



A CASE STUDY:

USING STATISTICAL ANALYSIS IN PLACE OF RE-QUALIFICATION TESTING FOR CTU'S

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In 2013 the Medicines and Healthcare Products Regulatory Agency (MHRA) conducted a routine GMP inspection. At the conclusion of the inspection, the following observation was issued in regard to Controlled Temperature Units (CTUs) and warehouse spaces:

MHRA OBSERVATION:

The thermometric assessment of cold storage devices was deficient in that:

- *The warehouses were not seasonally mapped to demonstrate compliance at the most challenging conditions.*
- *All areas were only mapped for 24-hours irrespective of their size which failed to provide sufficient information with respect to their compliance.*
- ***There was no periodic requalification plan in place.***

Guidance Documents

In formulating the site's response the following regulatory guidance documents were referenced:

- Good Practice Bulletin for Thermal Mapping of Controlled Temperature Units (CTUs)
- ISPE guide on Controlled Temperature Chamber Mapping, April 2012
- Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, Irish Medicines Board (IMB)
- European Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use(2013/C 68/01)
- USP General Chapter <1079> “Good Storage and Shipping Procedures”
- PDA Technical Report No. 64. Active Temperature-Controlled Systems: Qualification Guidance.

Guidance Documents

- PDA Technical Report No. 64. Active Temperature-Controlled Systems: Qualification Guidance.

*“Since all process and systems vary over time, periodic review are necessary to ensure that temperature control system performance remains within the defined parameters. Periodic review activities can be based on historical performance as documented in system history files. **If there is an indication that the system has changed its performance level, this should trigger an assessment, repair or replacement, and requalification process.**”*

page. 21- Section 4.6.2, Periodic Review of Qualifications

Observation Response

Upon receiving the observation from the MHRA, the following response was issued detailing the corrective actions the site would take:

- A stand-alone formal risk assessment will be performed on each CTUs in active service used to store GxP materials for the purposes of assigning a level of risk to each unit.
- Those units that are determined to be a high risk will be enrolled in a program to analyze internal temperature data on a periodic basis in order to evaluate the unit's performance and look for signs of system degradation.
- Those CTUs determined to be a high risk as a result of the risk assessment will be temperature mapped if they show signs of system degradation under the periodic evaluation.
- A periodic review of the risk assessment will be performed every two years to include new CTUs as well as evaluate whether any changes have occurred to existing CTUs that would impact their level of risk.

Risk Assessment

Severity, Probability, Detection Ratings Scales

Severity		Probability		
Rating	Description	Rating	Description	
Critical	Effects are severe: <ul style="list-style-type: none">▪ Very significant Non-Compliance Event (Critical BOH observation)▪ Potential loss of final drug substance batch/Significant Production Disruption and/or Potential Significant Patient Injury	High	multiple	≥ 34.1% of like-CTUs have had a GMP event or corrective work orders issued
			Single	CTU has a history of GMP events
Moderate	Effects are moderately severe: <ul style="list-style-type: none">▪ Significant Non-Compliance Event (Major BOH observation)▪ Potential loss of intermediate or final drug substance batch and/or/ Moderate Production Disruption▪ Potential moderate Patient Impact	Medium	multiple	5.1-34.0% of like-CTUs have had a GMP event or corrective work orders issued
			Single	CTU has a history of corrective work orders
Minor	Effects are not severe: <ul style="list-style-type: none">▪ Minor GMP concerns may be noted by BOH▪ No loss of intermediate batch /No or minor Production Disruption and/or No Patient Impact▪ Investigation with no product impact	Low	multiple	≤ 5.0% of like-CTUs have had a GMP event or corrective work orders issued.
			Single	CTU has no history of GMP events or corrective work orders.
Detection				
Rating	Description			
High	The current controls are highly likely to detect an out-of-specification condition.			
	More than one location in the CTU is continuously monitored through a dual or single monitoring probe.			
	Out of specification conditions are alarmed immediately with no programmed delay.			
Medium	Secondary measures are employed to test environmental conditions of the material stored.			
	The current controls are likely to detect an out-of-specification condition.			
	One location in the CTU is continuously monitored through a dual or single monitoring probe.			
Low	Out of specification conditions are alarmed after a programmed delay has elapsed.			
	Current controls will not detect an out-of-specification condition.			
	The CTU is not continuously monitored			

Risk Assessment

Final Risk Determination and Action Thresholds

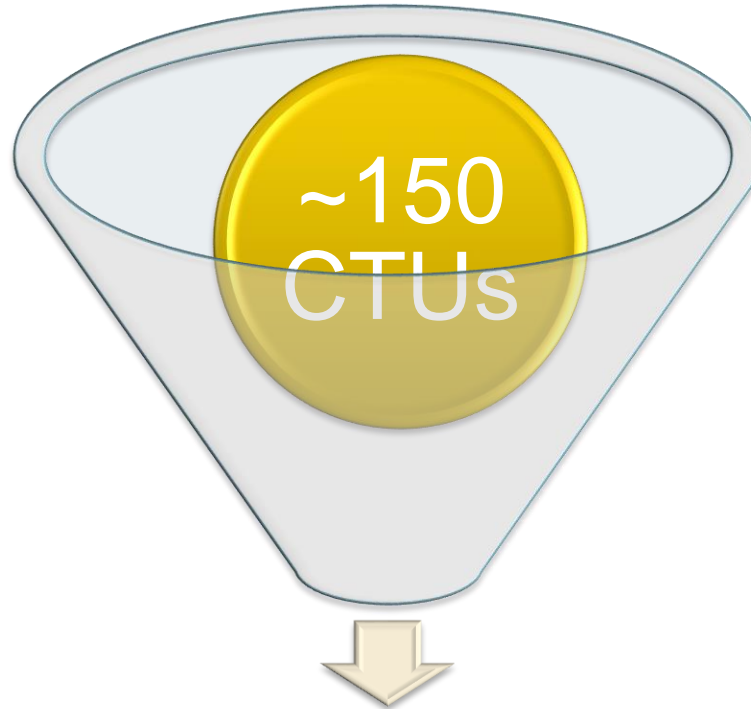
Initial Risk Determination				Final Risk Determination			
	Minor Severity	Moderate Severity	Critical Severity		Low Detection	Medium Detection	High Detection
High Probability	Medium	High	High	High Initial Risk	High	High	Medium
Medium Probability	Low	Medium	High	Medium Initial Risk	Medium	Mod. Sev.	Low
						Min. Sev.	
Low Probability	Low	Low	Medium	Low Initial Risk	Low	Low	Low

