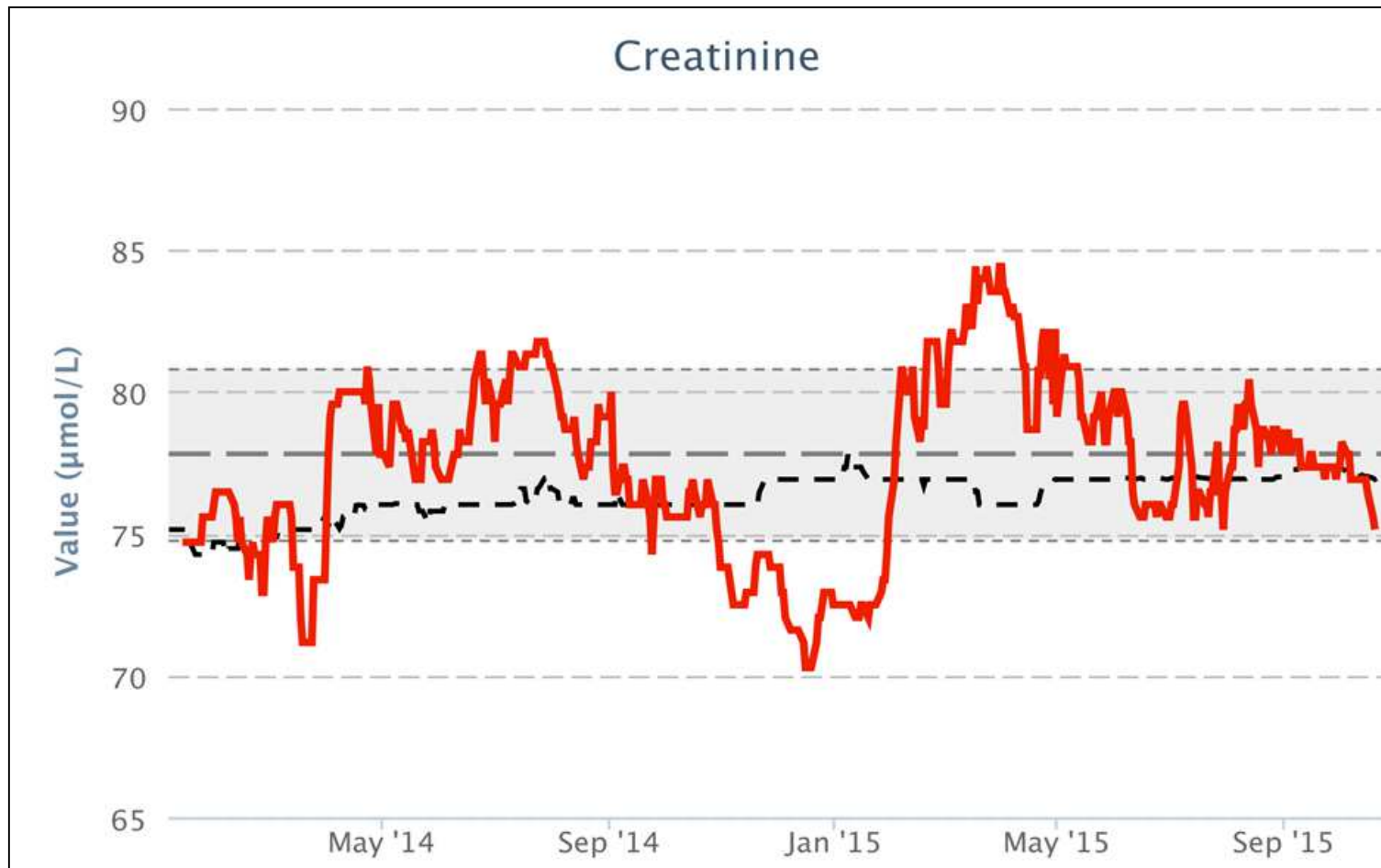




# Percentiler Applications

Identifying problem analytes (peer-specific)

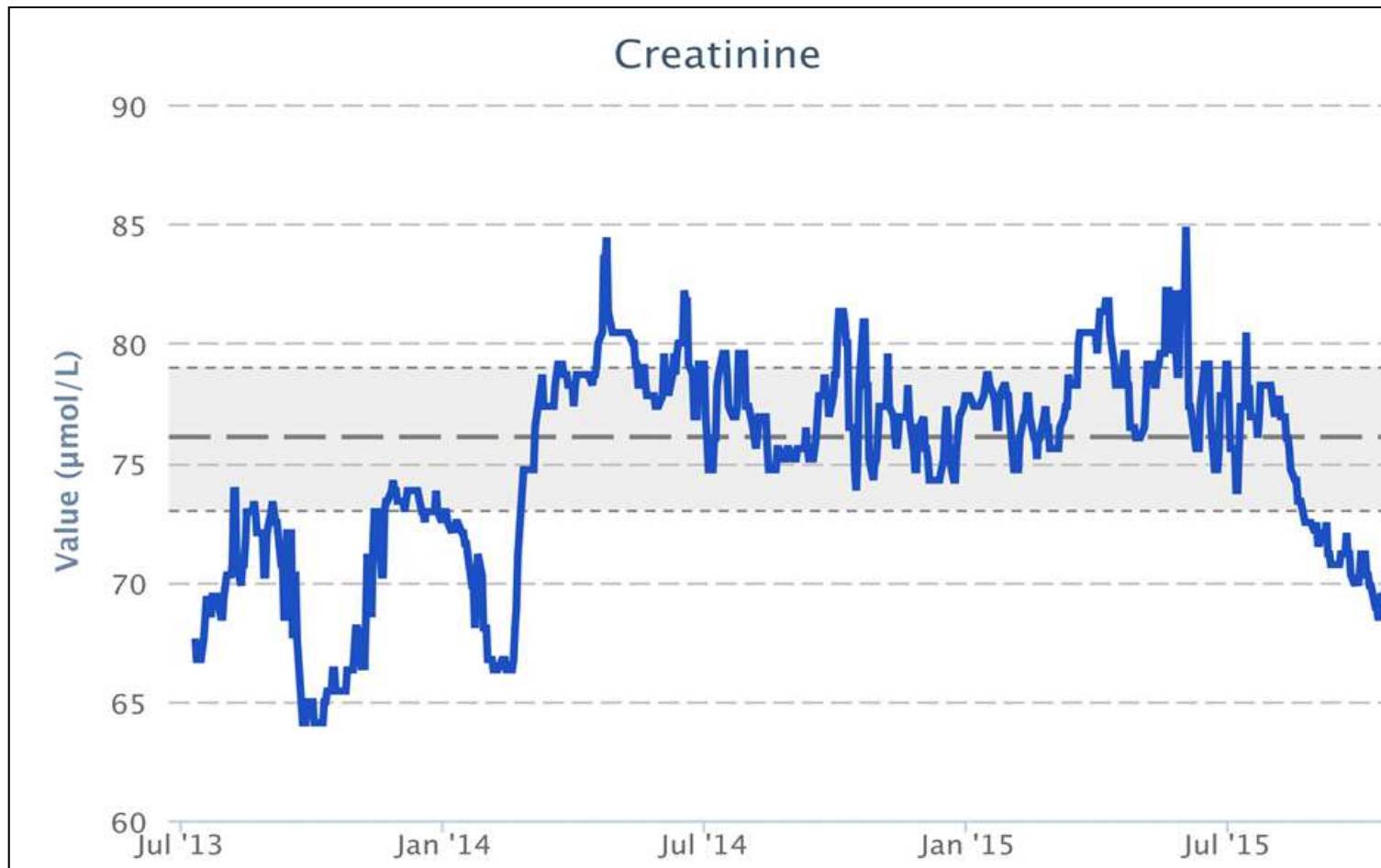
**Creatinine – Manufacturer B**



# Percentiler Applications

Identifying problem analytes (peer-specific)

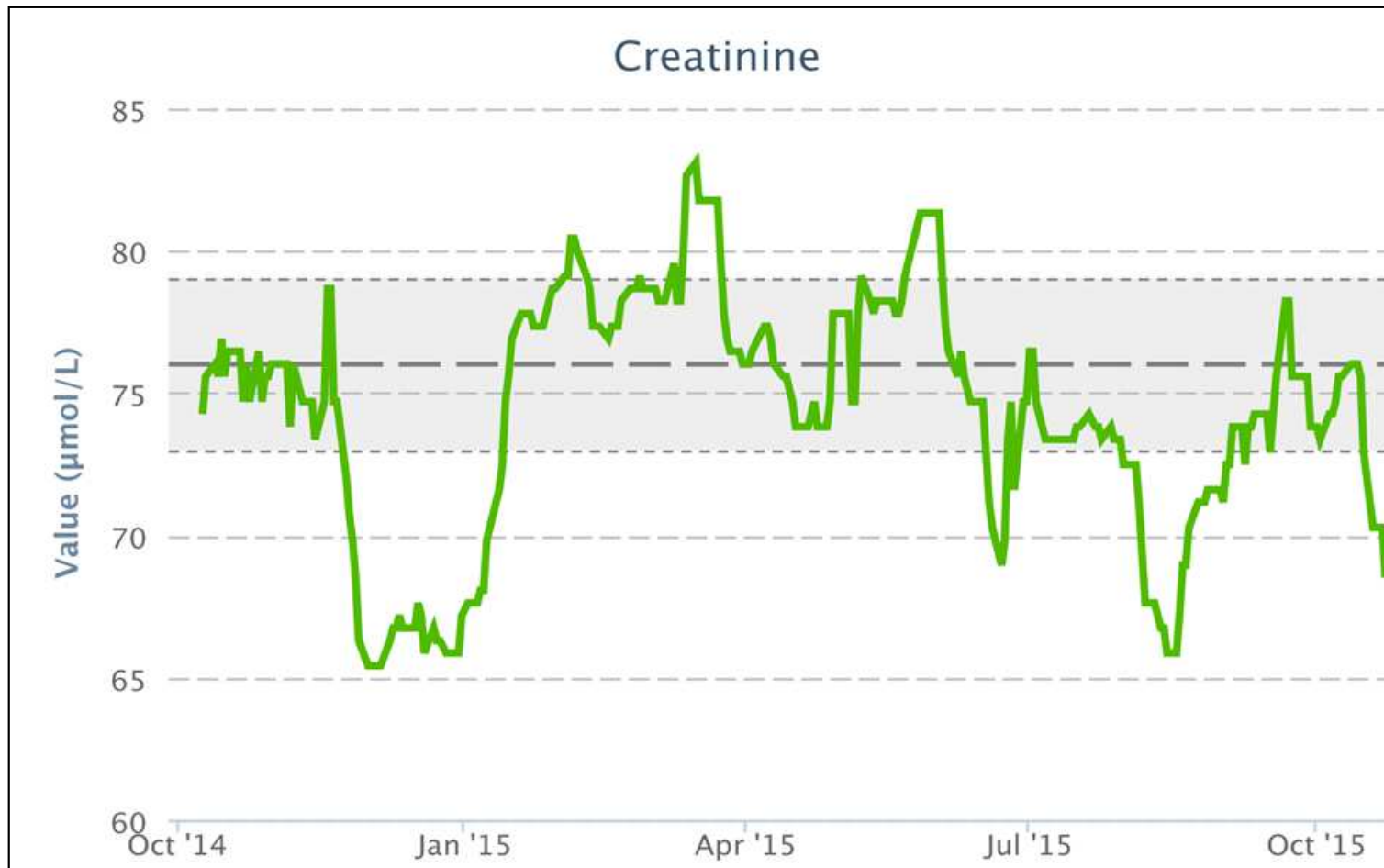
**Creatinine – Manufacturer B**



# Percentiler Applications

Identifying problem analytes (peer-specific)

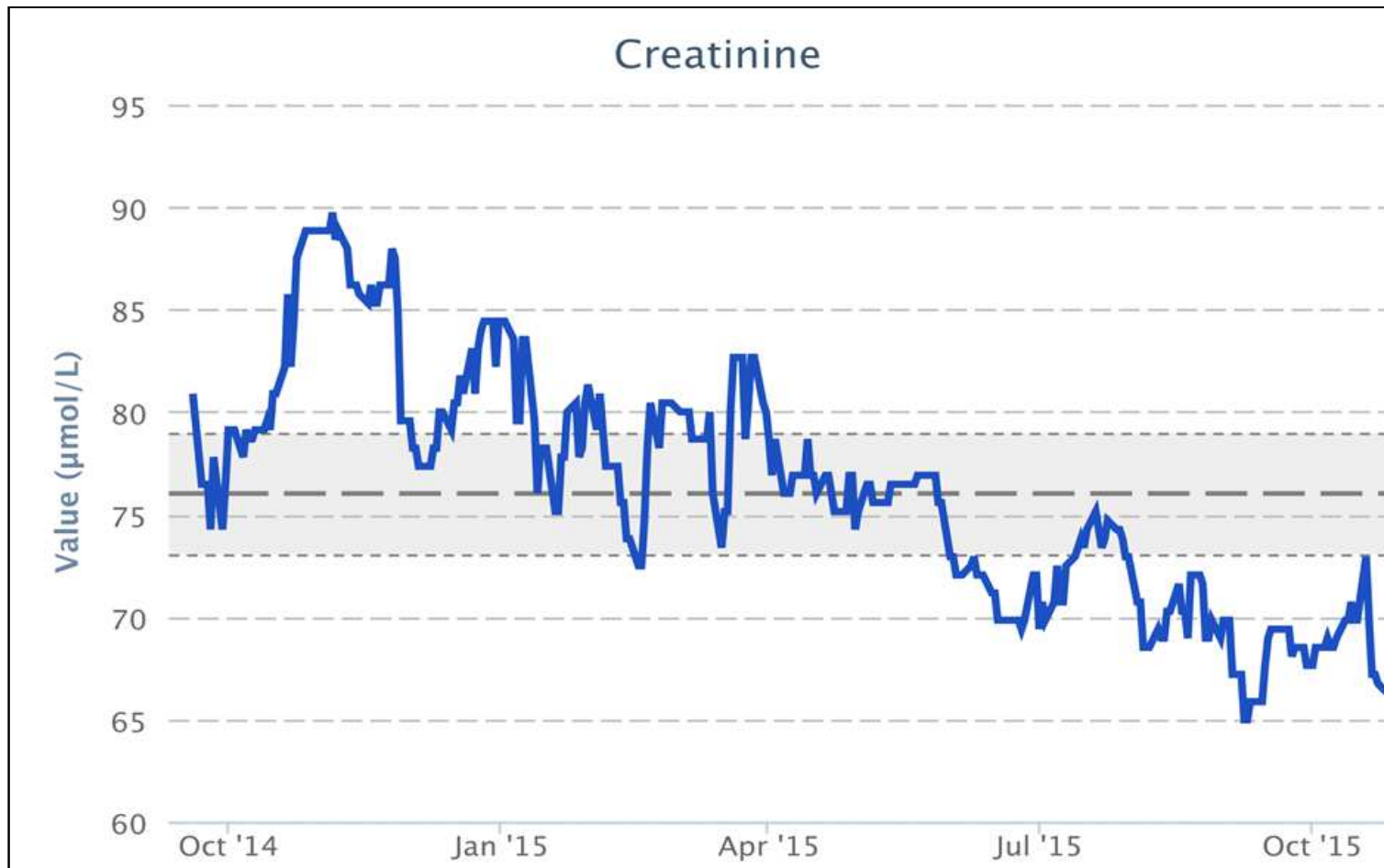
Creatinine – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

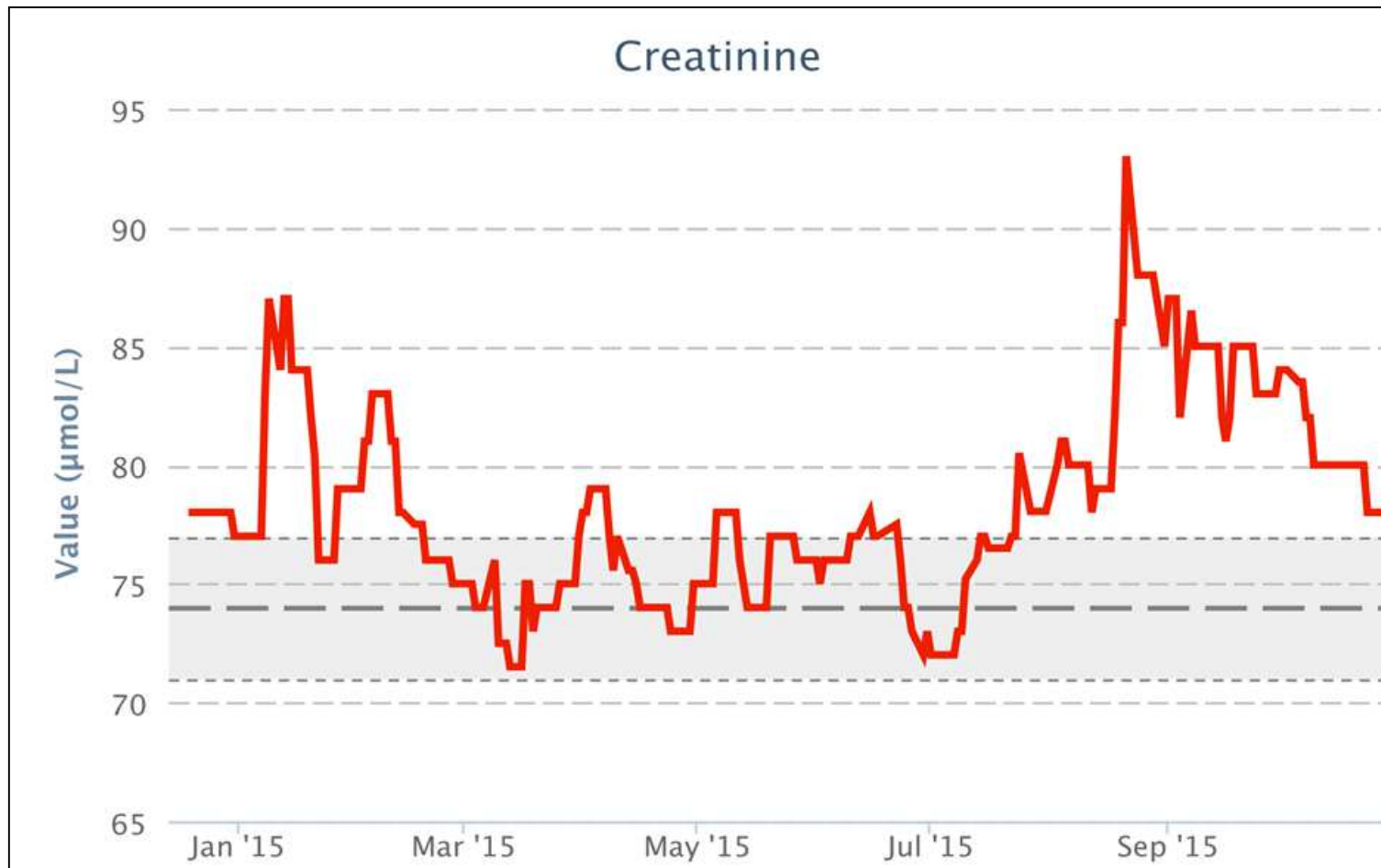
**Creatinine – Manufacturer B**



# Percentiler Applications

Identifying problem analytes (peer-specific)

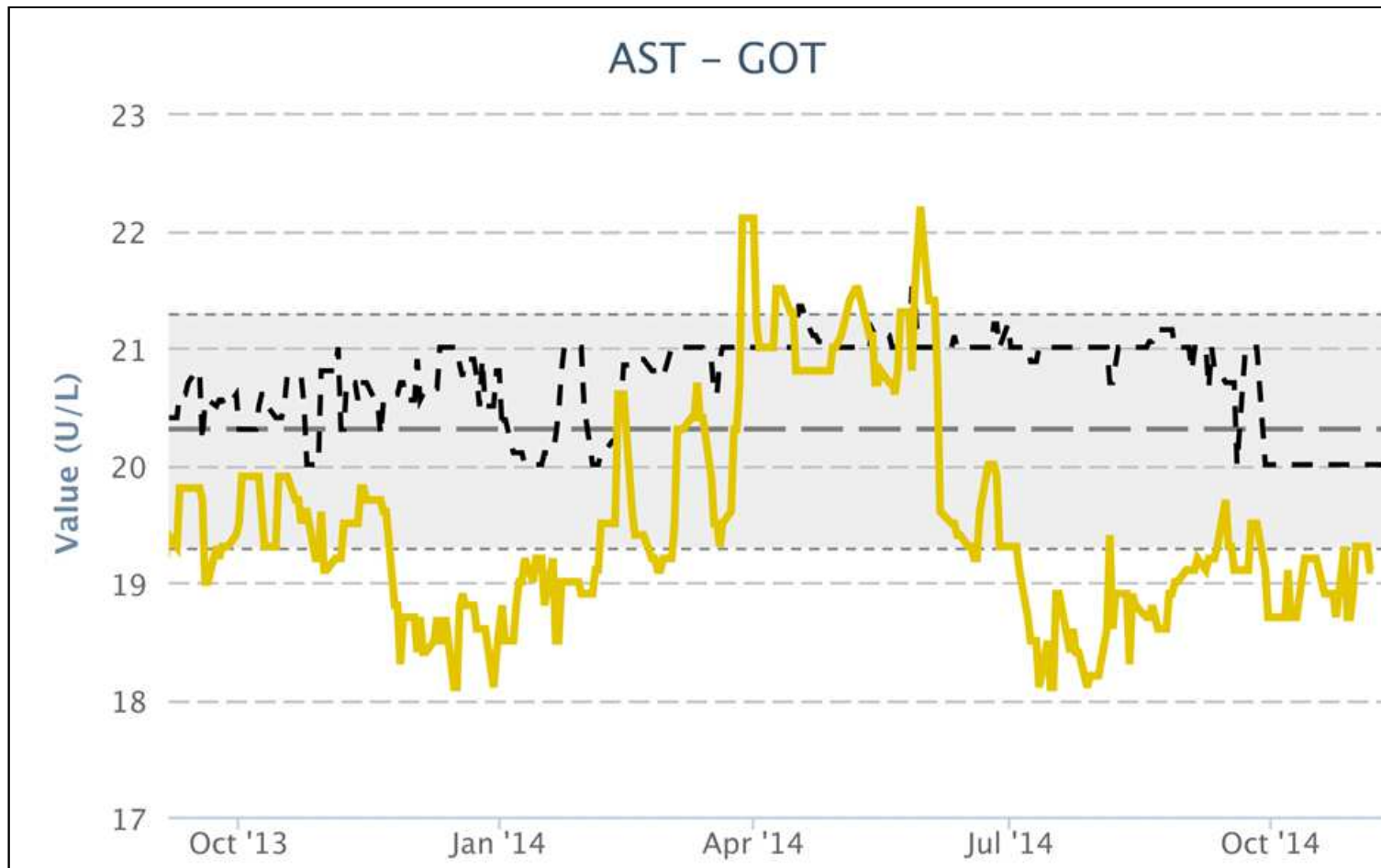
Creatinine – Manufacturer F



# Percentiler Applications

Identifying problem analytes (peer-specific)

