Module #4-Risk-based Analytical and Sample Method Selection, Continued

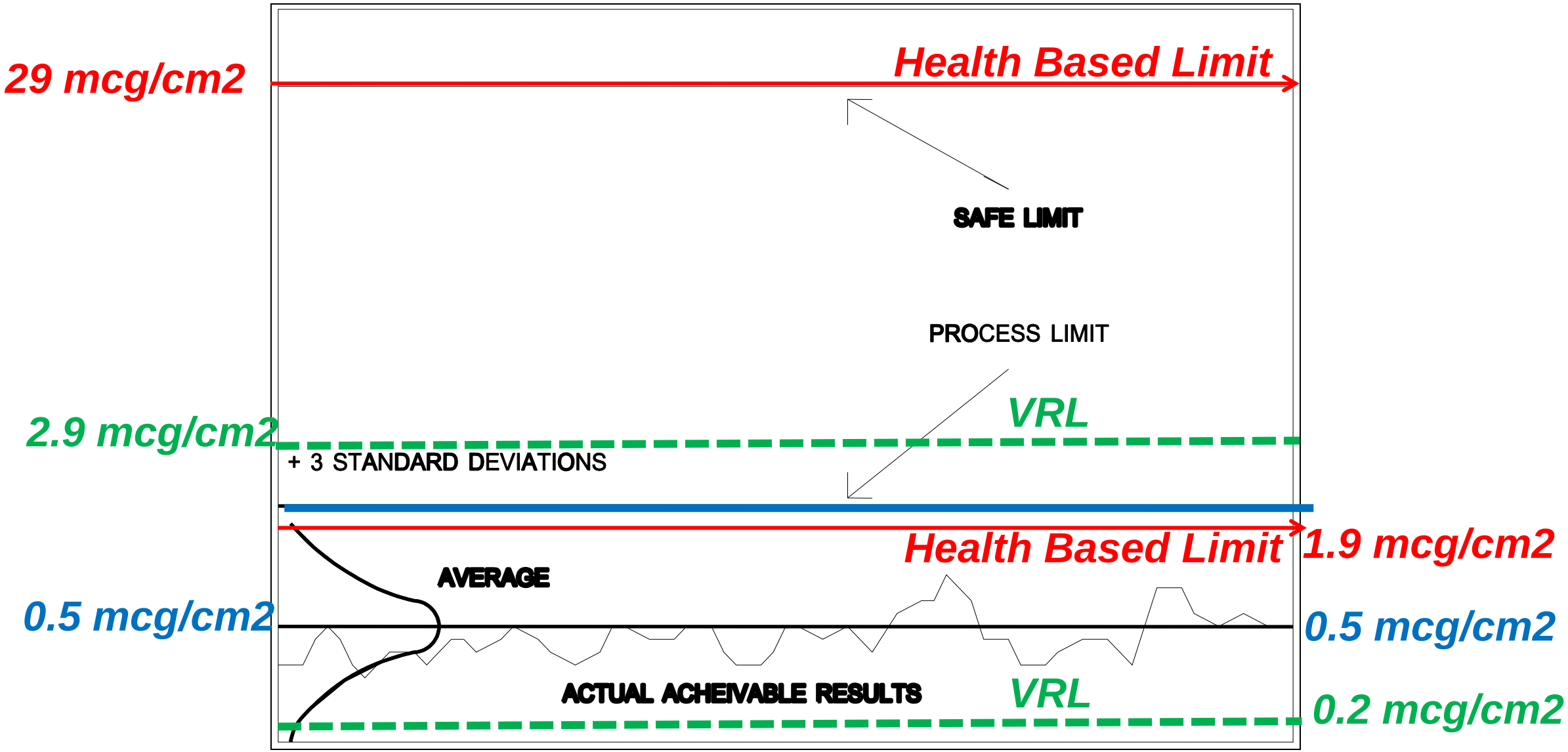
- Justification and Statistics-based Qualification of Visual Inspection
- Detection Limits and New Detectability Scales
- Establishing Risk-Based Surface Residue Acceptance Levels

CASE STUDY – Risk Assessment, Limits and Inspection Approach

Max. Safe Surface Residue level by multiple Criteria

Product	ADE/PDE	1/1000 LDose	10 ppm	**Visually Clean (0.4-4.0 µg/cm2)**
A				1
B				1
C				1
D				1
E				
F				

Safety Limit vs. Process Limit vs, Visual Detection Threshold



Visual Criteria Case Study Article

Pharmaceutical Technology

Application of Visible-Residue Limit for Cleaning Validation
Richard J. Forsyth and Vincent Van Nostrand

Oct 2, 2005
By: Richard J. Forsyth, Vincent Van Nostrand
Pharmaceutical Technology

Pharmaceutical plants must have visually clean equipment to operate according to good manufacturing practices. Formulators must visually inspect manufacturing equipment for cleanliness before formulation work begins (1). Manufacturers establish and perform visible cleanliness and analytical methods to ensure regulatory compliance. An analyst conducts a visual inspection and confirms visible cleanliness before taking swab samples for chemical analysis (2). The formulator of the subsequent batch conducts a visual inspection before manufacturing work begins. A correlation between available analytical data and visible cleanliness of manufacturing equipment over an extended period of time can expand the practice of performing visual inspections in lieu of swab sampling.

“Application of Visible-Residue Limit for Cleaning Validation”, Richard J. Forsyth and Vincent Van Nostrand ,Oct 2, 2005 Pharmaceutical Technology

Figure 2: Observers viewed formulation stainless steel coupons from various distances and angles.