Risk Assessment

CTUs Quality Risk Assessment Rating

Area	CTU Function	Potential Failure Mode	Failure Effect/Severity (S)	Probability (P)	Initial Risk	Detection (D)	Final Risk	Recommendations
Production	Incubator	Temperature Excursions	Moderate Incubates in-process purity plates. Temp excursion could delay production, loss of intermediate.	Low No GMP critical events	Low	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	Low	Periodic Re-Evaluation Not Required
Production	Refrigerator	Temperature Excursions	Minor Sample storage prior to QC delivery. Use of the CTU is optional as samples may be submitted directly to QC if needed.	Low No GMP critical events	Low	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	Low	Periodic Re-Evaluation Not Required
Production	Incubator	Temperature Excursions	Minor Used to warm buffers and sucrose. Temp. excursion could cause minor delay.	Low No GMP critical events	Low	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	Low	Periodic Re-Evaluation Not Required
Production	Cold Room	Temperature Excursions	Moderate Storage of bulk fill drug. intermediate. Temp excursion could delay production, loss of intermediate.	High Multiple Corrective Work Orders	High	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	High	Periodic Re-Evaluation Required
Production	Cold Rooms	Temperature Excursions	Moderate Storage of clinical intermediates. Temp excursion could delay production, loss of intermediate.	High Multiple Corrective Work Orders	High	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	High	Periodic Re-Evaluation Required
Production	Static Incubator	Temperature Excursions	Moderate Incubates clinical material. Temp excursion could delay production, loss of intermediate.	Medium CTU has experienced a corrective work order	Medium	Medium Single Temperature Probe Critical Alarms: 1800 sec. delay Warning Alarms: 1800 sec. delay	Medium	Periodic Re-Evaluation Not Required

Risk Assessment



33 High-Risk Units

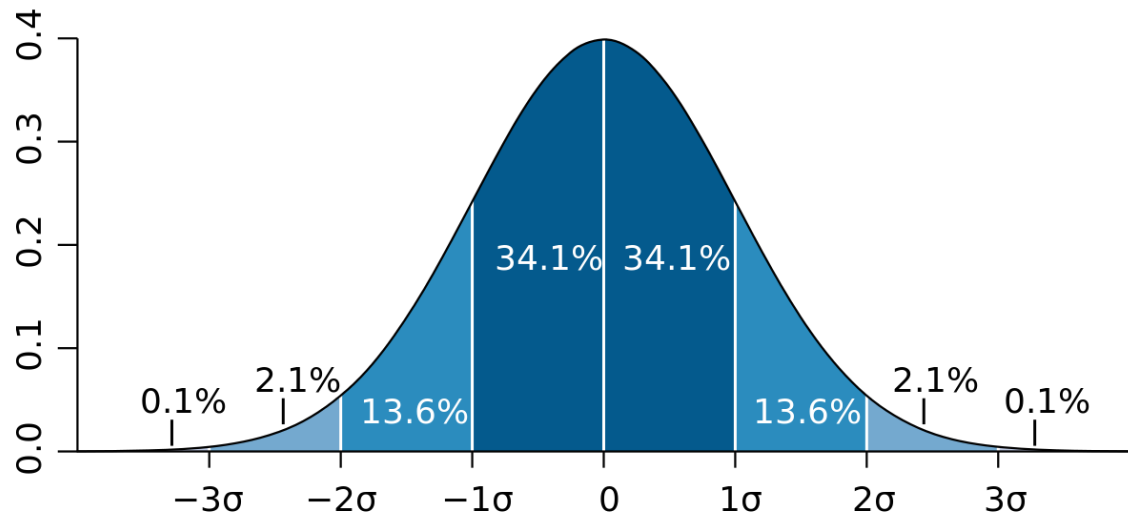
Next Step: performing a quarterly report focusing on standard deviation and average temperature

CTU Evaluation – Phase 1

...Analyzing Average Temperature and Standard Deviation on a quarterly basis

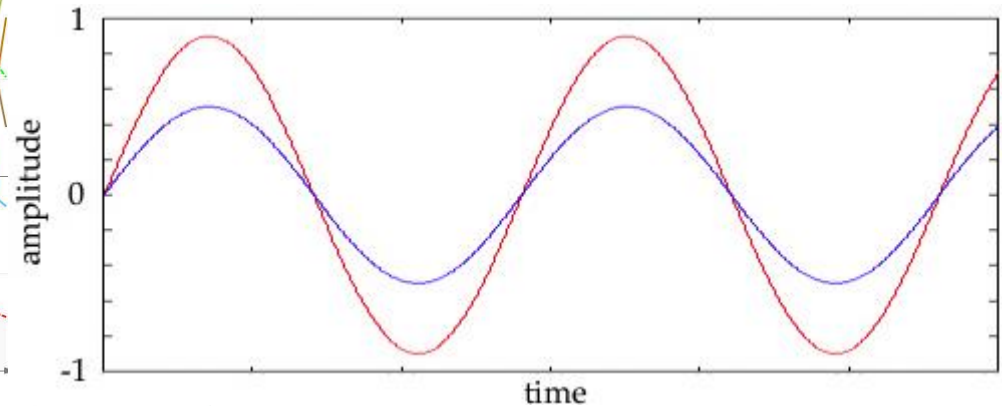
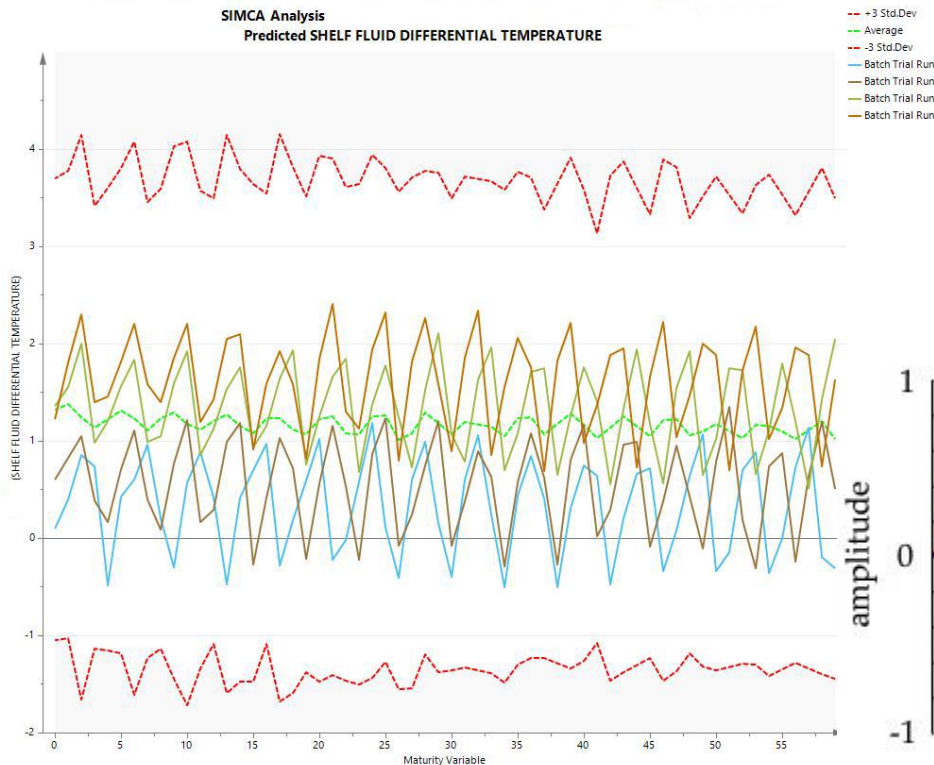
Standard Deviation: A measure used to quantify the amount of variation or dispersion in a set of data values.