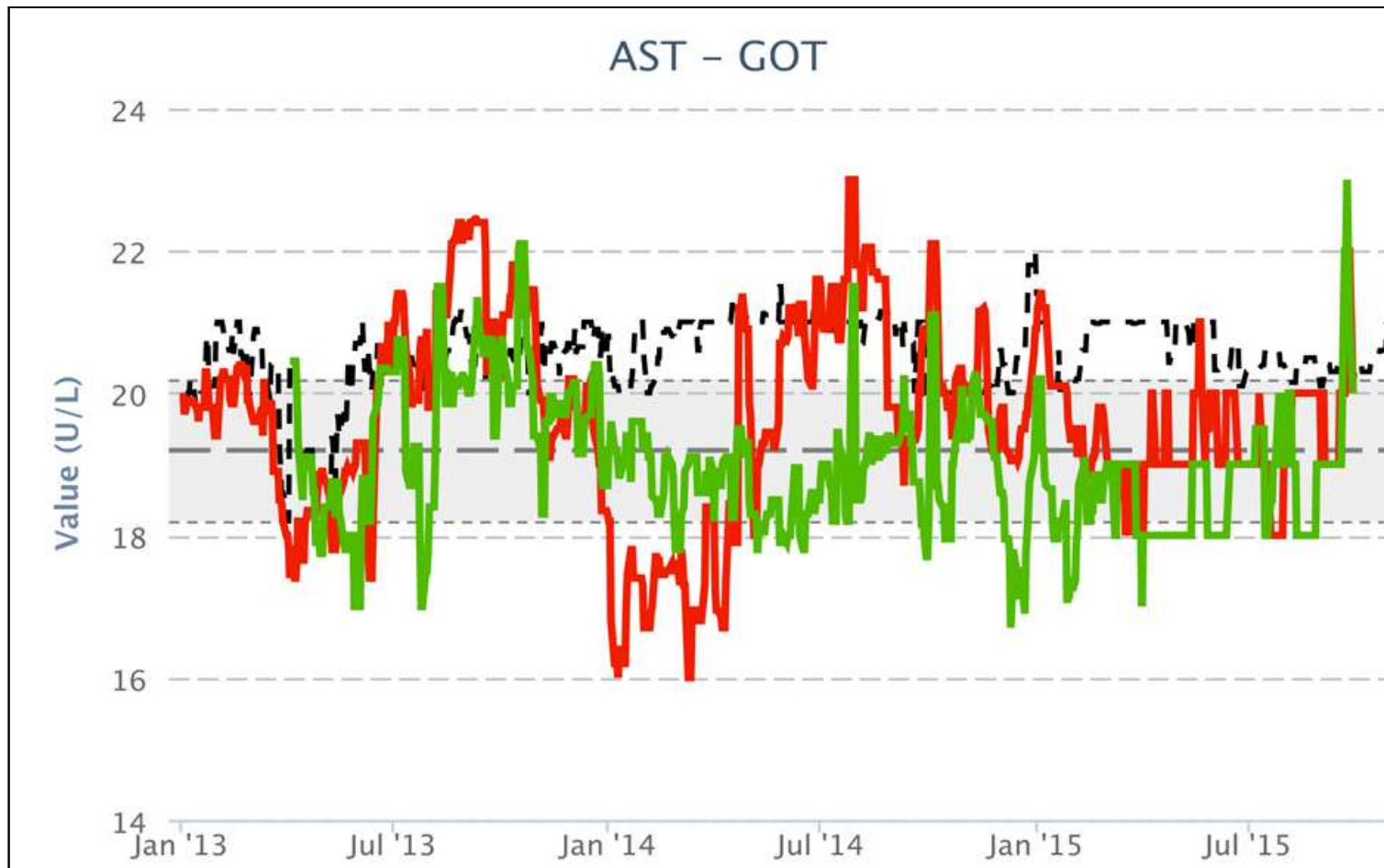
AST – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

AST – Manufacturer B

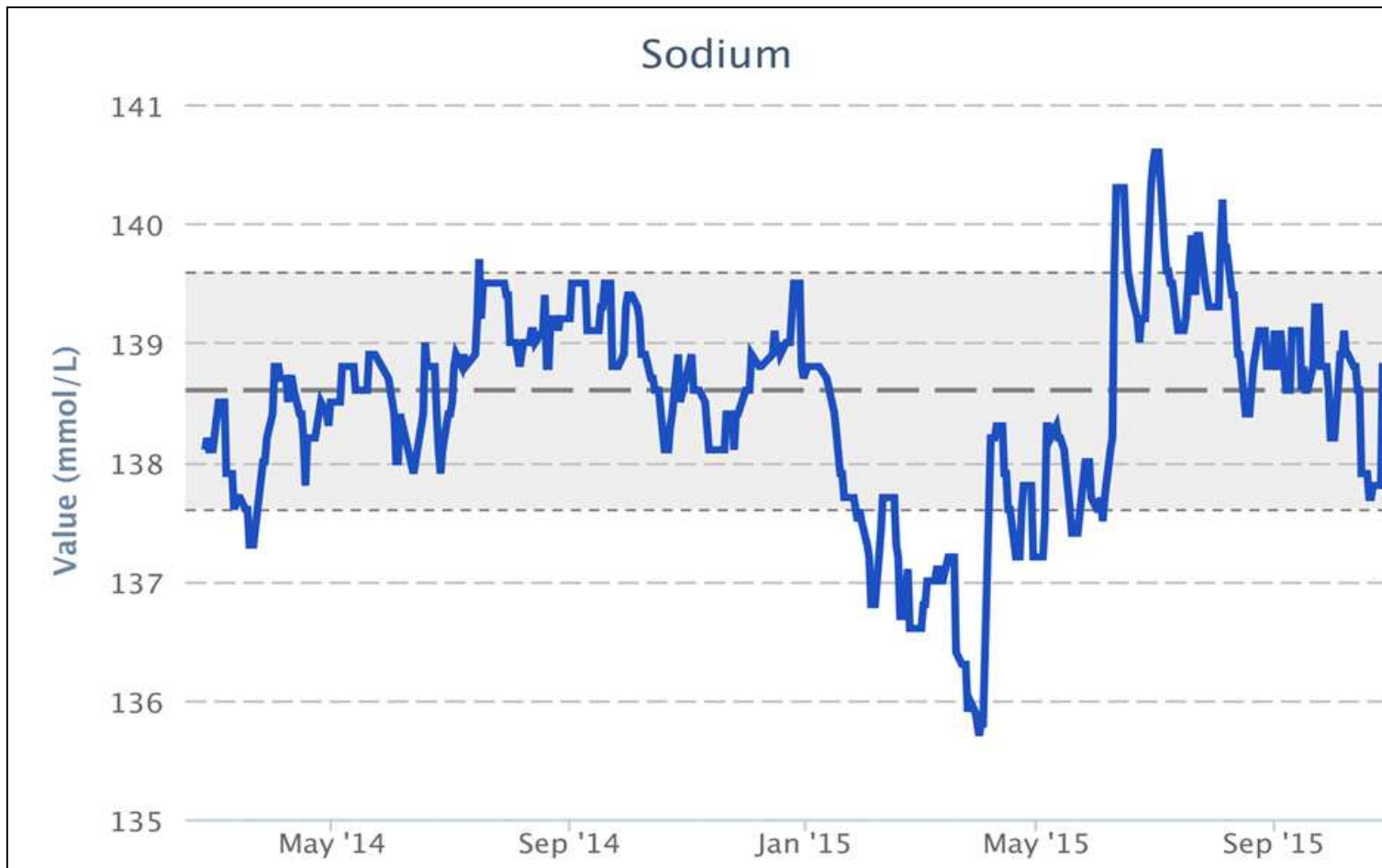




# Percentiler Applications

Identifying problem analytes (peer-specific)

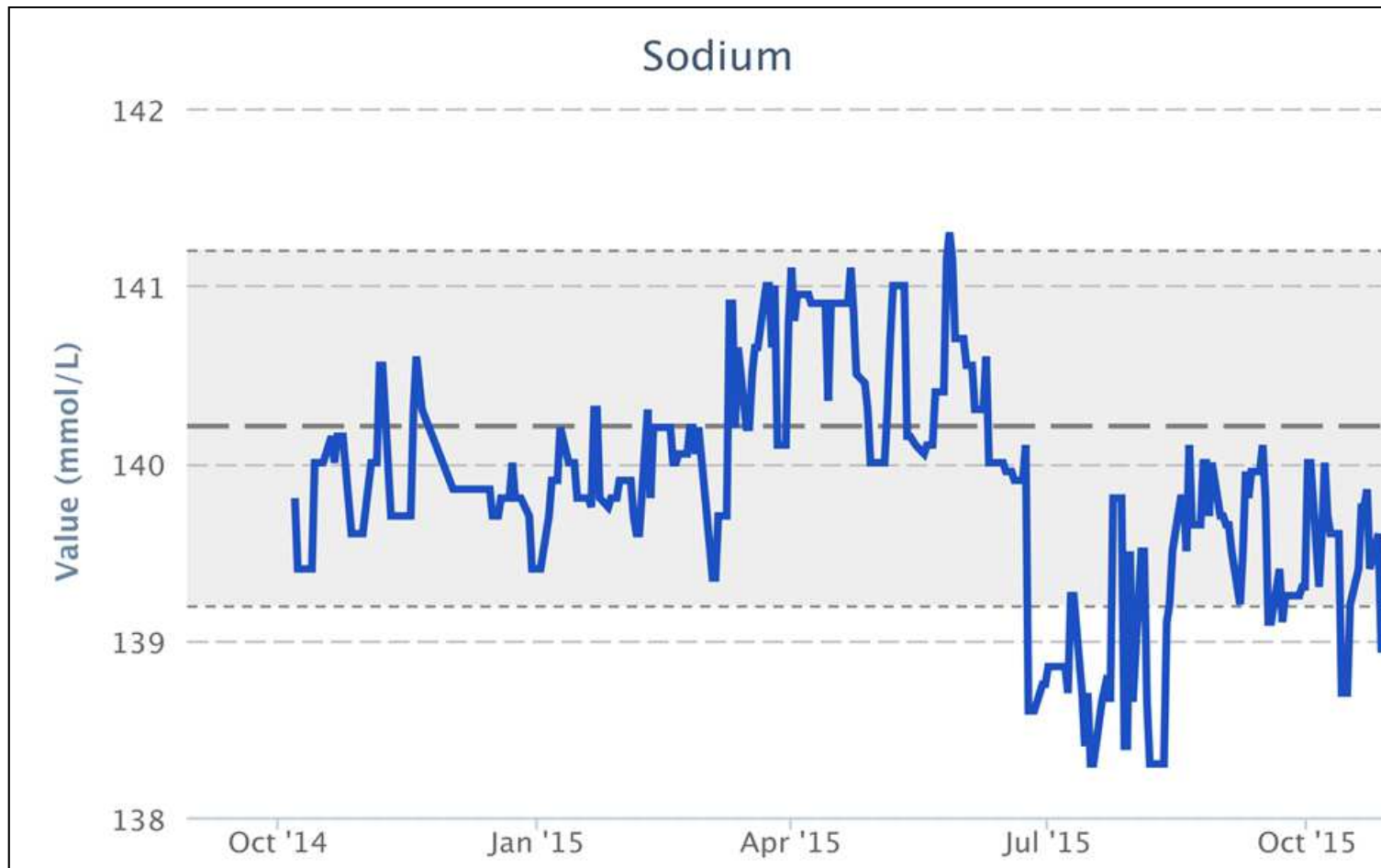
Sodium – Manufacturer A



# Percentiler Applications

Identifying problem analytes (peer-specific)

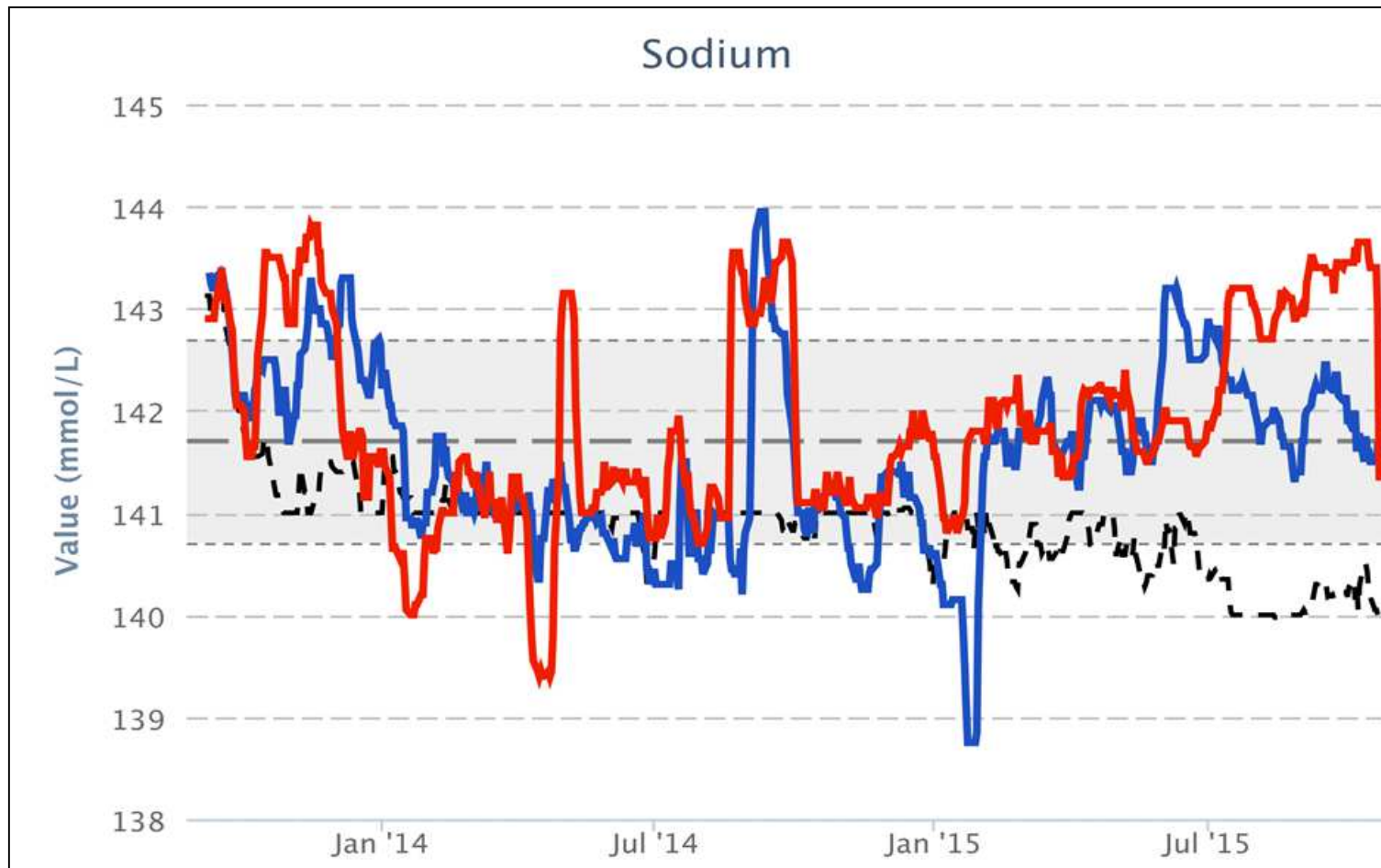
Sodium – Manufacturer A



# Percentiler Applications

Identifying problem analytes (peer-specific)

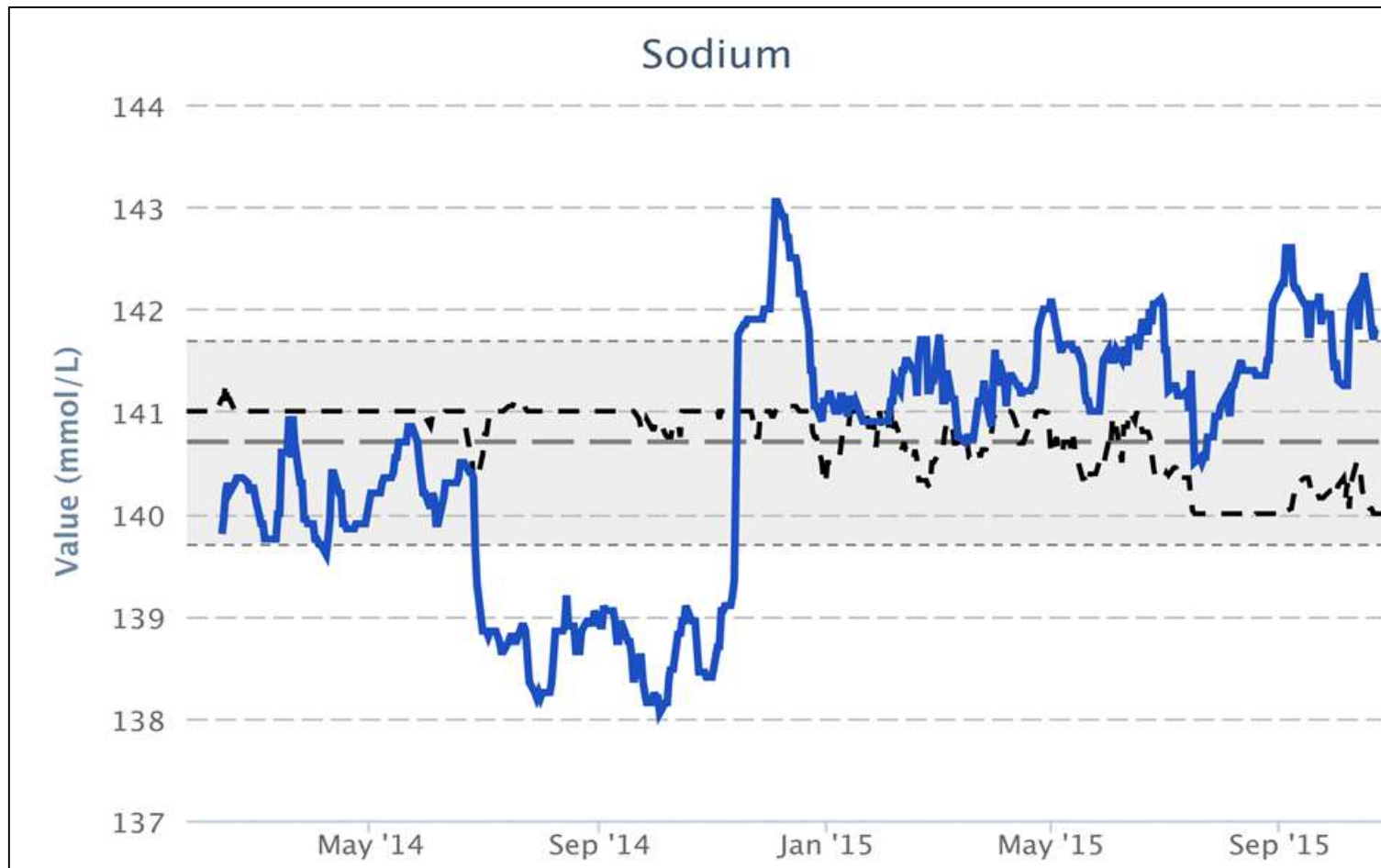
Sodium – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

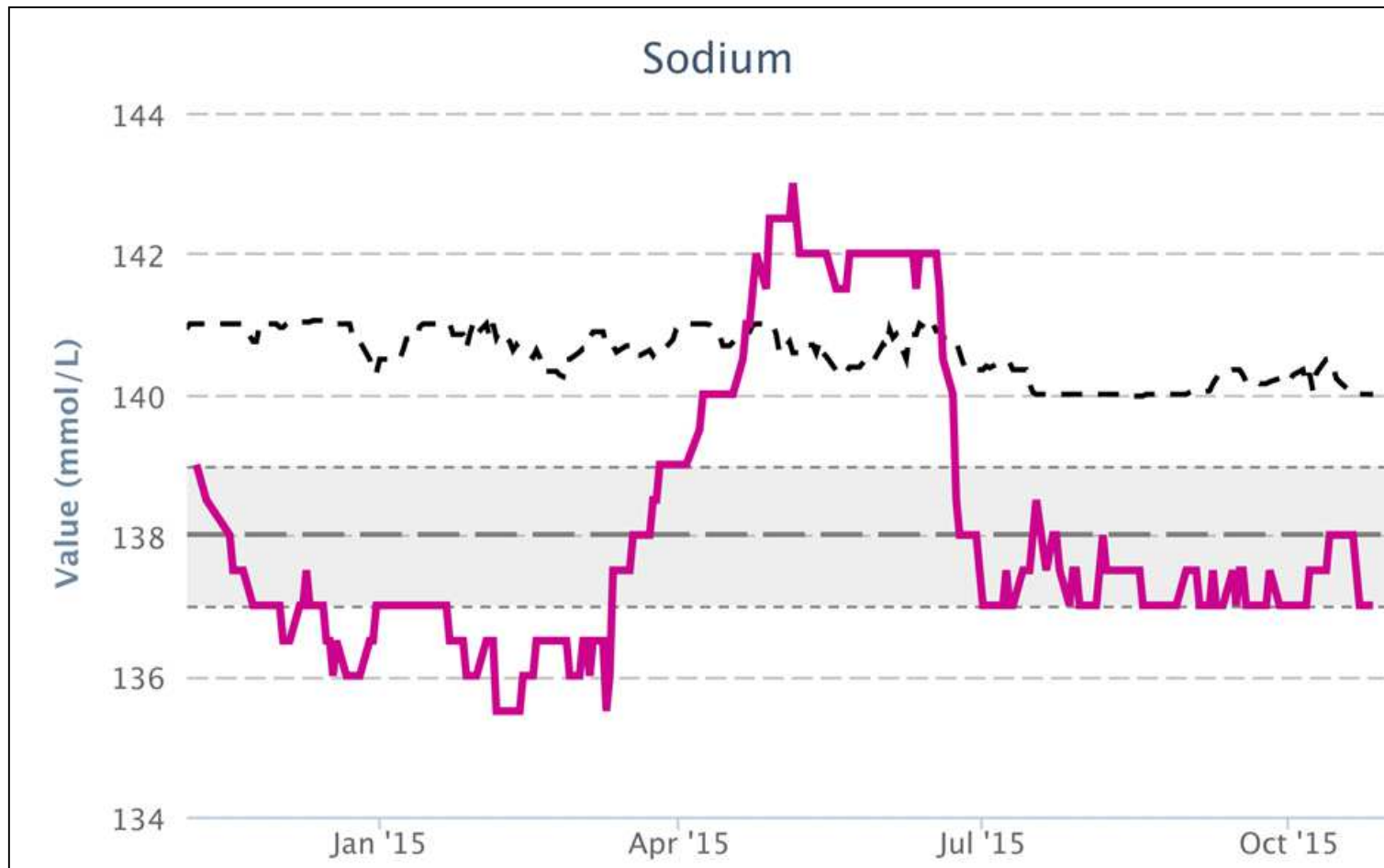
Sodium – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

