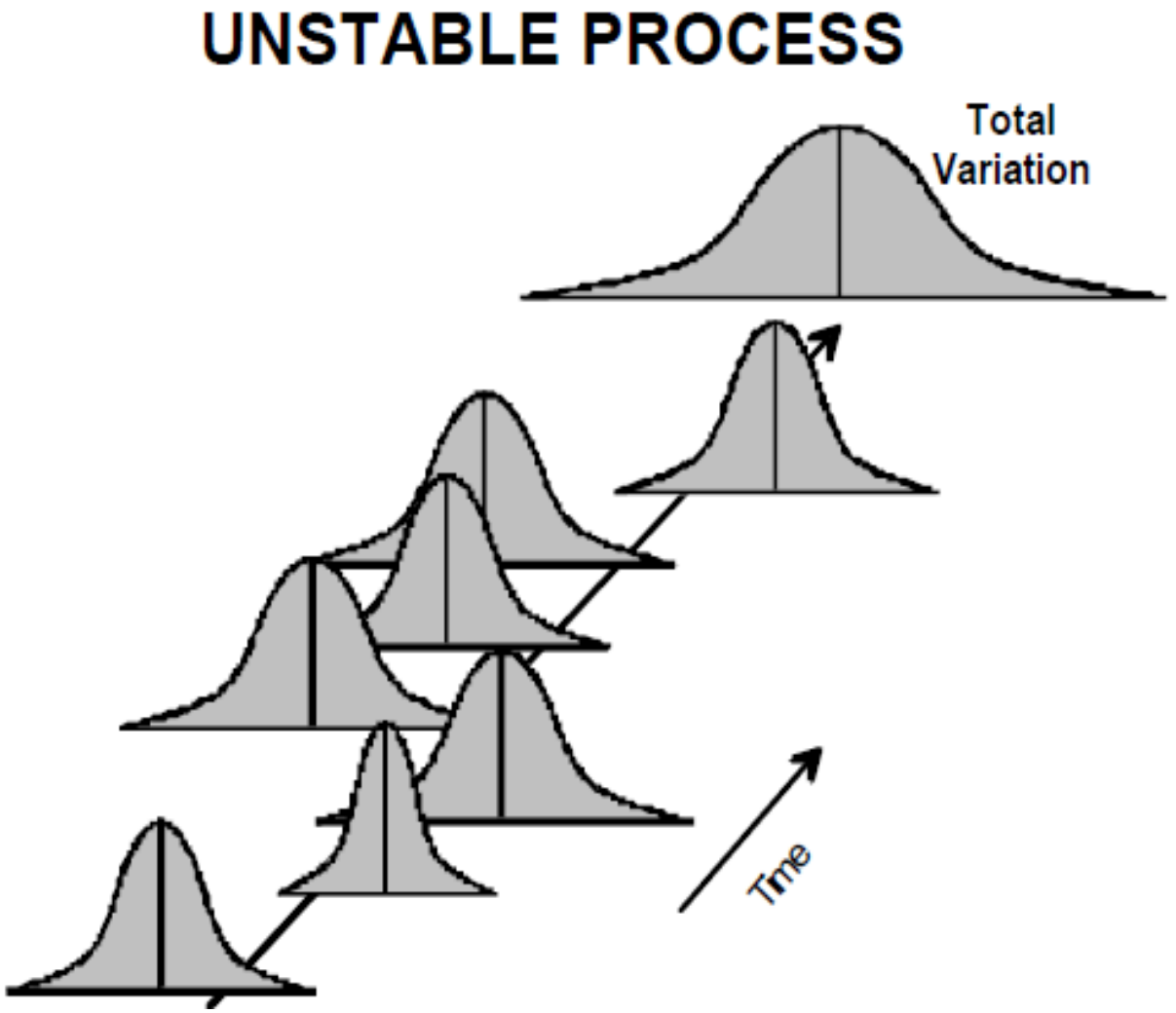
Module #5 –
Risk Reduction and Risk Acceptance

- Evaluation of Cleaning Processes using Process Capability
- New CPU-based Scale based on Process Capability
- Cleaning Statistical Process Control (SPC)

CASE STUDY – On-Line PAT Using TOC

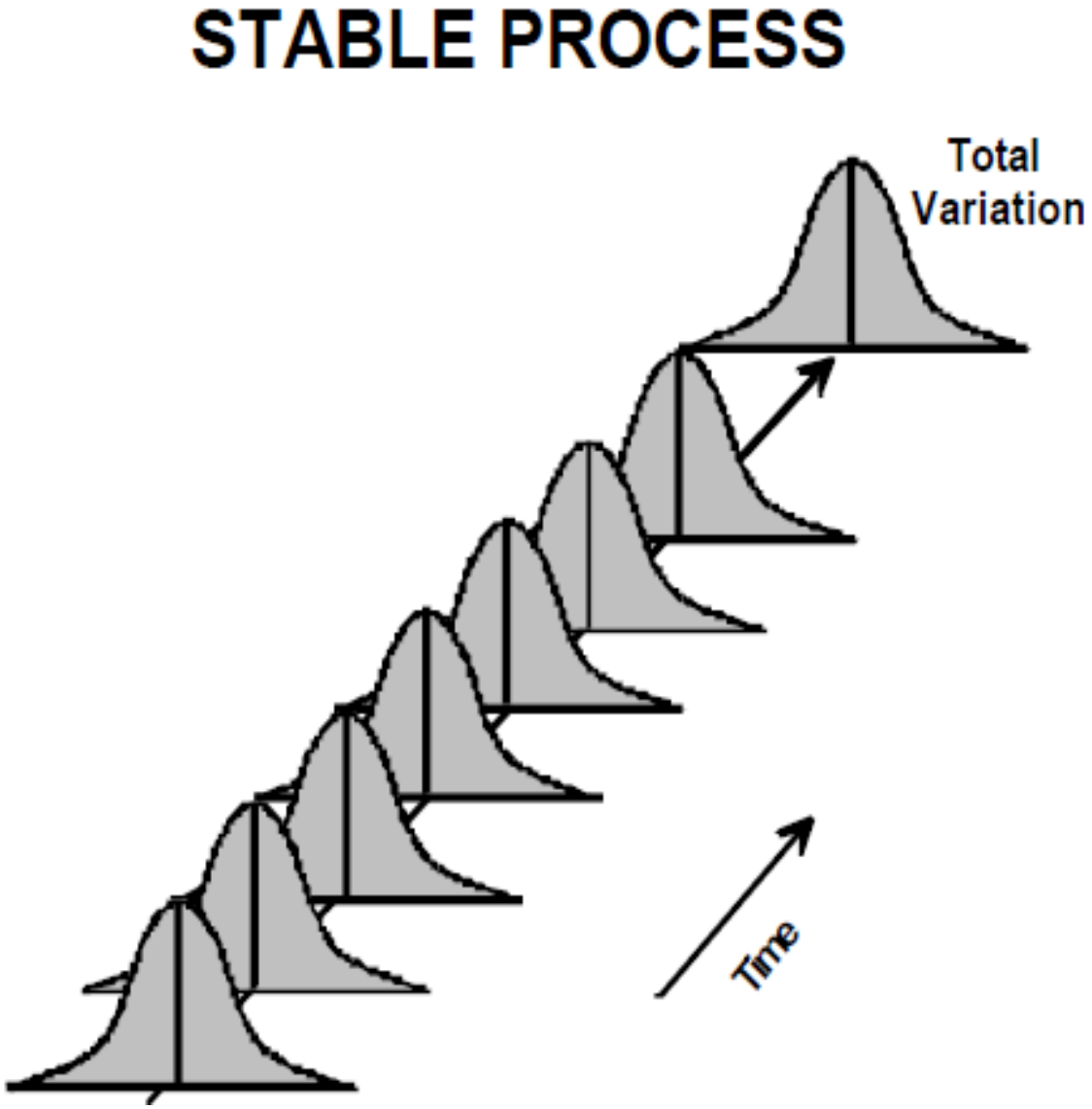
Reducing variation

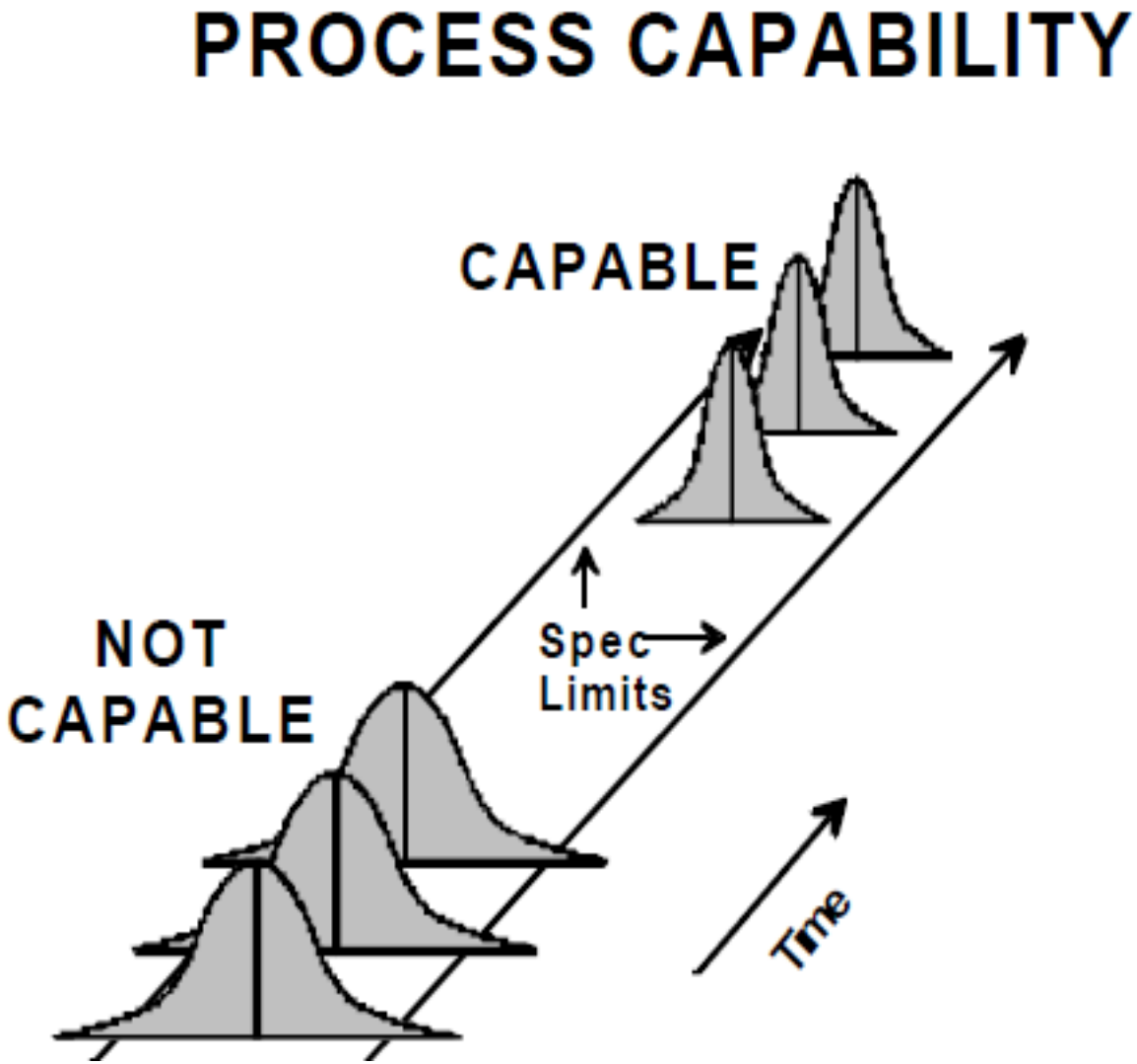
- Requires the achievement of stable and capable processes.
- In an unstable process, the process is constantly changing.
- The average shifts up and down. The variation increases and decreases. The total variation increases due to the shifting.