A low standard deviation indicates that the data points tend to be close to the mean of the set, while a high standard deviation indicates that the data points are spread out over a wider range of value.



CTU Evaluation – Phase 1

Analyzing the standard deviation value is very useful when determine performance for equipment that is designed to run at a steady state. The larger the standard deviation value, the more variability there is an equipment's performance.



CTU Evaluation – Phase 1

Through recording and charting both average temperature and standard deviation a picture of an equipment's performance emerges. By comparing a CTUs current performance against its historical averages, it can be determined if a unit has *“changed its performance level”*.

But How? – By using PI



Table 3. -25°C Warehouse Freezer Room

Year						
	Quarter	Average Temperature	Standard Deviation	Quarter	Average Temperature	Standard Deviation
2013	1 st	-26.852	0.393	1 st	-26.772	0.363
2013	2 nd	-26.277	0.903	2 nd	-26.211	0.910
2013	3 rd	-25.005	1.096	3 rd	-24.942	1.077
2013	4 th	-24.911	1.168	4 th	-24.725	1.282

Table 4. -20°C Warehouse Freezer Room

Year						
	Quarter	Average Temperature	Standard Deviation	Quarter	Average Temperature	Standard Deviation
2013	1 st	-19.996	0.848	1 st	-20.282	0.852
2013	2 nd	-19.962	0.870	2 nd	-20.253	0.870
2013	3 rd	-19.904	0.774	3 rd	-20.194	0.762
2013	4 th	-20.072	0.831	4 th	-20.360	0.829

Table 5. 32°C Production Incubator

Year	Quarter	Average Temperature	Standard Deviation
2013	1 st	32.185	0.070
2013	2 nd	32.165	0.075
2013	3 rd	32.142	0.064
2013	4 th	32.203	0.059

CTU Evaluation – Phase 2



...after all of that work, it was decided to not only focus on the “high-risk” units, but evaluate ALL CTUs on site. (current count: 163)

Table 1. CTU Evaluation Results

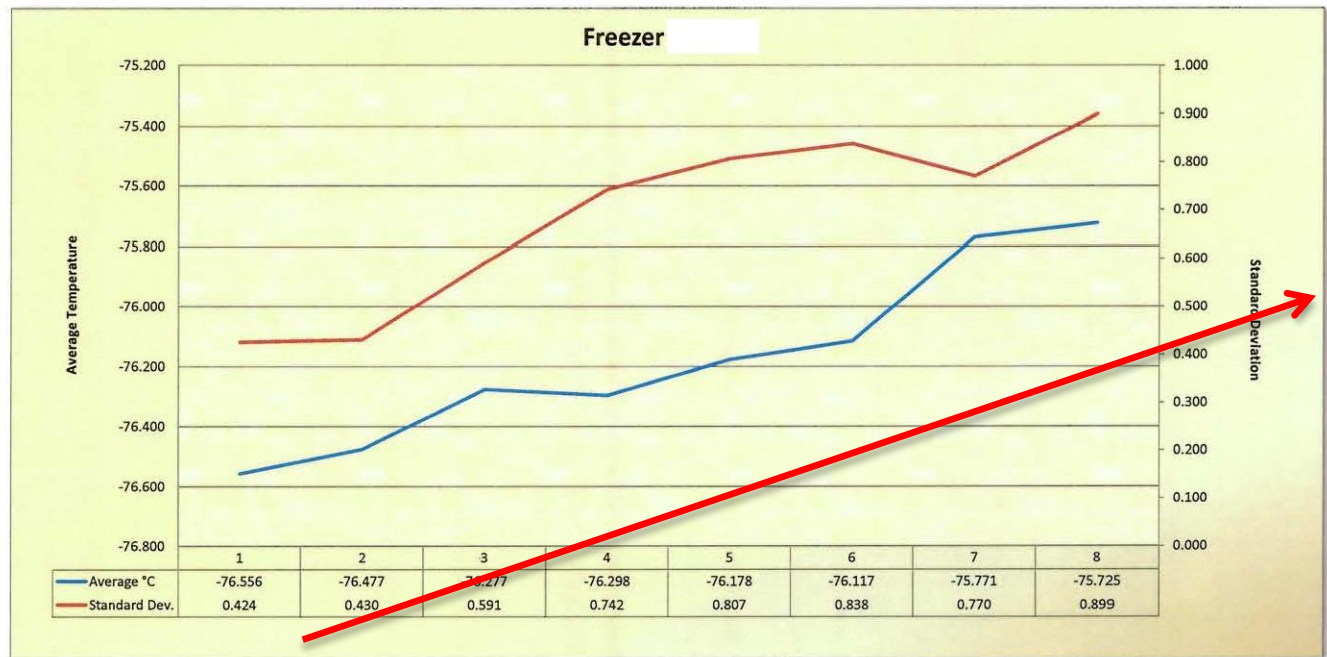
Equip. No.	CTU Type	Qualified Range	Evaluation Result	Equip. No.	CTU Type	Qualified Range	Evaluation Result
	Freezer	-75 ± 5C	✓		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✗		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	■		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	■		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	■		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	■		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	■		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓ ¹		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓ ¹		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓ ¹		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✗		Freezer	-50 ± 10C	✓
	Freezer	-75 ± 5C	✓		Freezer Rm.	-20/-25 ± 5C	✓
	Freezer	-75 ± 5C	✓		Cold Room	5 ± 3C	✓
	Freezer	-75 ± 5C	■		Freezer Rm.	-20/-25 ± 5C	✓
	Freezer	-75 ± 5C	NA ²		Cold Room	5 ± 3C	✓
	Freezer	-75 ± 5C	NA ²		Refrigerator	5 ± 3C	✓
	Freezer Rm.	-25 ± 5C	✓		Freezer Rm.	-20 ± 5C	NA ³
	Cold Room	5 ± 3C	✓		Freezer	-75 ± 10C	✓ ⁴