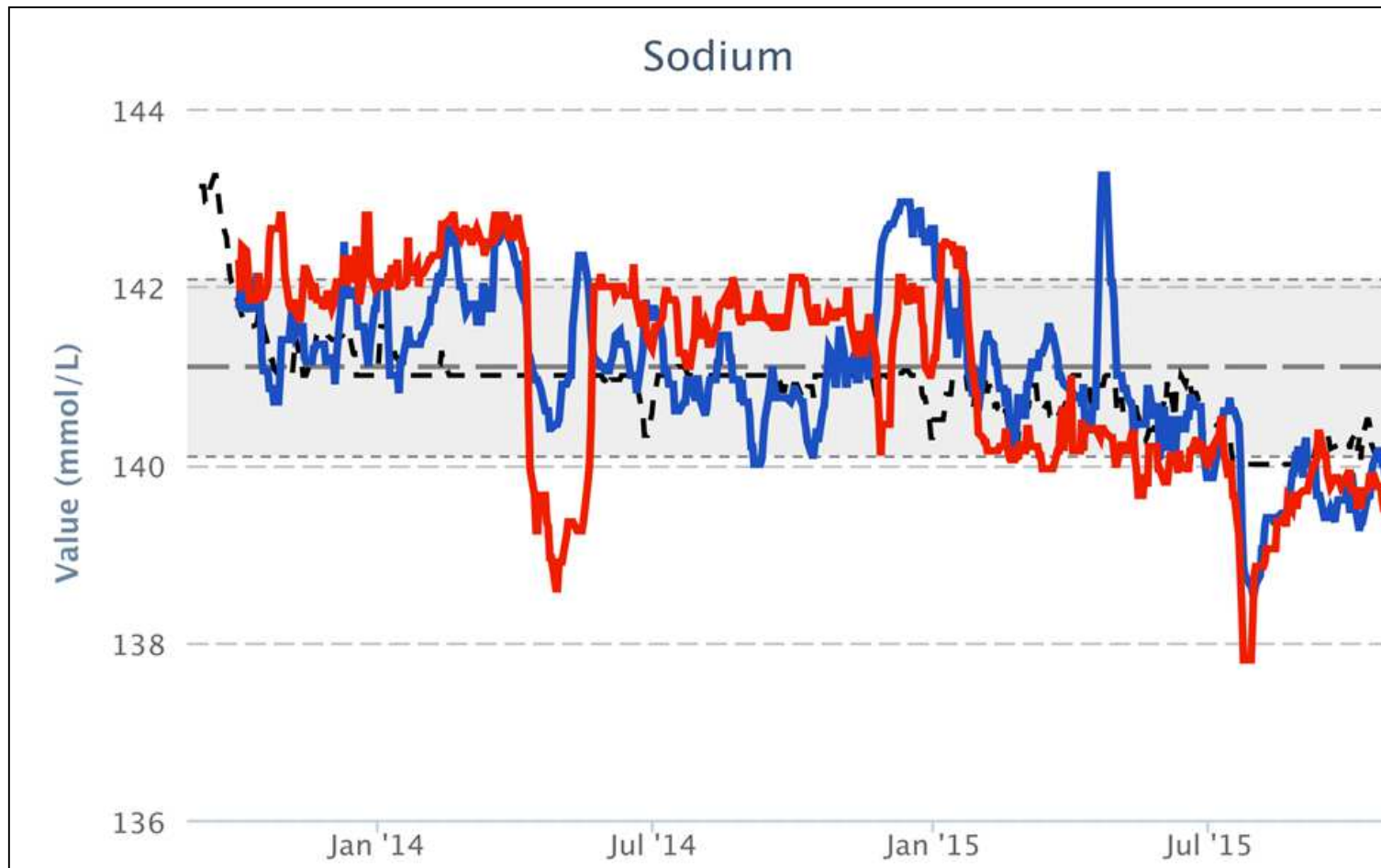
Sodium – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

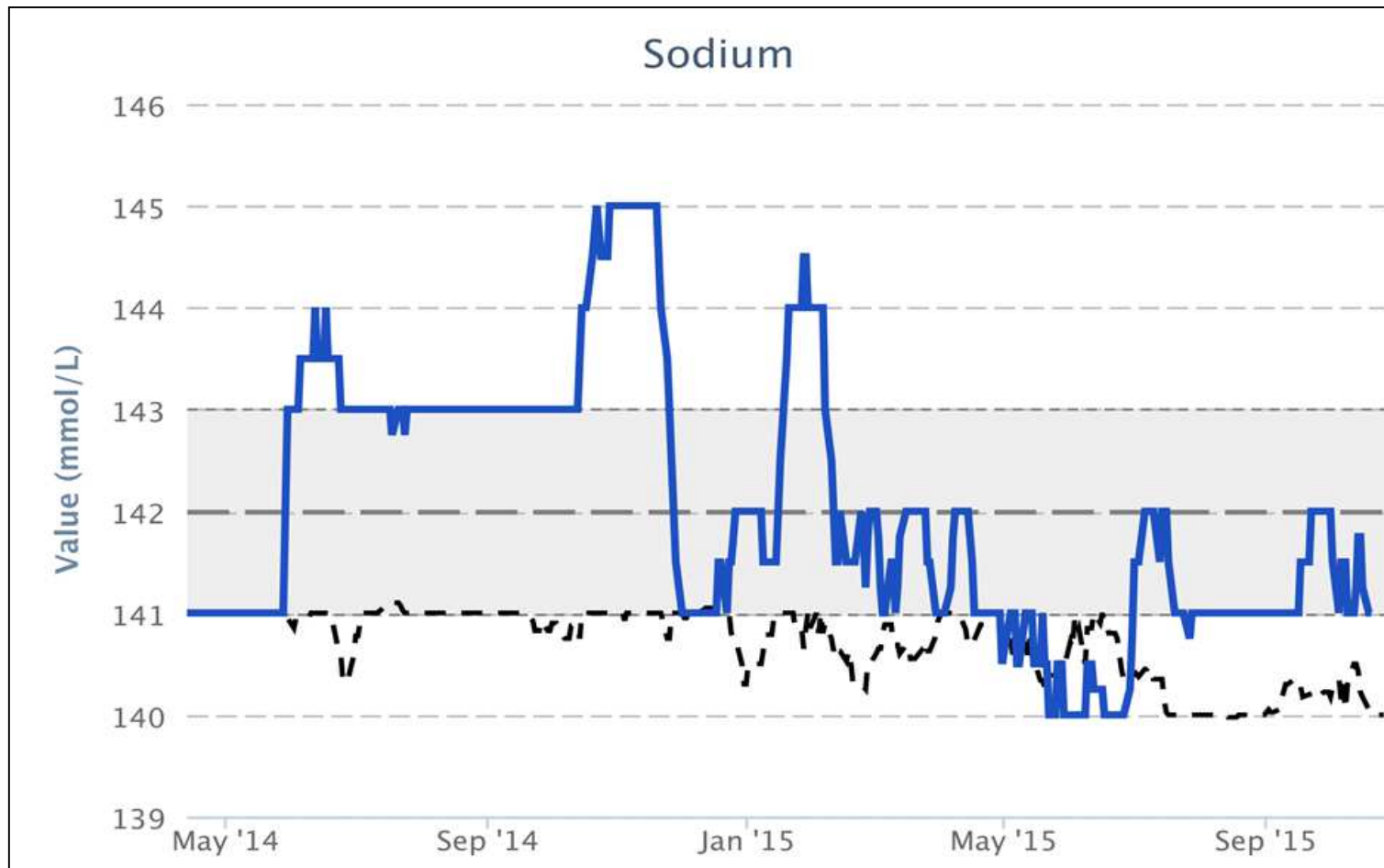
Sodium – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Sodium – Manufacturer C

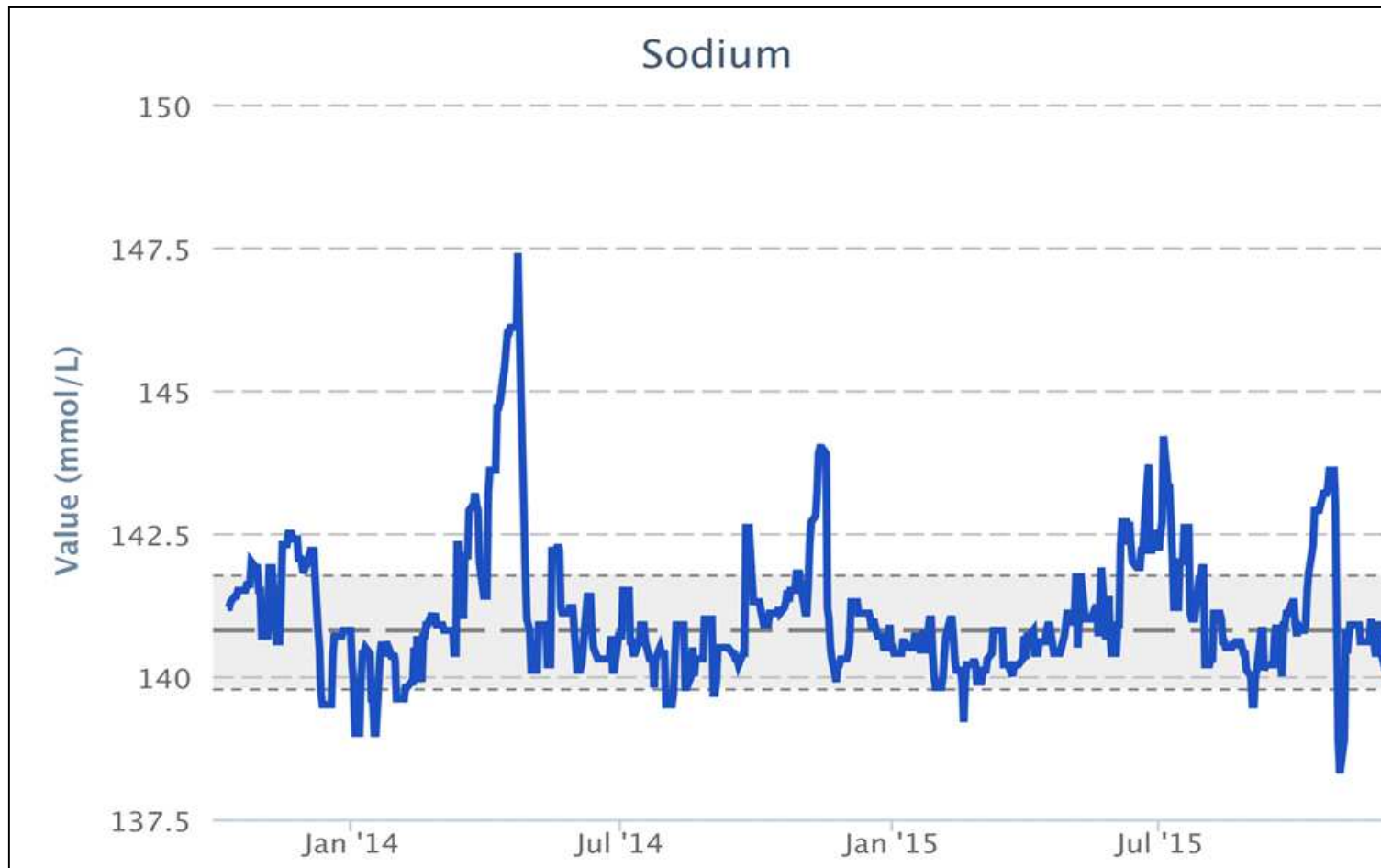




# Percentiler Applications

Identifying problem analytes (peer-specific)

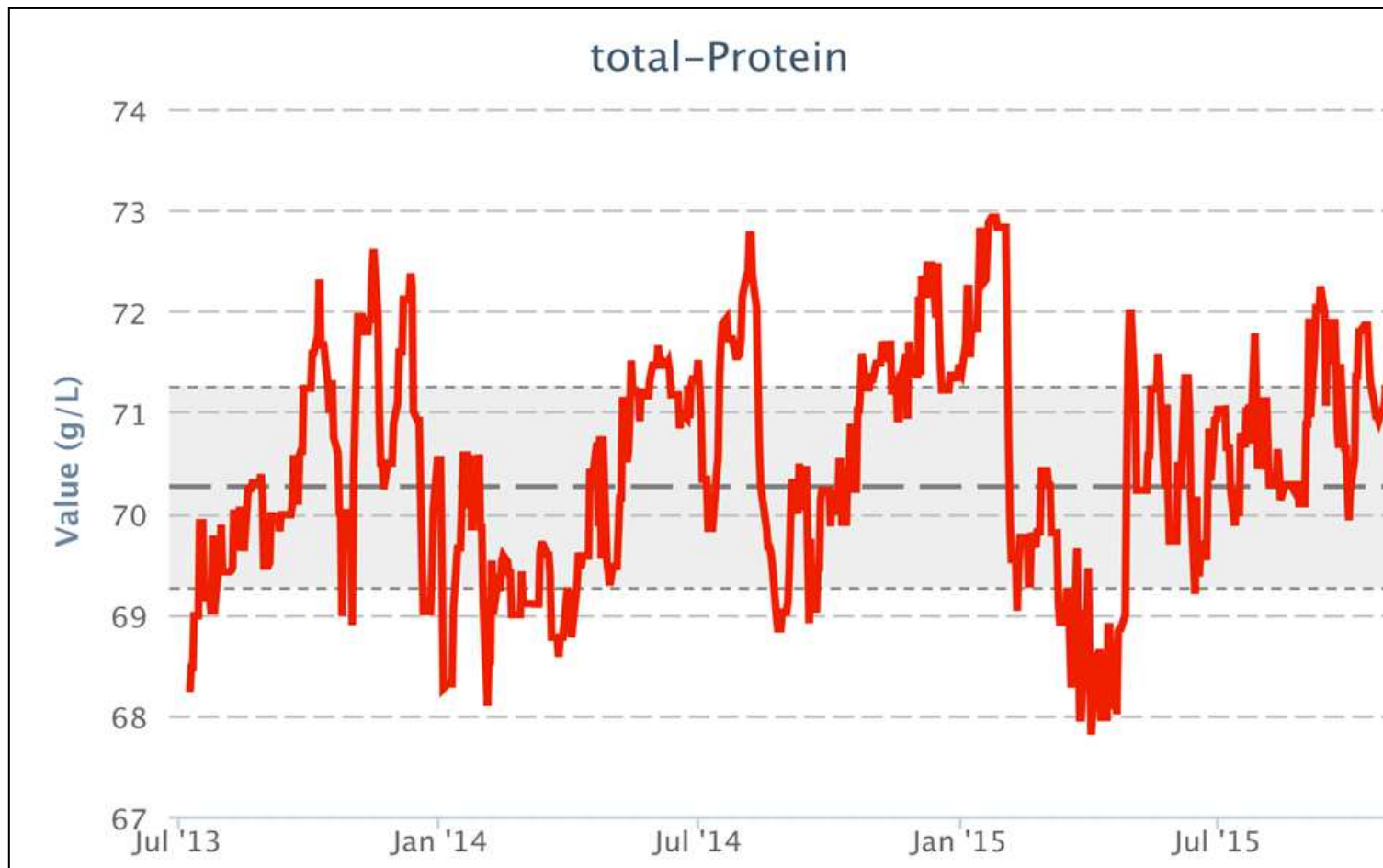
Sodium – Manufacturer F (several labs, upwards trend)



# Percentiler Applications

Identifying problem analytes (peer-specific)

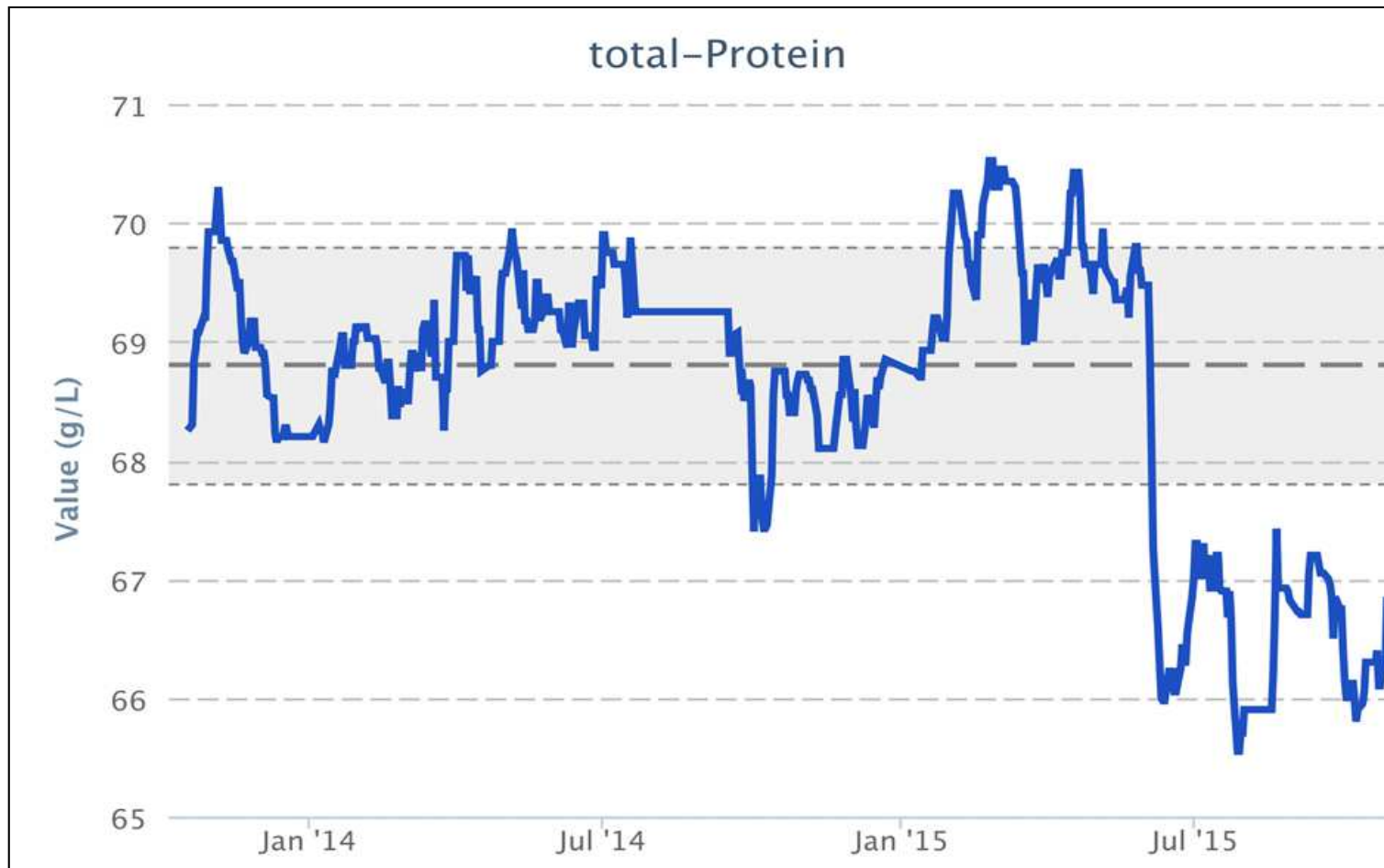
Total-protein – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

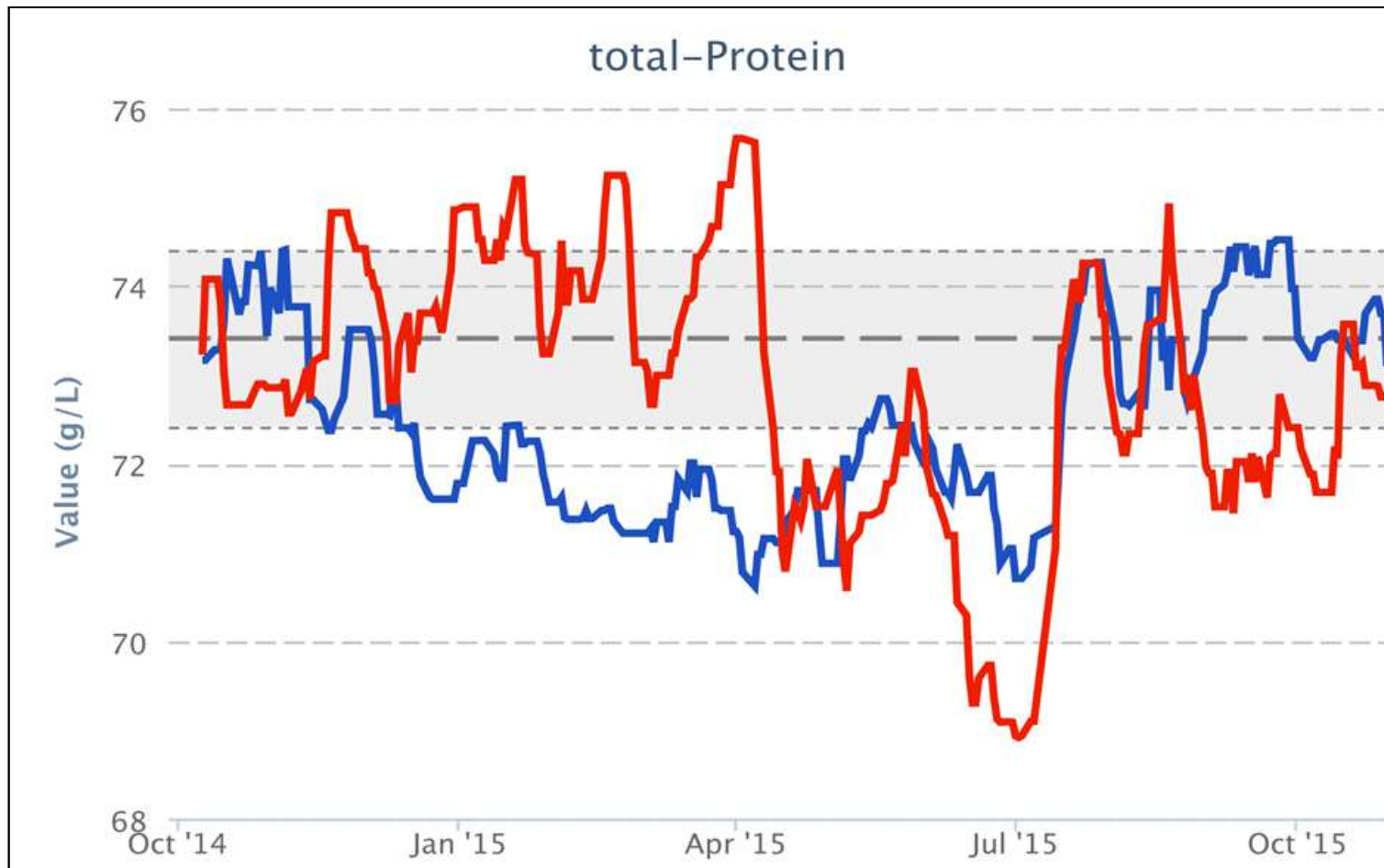
Total-protein – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

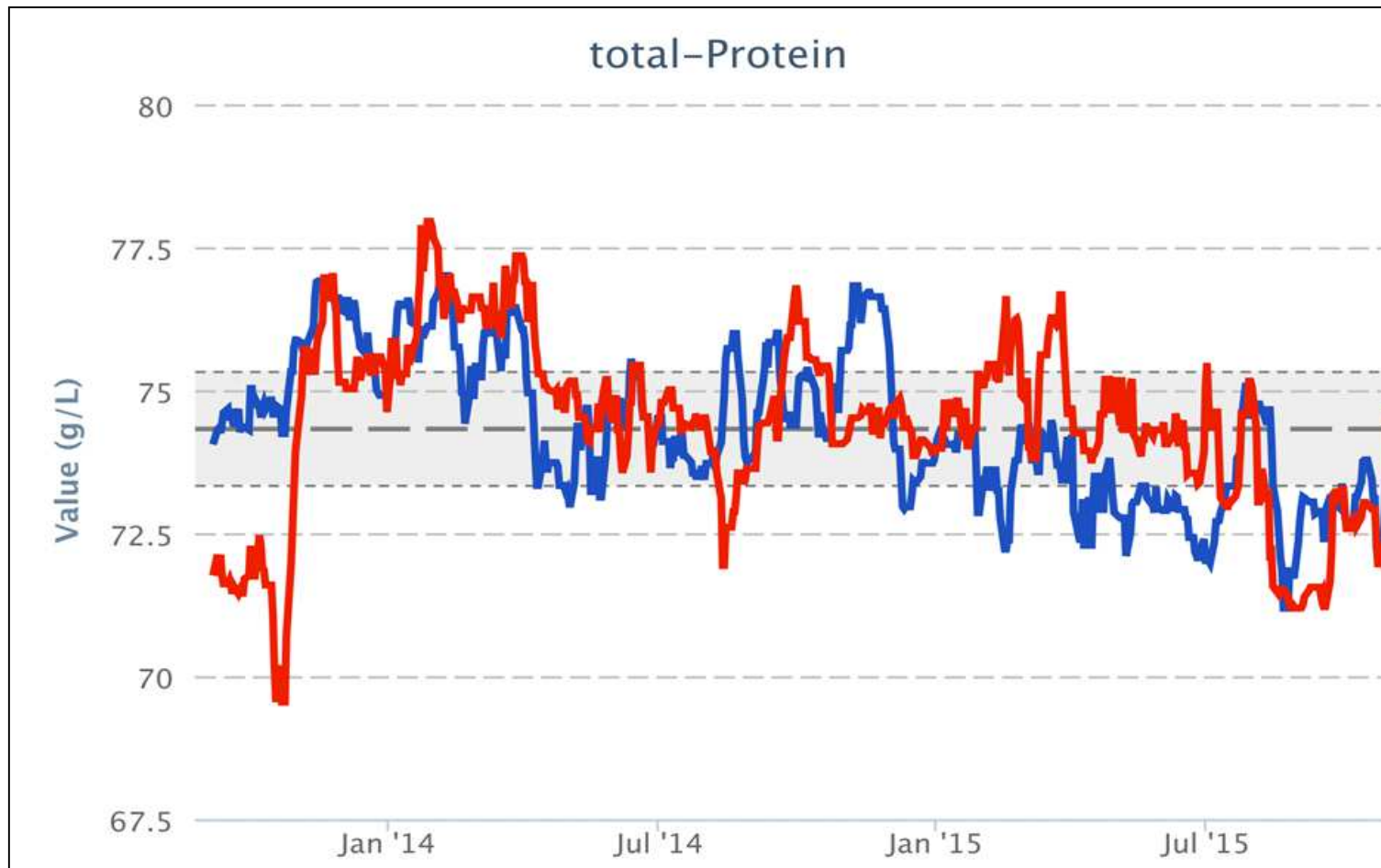
Total-protein – Manufacturer B



# Percentiler Applications

Identifying problem analytes (peer-specific)