GHTF Study Group 3 - Quality Management Systems, Process Validation Guidance – January 2004

Reducing variation AND within specs





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HBEL Limit vs. TOC Process Limit vs. TOC LOD/LOQ

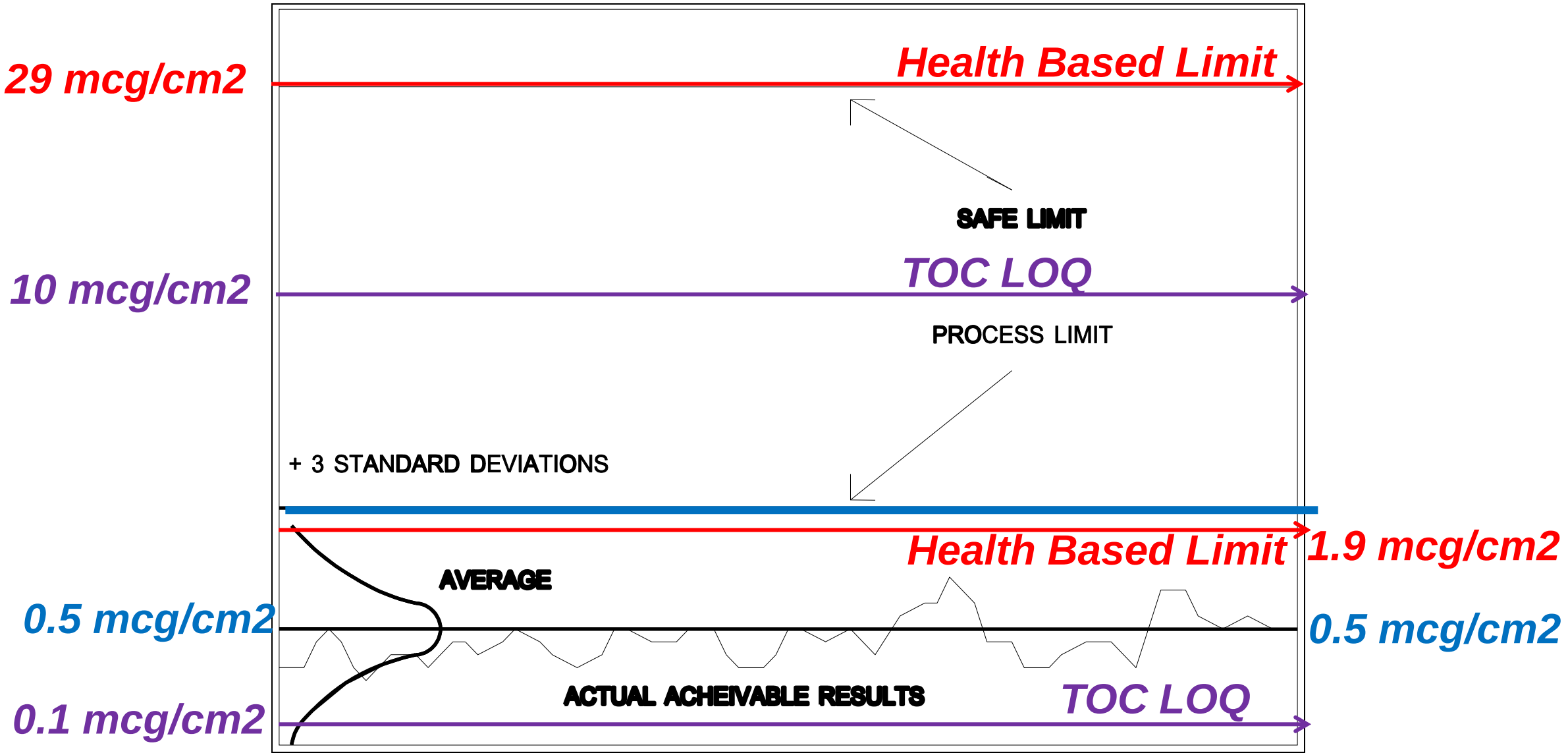
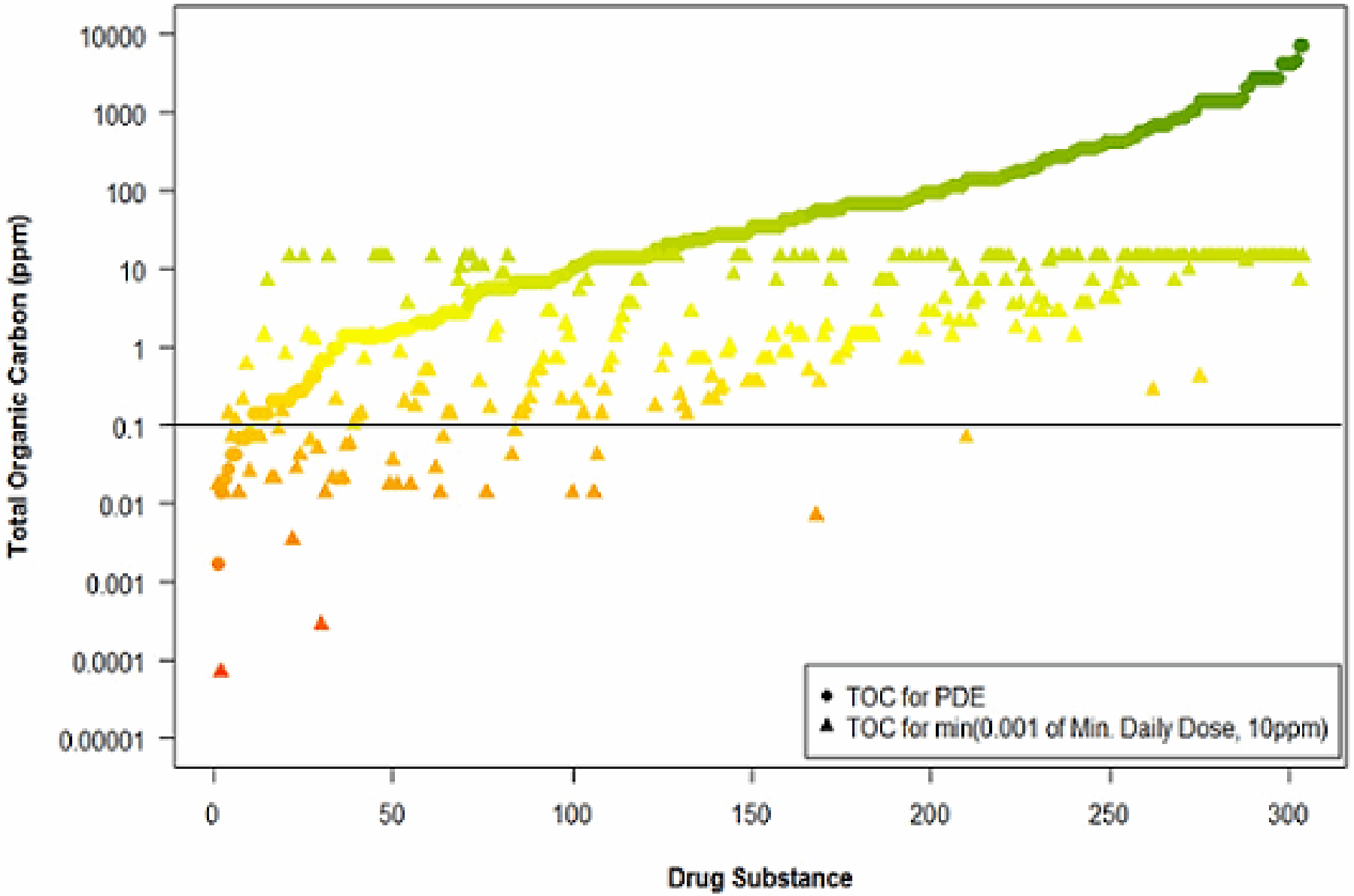


Figure 2: *Comparison of HBEL, 1/1,000th and 10 ppm to TOC Detection Limits (100 ppb)*



A Swab Limit-Derived Scale For Assessing The Detectability Of Total Organic Carbon Analysis; **Pharmaceutical Online, January 24, 2018;** By Andrew Walsh; Thomas Altmann; Alfredo Canhoto, Ph.D.; et al.

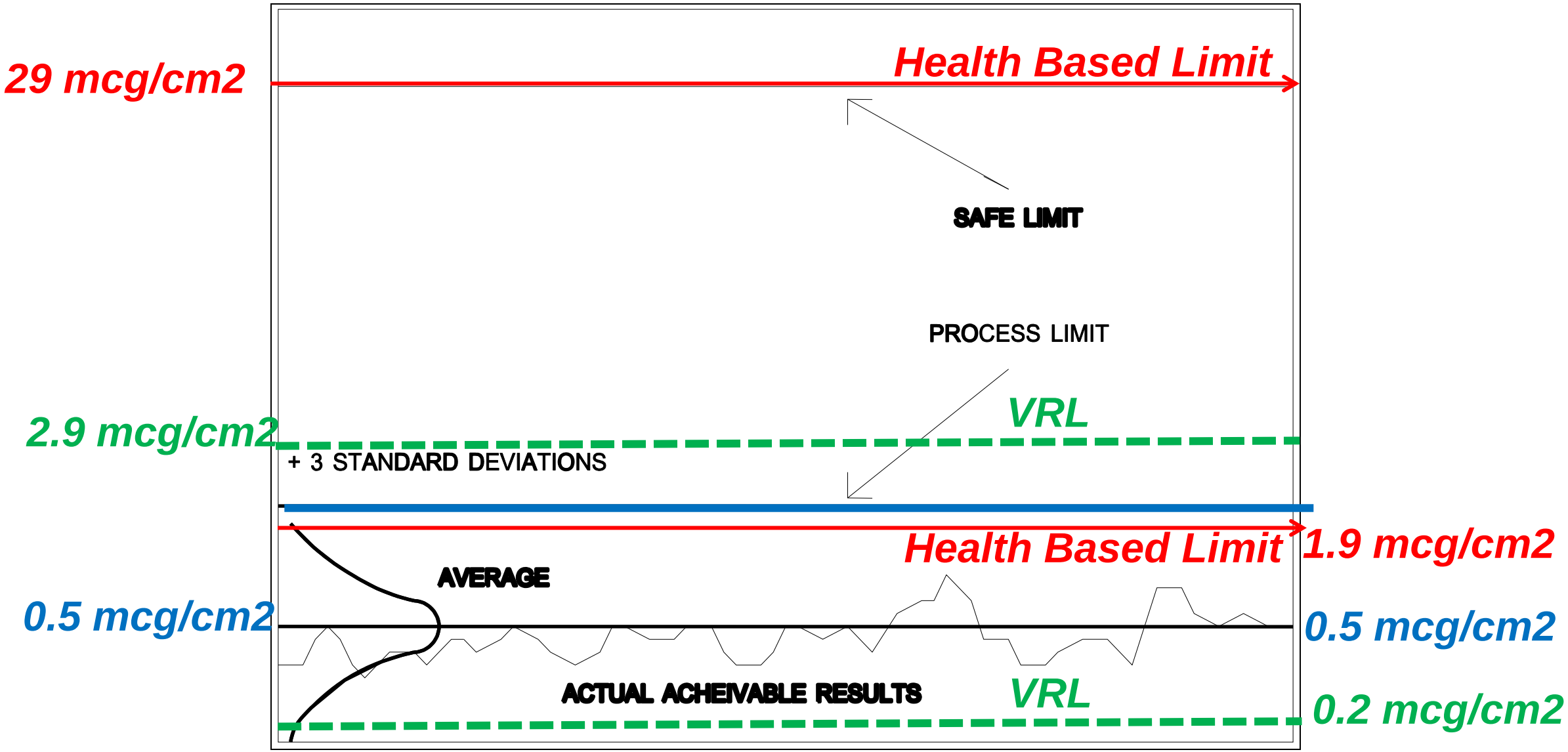
CDI = Carbon Detection Index
DL_{TOC} = TOC Detection Limit
SL_{TOC} = TOC Swab Limit