CTU Evaluation Examples

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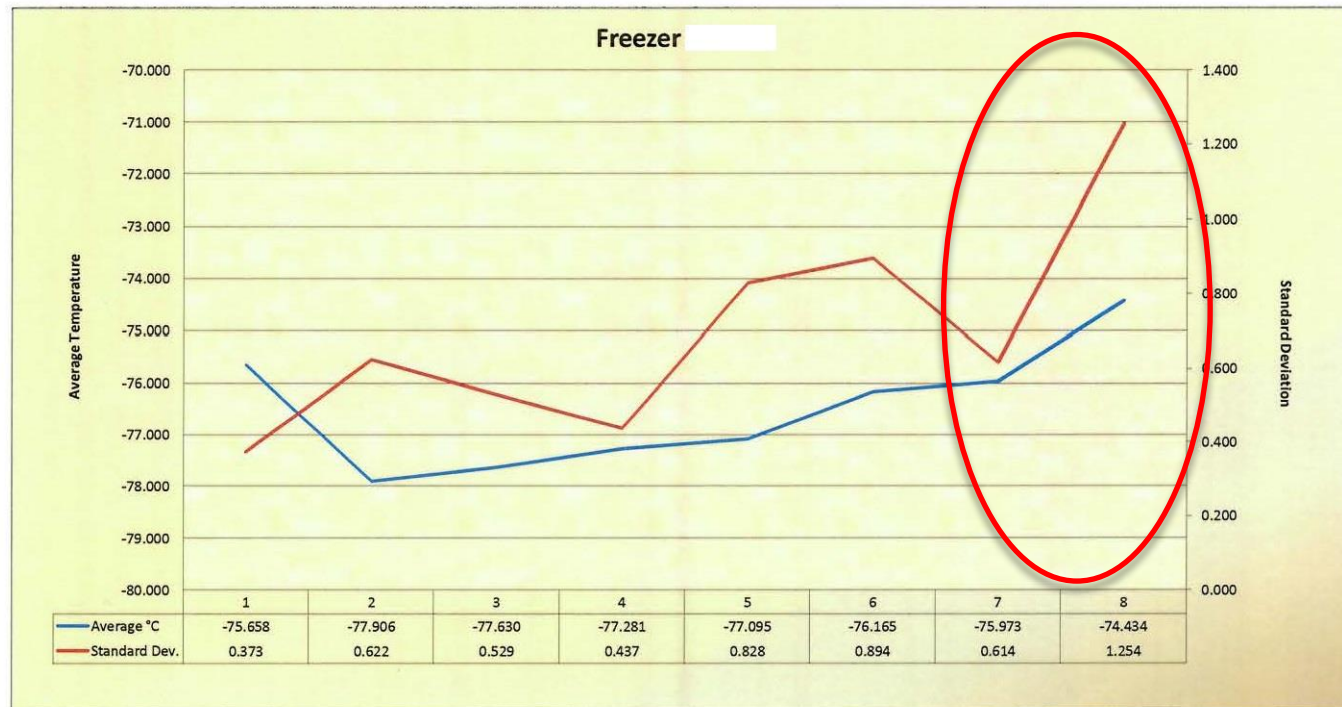
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-76.556	0.424
-76.477	0.430
-76.277	0.591
-76.298	0.742
-76.178	0.807
-76.117	0.838
-75.771	0.770
-75.725	0.899



Following this trend the freezer was re-temperature mapped where it failed.

CTU Evaluation Examples

Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-75.658	0.373
-77.906	0.622
-77.630	0.529
-77.281	0.437
-77.095	0.828
-76.165	0.894
-75.973	0.614
-74.434	1.254

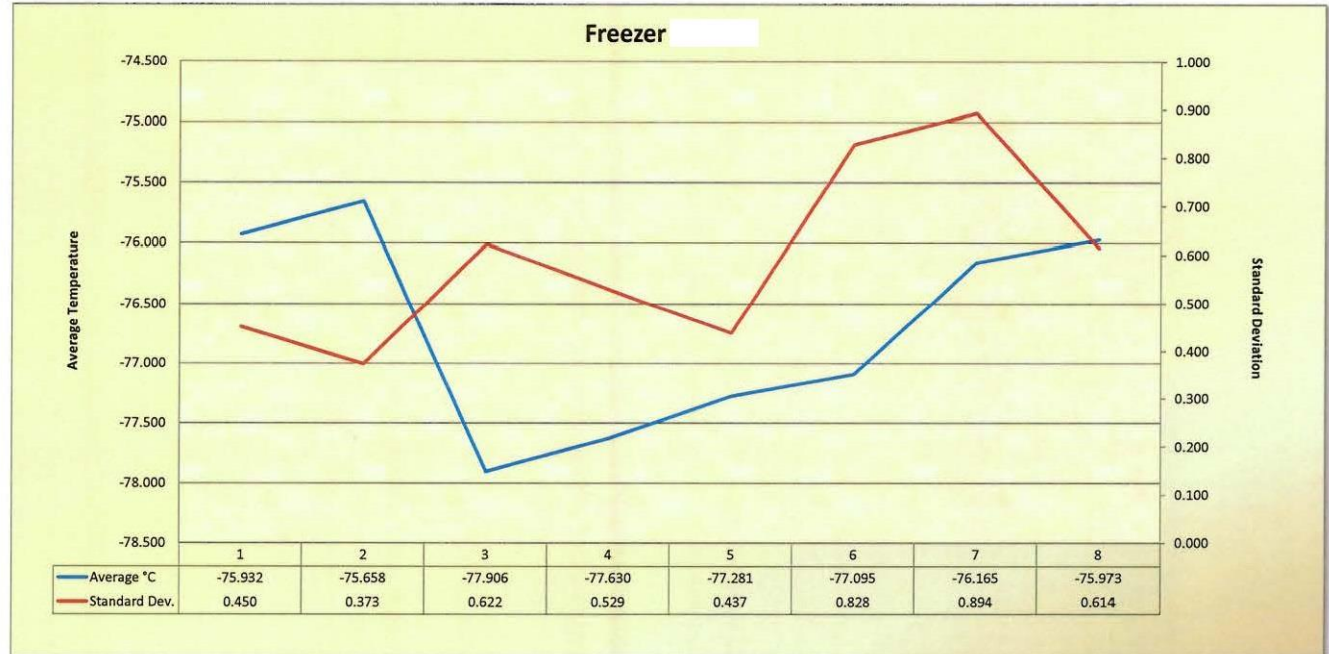


The spike in standard deviation and increase in temperature was the result of the freezer being shut down for cleaning.