Web Table II: Effect of viewing distance on visible-residue detection.*

400 lx, 15°	10 ft				15 ft				20 ft			
	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL
Pepcid			1		2	2	2		4	4	2	1
Proscar									3	2	2	
Singulair									2	2	1	
Syprine	4	4	4	4	4	4	4	4	4	4	4	4

WEB ONLY: Table III: Effect of light intensity on visible-residue detection.*

15 ft, 45°	400 lx				300 lx				200 lx				100 lx			
	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL	75% VRL	VRL	125% VRL	ARL
Pepcid	1	1	1										1	1	1	
Proscar													1	1	1	
Singulair													1	1	1	
Syprine	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

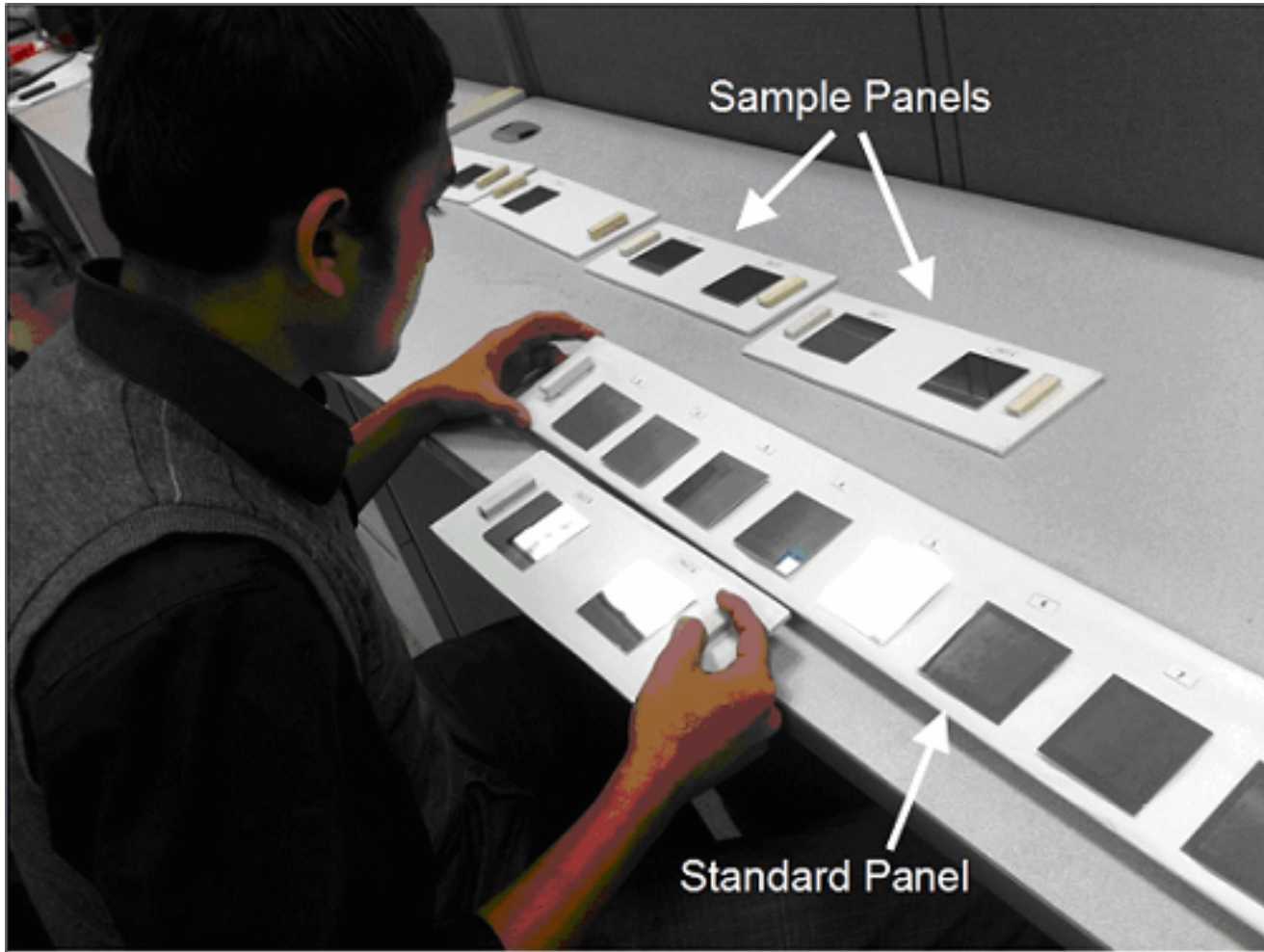
"Application of Visible-Residue Limit for Cleaning Validation", Richard J. Forsyth and Vincent Van Nostrand ,Oct 2, 2005 Pharmaceutical Technology

Validation Of Visual Inspection As An Analytical Method For Cleaning Validation

Pharmaceutical Online; September 11, 2017 Parth Desai and Andrew Walsh

A value of 1-9 was then selected for the unknown coupon by choosing the closest match with the visual standard coupons; it was then recorded in the spreadsheet. If any residue was seen that did not match a standard, meaning a concentration greater than #9 (410 microgram/25 cm^2), the analyst reported it as a 10 in the spreadsheet.

Standard Coupon Number	Surface Residue Level (µgram/25 cm^2)	Surface Residue Level (µgram/cm^2)
0	0	0
1	10	0.4
2	25	1
3	50	2
4	86	3.4
5	131	5.2
6	186	7.4
7	251	10
8	325	13
9	410	16.4