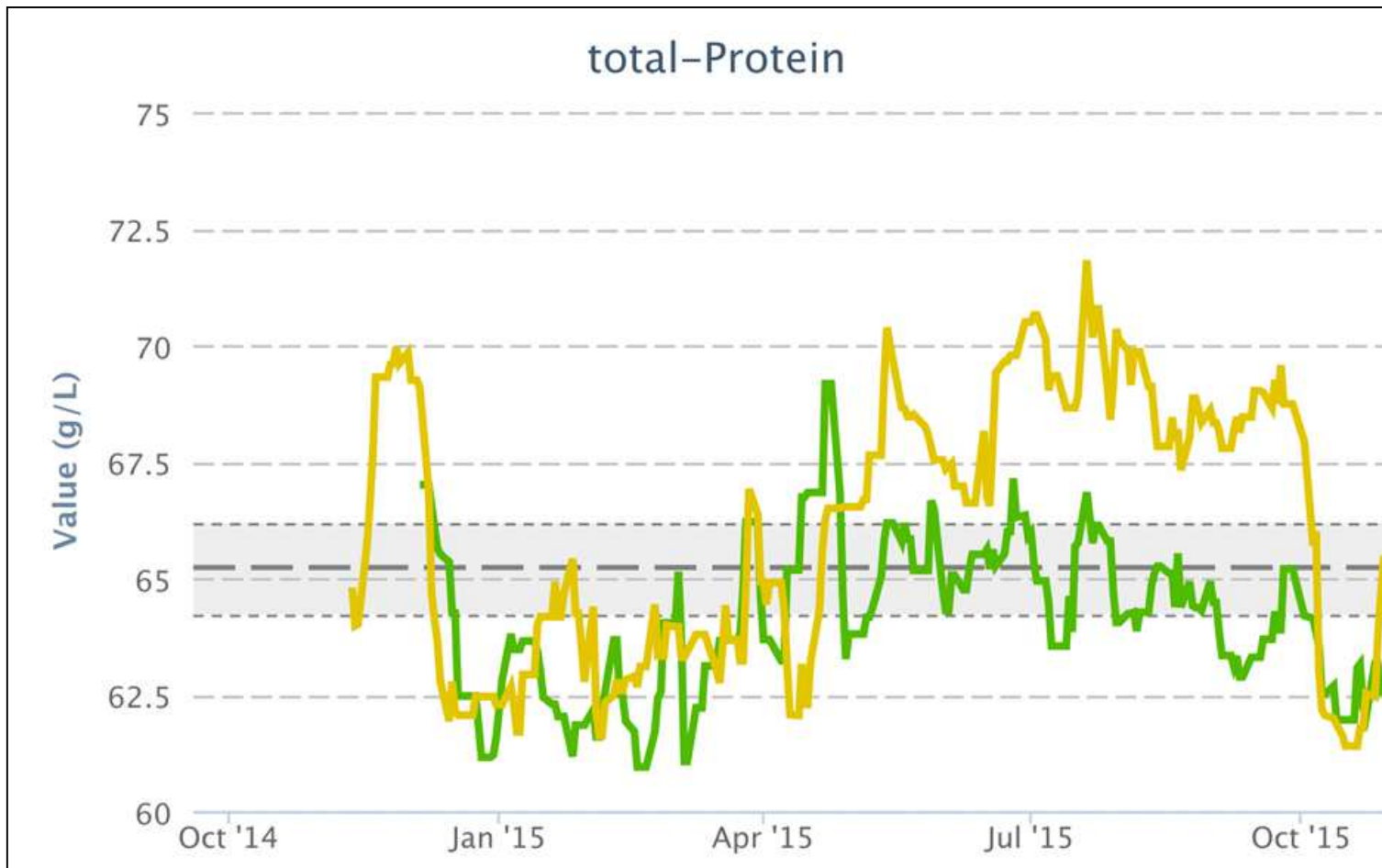
Total-protein – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

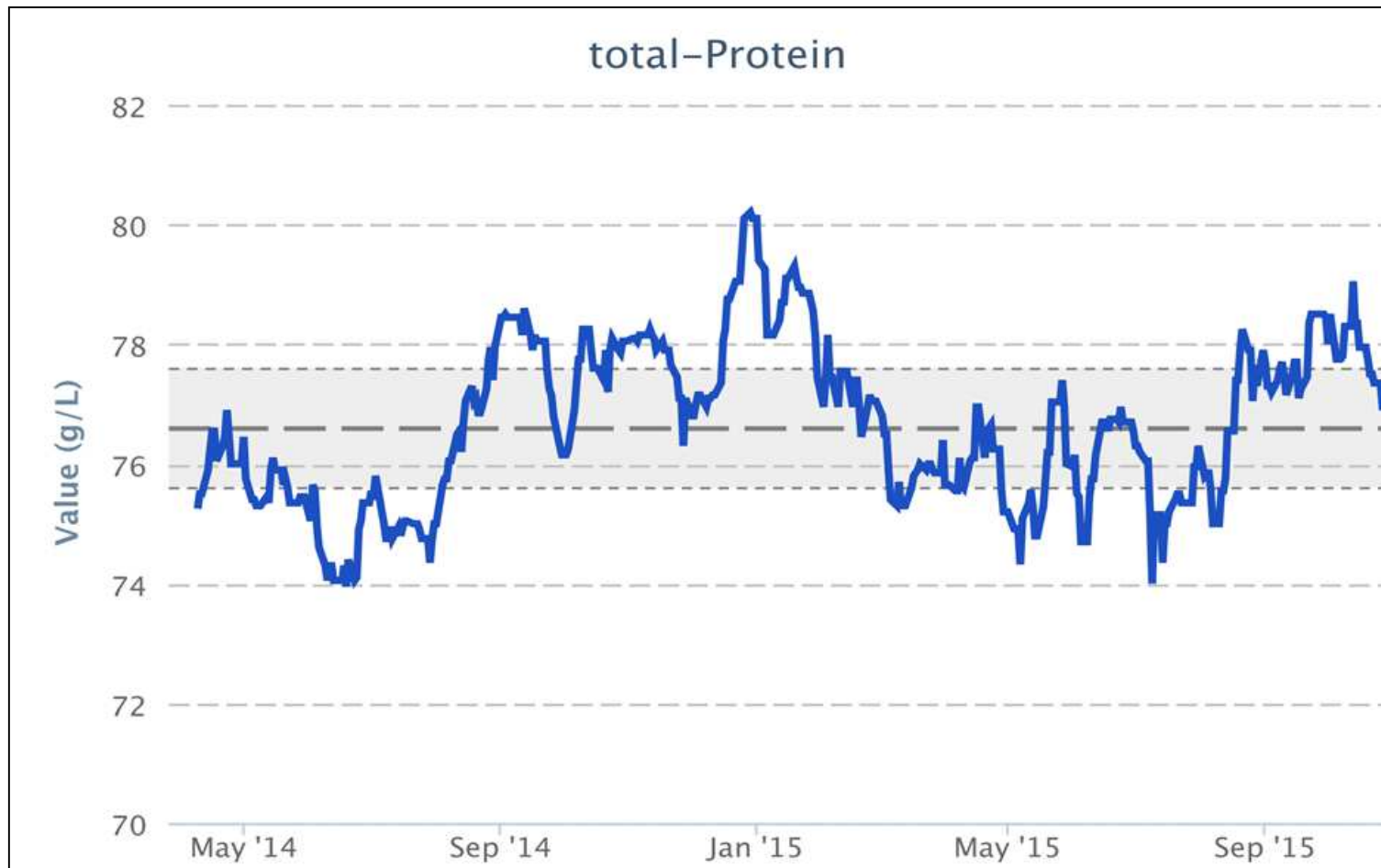
Total-protein – Manufacturer C



# Percentiler Applications

Identifying problem analytes (peer-specific)

Total-protein – Manufacturer C

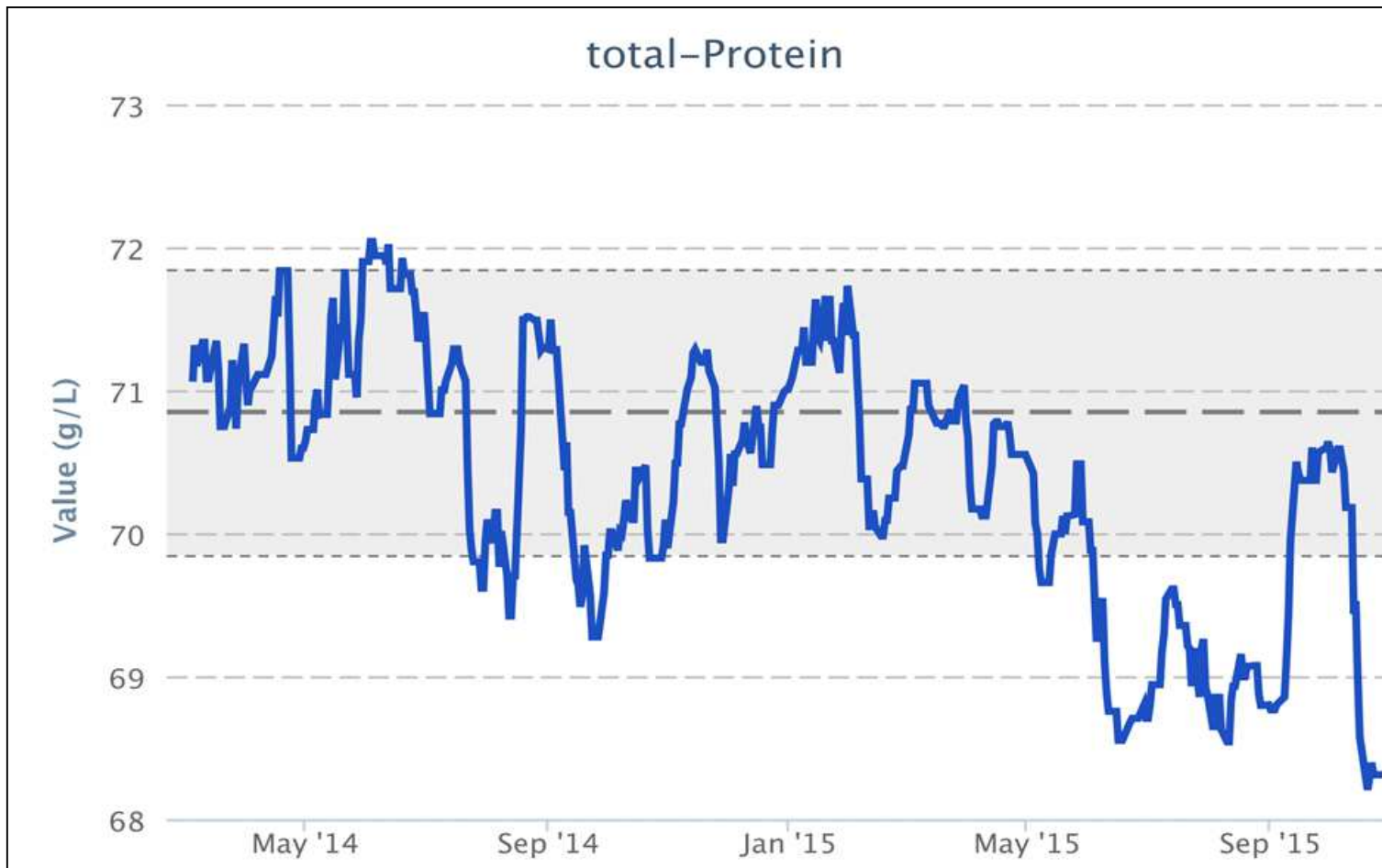




# Percentiler Applications

Identifying problem analytes (peer-specific)

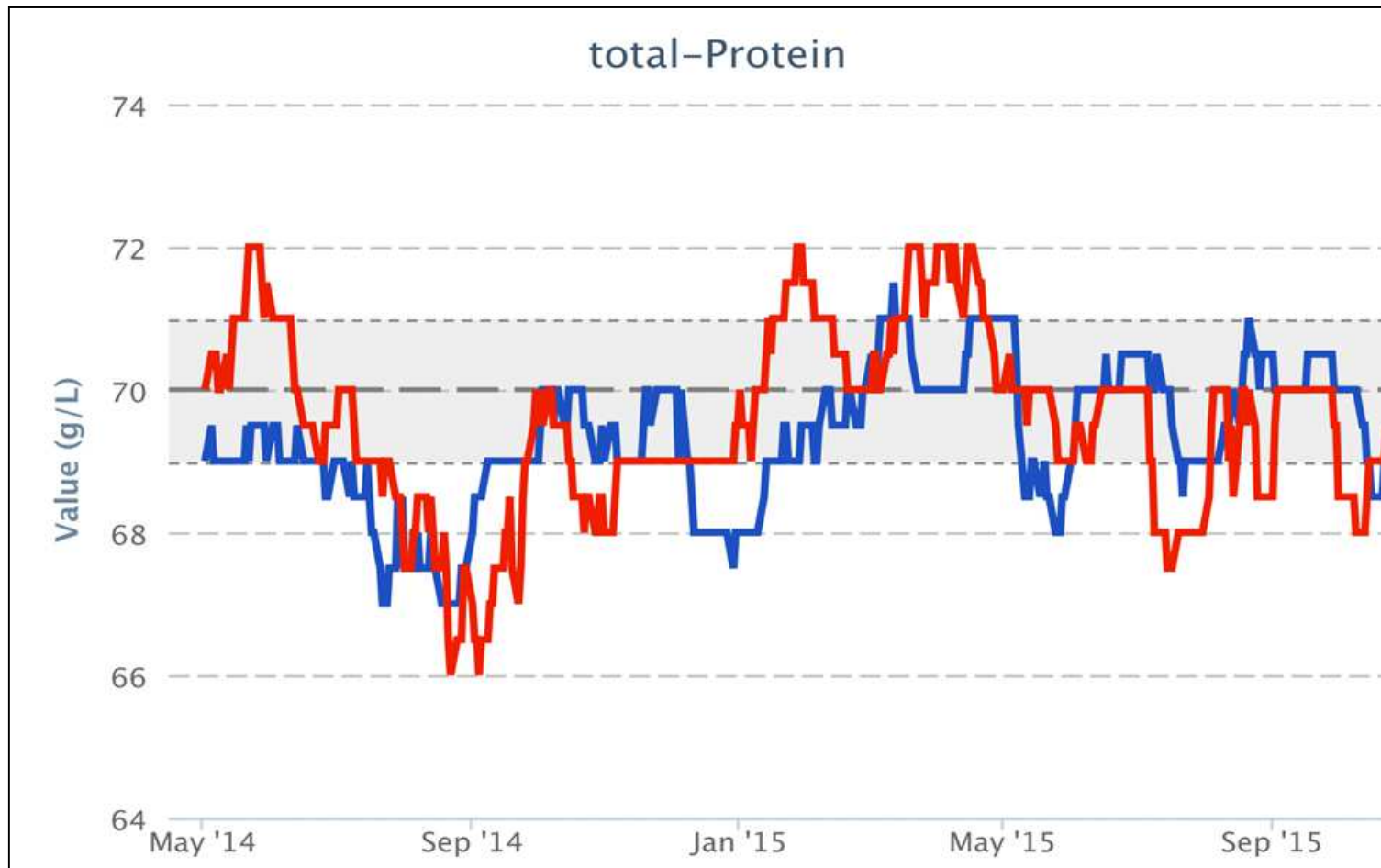
Total-protein – Manufacturer F



# Percentiler Applications

Identifying problem analytes (peer-specific)

Total-protein – Manufacturer G

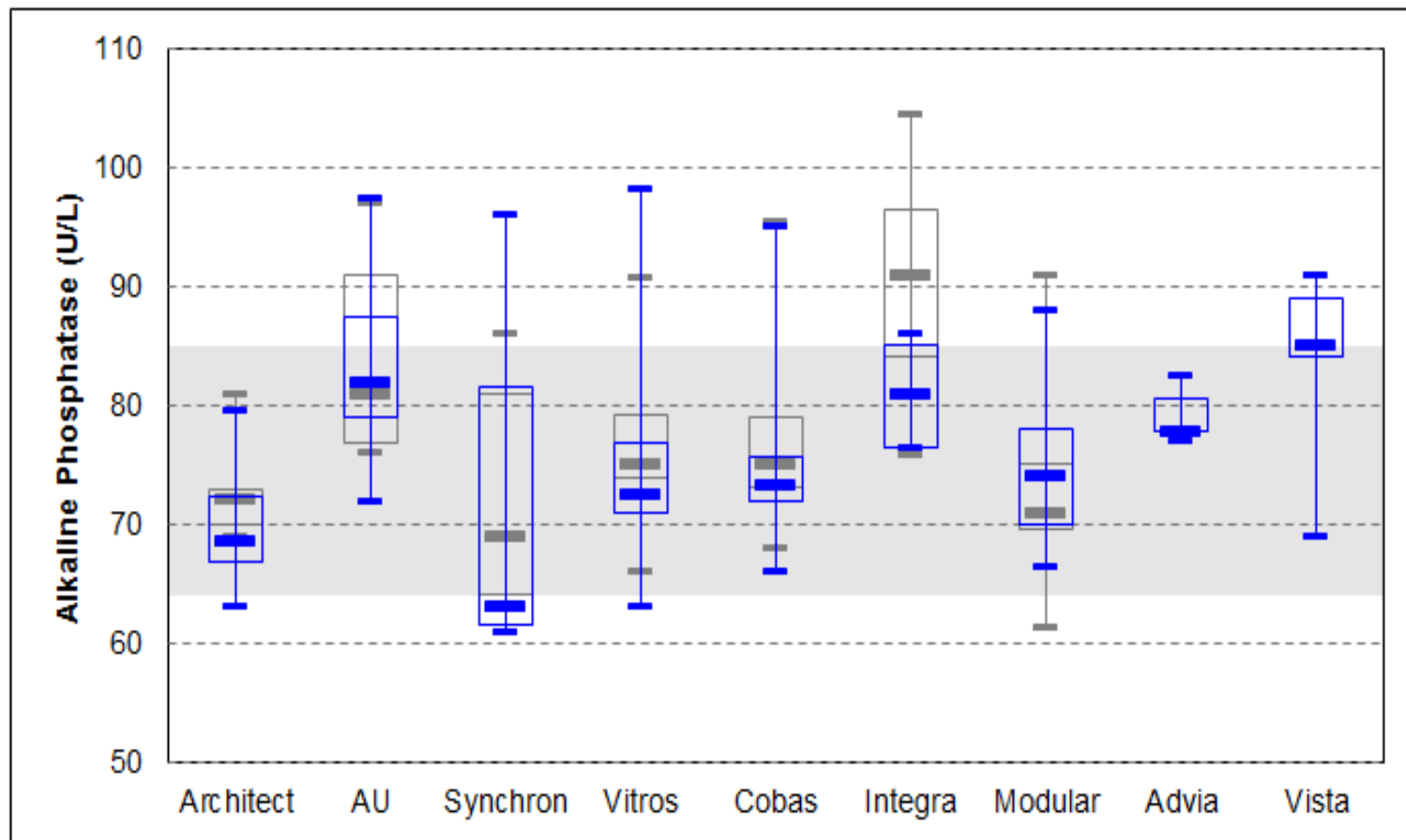


# Percentiler Applications

## Peer group overviews

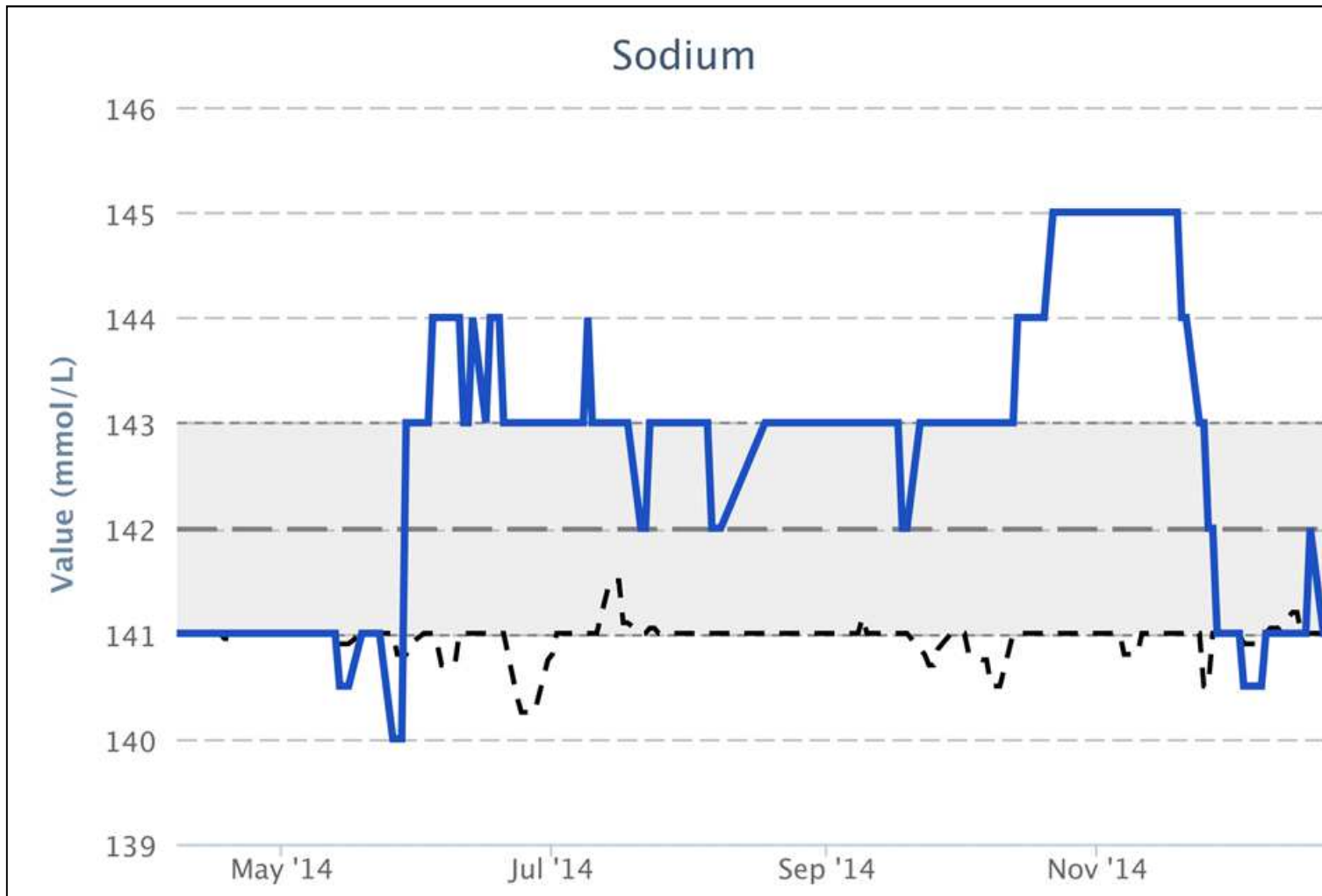
Peer Group report #1 (March 2014)