CTU Evaluation Examples

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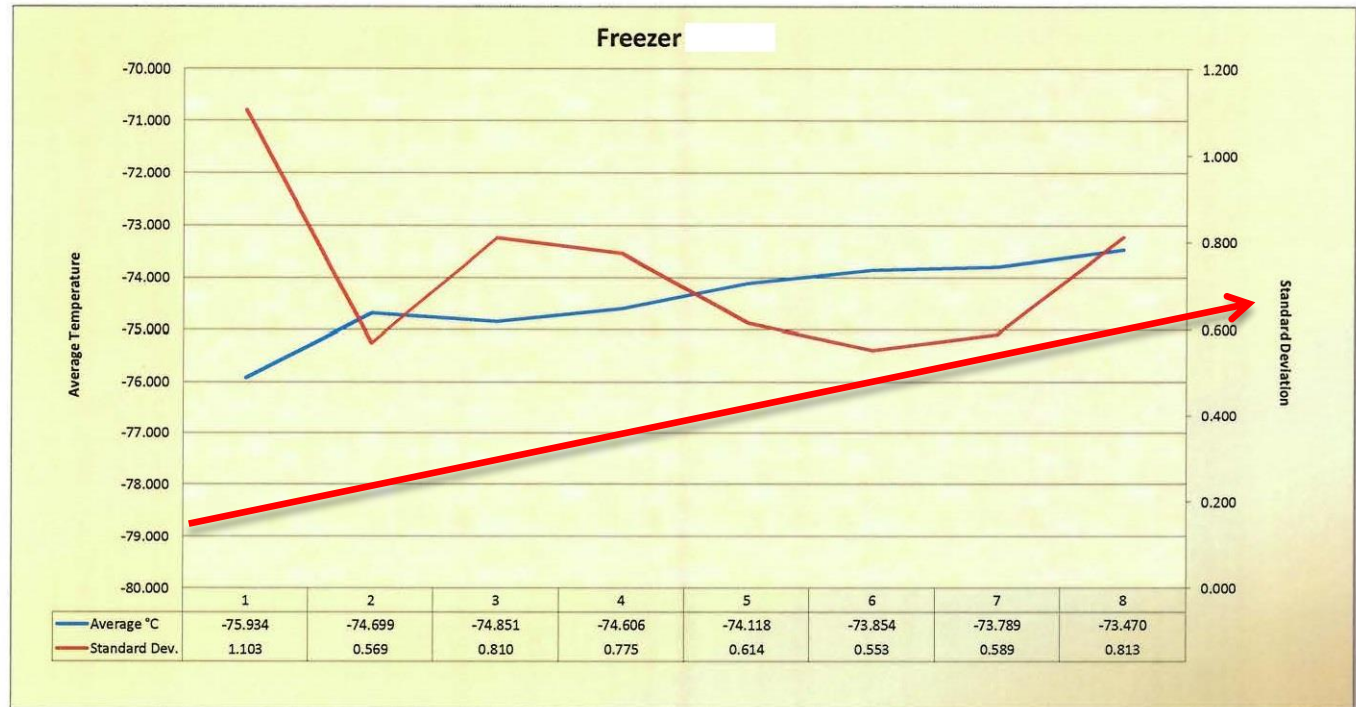
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-75.932	0.450
-75.658	0.373
-77.906	0.622
-77.630	0.529
-77.281	0.437
-77.095	0.828
-76.165	0.894
-75.973	0.614



The freezer was temperature mapped following a quarter-over-quarter increase in average temperature. The mapping was successful.

CTU Evaluation Examples

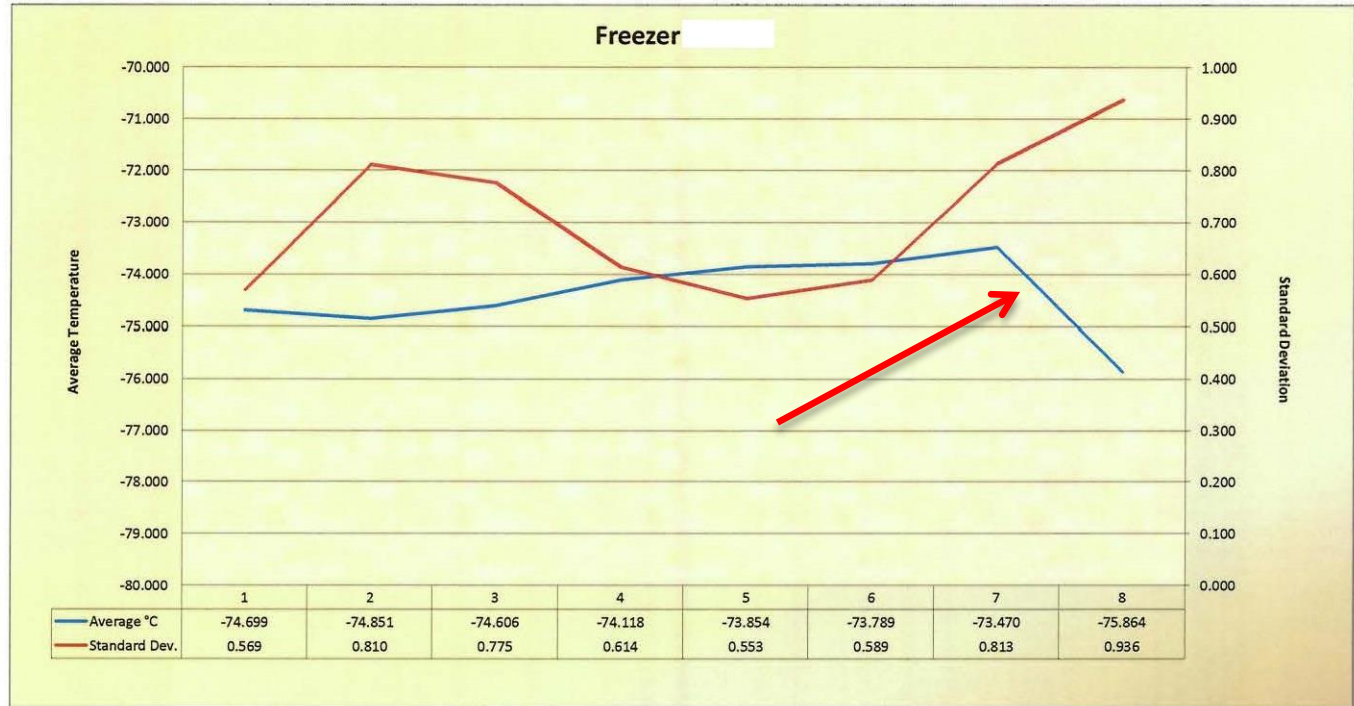
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-75.934	1.103
-74.699	0.569
-74.851	0.810
-74.606	0.775
-74.118	0.614
-73.854	0.553
-73.789	0.589
-73.470	0.813



The freezer experienced a slight, but steadily increasing quarter-over-quarter increase in average temp. A work order was issued to defrost.