Table 4 - Detection Limit-based Scales for Detectability of Residues by TOC

SL_{TOC} (ppb)	CDI Log (DL_{TOC} / SL_{TOC})		
	DL_{TOC} =30 (ppb)	DL_{TOC} = 100 (ppb)	DL_{TOC} = 1000 (ppb)
0.1	2.5	3.0	4.0
1	1.5	2.0	3.0
3	1.0	1.5	2.5
30	0.0	0.5	1.5
100	-0.5	0.0	1.0
350	-1.1	-0.5	0.5
1000	-1.5	-1.0	0.0
10000	-2.5	-2.0	-1.0
100000	-3.5	-3.0	-2.0

A Swab Limit-Derived Scale For Assessing The Detectability Of Total Organic Carbon Analysis; Pharmaceutical Online, **January 24, 2018;** By Andrew Walsh; Thomas Altmann; Alfredo Canhoto, Ph.D.; et al.

Health Based Limit vs. VRL



$$VDI = \log_{10}\left(\frac{VRL}{MSSR}\right) \qquad \text{(Equation 1)}$$

where:

VDI = Visual Detection Index
MSSR = Maximum Safe Surface Residue
VRL = Visual Residue Limit

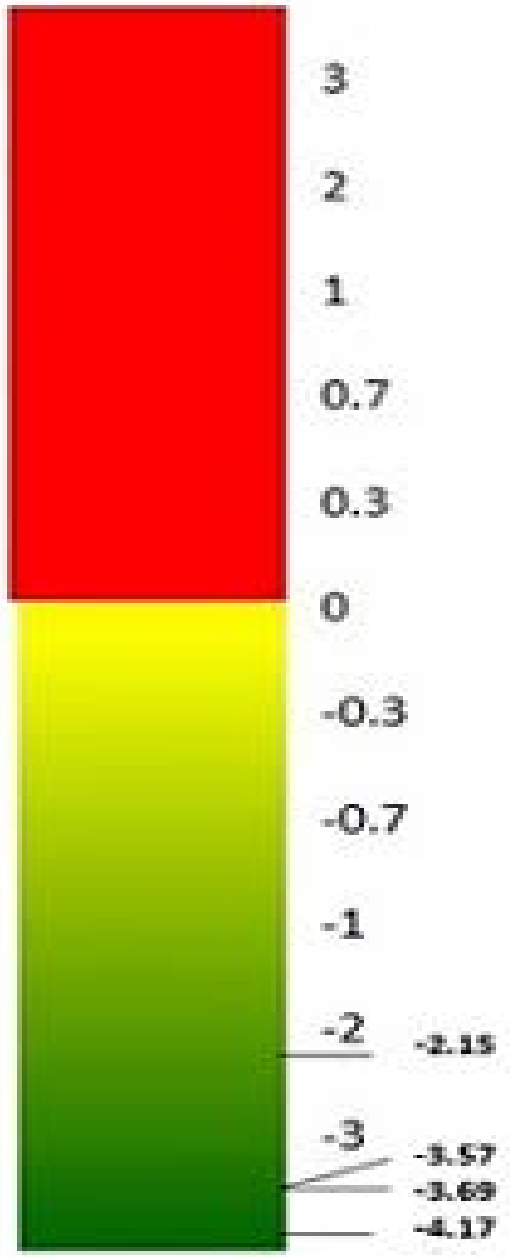
Calculation for **API-1** where:

MSSR = 28 µg/cm^2
VRL = 0.2 µg/cm^2 (based on the results of this study)

$$VDI = \log_{10}\frac{0.2\ \mu g/cm^2}{28\ \mu g/cm^2}$$

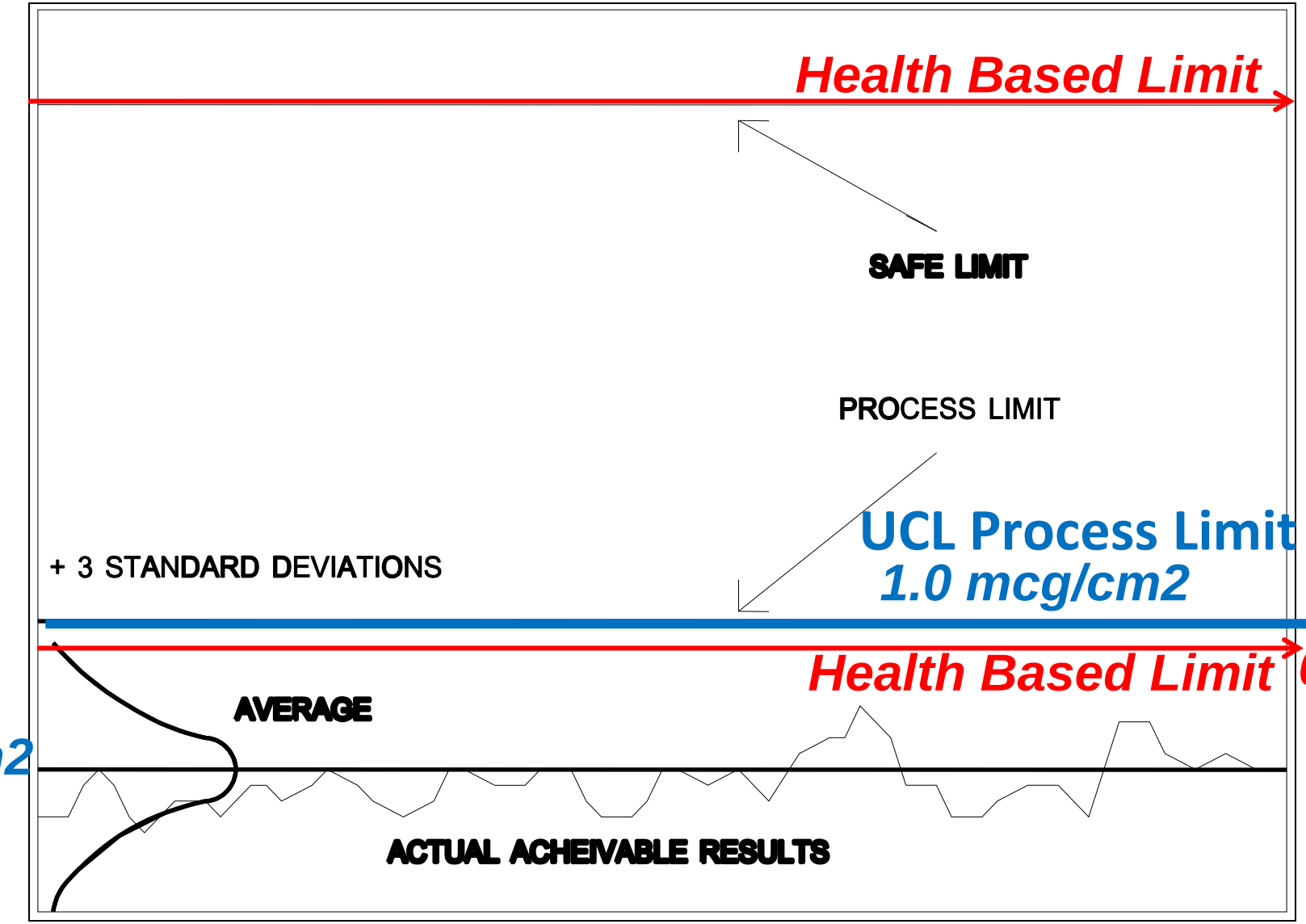
$$VDI = \log_{10} 0.007\ \mu g/cm^2$$

VDI = -2.15



Justification & Qualification Of Visual Inspection For Cleaning Validation In A Low-Risk, Multiproduct Facility, Pharmaceutical Online August 3, 2018 ; Andrew Walsh, Dongni (Nina) Liu, and Mohammad Ovais

Health Based Limit vs. UCL Process Limit



A Process Capability-Derived Scale For Assessing The Risk Of Compound Carryover In Shared Facilities; Cleaning Validation for the 21st Century *series; Pharmaceutical Online;* August 9, 2017; By Andrew Walsh; David G. Dolan, Ph.D.; Andreas Flueckiger, M.D.; Igor Gorsky; Robert Kowal; Ester Lovsin Barle, Ph.D.; Mohammad Ovais; Osamu Shirokizawa; and Kelly Waldron

Risk = ***f*** (severity of a hazard, probability of exposure to that hazard) (Equation 2)

$$\text{Risk} = f(\text{Toxicity}_{\text{ResA}}, \text{probability of exposure}_{\text{ResA}})$$

Cleaning Risk = ***f*** (***toxicity score***$_{API}$, probability of exposure$_{API}$) (Equation 4)

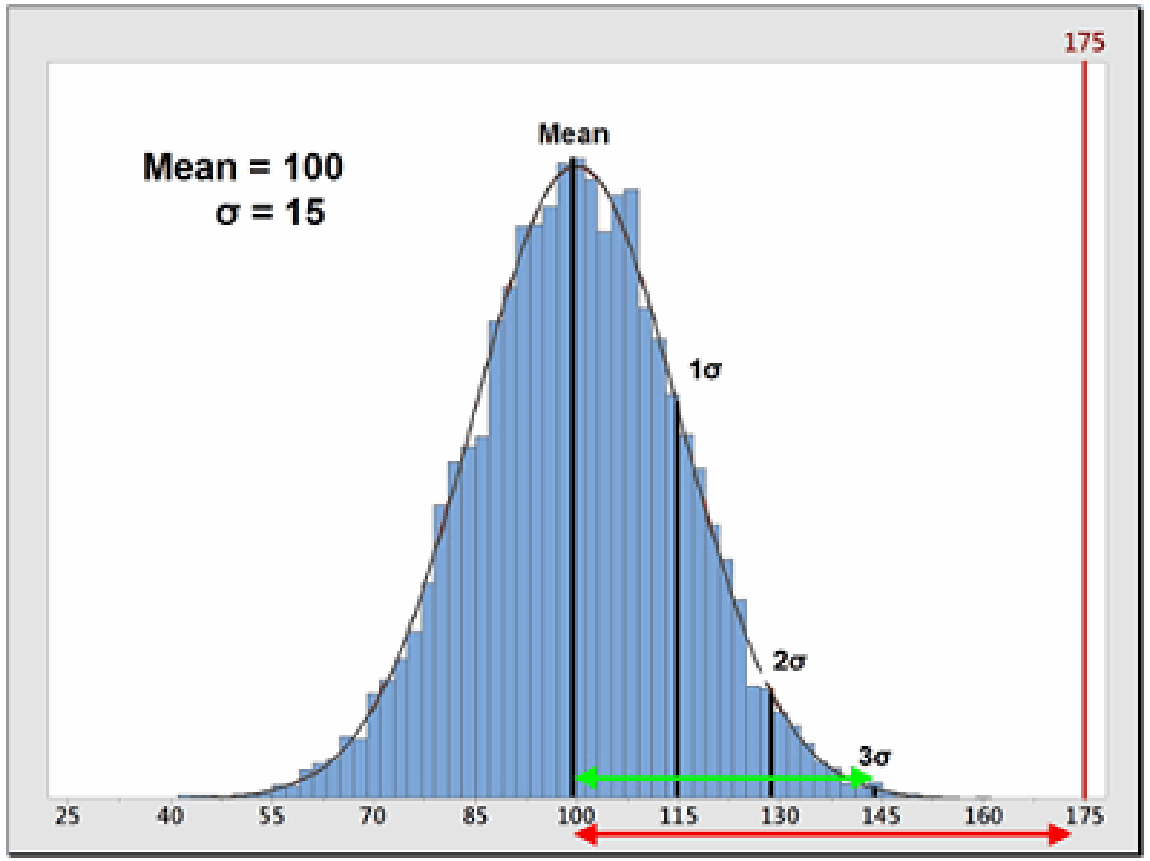
How do we estimate probability of exposure to residue (likelihood)?