Peer group report #2 (July 2015)



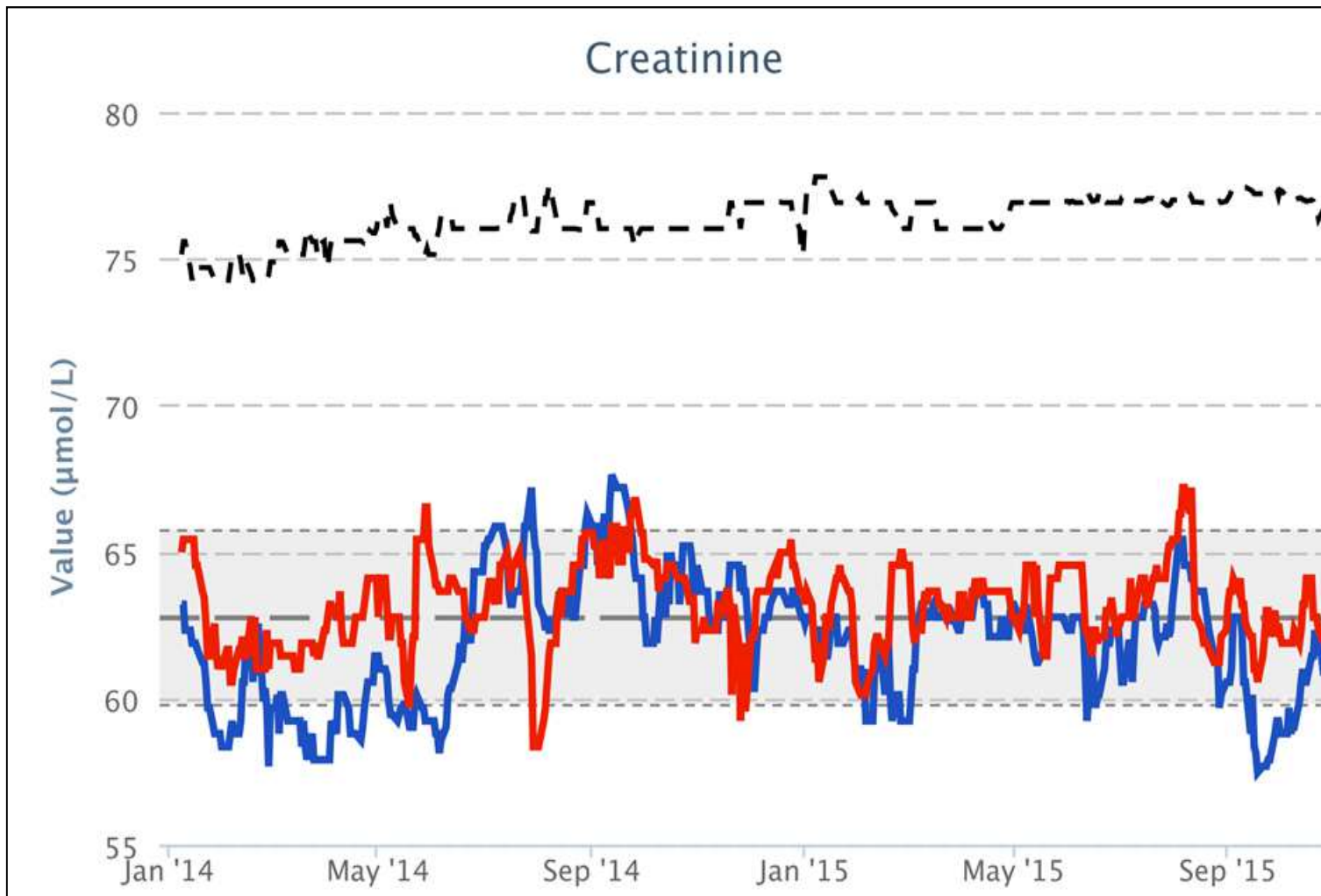
# Percentiler Applications

## Bias assessment versus peer



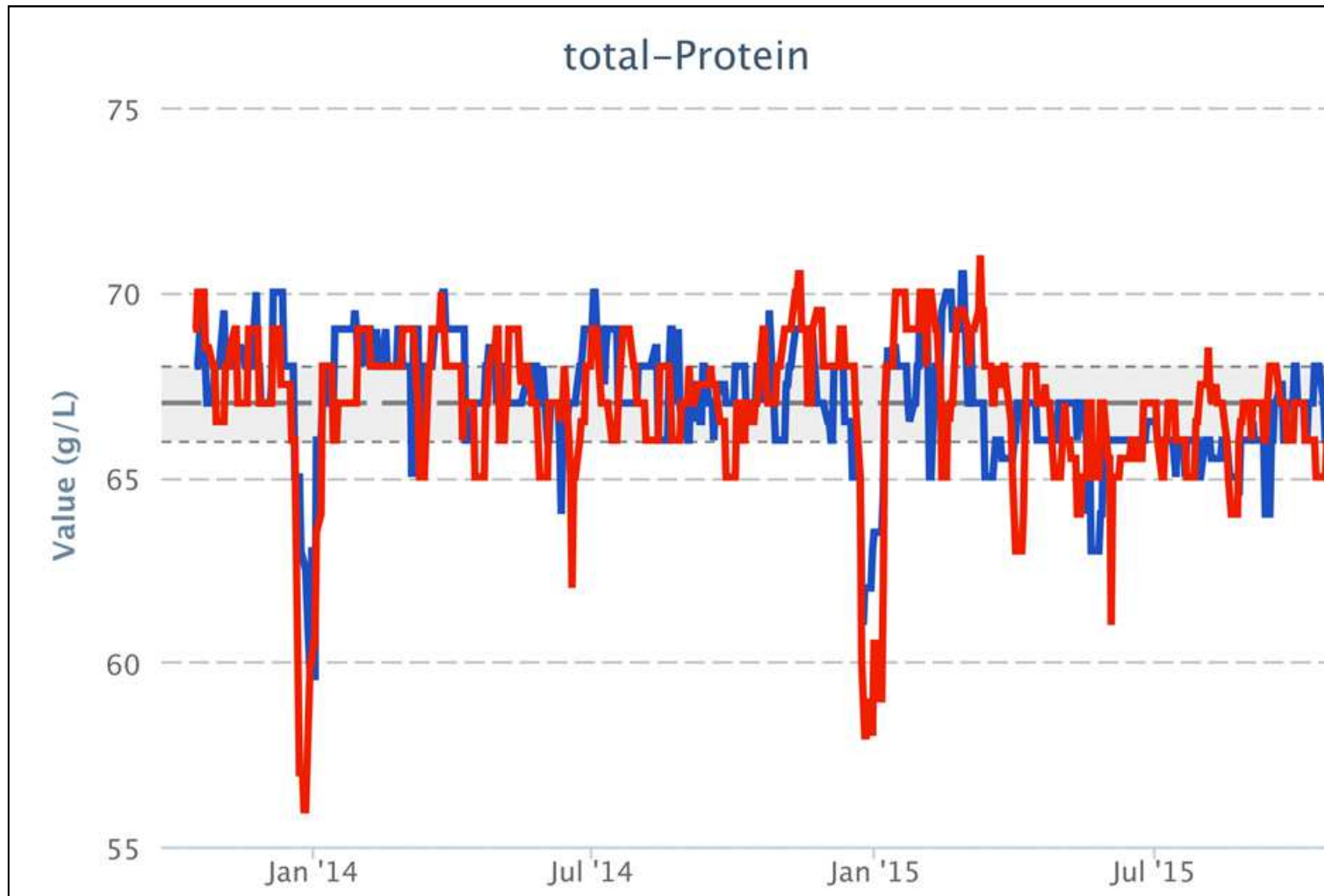
# Potential Issues

## Patient population effects & stratification problems



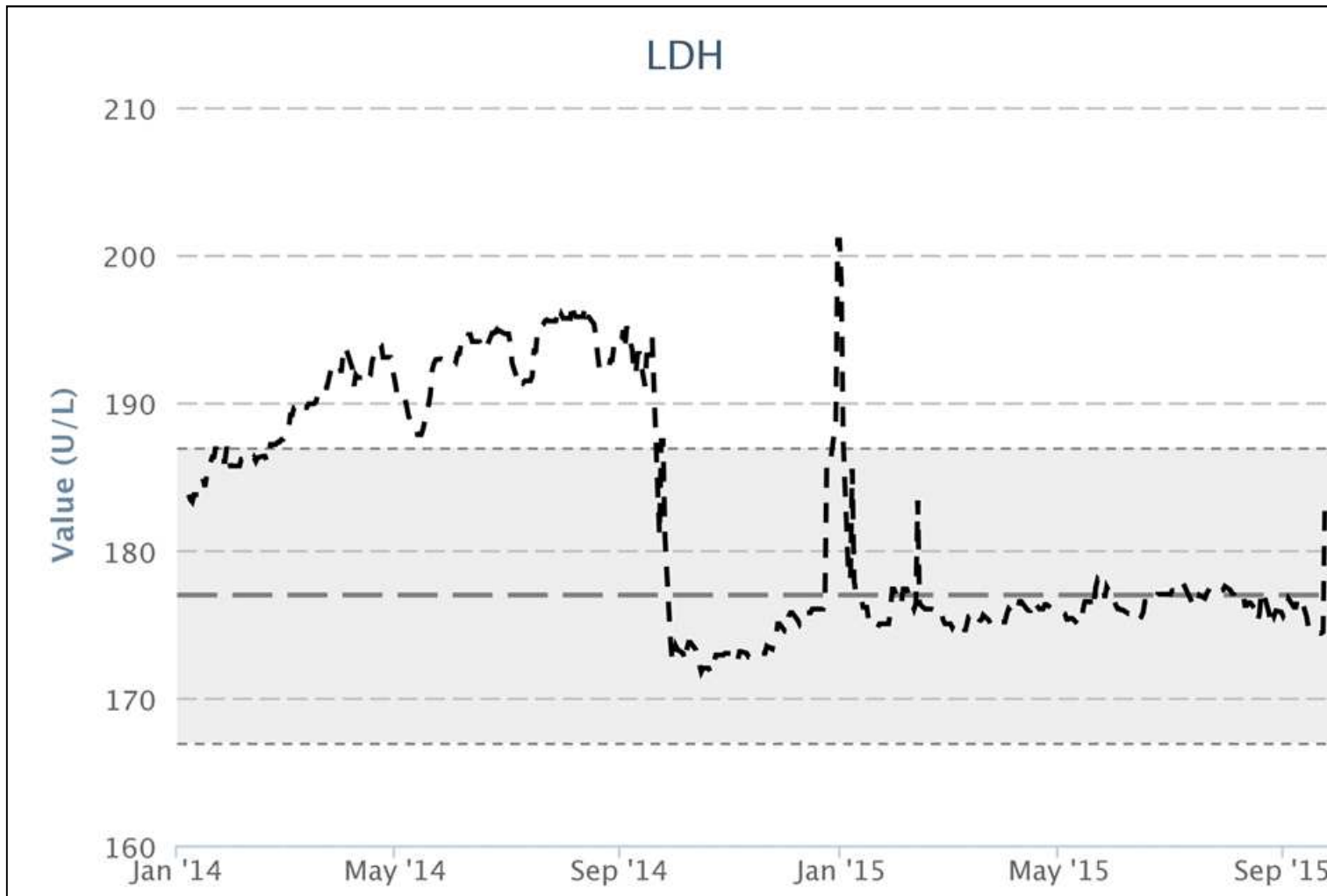
# Potential Issues

## Holiday periods



# Potential Issues

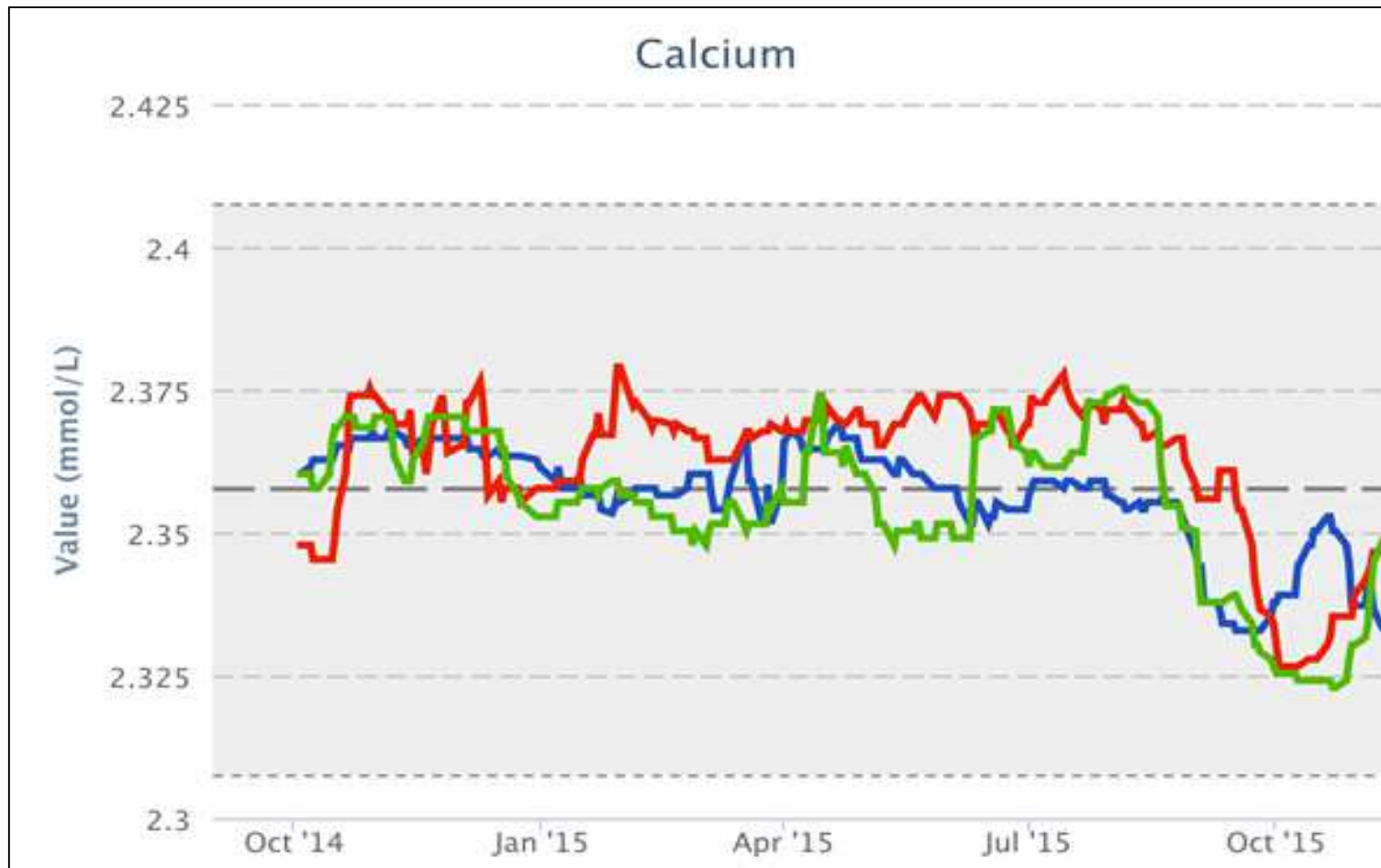
## Cobas peer influenced by lab chain





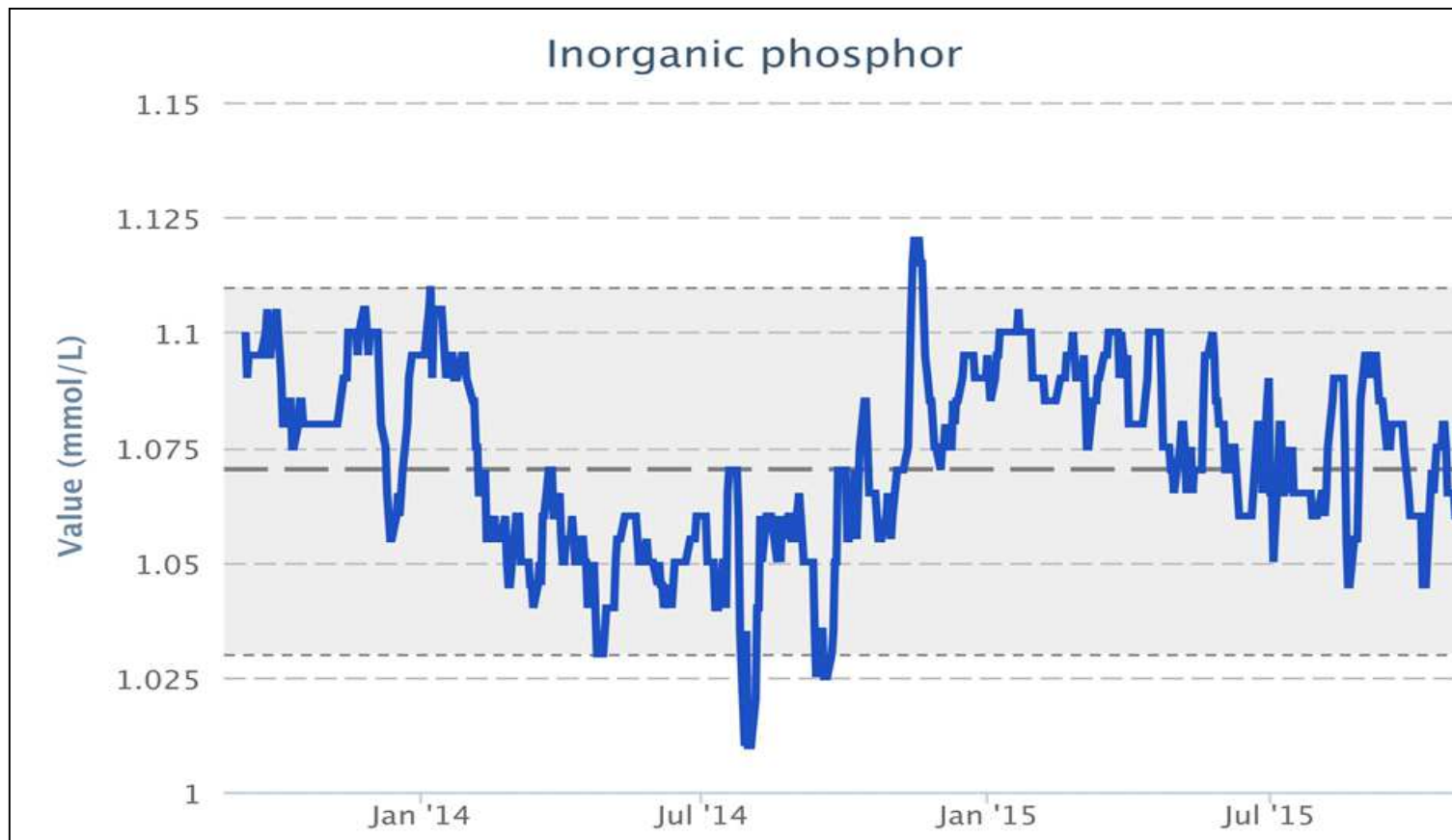
# Low population variation

Observation of small (insignificant) effects on a short(er) time-scale



# Low population variation

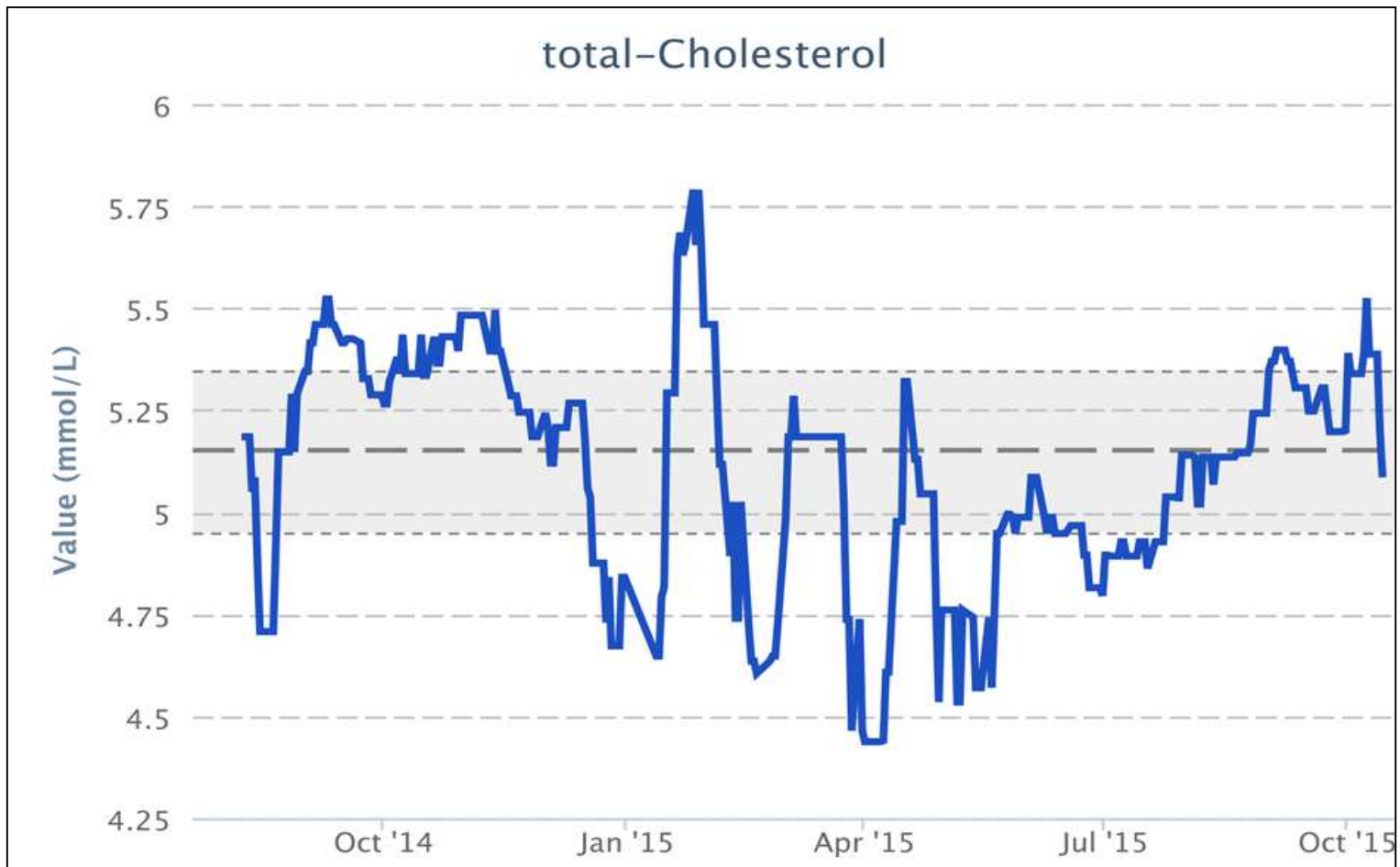
Observation of small (insignificant) effects on a short(er) time-scale



# High population variation

Counteract by using high “ $n$ ”