CTU Evaluation Examples

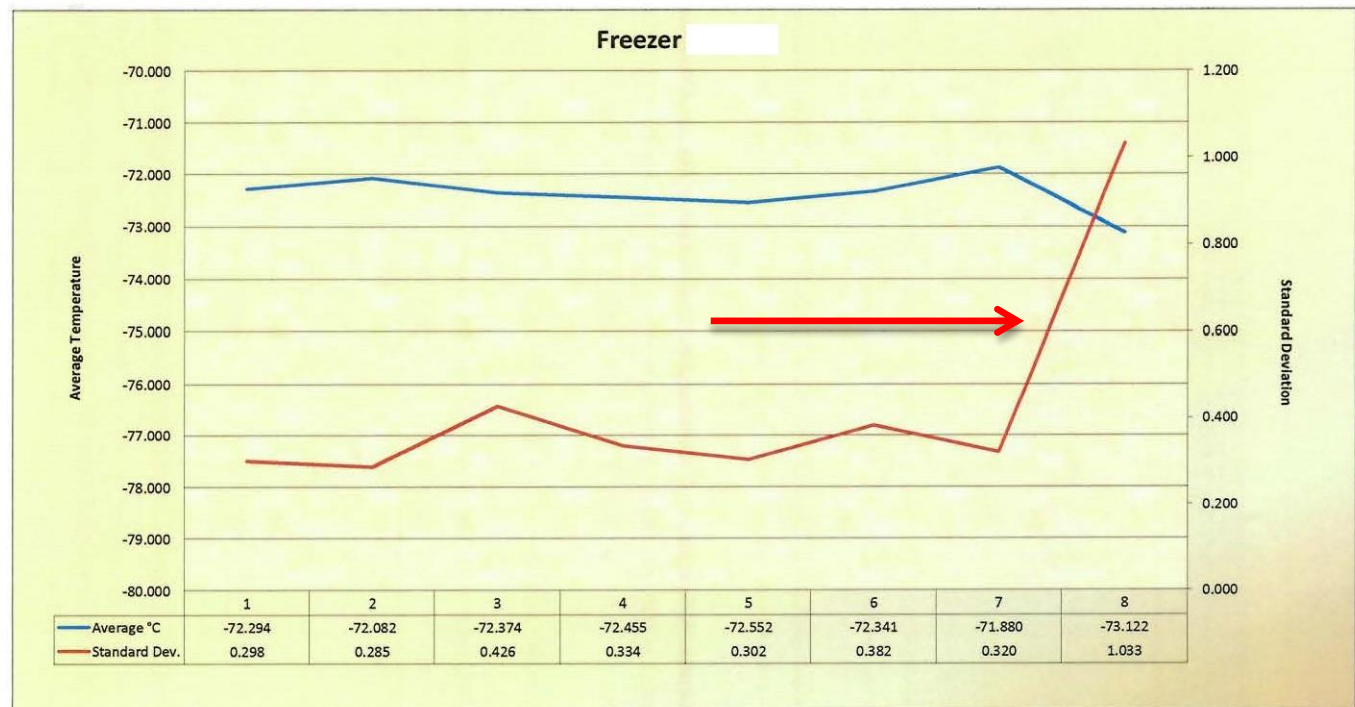
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-74.699	0.569
-74.851	0.810
-74.606	0.775
-74.118	0.614
-73.854	0.553
-73.789	0.589
-73.470	0.813
-75.864	0.936



Following the defrost, there was a sharp decrease in average temperature bringing it back closer to its prior performance. The S.D. did spike, but that was due to the defrost.

CTU Evaluation Examples

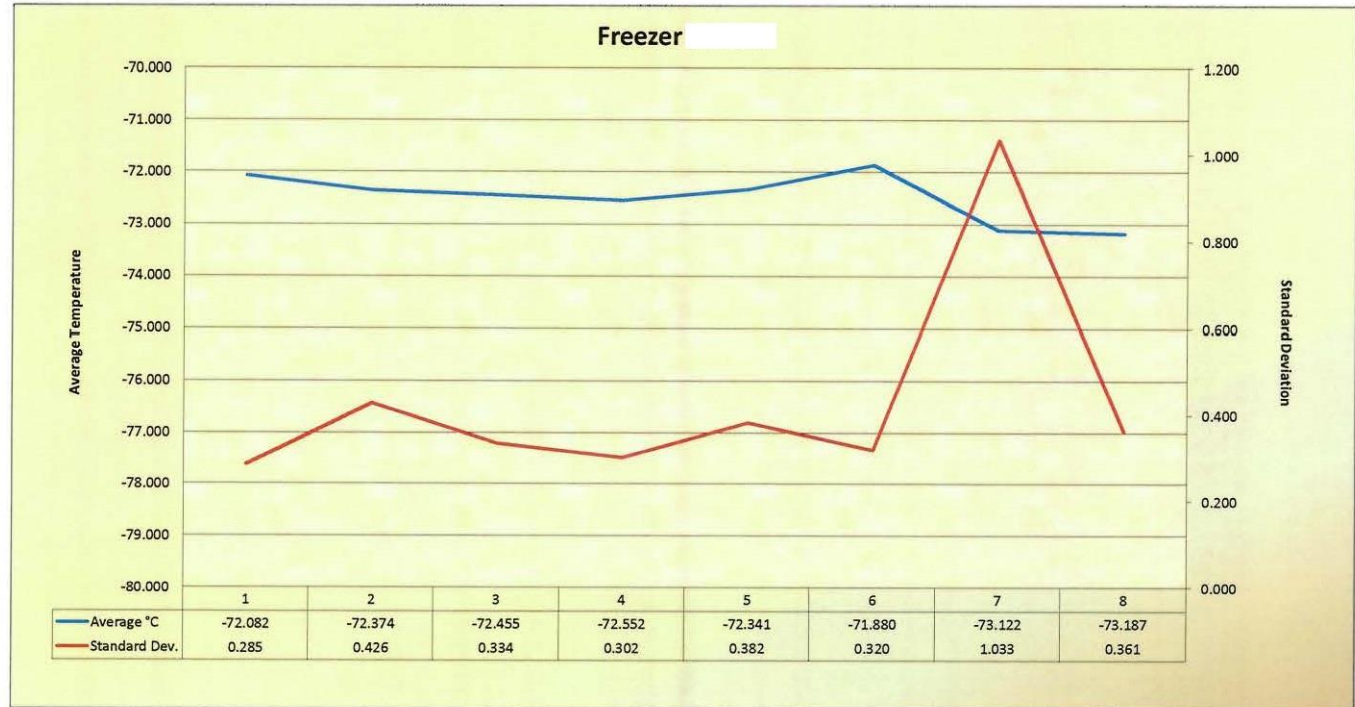
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-72.294	0.298
-72.082	0.285
-72.374	0.426
-72.455	0.334
-72.552	0.302
-72.341	0.382
-71.880	0.320
-73.122	1.033



Another example of a spike in standard deviation due to a defrost.