Consequently, what we are looking to measure is the probability of cleaning validation samples failing the limit calculated from the ADE, which can be simplified as the probability of cleaning failure. This article will explore the use of the process capability of the cleaning process as a means to measure the probability of cleaning failure$_{\mathbf{API}}$ as shown in Equation 5.

$$\text{Cleaning Risk} = f(\text{toxicity score}_{API}, \textit{cleaning process capability}_{API}) \qquad \text{(Equation 5)}$$

(Note: This equation can be used with any compound that has a calculated ADE/PDE [permitted daily exposure], including cleaning agents).

$$Cpu_{(upper\ limit)} = \frac{\text{Upper Specification Limit} - \text{Mean}}{3\sigma} \qquad \text{(Equation 8)}$$



$$Cpu_{(ADE\ limit)} = \frac{\text{ADE} - \text{derived Limit} - \text{Mean of Swab Data}}{3\sigma \text{ of Swab Data}} \qquad \text{(Equation 9)}$$

$$Cpu = \frac{175 - 100}{3 \times 15} = \frac{75}{45} = 1.67 \qquad \text{(Equation 10)}$$

A Process Capability-Derived Scale For Assessing The Risk Of Compound Carryover In Shared Facilities;
By Andrew Walsh; David G. Dolan, Ph.D.; et al: Pharmaceutical Online, August 9, 2017

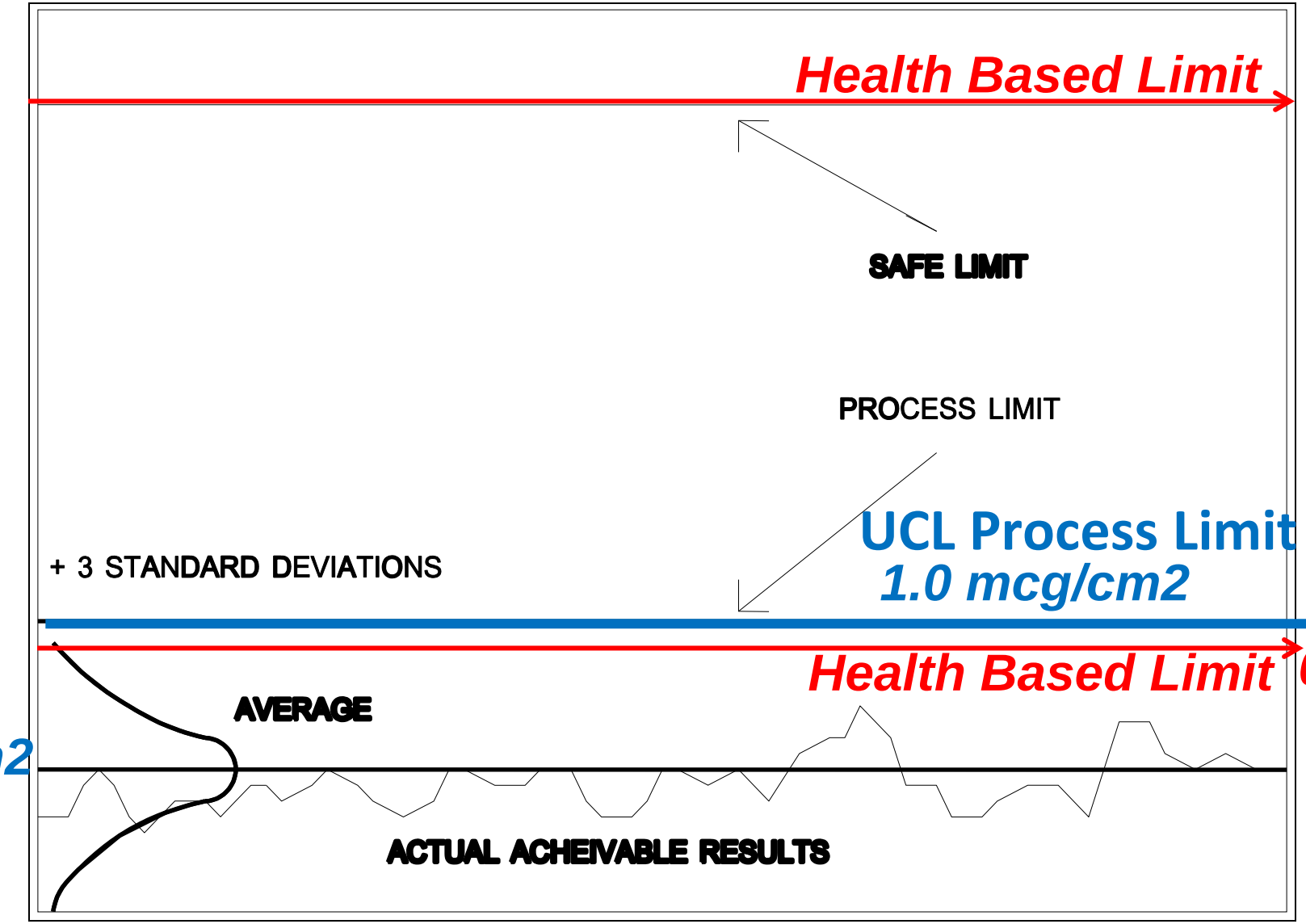
Table 2 - Cpu-based Scale for Probability of ~~Exposure~~

(Probability of) Exposure Scale			
Cpu (cleaning process)	(1/Cpu x 10)	Failures (PPM)*	Rating
1	10.0	1350	Unacceptable
1.11	9.0	434	Poor
1.25	8.0	88	Fair
1.42	7.0	10	Acceptable
1.66	6.0	0.3	Good
2	5.0	0.001	Very Good
2.5	4.0	3.19E-08	Excellent
3.3	3.0	2.08E-17	
5	2.0	3.67E-45	
10	1.0	4.91E-192	Exceptional
100	0.1	<2.23E-308	

* Potential failures (in parts per million) were calculated using Minitab 17 and without the 1.5 Sigma shift

A Process Capability-Derived Scale For Assessing The Risk Of Compound Carryover In Shared Facilities;
By Andrew Walsh; David G. Dolan, Ph.D.; et al: Pharmaceutical Online, August 9, 2017

Health Based Limit vs. UCL Process Limit



Cleaning Statistical Process Control (SPC)
You have to collect data to do SPC!

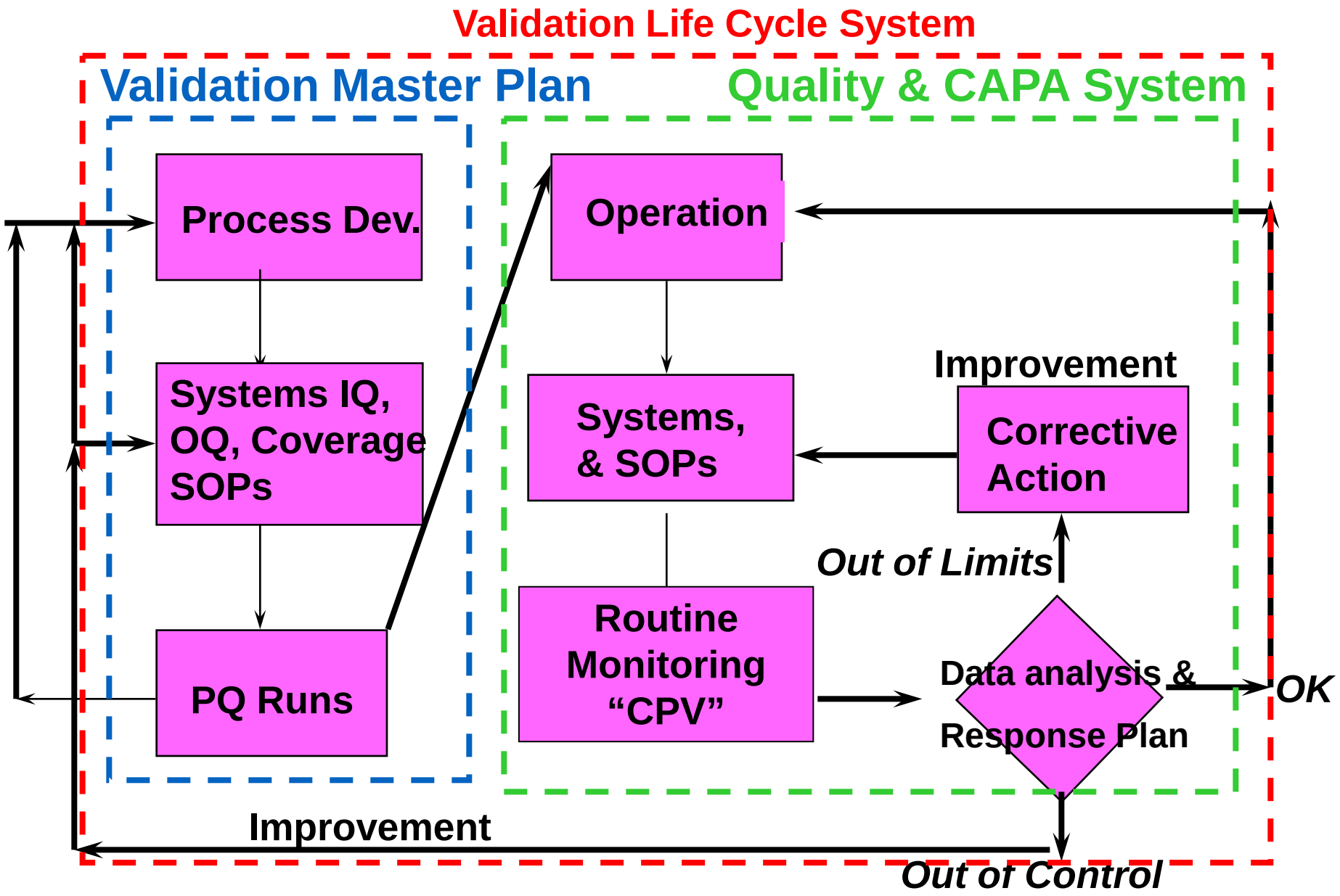
7.3 *Risk-Based Monitoring:*

7.3.1 Risk-based continued monitoring (levels and frequency of routine sampling) of cleaning process parameters and sampling of critical cleaning quality attributes should be based on the data collected during cleaning process development and qualification runs.