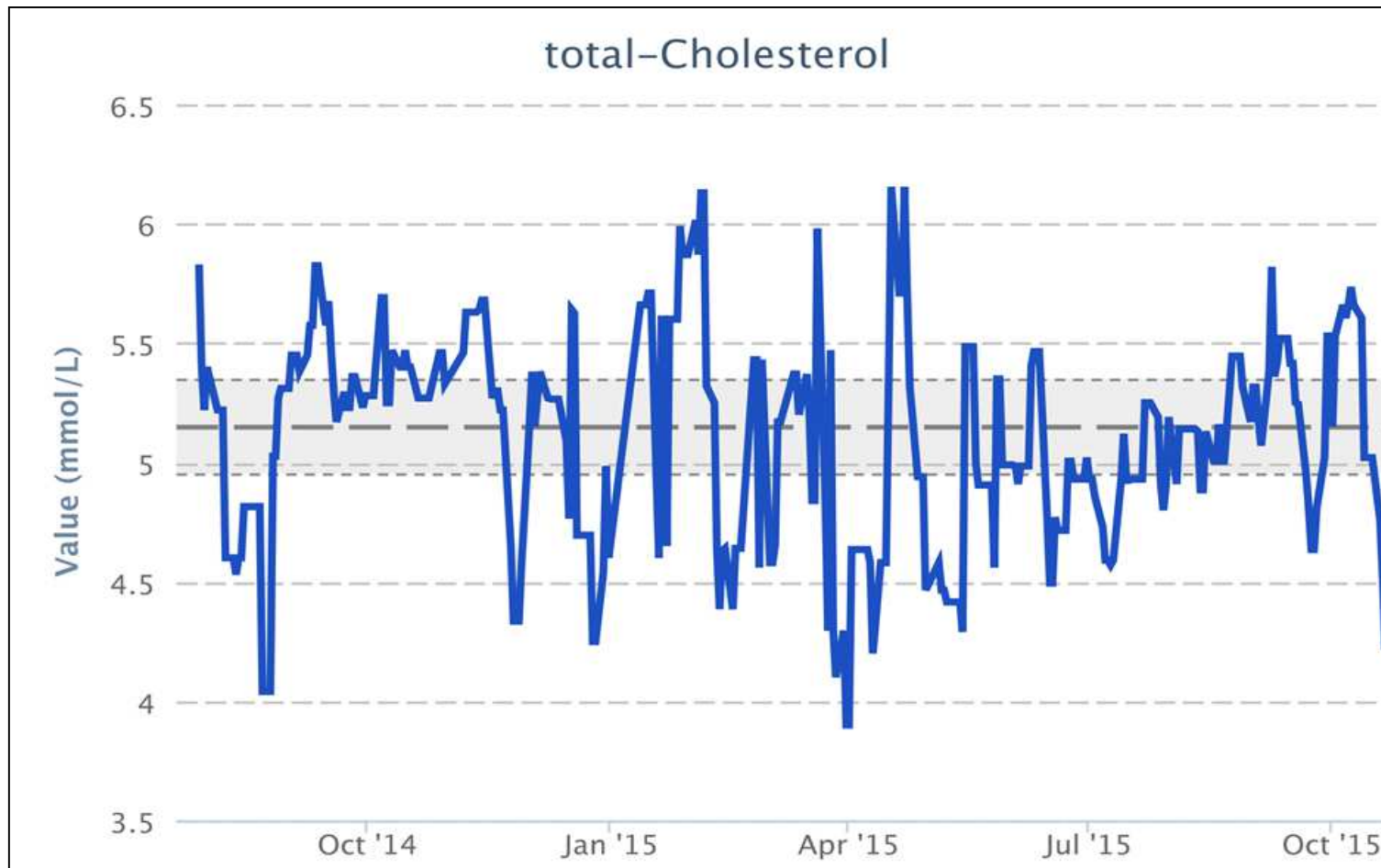
Example:  $n = 16$



# High population variation

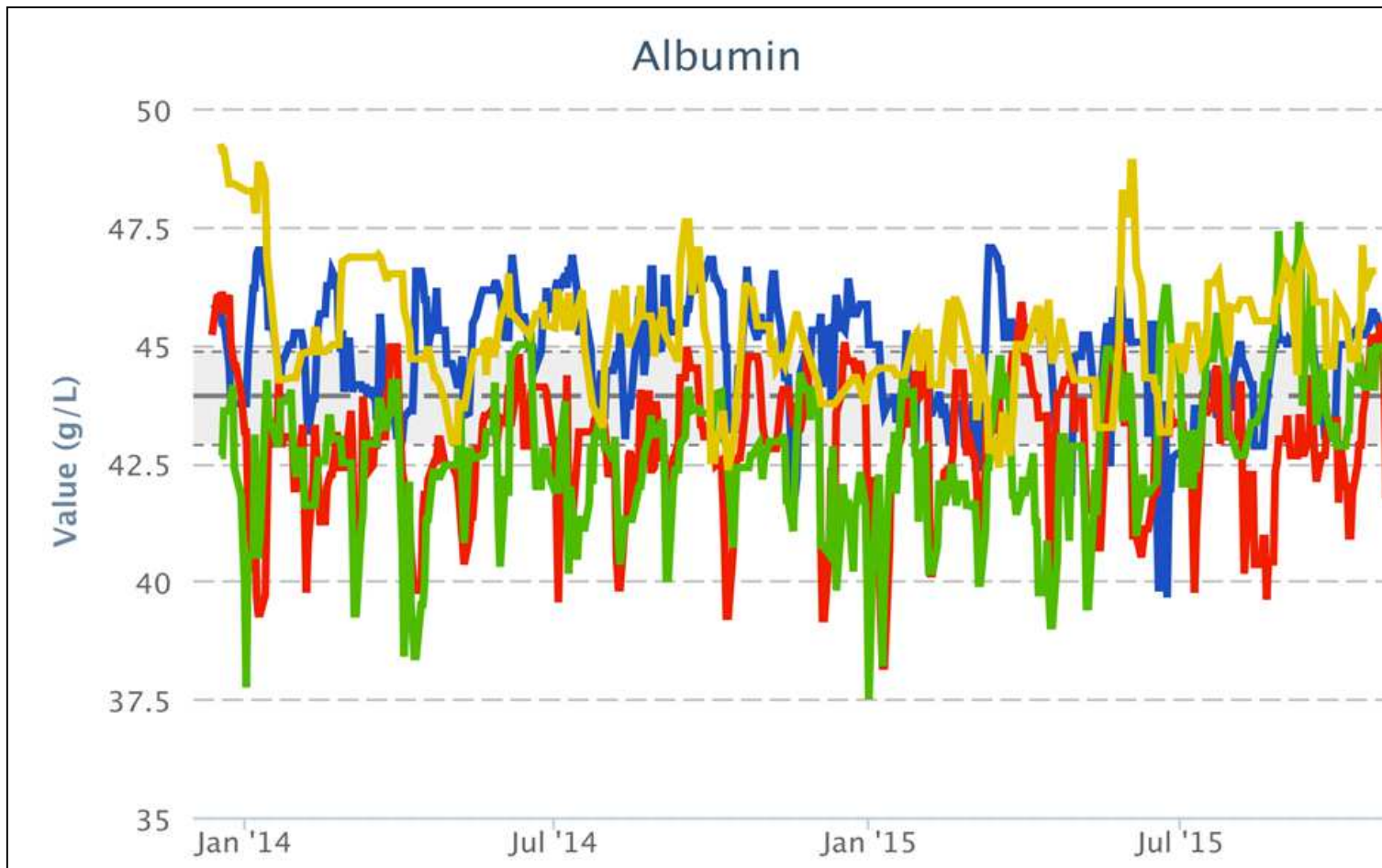
Cave when using high “*n*”

Verify at  $n = 5!$  (or  $n = 8$ )



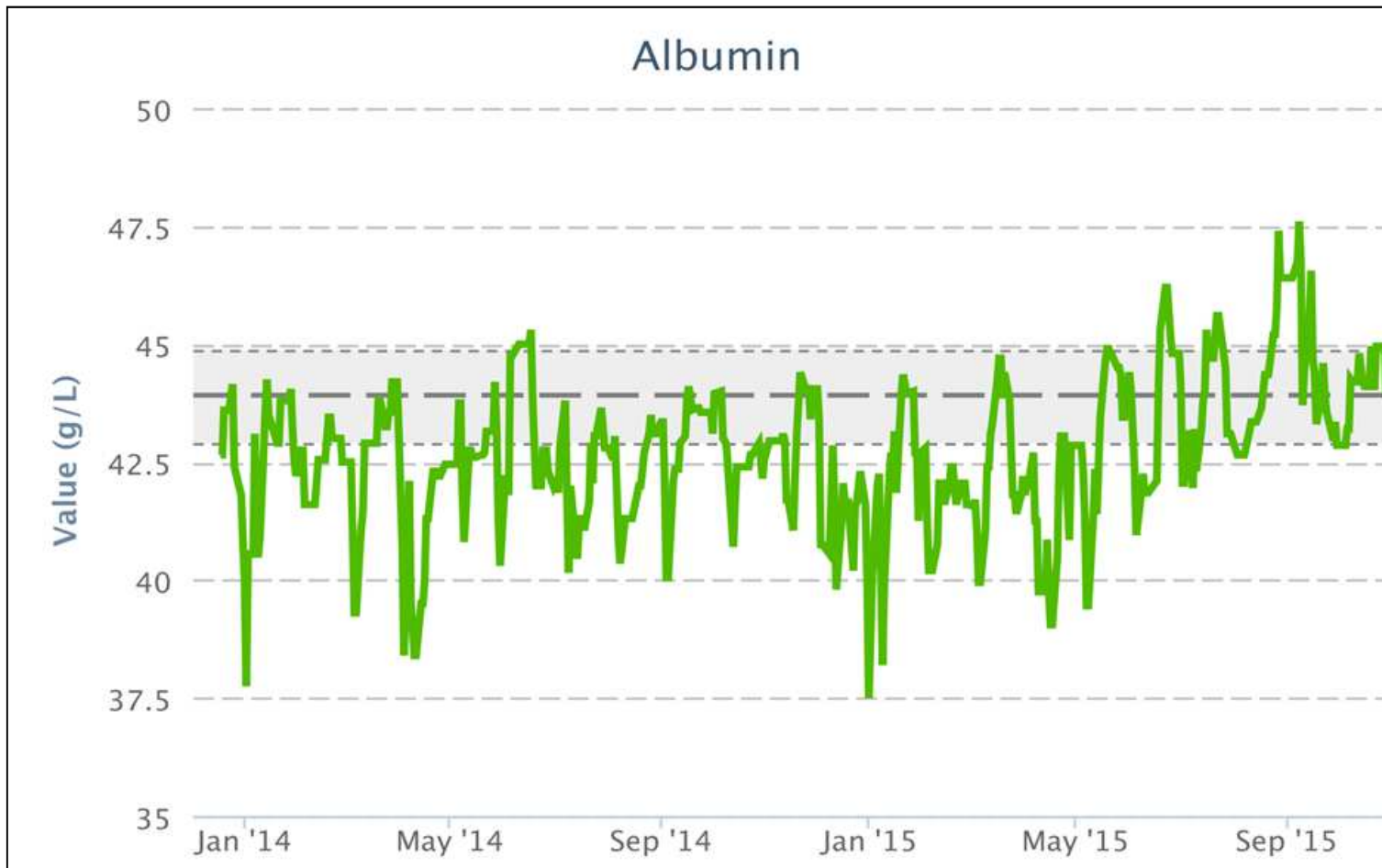
# High population variation

Still possible to observe effects on a mid- to long-term scale



# High population variation

Still possible to observe effects on a mid- to long-term scale



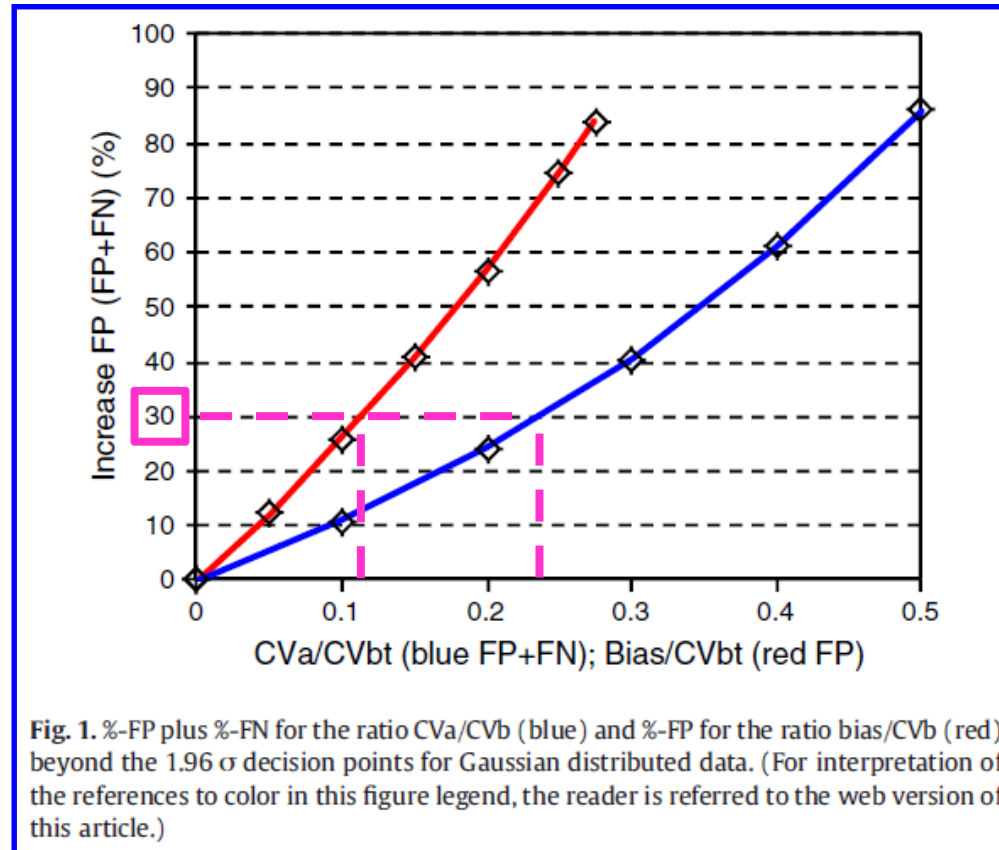
# The Flagger



# The Flagger – Application Concept

## Theory

### Effect of assay instability on surrogate medical decisions



A fresh look at analytical performance specifications from biological variation.

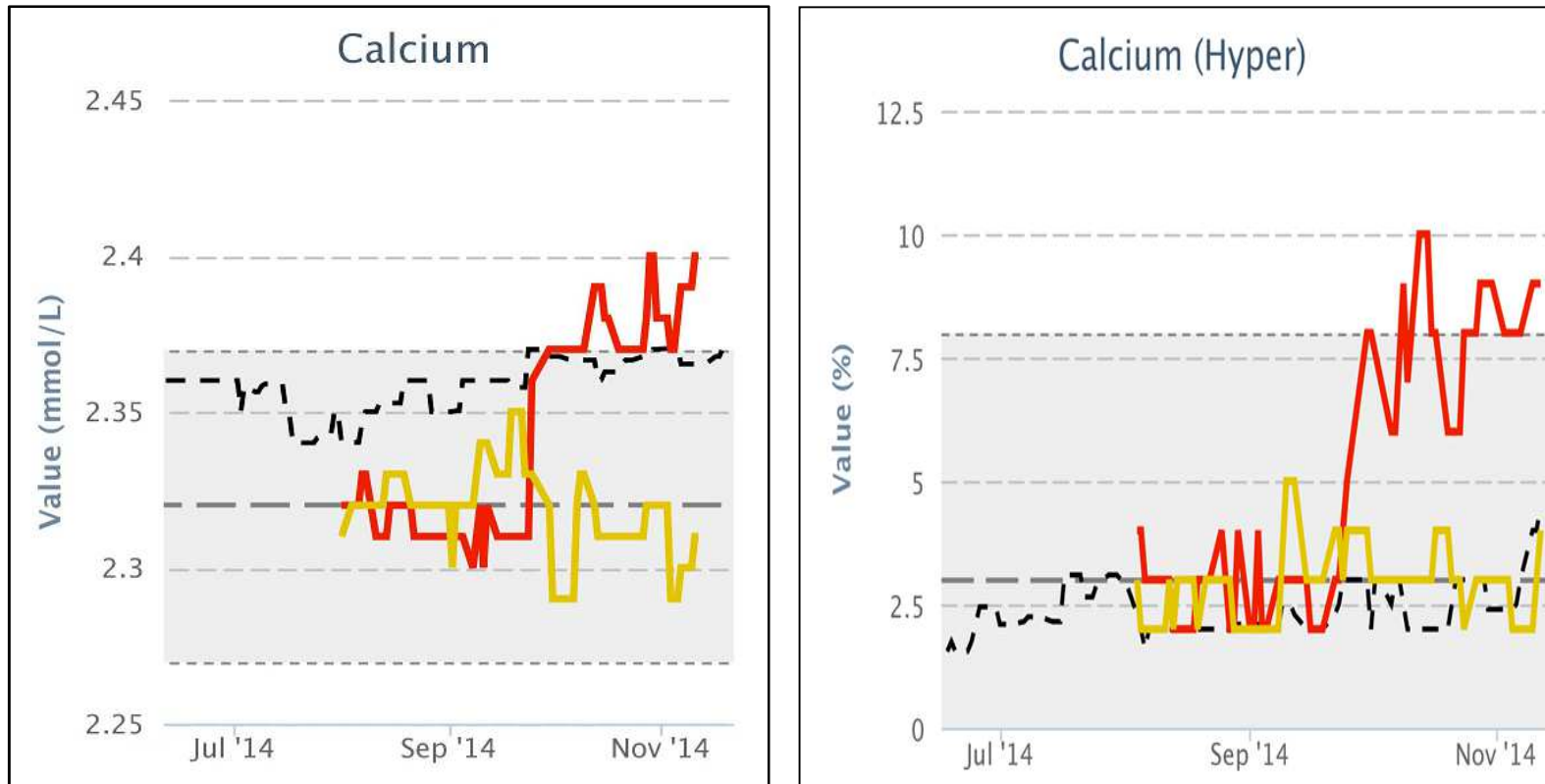
Stepman HC, Stöckl D, Twomey PJ, Thienpont LM. Clin Chim Acta 2013;421:191-2.

Empower Gent Dec 9 2015 – The Percentiler – The Flagger

# The Flagger – Application Concept

Example: hypercalcemia surrogate medical decision

**Triplication** of flagging rate in period with high vs low median values

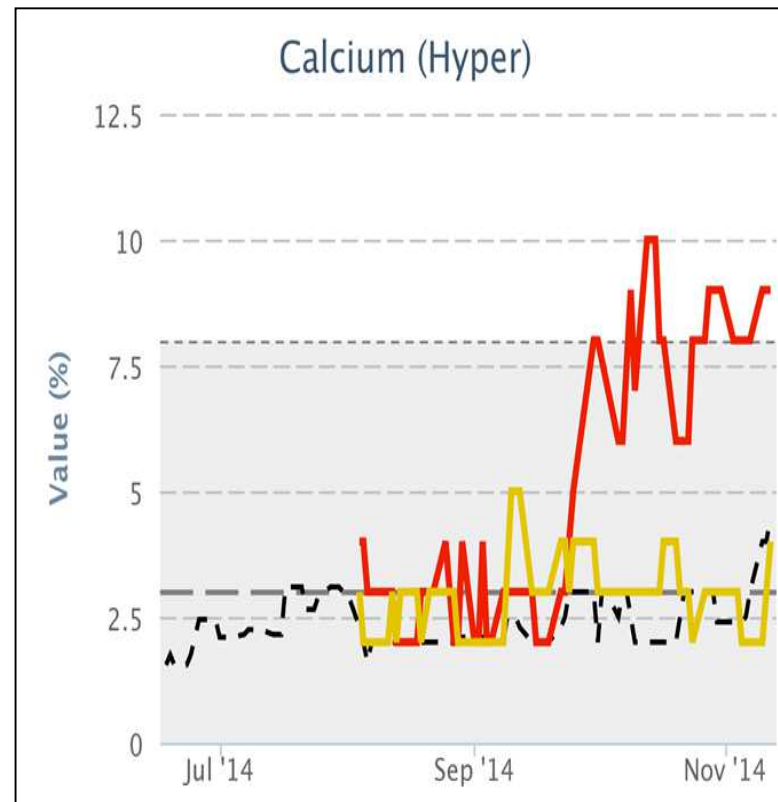
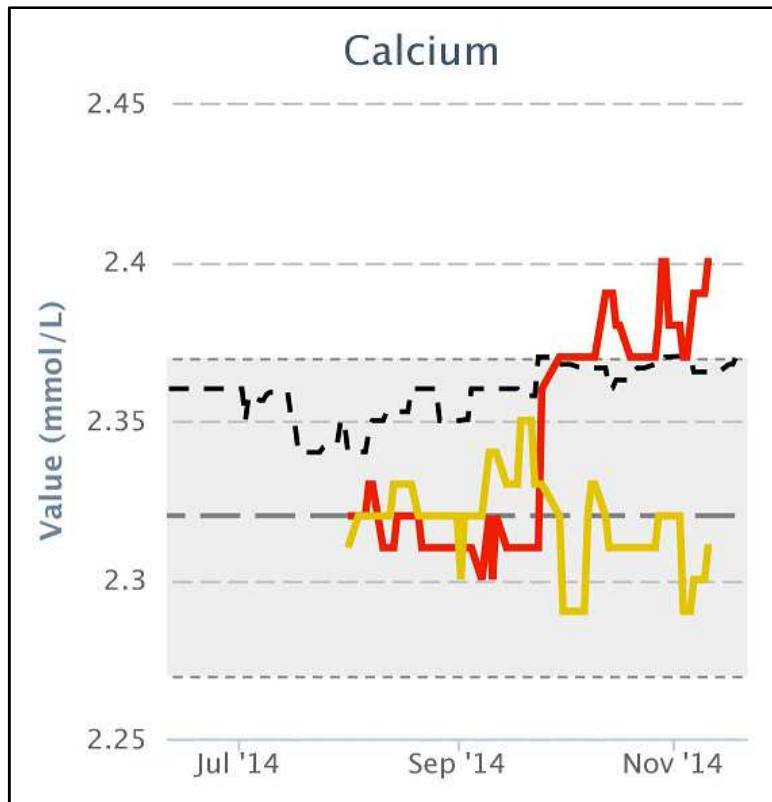


Goossens K et al. On-line flagging monitoring – A new quality management tool for the analytical phase. *Clin Chem Lab Med* 2015; doi: 10.1515/cclm-2015-0066.