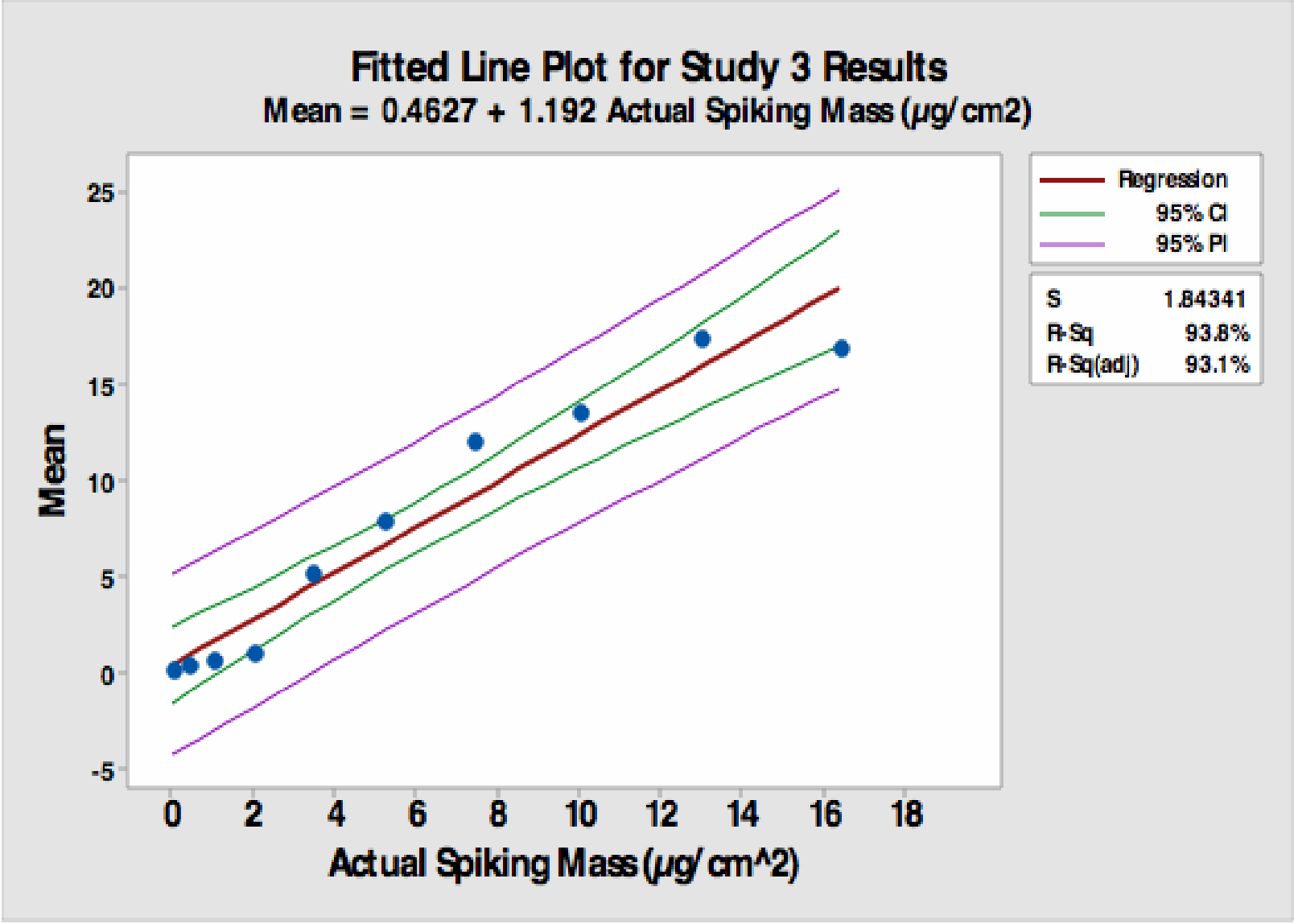


- 6 cm by 6 cm "coupons" of 316L stainless steel with a #8 surface finish

- 1 ml OTC sunscreen product spiked onto the coupons,

The first four responses (0.4 to 3.4 µgram/cm^2) were flat, indicating analysts reported them as clean (0).

Therefore, the amount spiked onto coupon number 4 (3.4 µgram/cm^2) could be considered as a possible detection limit (DL) in this visual inspection study.



Validation Of Visual Inspection As An Analytical Method For Cleaning Validation
Pharmaceutical Online; September 11, 2017 Parth Desai and Andrew Walsh

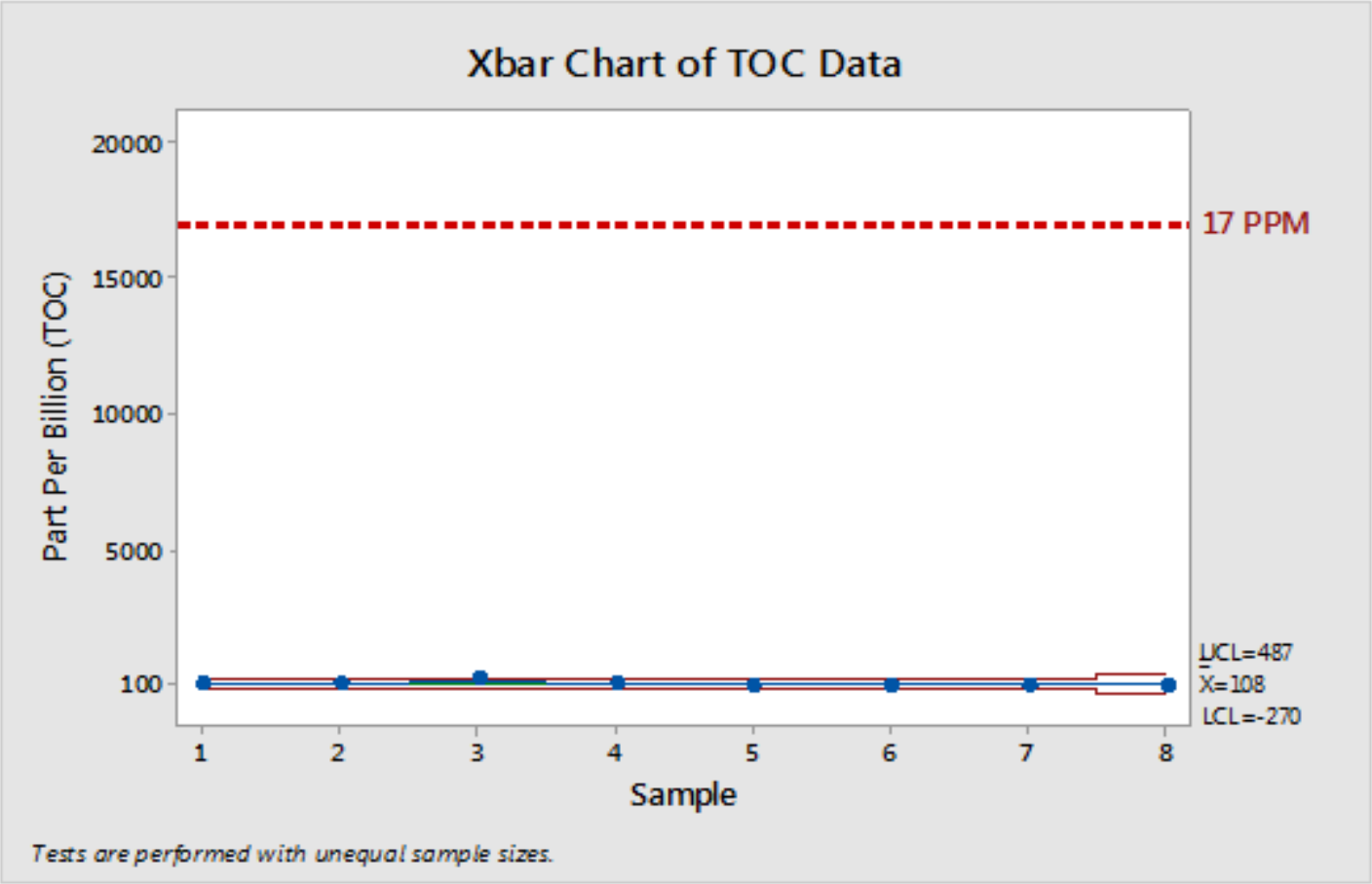
Justification & Qualification Of Visual Inspection For Cleaning Validation In A Low-Risk, Multiproduct Facility, Pharmaceutical Online August 3, 2018 ; Andrew Walsh, Dongni (Nina) Liu, and Mohammad Ovais