CTU Evaluation Examples

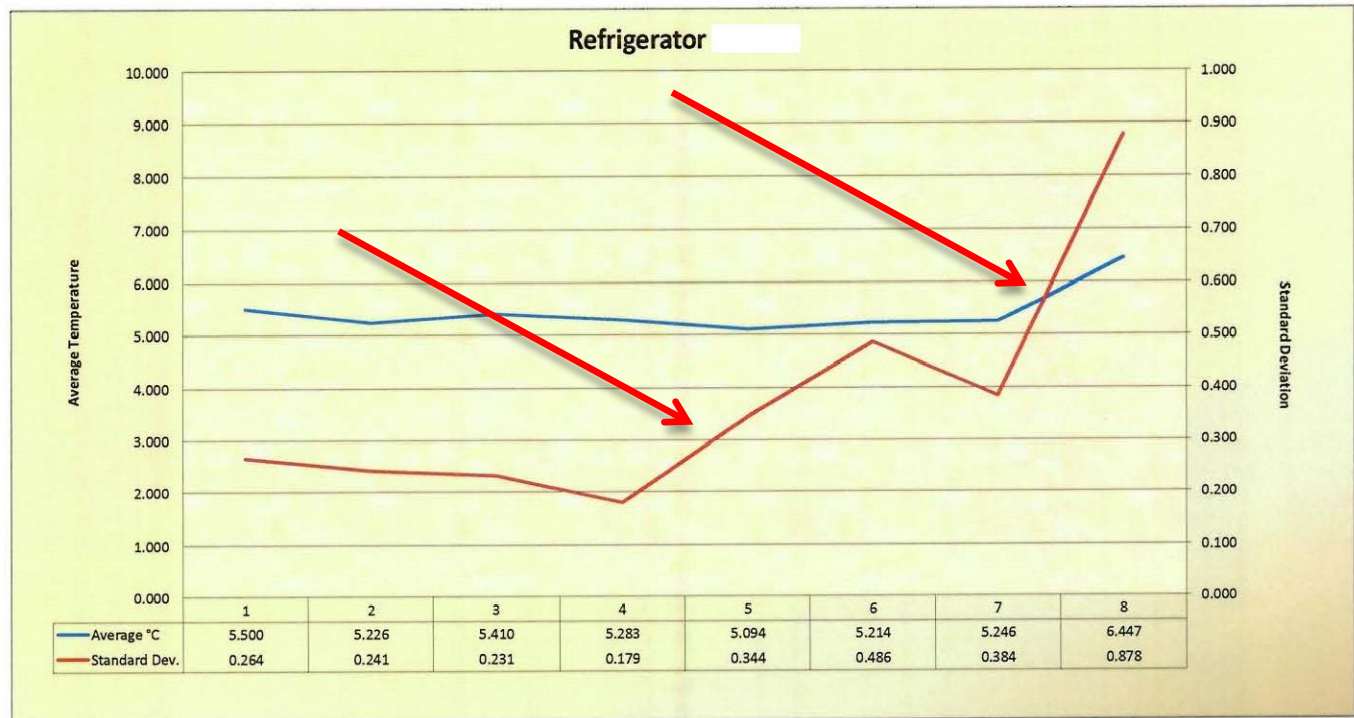
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-72.082	0.285
-72.374	0.426
-72.455	0.334
-72.552	0.302
-72.341	0.382
-71.880	0.320
-73.122	1.033
-73.187	0.361



Following the defrost, the standard deviation value returned to its previous historical context while the average temperature also decreased.

CTU Evaluation Examples

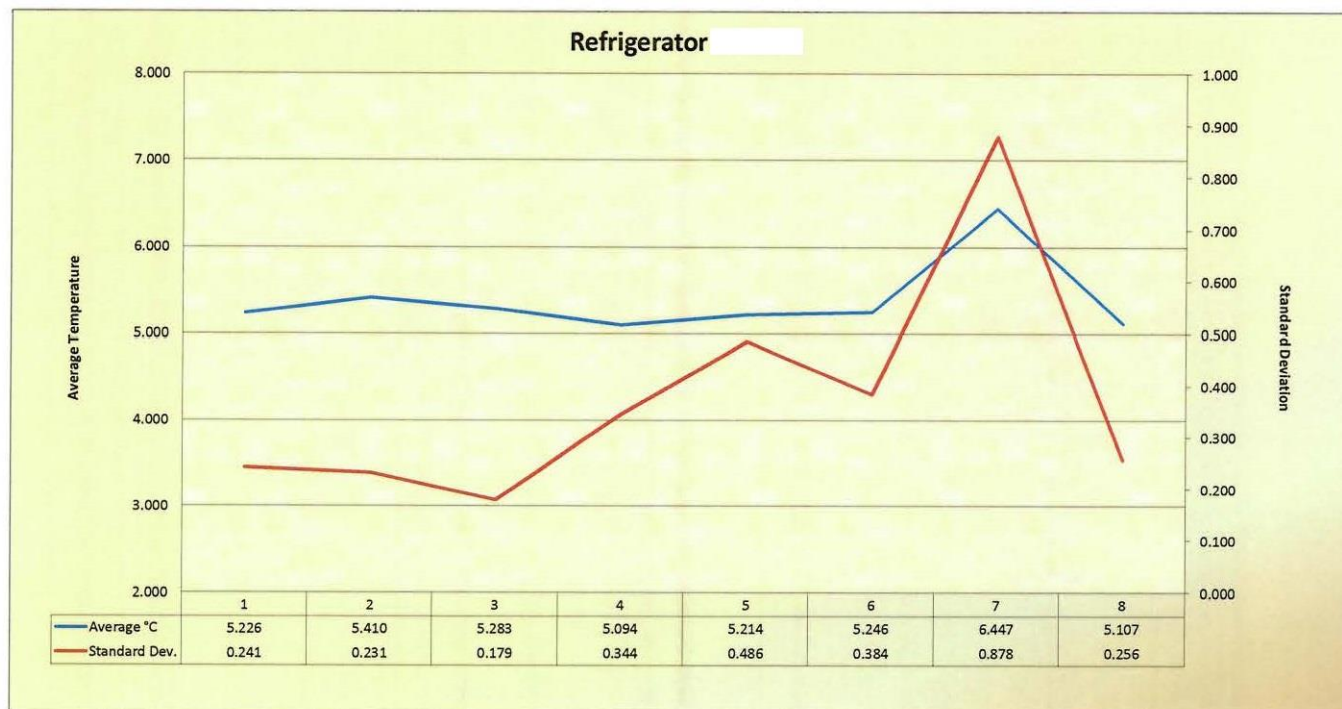
Refrigerator	
5 +/- 3C	
Average °C	Standard Dev.
5.500	0.264
5.226	0.241
5.410	0.231
5.283	0.179
5.094	0.344
5.214	0.486
5.246	0.384
6.447	0.878



The standard deviation trend indicated an issue with an increase of 0.307, and then another sharp increase a few quarters later, which resulted in an alarm condition and a work order to investigate.