# Flagger Limits

## Original Idea

Violation Flagger limits ~ Violation Percentiler limits



# Flagger Limits

## Original Idea

Violation Flagger limits ~ Violation Percentiler limits

Would require the use of **lab-specific limits**

Because:

- **Different laboratories apply different reference intervals**
  - **The long-term flagging rates lie at grossly different levels**
- **Assays are calibrated differently at different concentration ranges**

# Flagger Limits

**Current Limits = Analyte-specific limits**

**Calculated relatively to the long-term flagging rate**

**For example:**

**AST limit = relative 30% (absolute minimum = 1%)**

**Long term flagging rate = 10%**

**Limit =  $\pm 3\%$  (30% of 10%)**

**Long term flagging rate = 2.5%**

**Limit =  $\pm 1\%$  (NOT 0.75%)**

# Flagger Limits

**Current Limits = Analyte-specific limits**

**Violation Flagger limits  $\neq$  Violation Percentiler limits**

**Treat these limits differently:**

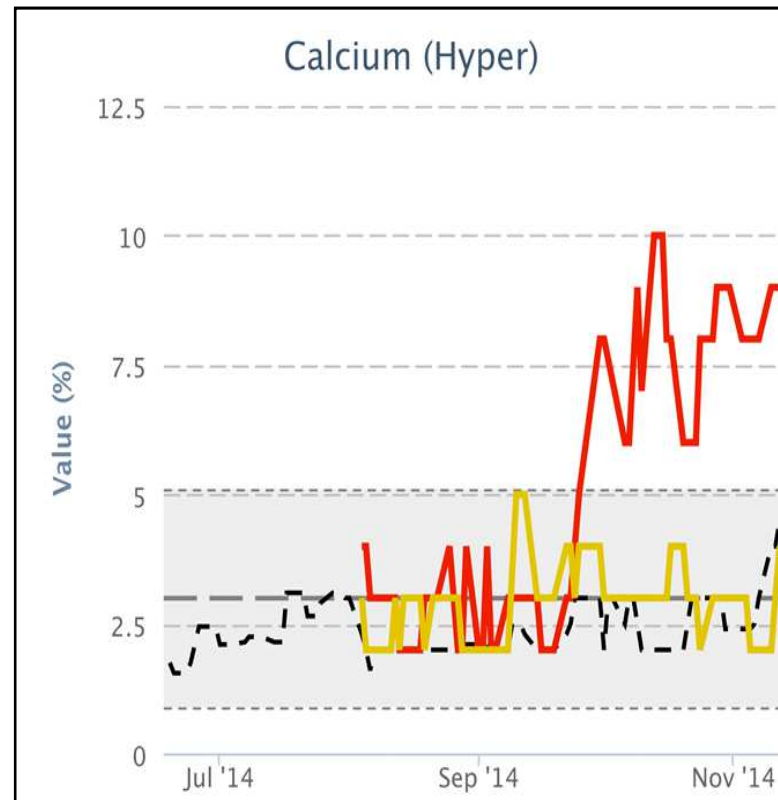
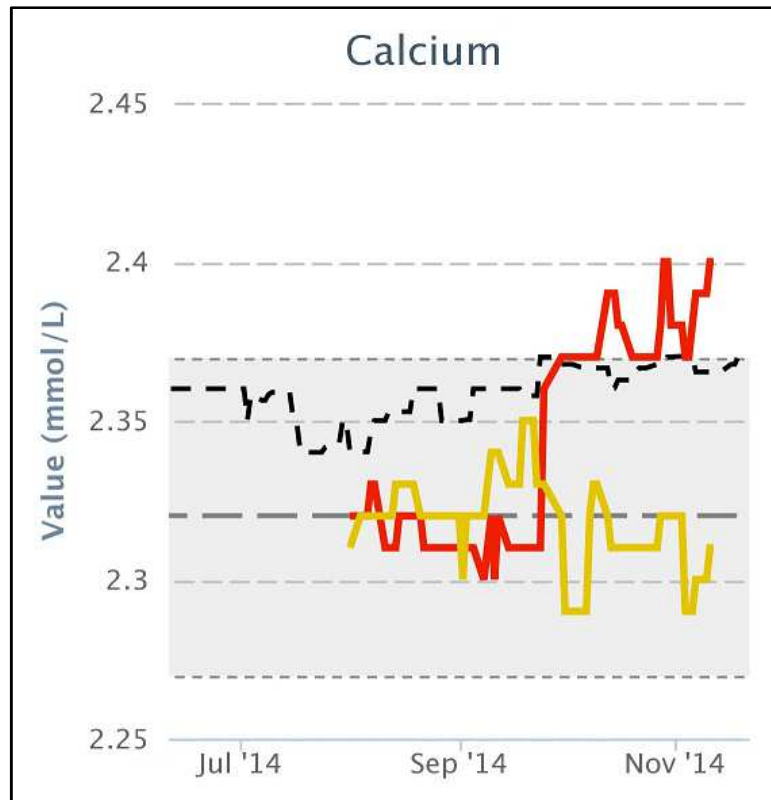
**They give different and additional information about your long-term performance**

- **Percentiler limits** ~ Biological variation/State-of-the-art performance at median concentration
- **Flagger limits** ~ State-of-the-art performance at low/high concentration

# Flagger Limits

**Current Limits = Analyte-specific limits**

**Violation Flagger limits  $\neq$  Violation Percentiler limits**





# Flagger Limits

	Percentiler		Flagger	
	Bias	Bias	Limit	Minimum
	Biology (%)	Empower (%)		Limit (Absolute %)
ALB	1.3	2.3	30	1
ALKFOS	6.4	7.0	40	1
ALT	11.4	11.0	30	1
AST	5.4	4.9	30	1
BILTOT	11.4	12.2	40	1
CA	0.8	2.1	70	1
CHOL	4	4.1	30	1
CL	0.5	1.0	50	1
CRP	21.8	11.0	30	1
GGT	10.8	9.4	50	1
GLUC	2.2	3.8	30	1
K	1.8	2.3	50	1
CREAT	4	4.1	40	1
LDH	4.3	5.4	50	1
MG	1.8	3.5	80	1
NA	0.3	0.7	100	1
P	3.2	3.6	70	1
PROT	1.2	1.4	60	1
UREA	5.5	5.5	30	1
URIC ACID	4.9	4.7	60	2
FT4	3.3	3.4	30	1
TSH	7.8	7.3	30	1

# Flagger Limits

**Preliminary!**

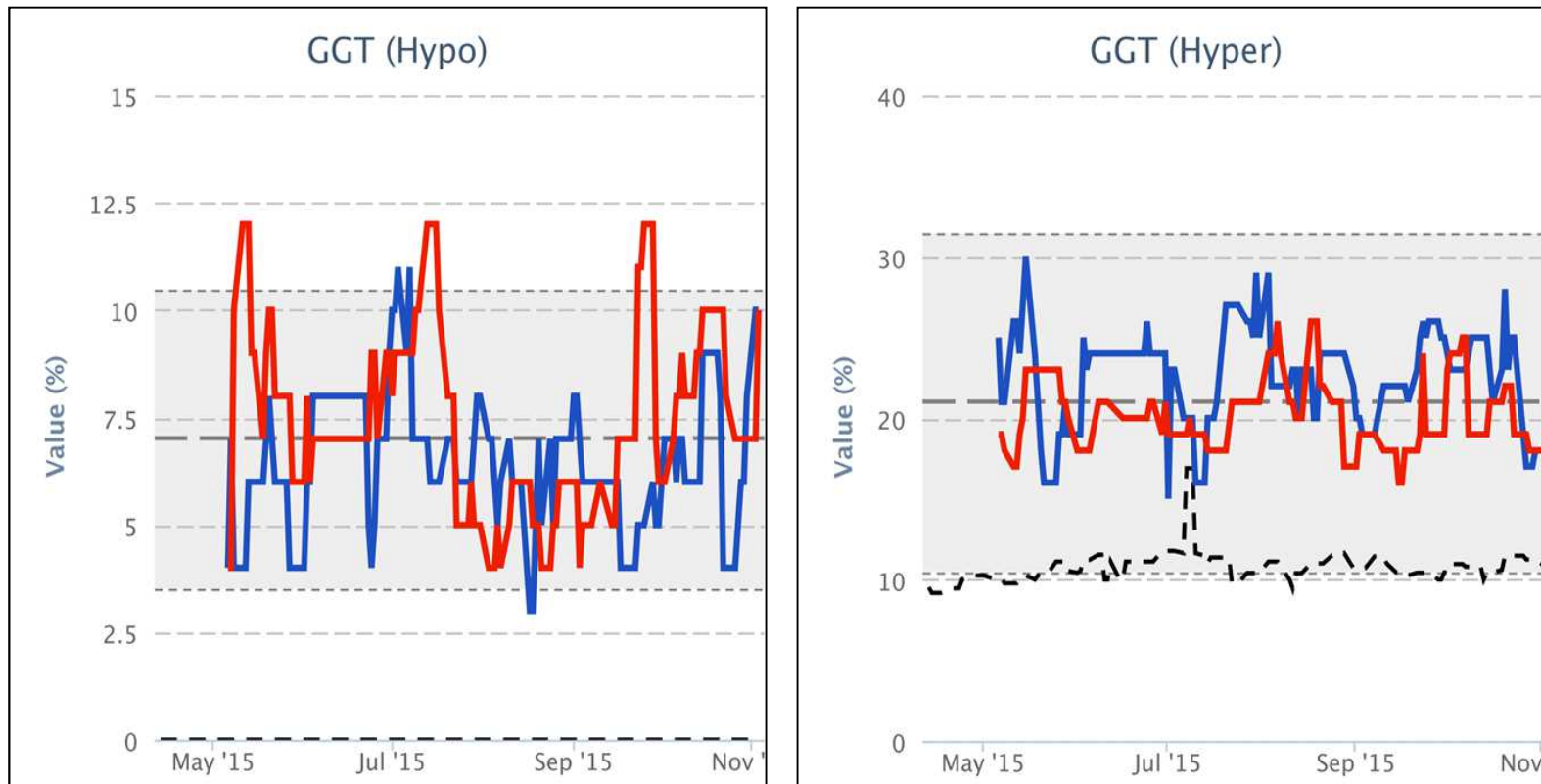
**Right now, the limits are biased towards Cobas performance**

**We need more instruments from other peer groups to set state-of-the-art related limits**

# Flagger – Peer Group Comparison

Similar as for the Percentiler:

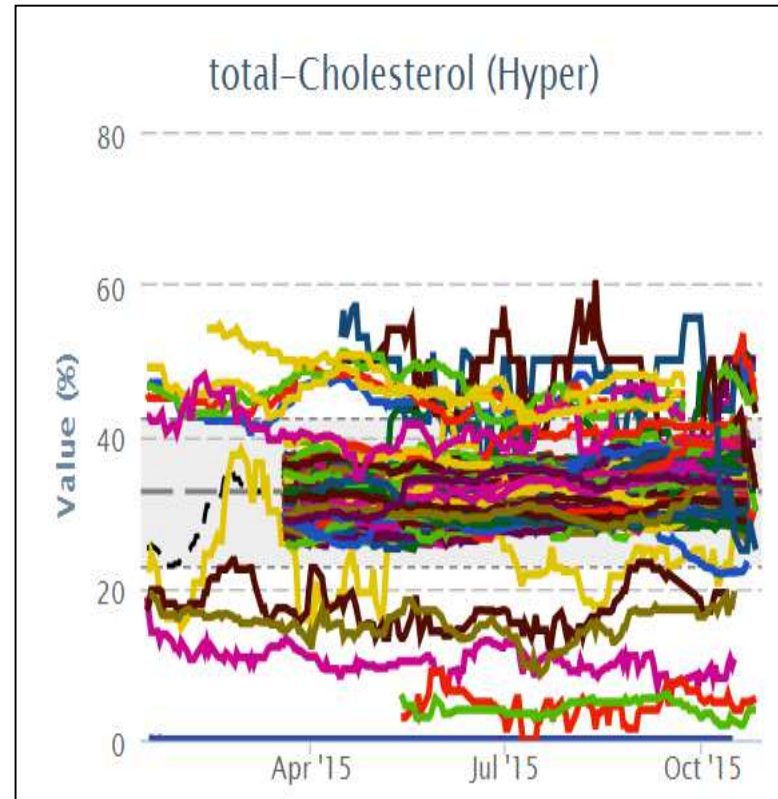
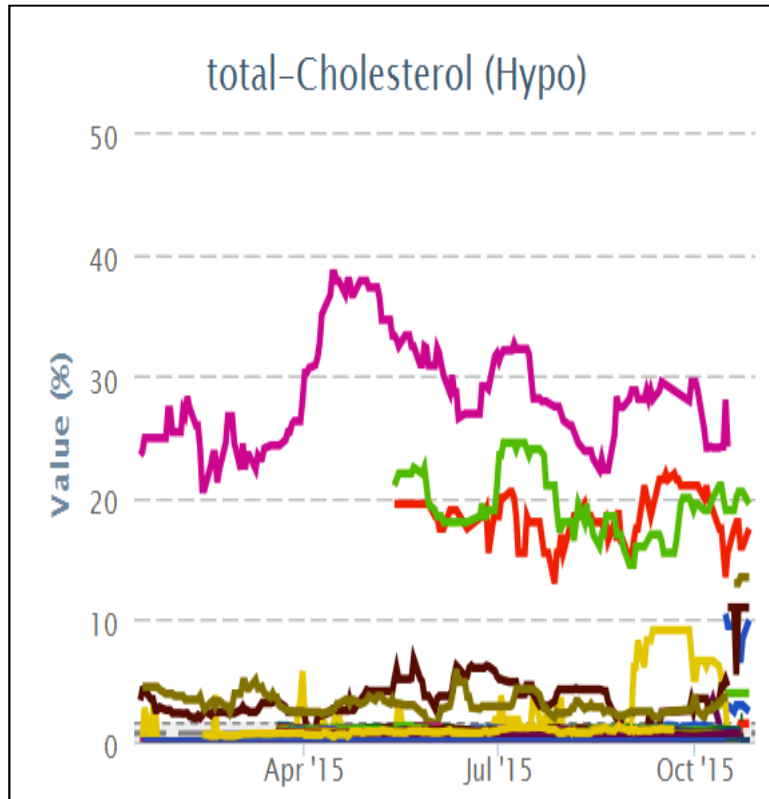
All or peer group median = black dotted line



# Flagger – Peer Group Comparison

Is peer group comparison useful?

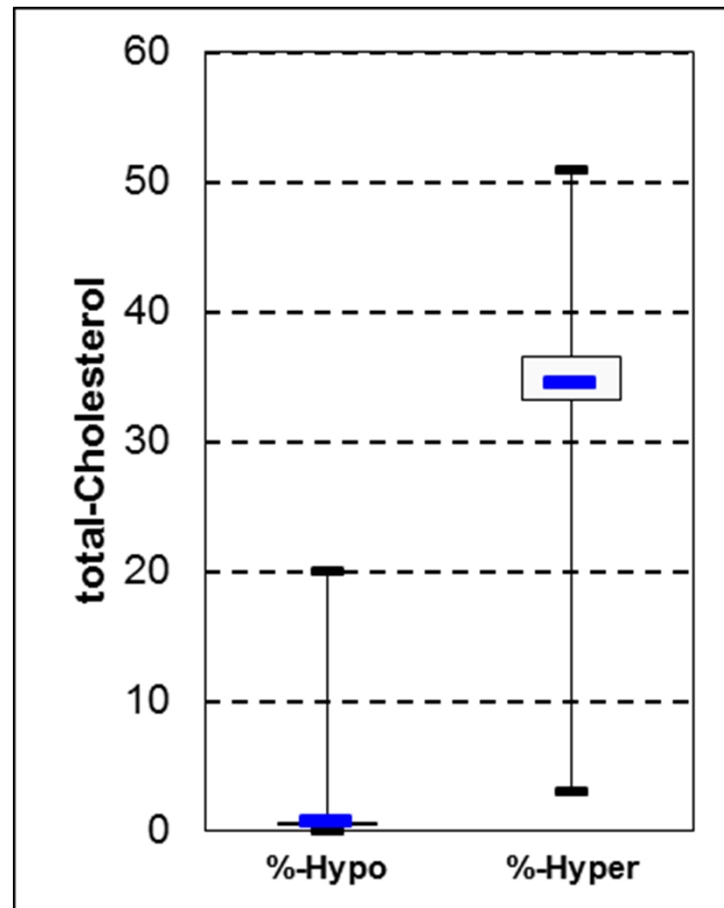
There is limited consensus on the applied reference limits in the lab!



# Flagger – Peer Group Comparison

Is peer group comparison useful?

There is limited consensus on the applied flagging limits in the lab!



# Percentiler - Flagger Link

## Principle

When values for patient medians  $\uparrow$ :

- %-hypo  $\downarrow$
- %-hyper  $\uparrow$

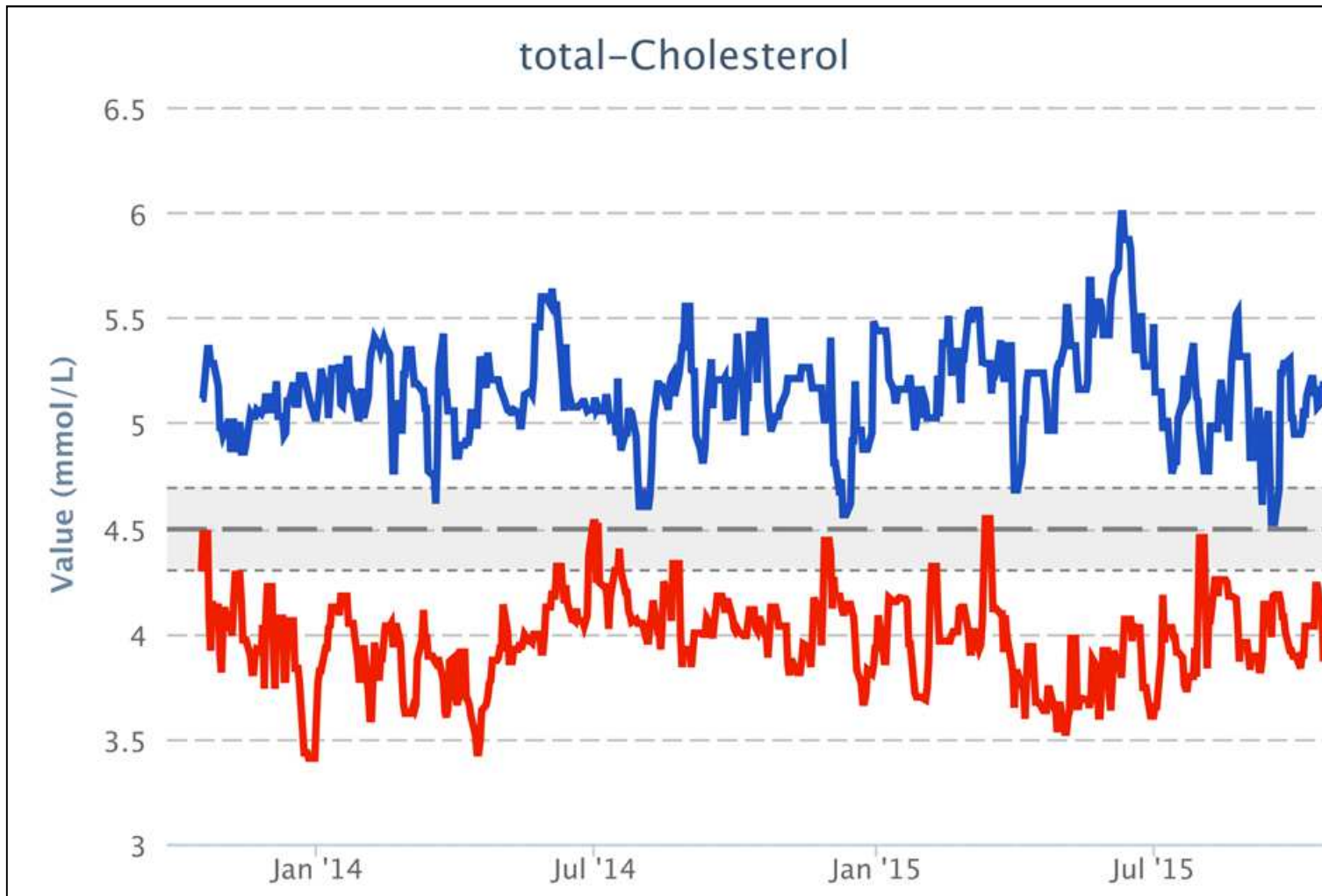
When values for patient medians  $\downarrow$ :

- %-hypo  $\uparrow$
- %-hyper  $\downarrow$

**It allows to translate analytical changes into their effect on the flagging rate**

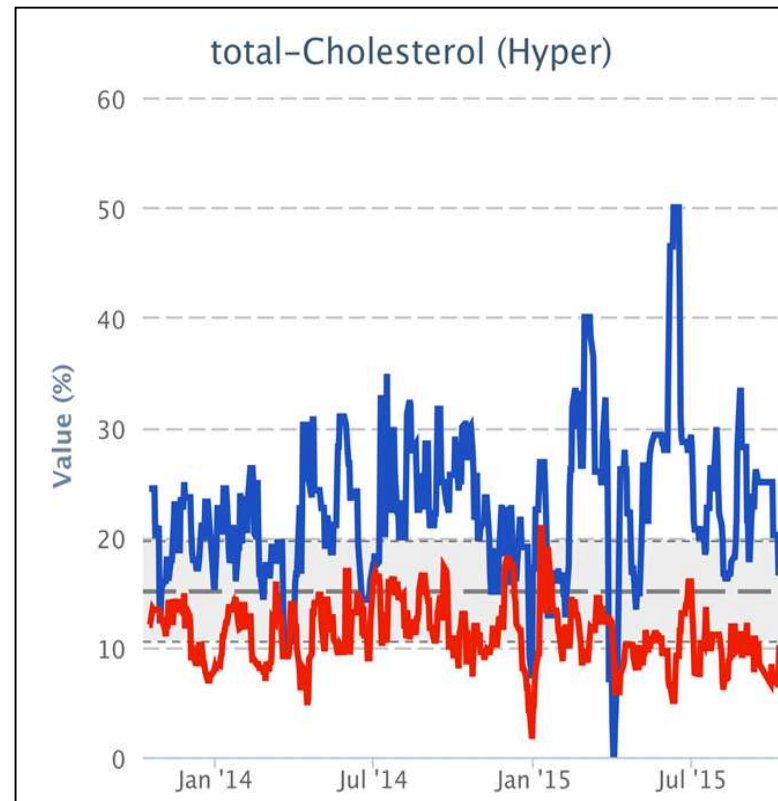
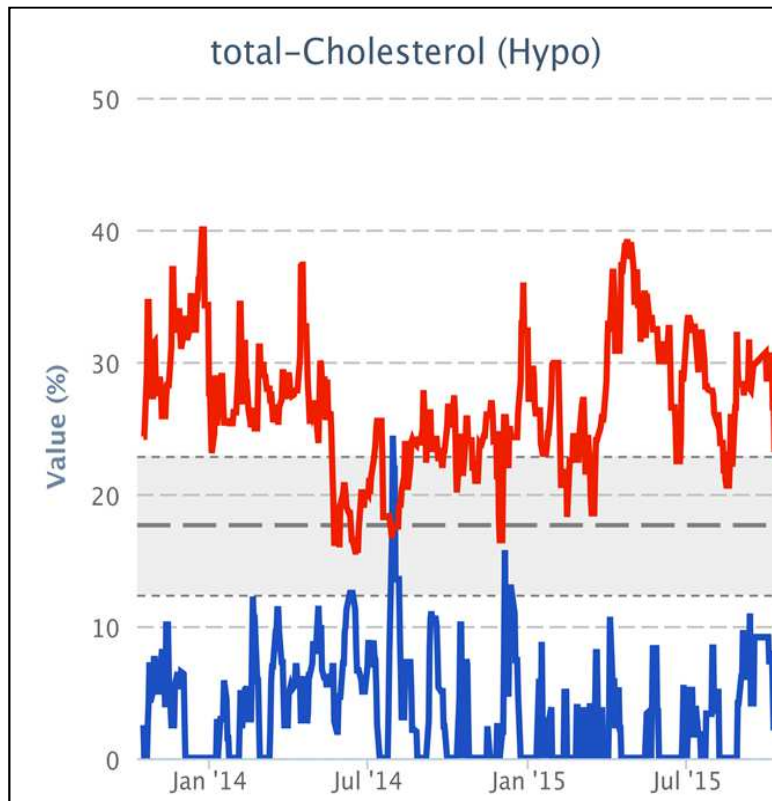
**But exceptions exist!**