Table 2 shows the lowest possible TOC swab limits calculated for all the tanks in the manufacturing area. The manufacturing tanks have the largest surface areas in the facility and, since limits are inversely proportional to the equipment surface area, only the limits in the manufacturing area were calculated. All TOC swab limits for the other areas (e.g., packaging) would be substantially higher.

Compound	ADE
API-1	80 µg/day
API-2	2,800 µg/day
API-3	8,300 µg/day
API-4	2,100 µg/day

Tanks and Kettles	API	Maximum Safe Surface Residue for API (µg/cm²)	TOC Swab Limits for API (ppm)
Tank-1	API-2	991	531
TANK-1	***API-1***	***28***	***17***
Tank-1	API-3	2939	1202
Tank-1	API-4	744	176
Tank-2	API-2	1983	1062
Tank-2	API-1	57	34
Tank-2	API-4	1487	351
Tank-3	API-3	7442	3044
Tank-3	API-4	1883	445

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

Visual Inspection Qualification Case Study

Coupon	Product Residue Level
Blank	0
Low Residue Level	0.02 mcg/cm^2
High Residue Level	0.2 mcg/cm^2
MSSR	**28 mcg/cm2**

30 ea 316L/#4 finish stainless-steel coupons, 10 sets of 0, 0.02 and 0.2 mcg/cm2

the inspectors should identify the blank coupons as clean and the low residue level and high residue level coupons as dirty. All personnel performed these inspections three times over the course of three days, 3X 30 observations

The acceptance criterion for the VRL was the level at which all inspectors could identify the dirty coupons correctly 100 percent of the time.

All inspectors were able to correctly identify all of the dirty coupons at the 0.2 mcg/cm^2 level 100 percent of the time but could not do so at the 0.02 mcg/cm^2 level (approximately 90 percent did so).

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

False Negatives? False Positives?

The misclassification rates show the rates that the clean coupons were rated dirty and the dirty coupons were rated clean. In this case, none of the dirty coupons were rated clean, ② while 19.5 percent of the clean coupons were rated dirty. This can be considered acceptable, since clean equipment that is suspected of being dirty will simply be cleaned again.

For the coupons, the percentage of dirty rated clean was 0% ①. For the percentage clean rated dirty, the graph reveals that two of the coupons (#066 and #055) were misclassified at a very high rate ②. These coupons were examined to determine why they had such high misclassification rates. Coupon #066 was found to have a slight discoloration on its surface that was not noticed while preparing the coupons, which many inspectors mistakenly identified as residue.

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

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

where:

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

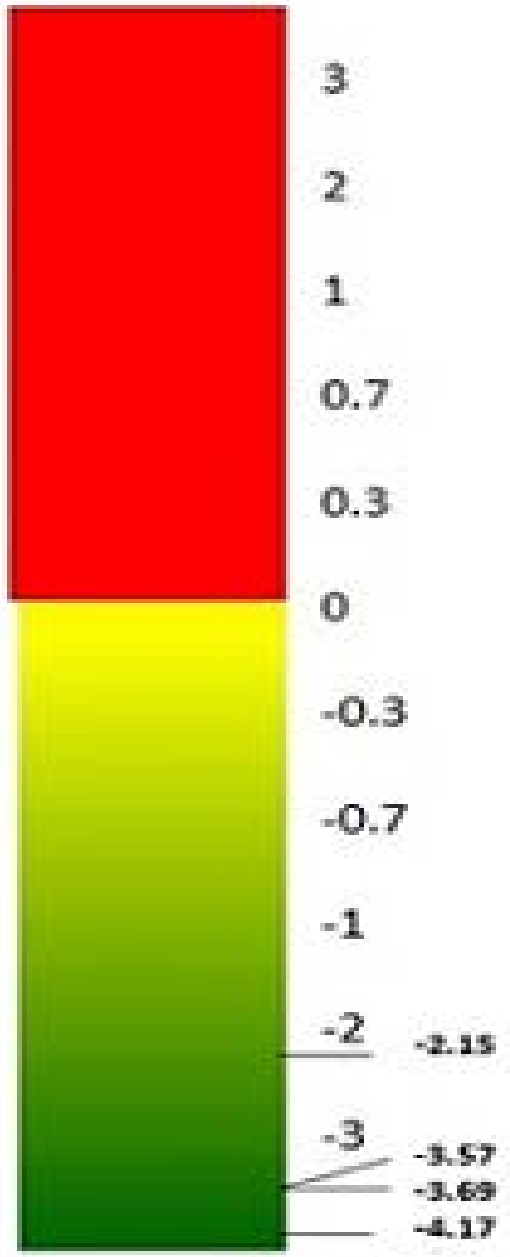
Calculation for **API-1** where:

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



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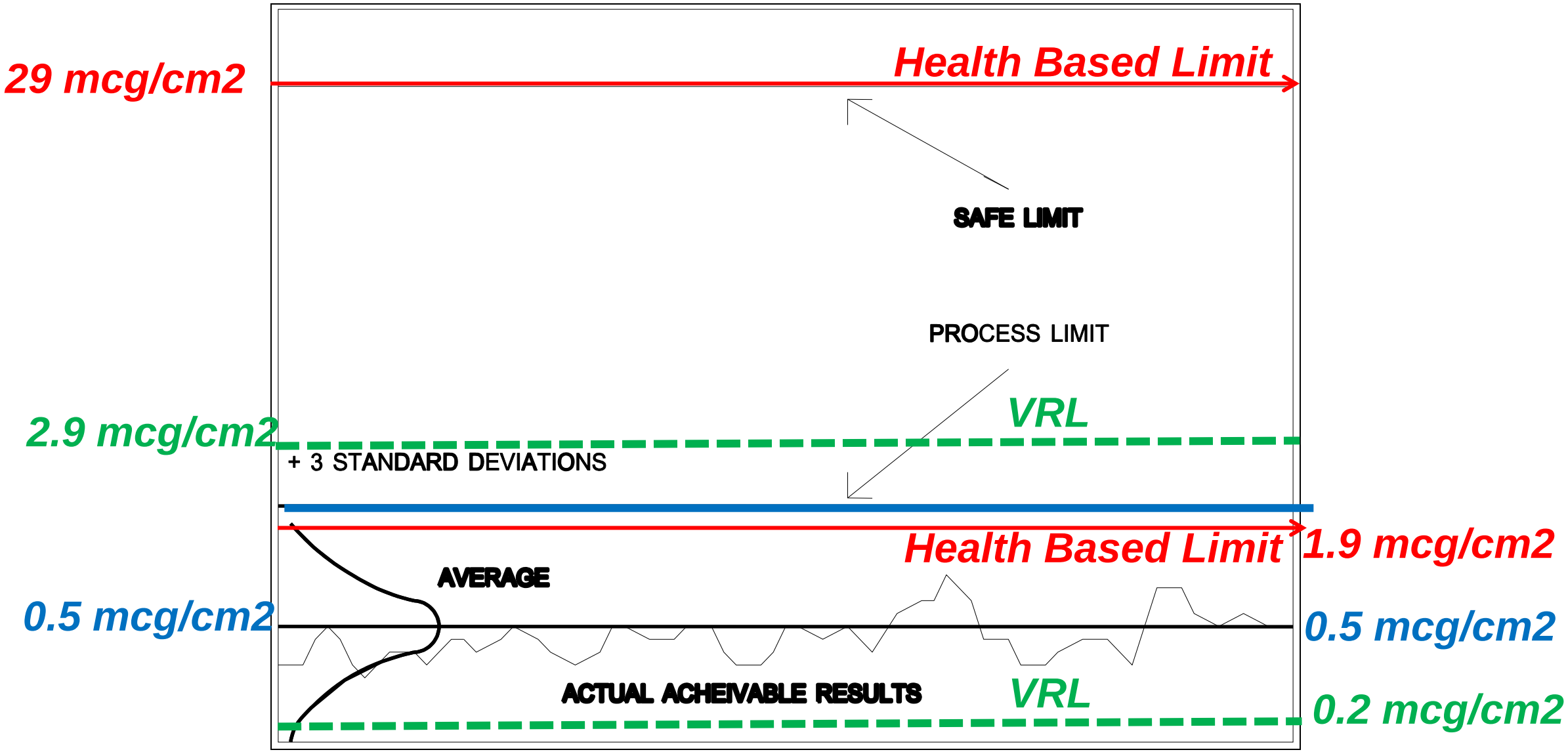
Health Based Limit vs. Process Limit



Establishing Risk-Based Surface Residue Acceptance Levels

- Limits combine policy, risk objectives and assumptions.
- Limits must be converted to a measurable (analytical) qty. or acceptance criteria.
- You must know sample methods first
- Acceptance criteria convert limits criteria to specific sample result based on sample method, recovery studies, data , calculation of contamination and transfer assumptions, observation and qualification studies.

Quantitative Basis for Surface Limits

- Residue level in next product unit

  (L1: ppm, (μg API A/day)/(g drug product B/day)

- Residue level in next batch

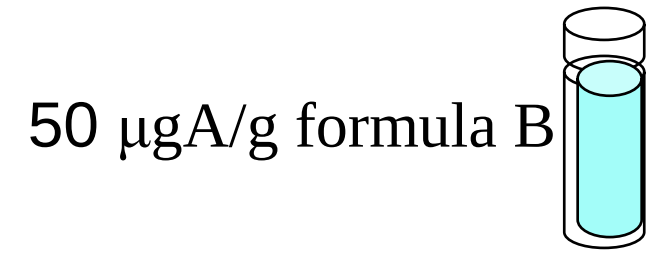
  (L2, MSC: mg/kg x kg batch size=mg)

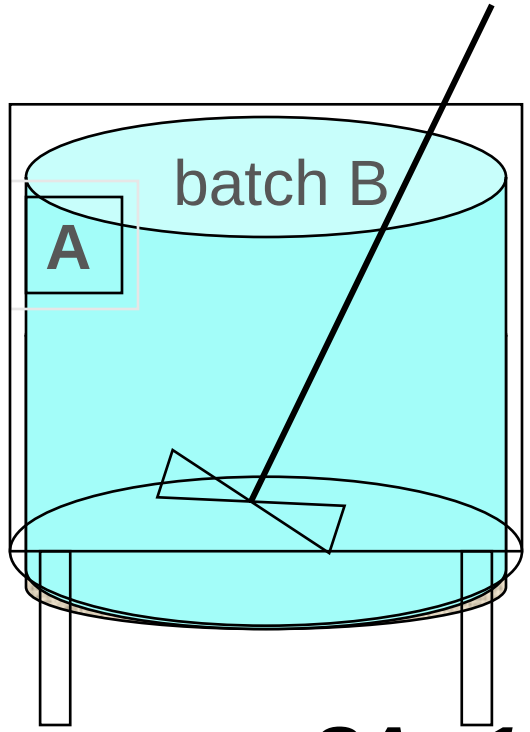
- Residue level on equipment surface?