7.3.2 Monitoring and sampling do not have to continue at the level used during the cleaning process development and qualification runs and can be modified based on the data and level of risk. The level of monitoring and sampling can be adjusted to a statistically appropriate level and be representative of the equipment.

ASTM E3106 − 18, Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation

Cleaning Process Validation Life Cycle Overview



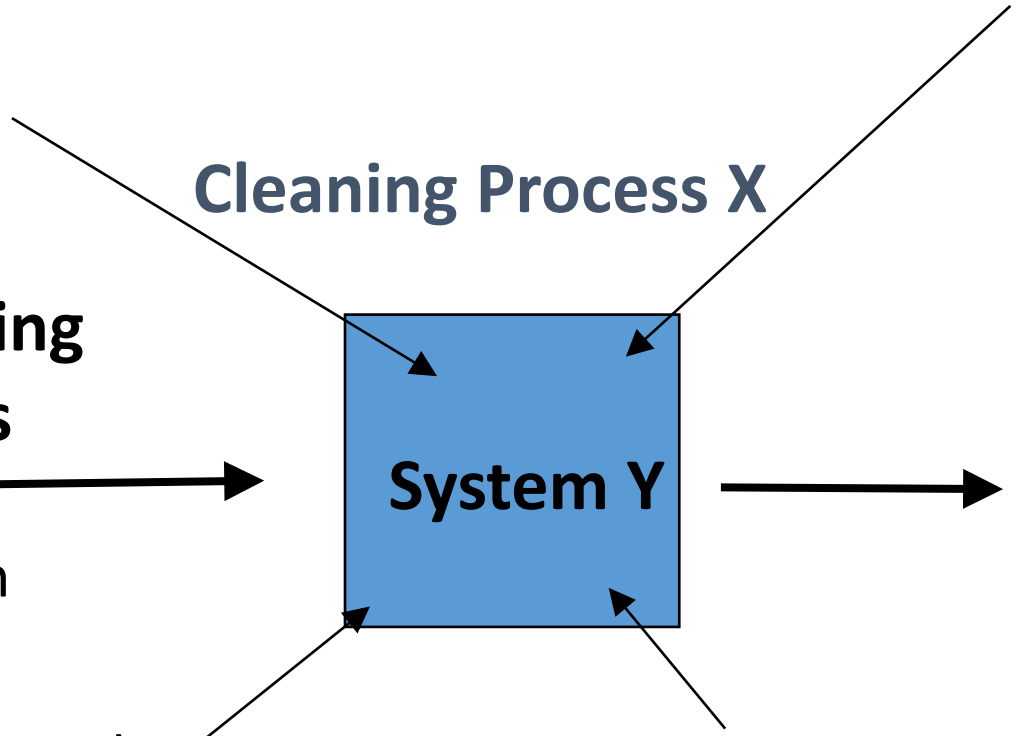
7.3.4 *Use of PAT in Cleaning Validation:*

7.3.4.1 PAT can be used as a system for designing, analyzing, and controlling cleaning processes. This includes timely measurements of critical cleaning input/output variables identified and documented *during risk assessment and during cleaning process development* with the goal of ensuring patient safety and product quality.

Cleaning Validation Design Space, Two product system

Methods, Conditions, Parameters (CPPs)
Pressure, Temp, flow, rpm, concentration, timing, position

Facility, Systems, Tools,
Equipment



DHT, Starting Conditions
Quality, Composition

Output CQAs, Attributes
Surface Quality, residues, bacteria
Bioactive Residue A, B
Surface (µg/cm2);
Rinse (mg/L);

Media, agents, consumables

Procedure-
sequence, duration, interval, control

Strategies for Developing a Robust Cleaning Process Part I: Application of Quality by Design to Cleaning; *American Pharmacetical Review,* July 1, 2010; R. Sharnez

Critical Process Parameter	Operating Range (Control Space)		Characterization Strategy	
	Lower Acceptable Limit (LAL)	Upper Acceptable Limit (UAL)	Traditional Approach: Characterize with CPPs at set point or typical operating conditions	QbD Approach: Characterize with CPPs at their respective worst-case operating points
Hold Time (days)	1	7	4	5
Concentration of cleaning solution (%)	0.75	1.25	1.0	0.75 (for wash) 1.25 (for rinse)a
Temperature of cleaning solution (°C)	60	80	70	60
Flow rate (gpm) or Pressure [b] (psig) of cleaning solution or rinse water	12 10	18 14	15 12	12 10

[a] Rinse out studies may not be required if the equipment is cleaned with process solvents (i.e. formulated cleaning agents are not used)
[b] At sprayball or other suitable location where pressure can be correlated to flow rate

Continuous Process Verification
"Process Indicators" (PIs)

Is process operating under control, within validated parameters? This time? Every time?

- On-line instrumentation
  - Chemical: Conductivity, pH,
  - Temperature
  - Hydrodynamic: Pressure, flow, function
- Computer controller, data acquisition
- Batch record- "checked by"
- Cleaning logs and status tags
- *Samples- visual, rinse, swab*

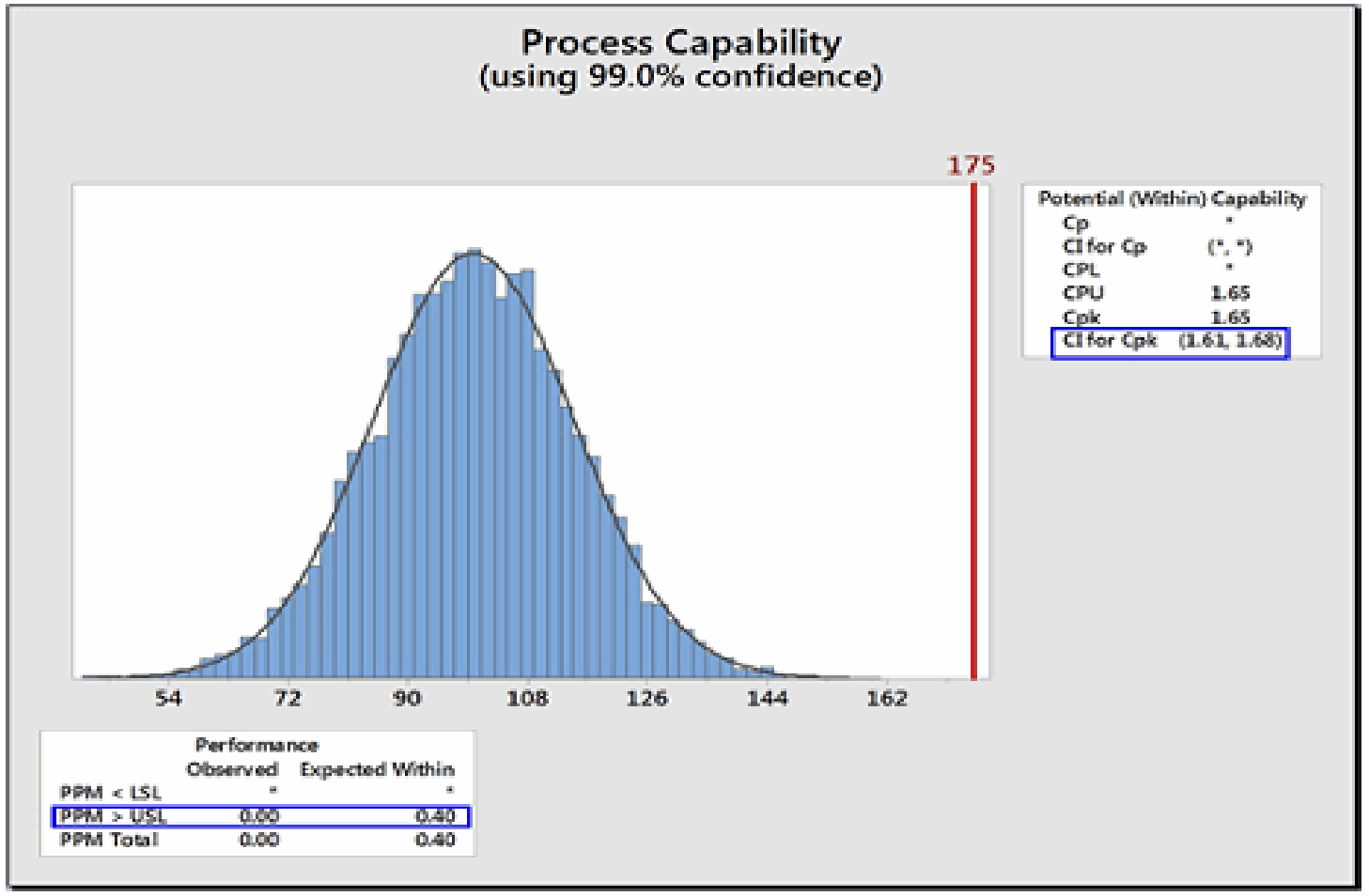
7.3.3 *Statistical Process Control (SPC) Limits*—Data that has been collected in the risk evaluation or risk control stages can have SPC limits calculated from these data. These SPC limits should then be used for monitoring cleaning processes and in place of the MSSR limits used for the risk analysis in risk evaluation.

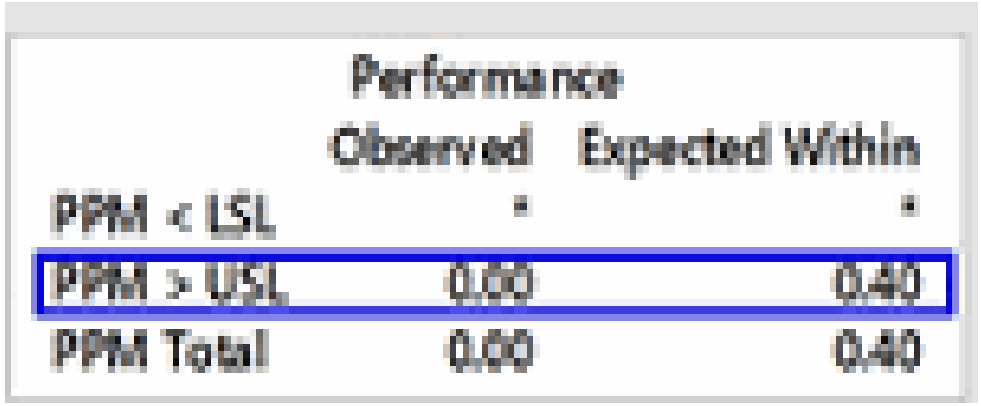
7.3.4.3 The data from these approaches can be evaluated statistically. Models can be developed and subsequent runs can be compared to the model to determine whether the cleaning is equivalent to the model or used for real-time release of equipment.