CTU Evaluation Examples

Refrigerator	
5 +/- 3C	
Average °C	Standard Dev.
5.226	0.241
5.410	0.231
5.283	0.179
5.094	0.344
5.214	0.486
5.246	0.384
6.447	0.878
5.107	0.256

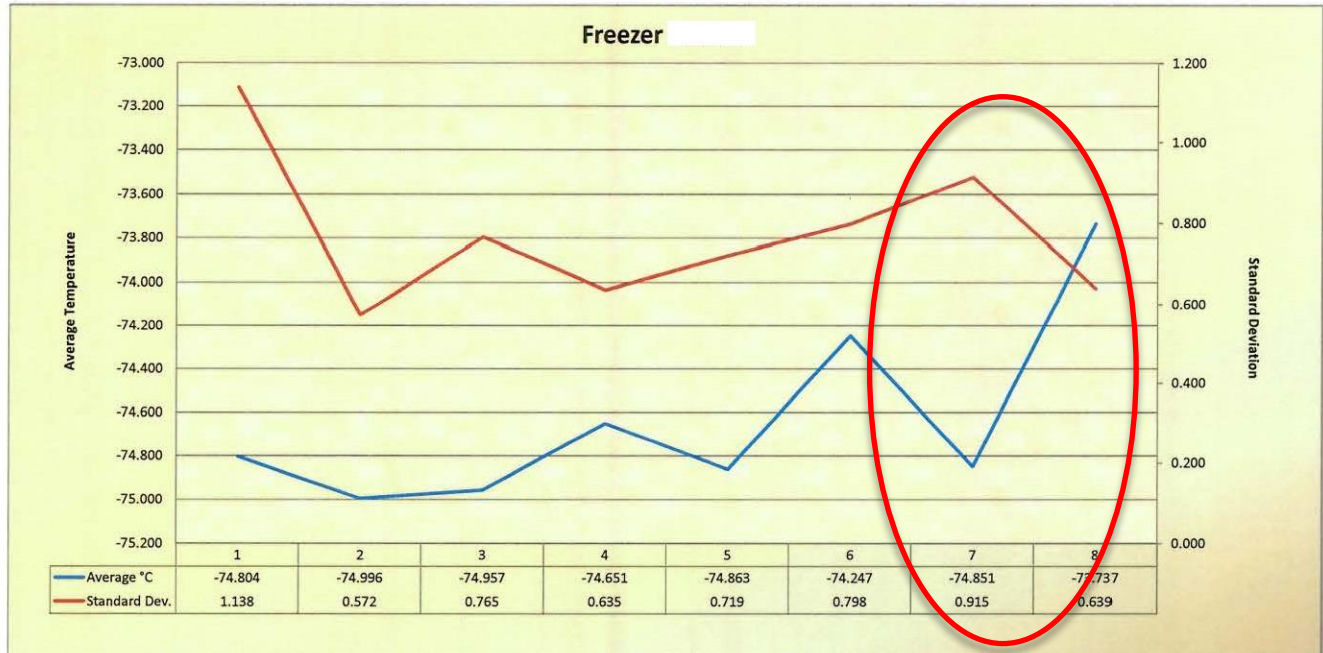


Following corrective actions, both the standard deviation value and average temperature fell back down to their previous levels.

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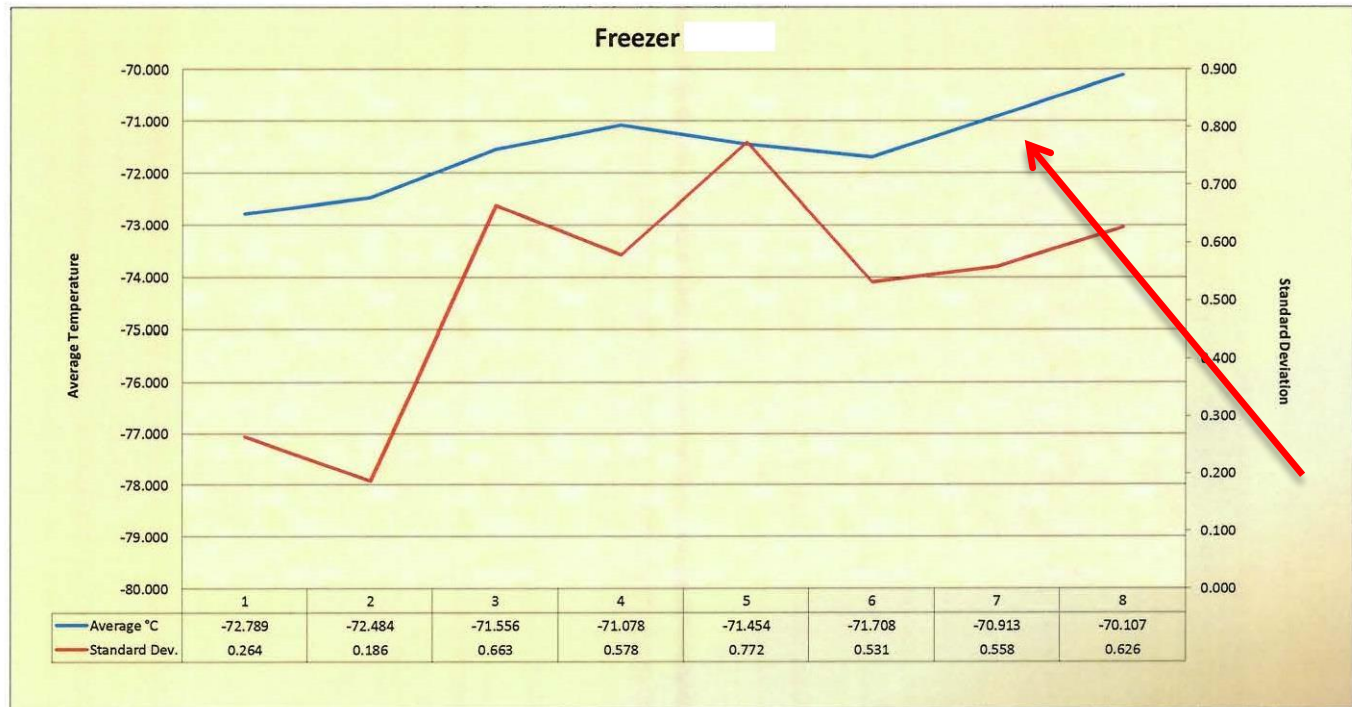
Freezer	
-75 +/- 5C	
Average °C	Standard Dev.
-74.804	1.138
-74.996	0.572
-74.957	0.765
-74.651	0.635
-74.863	0.719
-74.247	0.798
-74.851	0.915
-73.737	0.639



Freezer experienced a sharp increase in average temperature. As a result of the spike, the freezer was emptied, defrosted and tagged out of service for mapping. The mapping was not passing, and as a result the freezer was removed from service and decommissioned.

CTU Evaluation Examples

Freezer	
-75 +/- 10C	
Average °C	Standard Dev.
-72.789	0.264
-72.484	0.186
-71.556	0.663
-71.078	0.578
-71.454	0.772
-71.708	0.531
-70.913	0.558
-70.107	0.626



The average temperature for the -75°C freezer was trending warm. While still within the operating range, the unit was flagged for re-mapping to adjust the operating set point to bring the unit's average temperature back closer to -75°C.

Performing statistical analysis on CTUs is more than using that data to replace across-the-board periodic testing. While reviewing data on a standard basis does allow for targeted re-mapping or other corrective actions based on performance, it also **demonstrates control your equipment** by being proactive in looking for areas of concern. Regulatory agencies seemed to agree with this method as the approach taken was discussed without issue during a recent FDA general GMP inspection in 2016. Additionally, CTUs did not come up during the 2016 general GMP inspection performed by the MHRA. In 2016, the site received no BOH observations or comments in regards to any CTUs.

Thank You

Questions?