  (L3: mg per batch ÷ common surface area=mg/cm2)

Critical Quality Attributes- ARL, MSSR

- **ADE** ≥ (1/1000) Dose A=50 mcg/day
- **L1**(MSC)=50 mcg A/1 g MDD B by ADE
  = 50 ppm, or 10 ppm default
- $L2_{ADE}$=50 µgA/gB x 40 kg B
  $L2_{10ppm}$=10ppmX 40 kg
  =2 g, 400 mg MSC
- **L3: Equipment surface limit (MSSR)**
  400mg/14,000 = 29 mcg/cm2
  2 g/ 14,000= 143 mcg/cm2

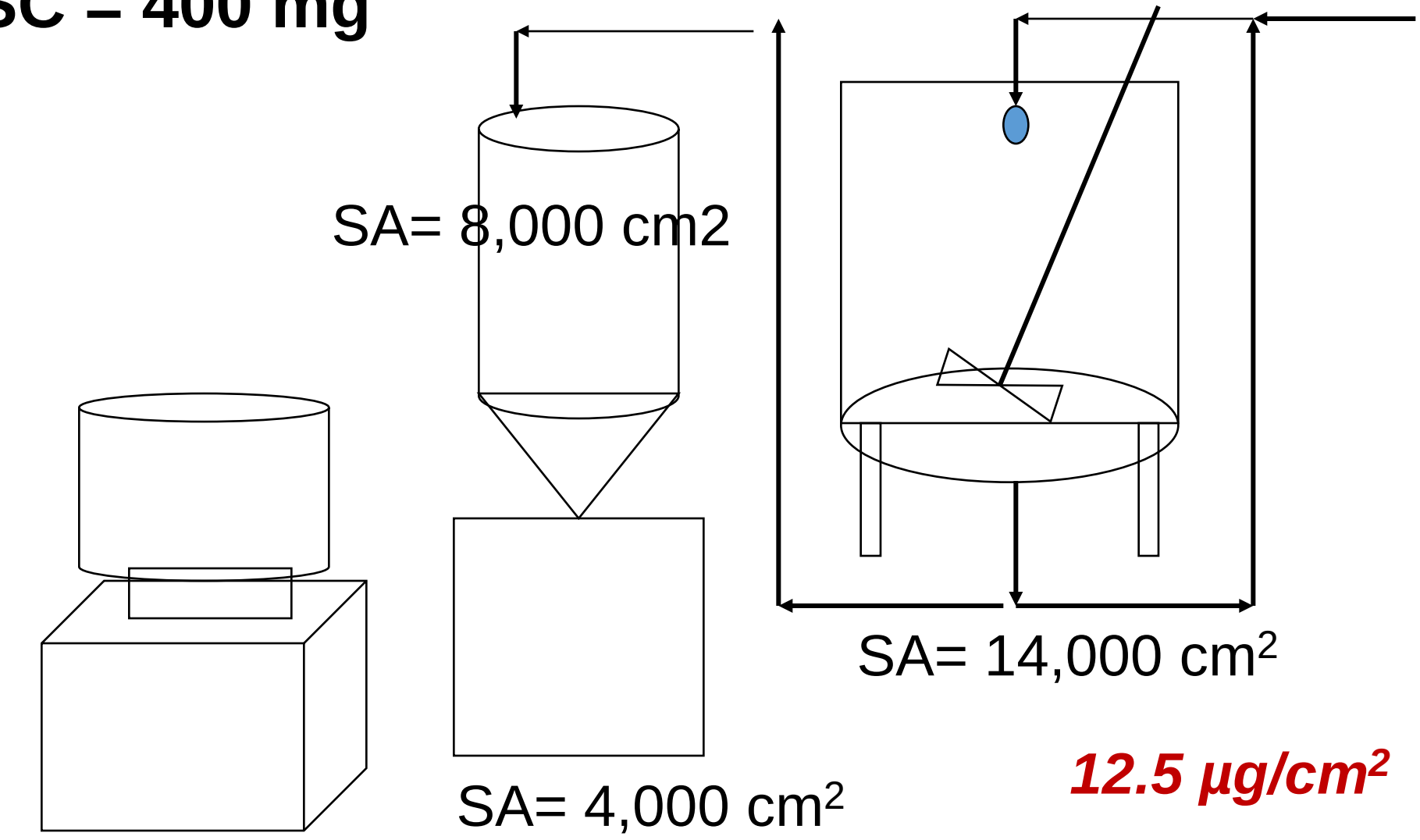




Simple Process

SA= 14,000 cm2

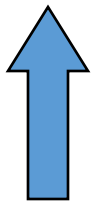
L2 MSC = 400 mg



12.5 µg/cm²

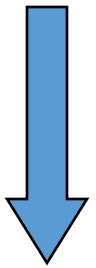
32,000 cm2; Surface limit = ??

- Surface Contamination Limit = MSC_{total}/SSA
- What surface area is used??
  - All surface area for all equipment?
  - Only direct product contact?
  - Only equipment in contact with API?



surface area

surface residue limit



Lilly Case: Multiple Products?Multiple Equipment?
Residue/Equipment Matrix

- Limits for *Multiple* Oral Solids in shared equipment train
  - ***surface area in common***
- Limits based on multiple criteria
  - Dose Criteria (1/1000 dose A> dose
  - Purity criteria (10ppm A>B)
  - Visual (100 mcg/4 sq.in.)

PharmaceuticalTechnology, 17(4),54-60 (1993)

Lilly Case: Multiple Products?Multiple Equipment?
Residue/Equipment Matrix

	Screen	Mill	Blender	Press	Coater
	2000 in^2	1000 in^2	3000 in^2	1500 in^2	2000 in^2
A	X		X	X	
B		X	X	X	
C	X		X	X	X
D			X	X	
E		X	X	X	