# Percentiler - Flagger Link

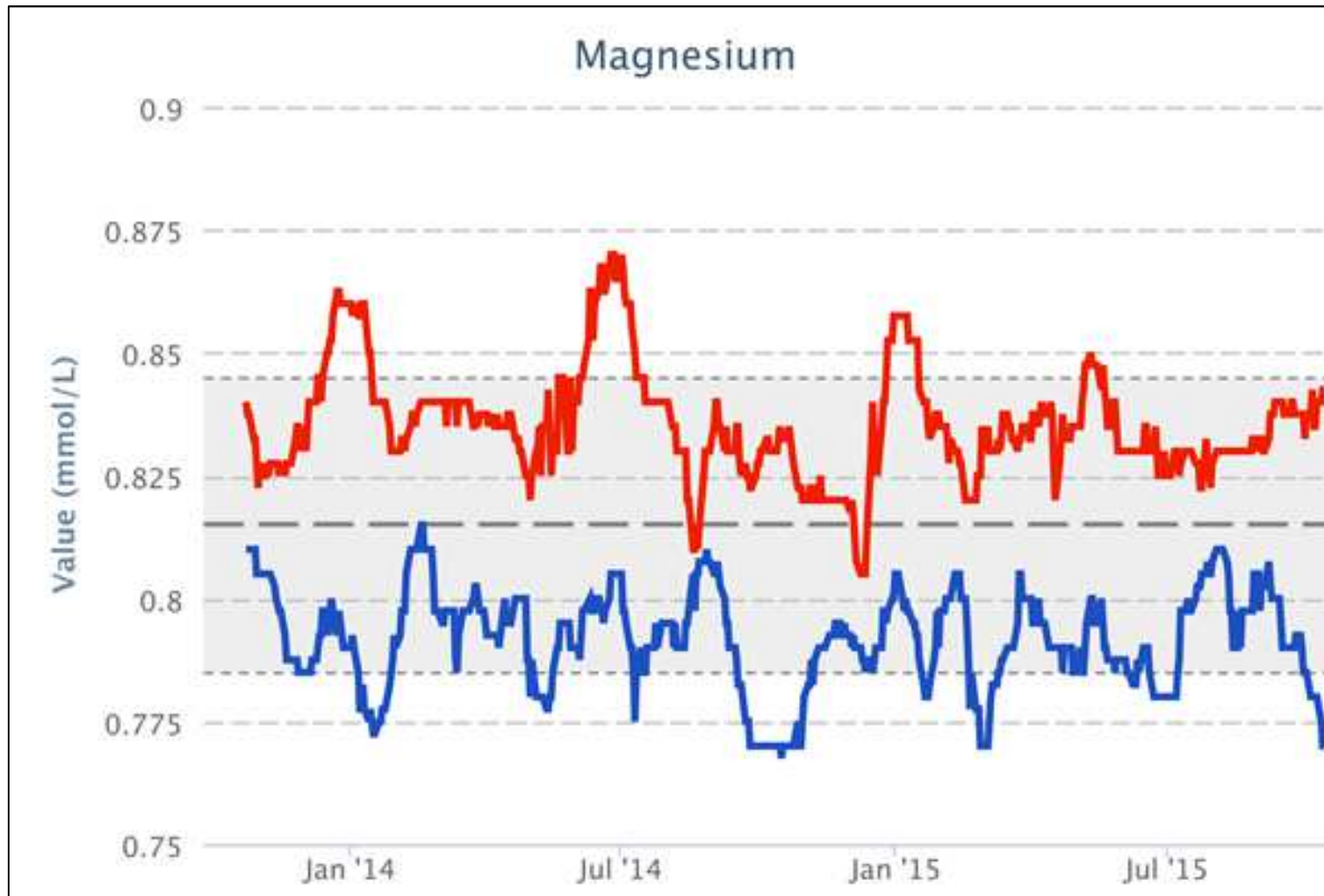




# Percentiler - Flagger Link

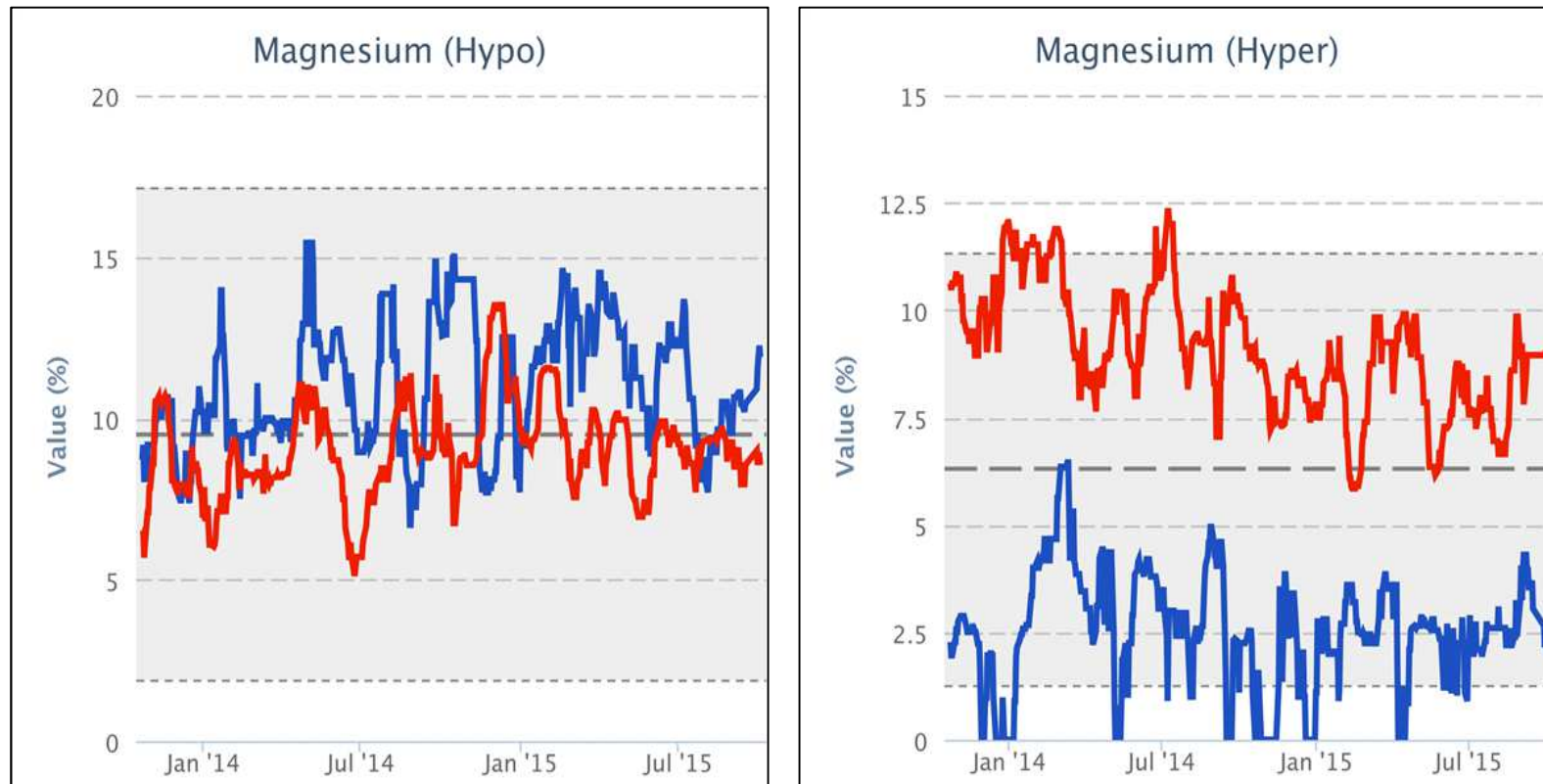


# Percentiler - Flagger Link



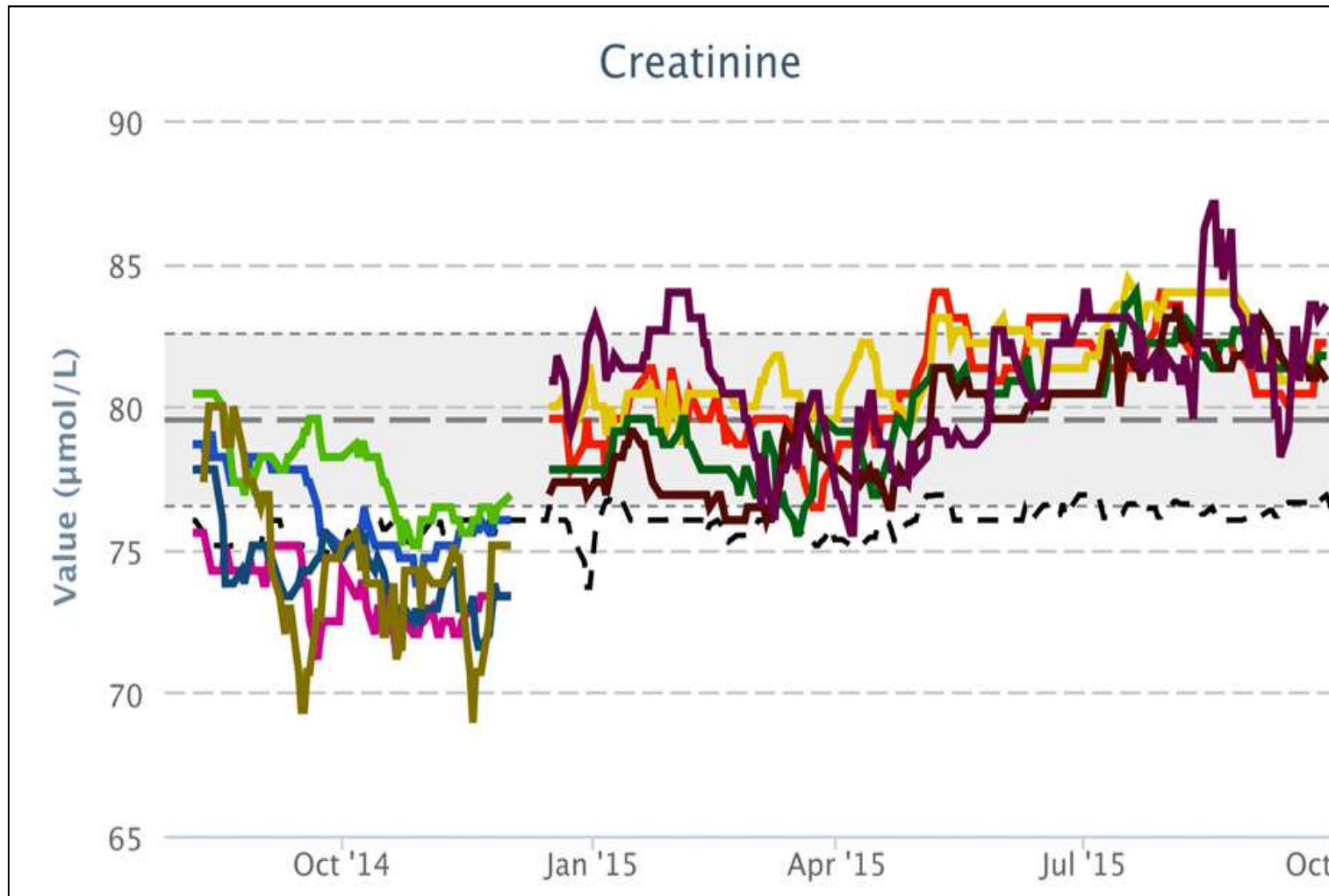
# Percentiler - Flagger Link

Hypo's comparable despite patient median bias



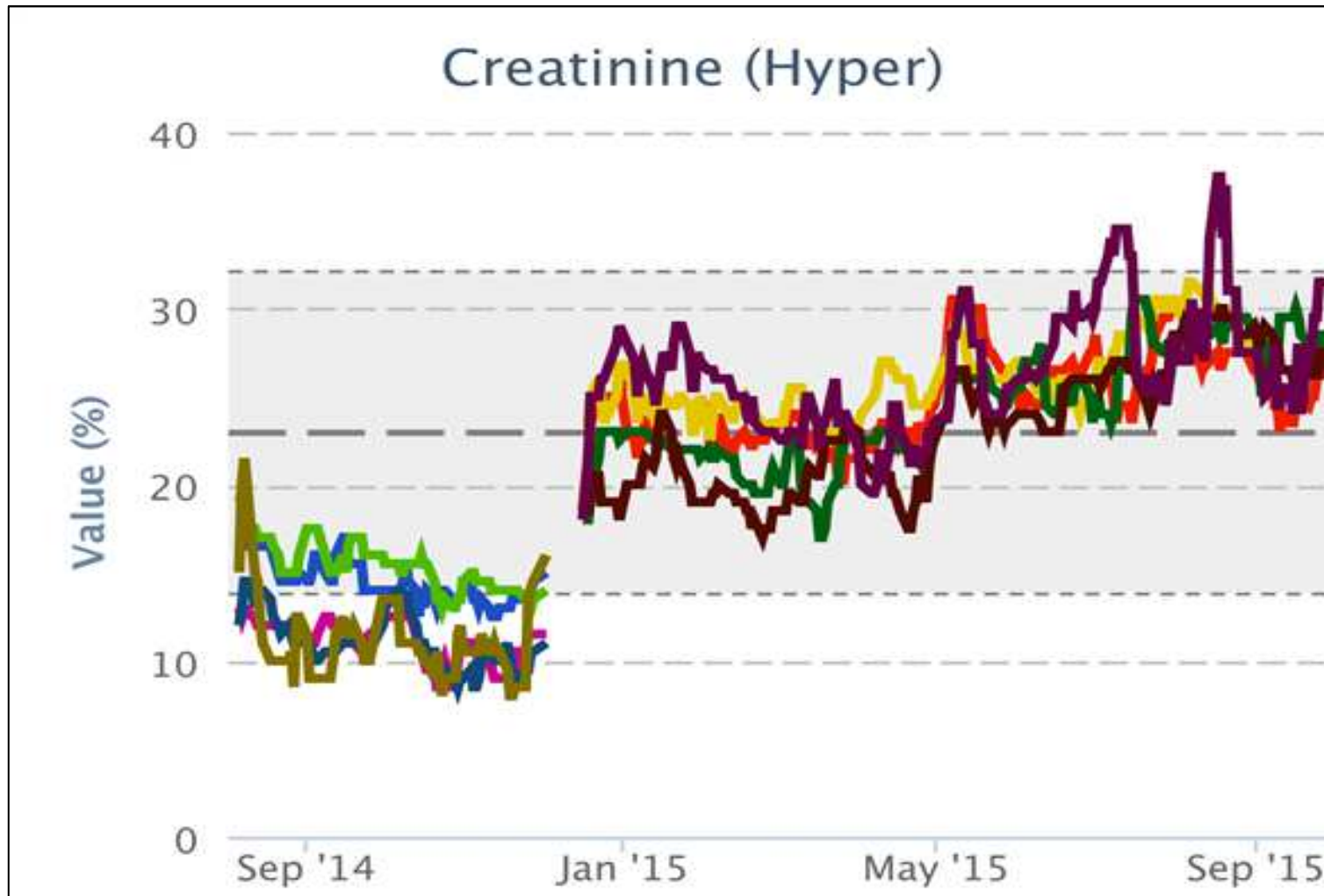
# Percentiler - Flagger Link

Instrument change



# Percentiler - Flagger Link

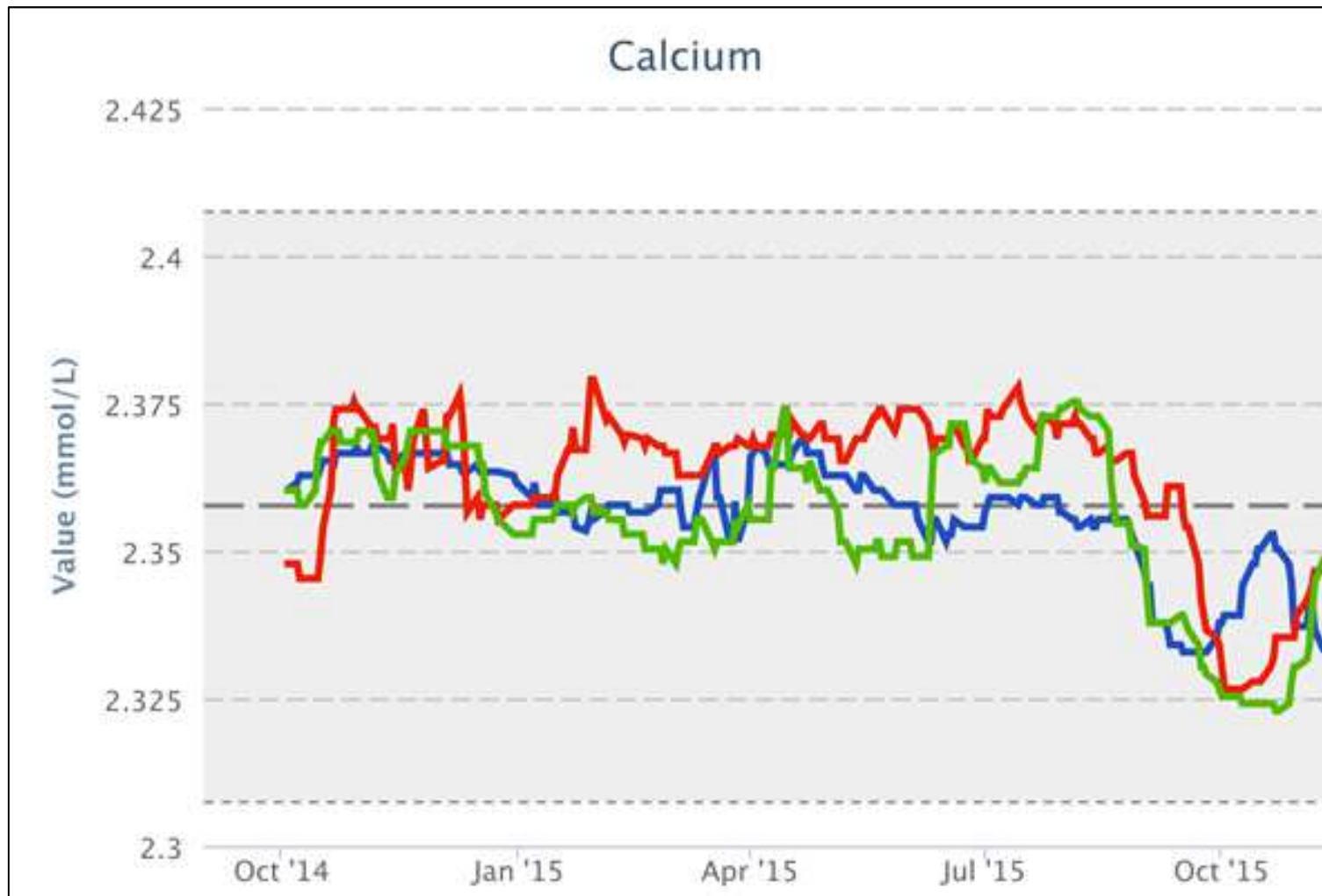
Instrument change





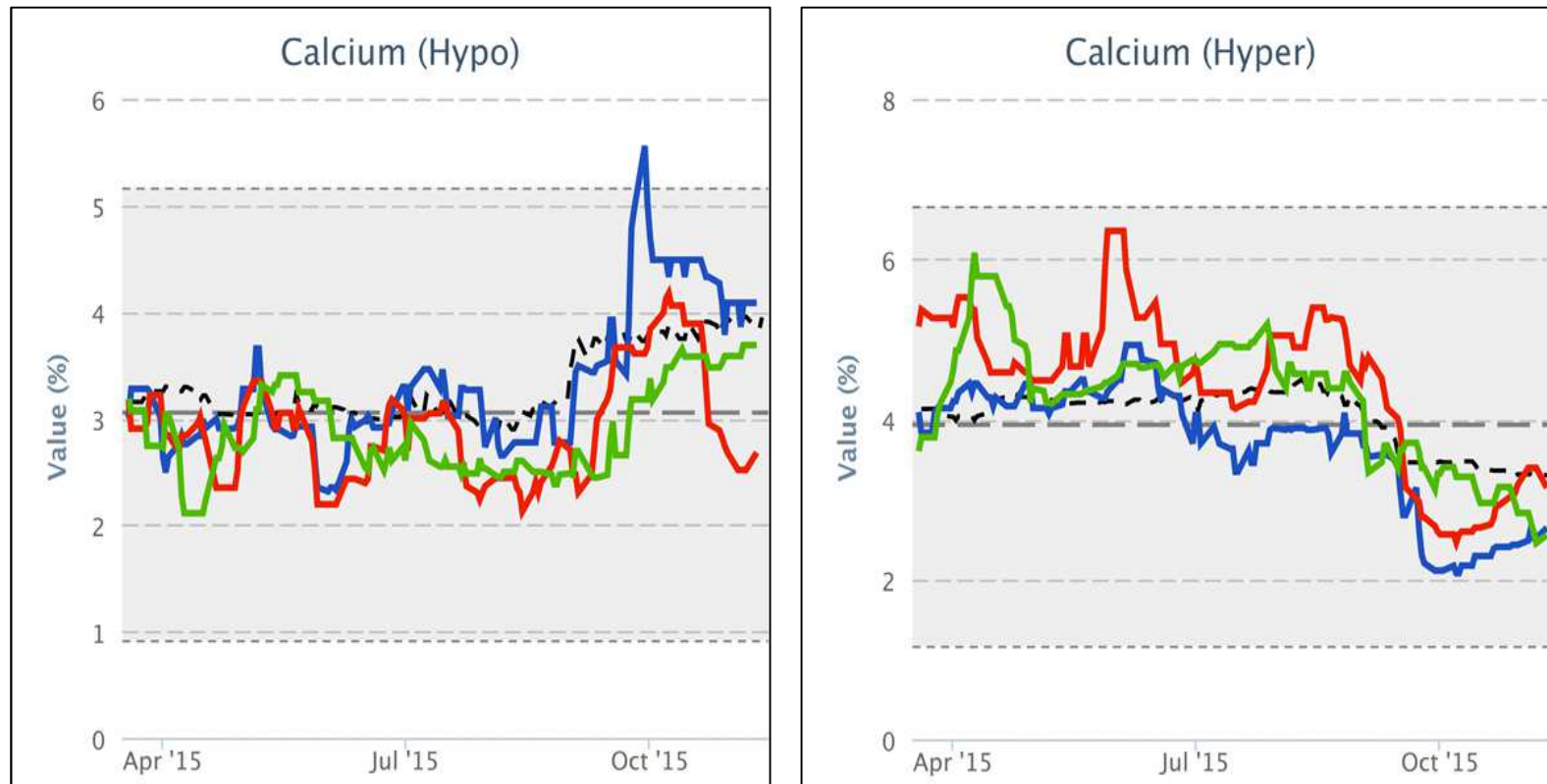
# Percentiler - Flagger Link

The effect of analytical changes on the flagging rate



# Percentiler - Flagger Link

The effect of analytical changes on the flagging rate





# Flagger accounts

[www.theflagger.be](http://www.theflagger.be)

**Percentiler login = Flagger login**

# Benefits

## Patient percentile (flagging) monitoring

- Gives evidence about stability of performance & the reasons for assay variation (manufacturer, lot-to-lot, calibration, instrument)
- Enables monitoring the effect of instability on “surrogate” medical decisions (“flagging” frequency)
- Strengthens the laboratory/manufacturer dialogue
- Strengthens the physician/laboratory interface by more transparent communication on performance
- Helps with establishment of realistic quality goals
- Provides basis for comparison across manufacturers

# Thank you

- **The Percentiler/Flagger Laboratories**
- **Belgian representatives (& headquarters) of Abbott, Beckman/Analys, Ortho, Roche, Siemens**
- **LIS companies**
- **Belgian Society for Clinical Chemistry**
- **Filip Migom (MIPS) & Tom Fiers (Gent University Hospital) & Gudrun Verween**
- **Bruno Neckebroek (IT)**
- **Sten Westgard, Hassan Bayat...**