ASTM E3106 − 18, Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation

Understand and select statistical tools

- Central tendency and Variation
  - batch samples against specs
- Control Charts X bar+/- 3σ
  - Monitor process results over time or batches
- Significance testing/equivalence tests
  - To determine if differences between lots are normal variation or not
  - To determine if a process change affects product quality attributes To determine number of samples to estimate the normal variation in the population of all products produced by a process
- ANOVA
- Multiple variable regression/Correlation

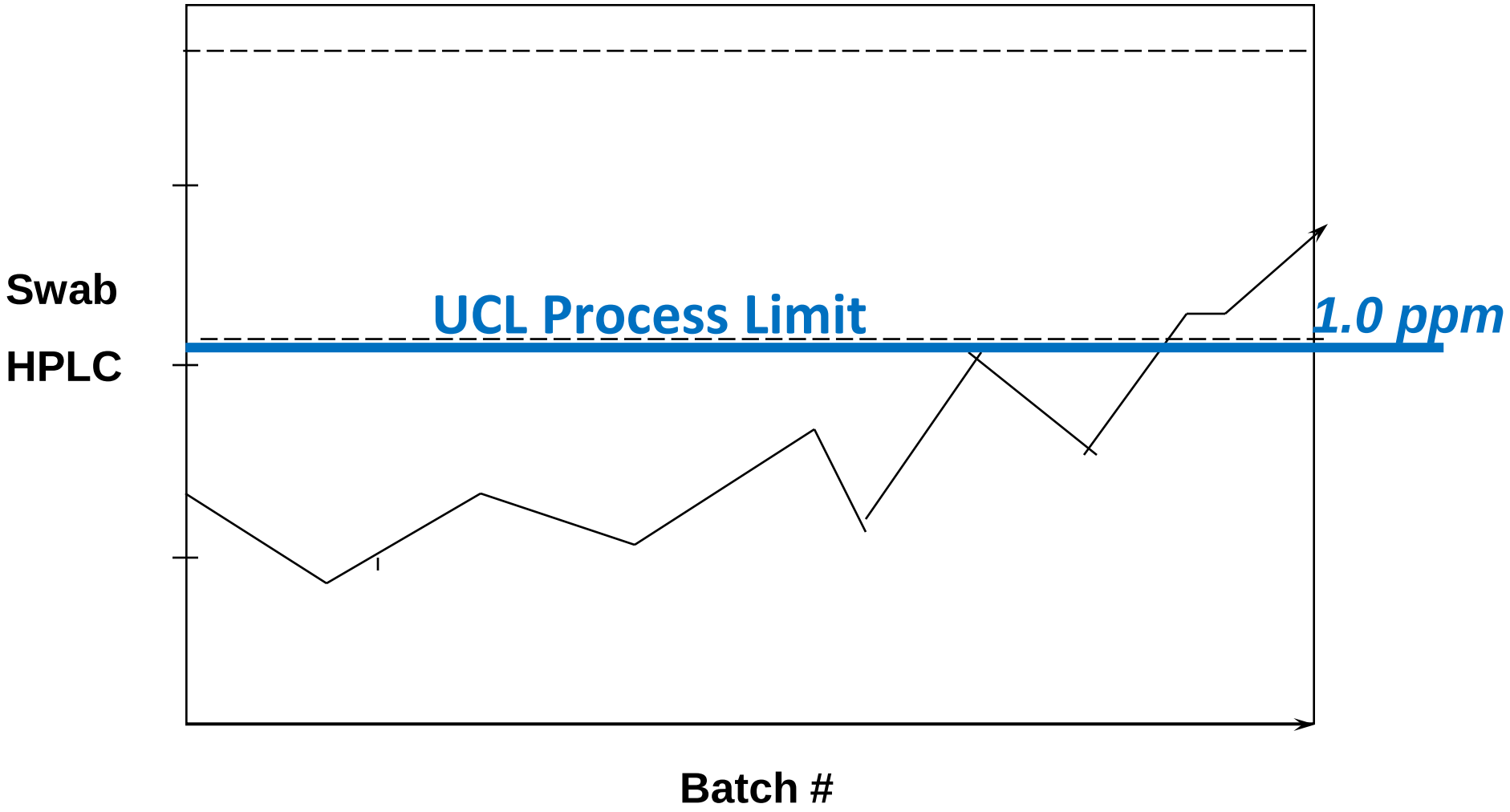




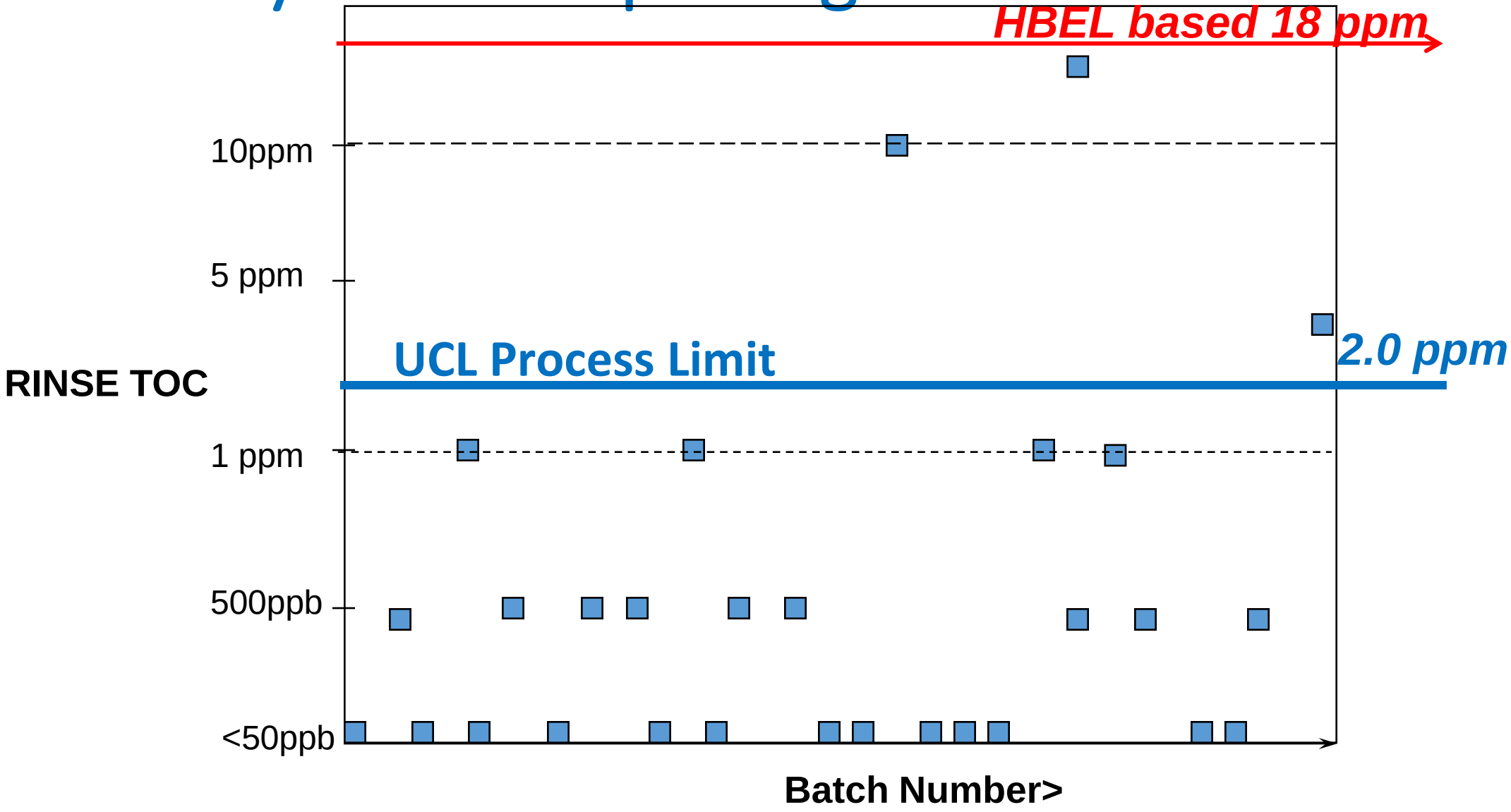
based on this data, that there are 0.4 possible failures out of 1 million

A Process Capability-Derived Scale For Assessing The Risk Of Compound Carryover In Shared Facilities;
By Andrew Walsh; David G. Dolan, Ph.D.; et al: Pharmaceutical Online, August 9, 2017