Lilly Case: Dose A>B: (0.001)I/J x K/L x M
10 ppm A>B: 10 x S/L x M

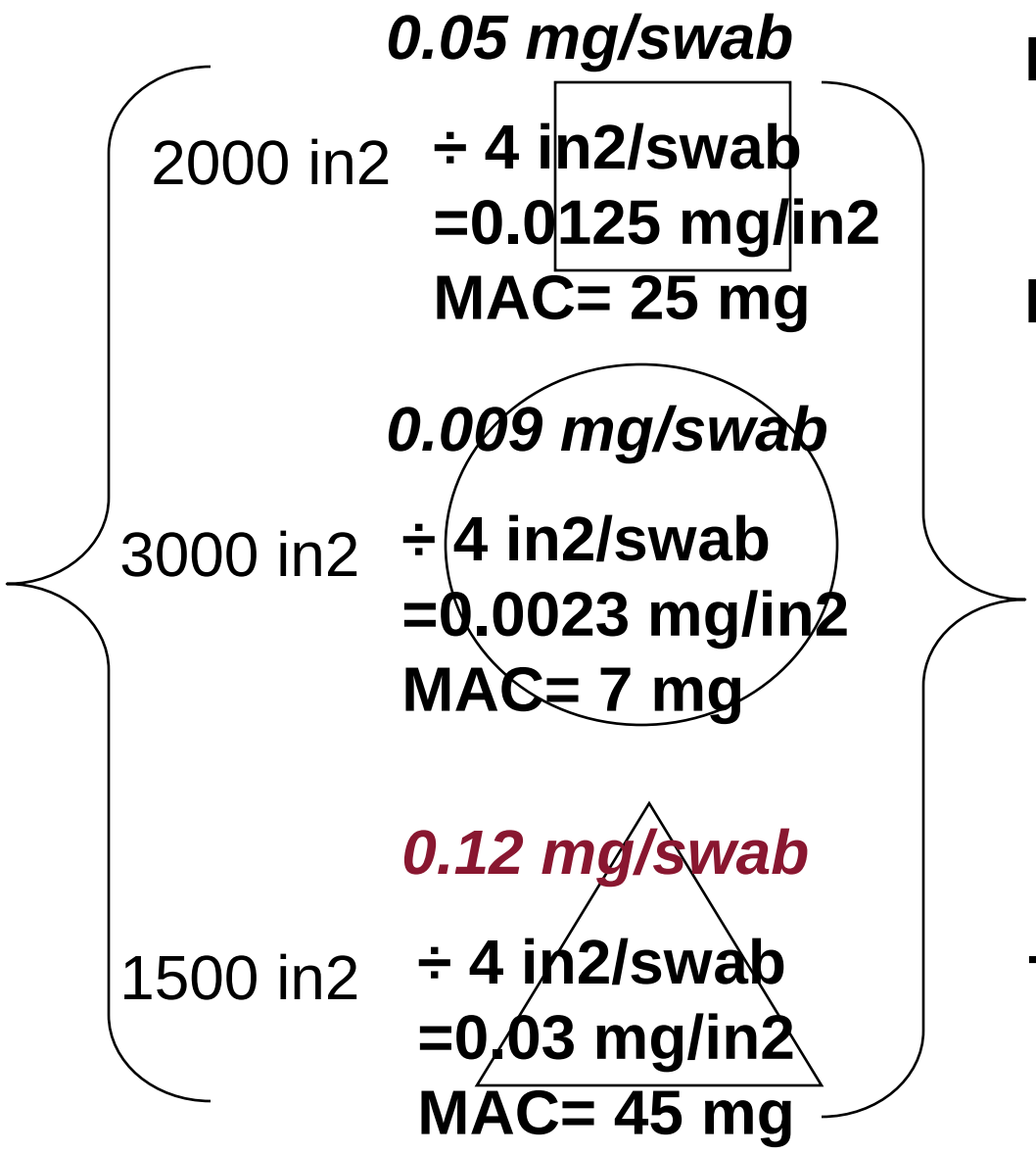
I = dose strength A; J= doses/day B
K=Batch size B (dose units); S= kg /batch B
L= common surface area (in2);
M= sample area (in2/swab)

ADE mcg/day	A J=1 K=40000 S=16 kg		B J=6 K=65000 S=13 kg		C J=3 K=90000 S=36 kg		D J=4 K=30000 S=15 kg		E J=8 K=35000 S=26 kg	
A			4500	0.481	6500	0.923	4500	0.333	4500	0.194
50 mg/day				0.116		0.222		0.133		0.231
B	4500	0.533			4500	0.400	4500	0.100	5500	0.048
15		0.142				0.320		0.133		0.189
C	6500	0.369	4500	0.144			4500	0.100	4500	0.058
15		0.098		0.116				0.133		0.231
D	4500	7.111	4500	1.926	4500	5.333			4500	0.778
200		0.142		0.116		0.320				0.231
E	4500	35.556	5500	7.879	4500	26.667	4500	6.667		
1000		0.142		0.095		0.320		0.133		

Common Industry Practice: “Worst-case” x “worst-case”

- One worst-case surface limit for all products
- *One surface residue limit for all equipment, all surfaces*
- One worst-case sample acceptance criteria for all samples
- One residue acceptance level for all products in a common cleaning SOP grouping