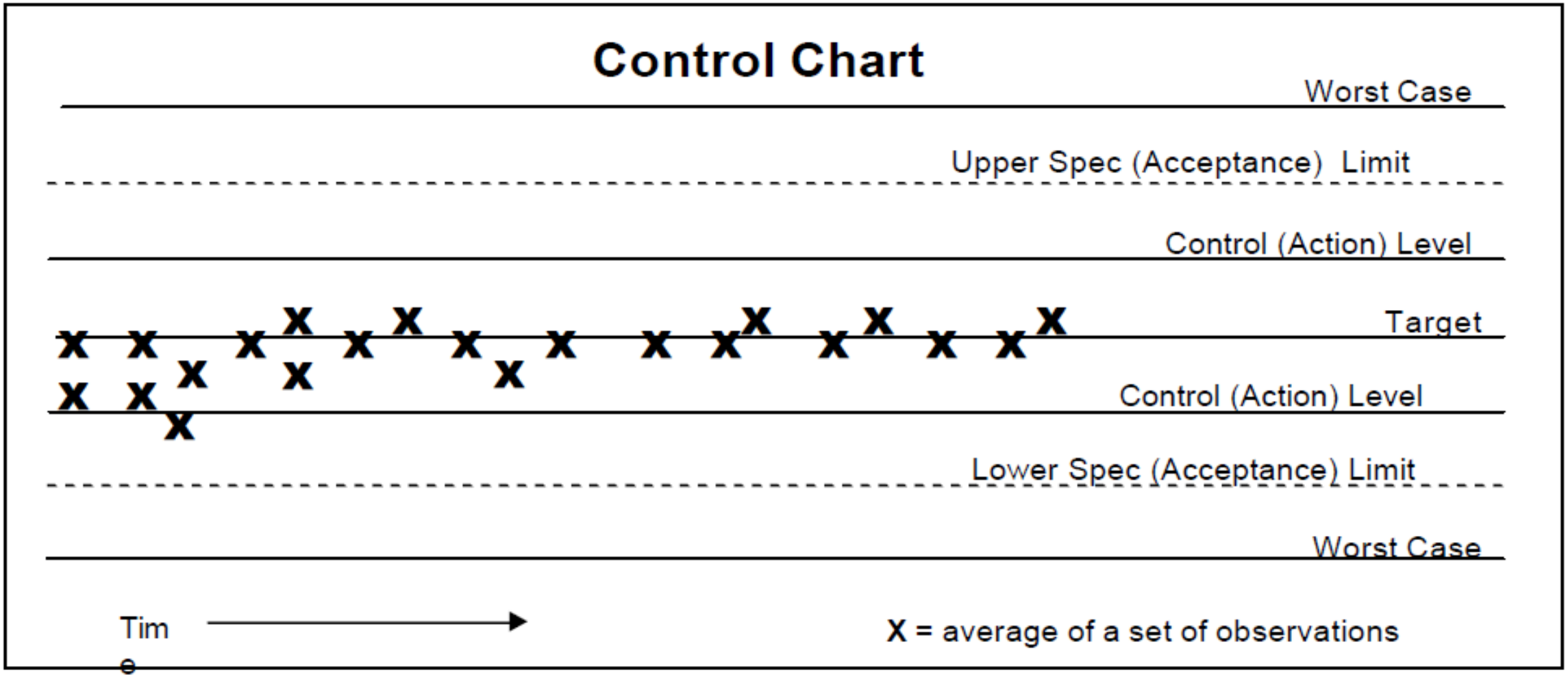
Data Analysis and Reporting



Data Analysis and Reporting



Capability Study

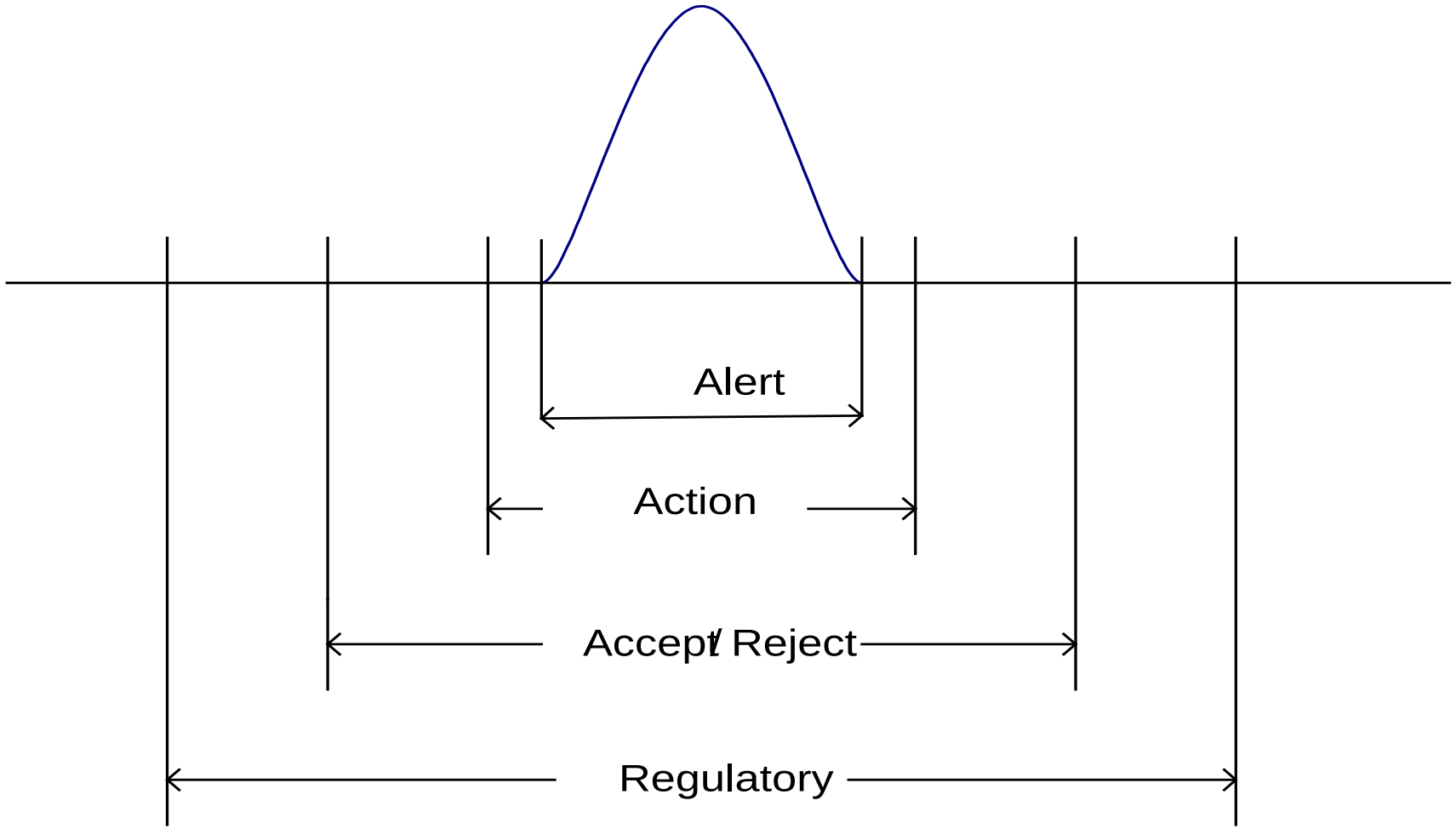


GHTF Study Group 3 - Quality Management Systems, Process Validation Guidance – January 2004

Capability Study

•Select a small number of units periodically over time. Each period of time is called a subgroup. For each subgroup, the average and range is calculated. The averages and ranges are plotted over time using a control chart
•If consistent, the samples are then combined to determine if centered and the variation is sufficiently small. This is accomplished by calculating capability indexes. Commonly used capability indices are Cp and Cpk.
•If acceptable values are obtained, the process consistently produces product that meets the specification limits. Capability studies are frequently used towards the end of the validation to demonstrate that the outputs consistently meet the specifications.
•They can also be used to study the behavior of the inputs in order to perform a tolerance analysis.

Idealized Specification Limits



Ten Deadly Statistical Traps in Pharmaceutical Quality Control, Lynn Torbeck, Pharmaceutical Technology, 29 March 2007

Mgmt. Response Plan

- Alert levels
  - …levels or ranges which, when exceeded, signal a potential drift from normal operating conditions and which may not require action, but may need to be monitored more closely than standard." - *PDA Technical Report #13*

- Action levels:
  - …quality levels or ranges which, when exceeded, signal an apparent drift from normal operating conditions and which require action." - *PDA Technical Report #13*

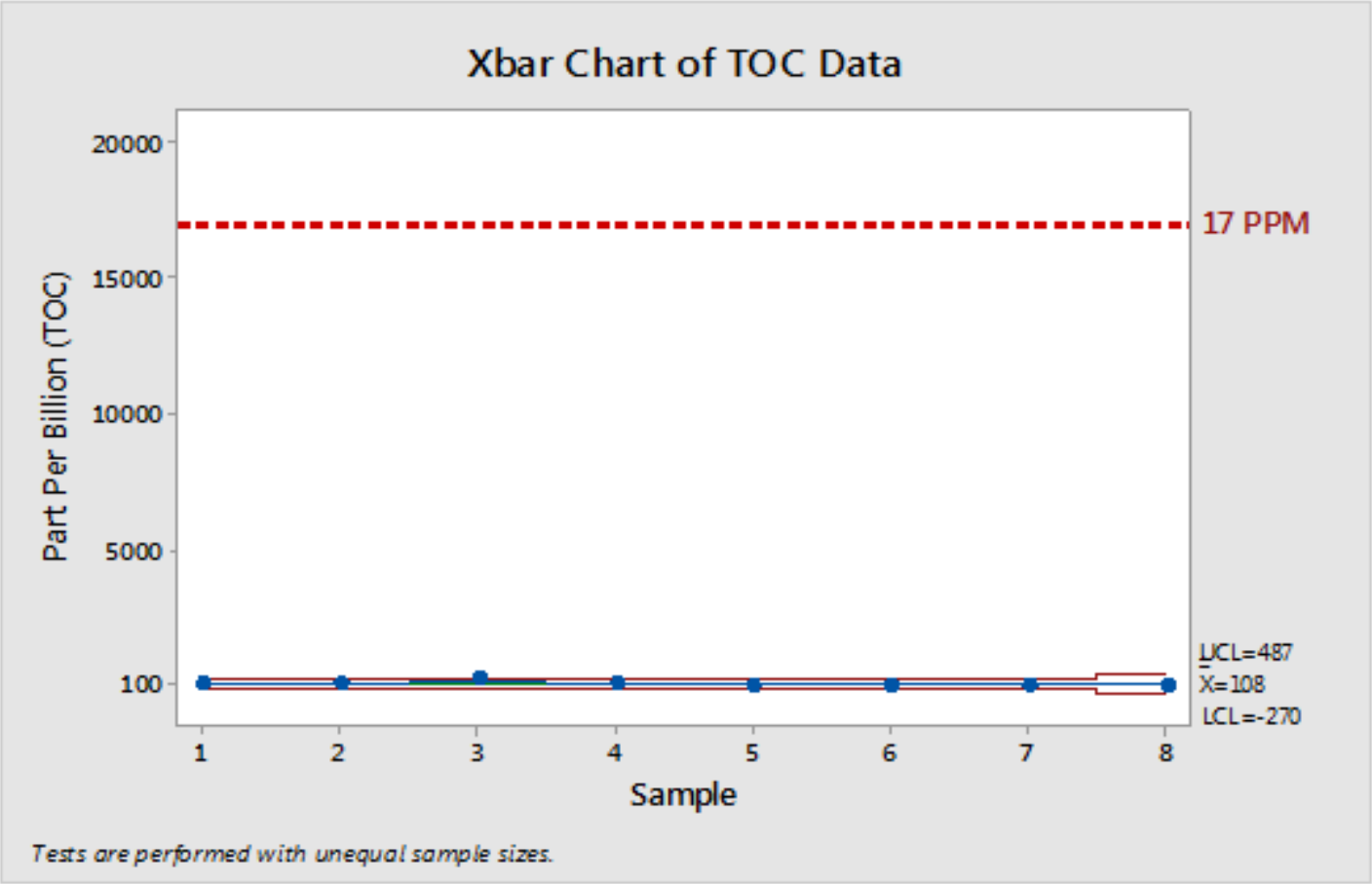
7.3.4 *Use of PAT in Cleaning Validation:*

7.3.4.2 It is recommended that cleaning processes use technologies to measure, control, and record these variables to detect critical failures and ensure reliable and consistent process performance.

7.3.4.4 On-line and in-line sampling have the most applicability for continuous monitoring of critical cleaning input/output variables such as temperature, flow rate, TOC, conductivity, and so forth.

7.3.4.5 At-line sampling may include TOC, conductivity, and visual inspection. Information collected during or after a cleaning process is complete can enable parametric release of equipment and improve manufacturing process efficiency
(Guide E2476).

TOC data was then collected for the cleaning procedures for five kettles, two packaging lines, and the raw material preparation area.



The upper control limit (UCL) for all of the TOC swab data was only 487 ppb, meaning that 99.87 percent of all the TOC swab data fell below this value.

Justification & Qualification Of Visual Inspection For Cleaning Validation In A Low-Risk, Multiproduct Facility, Pharmaceutical Online August 3, 2018 ; Andrew Walsh, Dongni (Nina) Liu, and Mohammad Ovais

PAT application: At-line TOC for cleaning validation and product changeover ; Water Technologies & Solutions application note; SUEZ

CASE

Equipment: large-scale Chromaflow chromatography column, cleaning study in 2006.

Sample Plan : Swab four "worst-case" locations; Rinse at CIP skid

Acceptance criteria: swab and rinse both1.25 ppm C.

Validation: Method suitability; PQ runs met acceptance;

Data from periodic sampling and changeover

Proposal: Use Sample plan for routine monitoring (Continuous Process Verification)

book or equipment use record. The sampling materials and the TOC analyzer were carried out to the production floor, where the sampling occurred at-line following a CIP of the column.

Equipment Swab Location	LIMS number	Swab Number	TOC Result TOC <1.25 ppm C	Pass/Fail*
Inlet Valve	120231	1	126 ppb	Pass
Column Gasket	120232	2	222 ppb	Pass
Base Gasket	120233	3	245 ppb	Pass
Outlet Valve	120234	4	134 ppb	Pass
Cleaning Circuit	**LIMS Number**	**Water Grade**	**TOC Result TOC <1.25 ppm C**	**Pass/Fail***
Column 1_A	120235	WFI Final Rinse	42.3 ppb	Pass

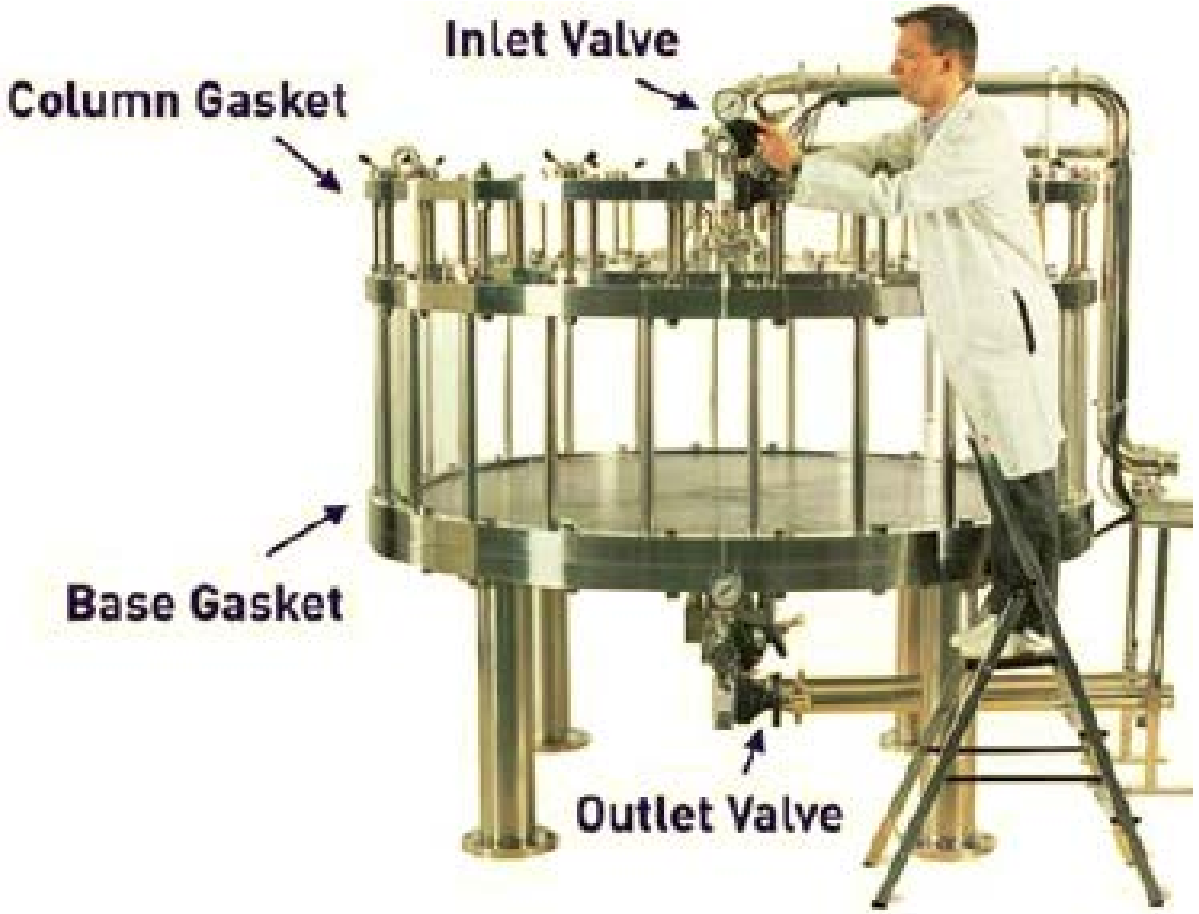
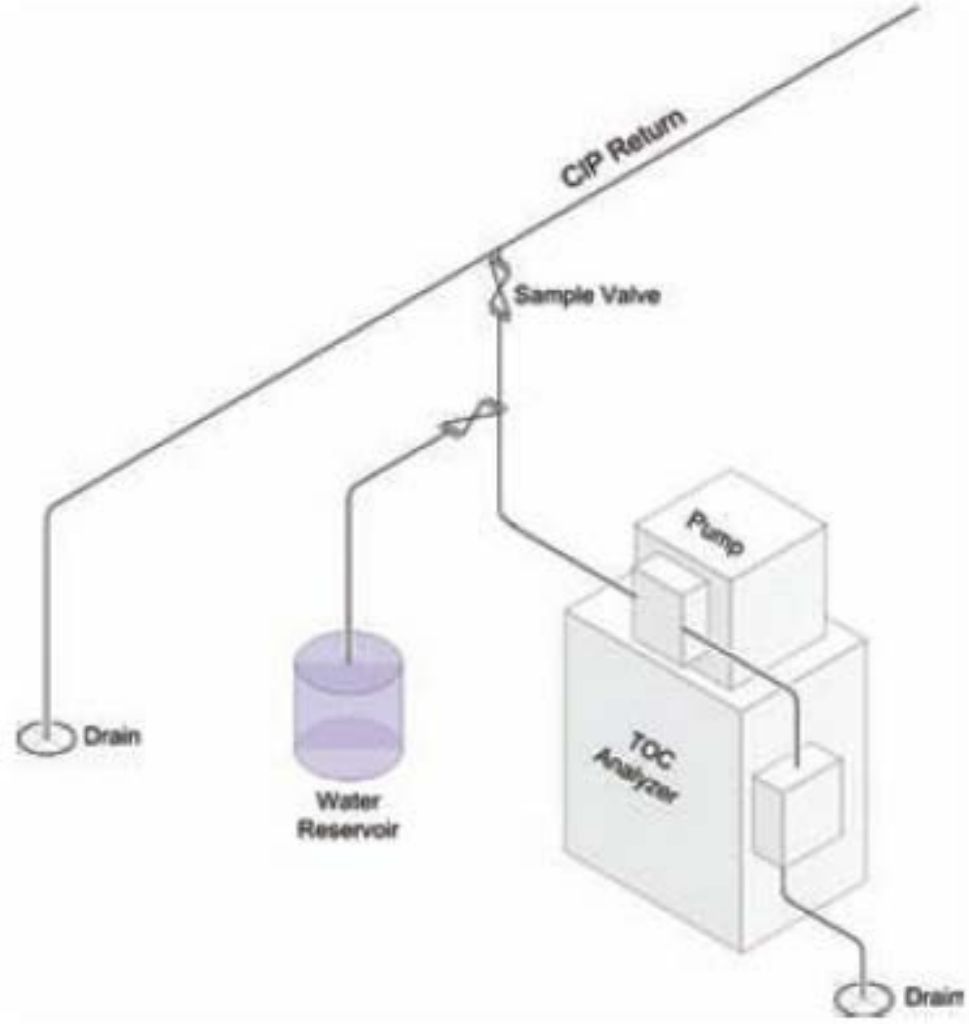


Figure 1. Worst-Case Locations for Swab Sampling

Streamlining the Process with Quality

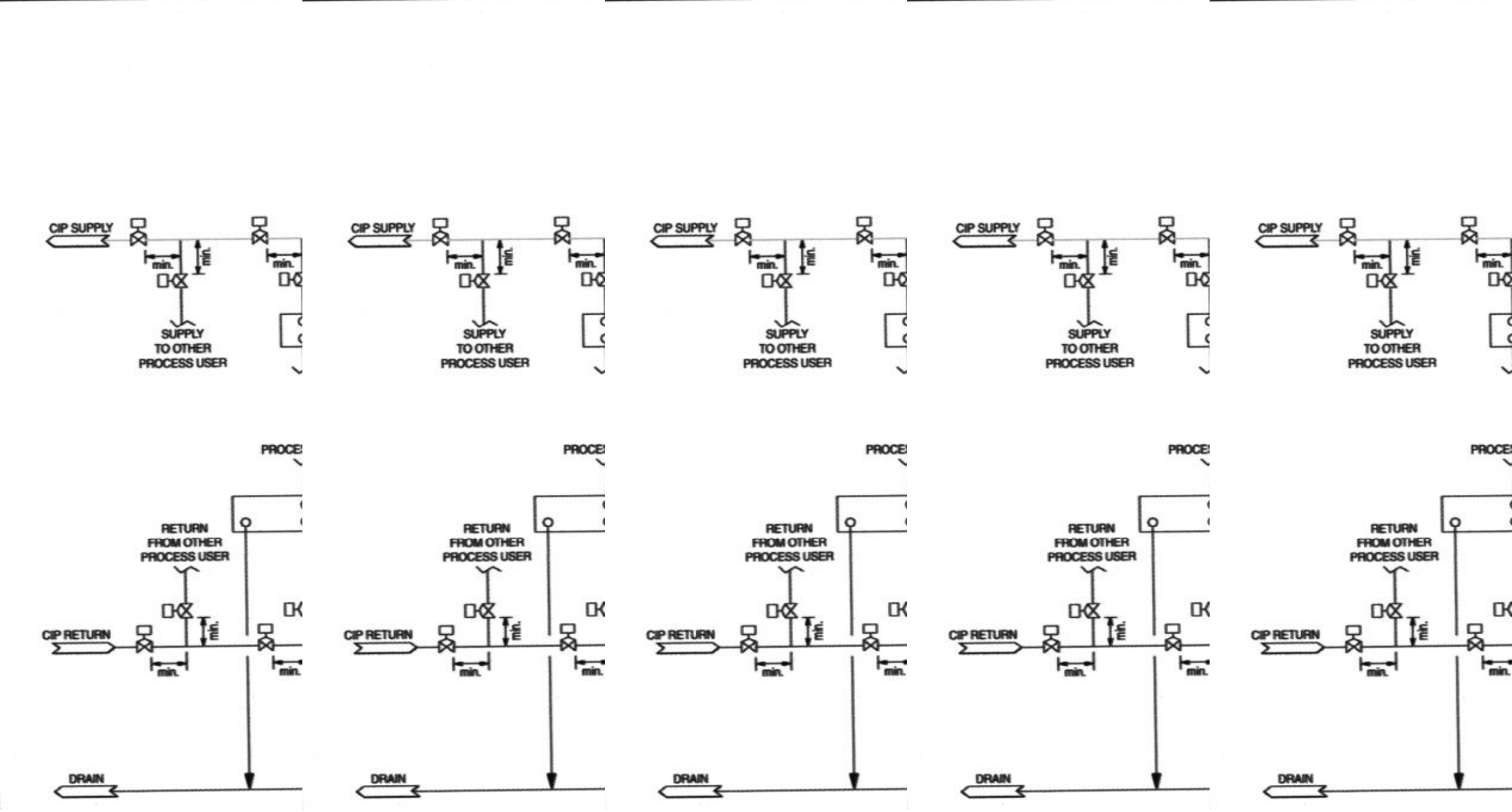
This example is one of many in using innovative instruments for PAT applications. Typically, product changeover or the periodic monitoring of samples can be completed within minutes or hours using the Sievers M9 Portable, providing efficiency gains for single or multi-product facilities. The



Online technologies like TOC that perform destructive analyses on a captive sample can exhibit delays on the order of 1 to 5 minutes for the oxidation reaction or equilibration of the instrument sensors before the results are available. While this is somewhat immaterial to a continuous water treatment process, the duration of the final rinse is on the same order as the equilibration. As such, the delay between when the result and the sampling time may be reduced by beginning the equilibration of the instrument prior to the time it is required.

Figure 3: Online TOC Analyzer Sample Configuration

Online Total Organic Carbon Analysis for Cleaning Validation Risk Management; American Pharmaceutical Review; October 1, 2010; *Keith Bader*



"Practical CIP System Design", David Greene, Pharmaceutical Engineering, March/April 2003

CIP Supply/Return Conductivity