C followed by A, ARL= 0.098 mg/swab



6500 in2

L3= 0.098 mg/swab ÷4 in2/swab

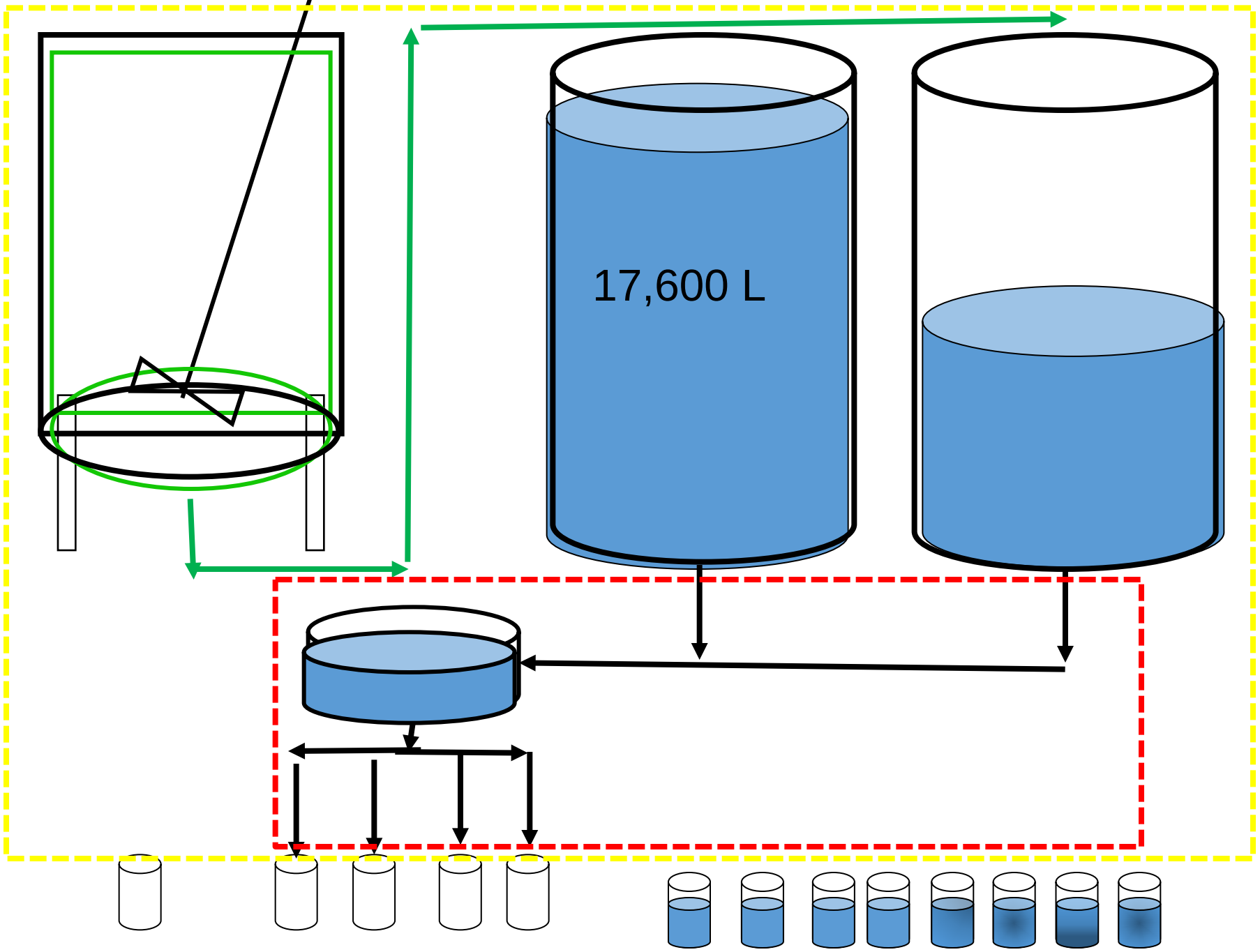
= 0.0245 mg/in2

L2(MAC)= 6500*0.0245 =159 mg

Total Actual CO= 77 mg

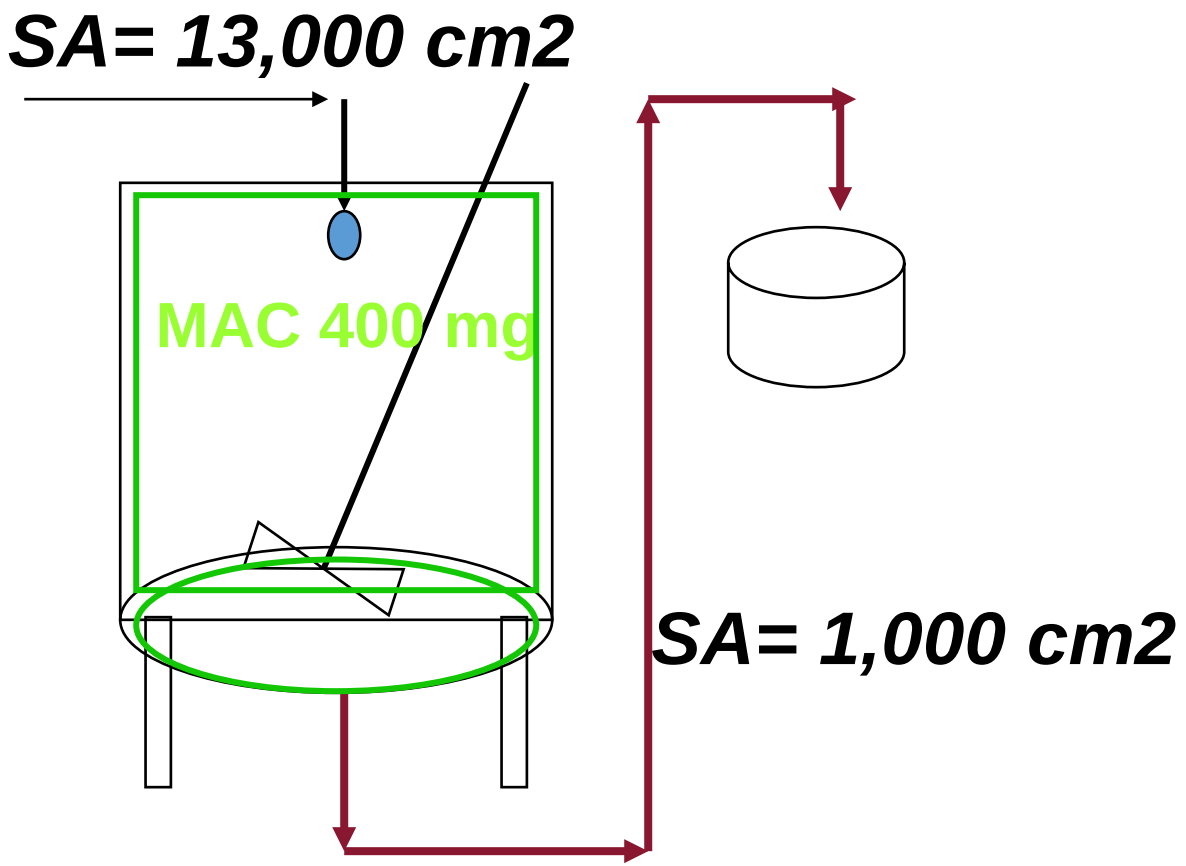
Caution!

- L3 ARL(MSSR) calculations assume Drug A residue is dispersed uniformly into Batch B. Assumptions on concentration and transfer must be made when calculating sample acceptance criteria


17,600 L

All Surfaces are NOT the same! Critical surface

	SA	µg/cm²	MAC
Tank	13000	29	371
Transfer Line	1000	29 ?	29 ?
Total	14000	29	400



To meet 10 ppm criteria, 29 mg /(10mg/kg)= 2.9 kg

Could 29 mg extract off in less than 2.9 kg?

Policy: Are firms required to use “Worst Case”?... that does not exist?

	“Z” J=8 K=30000 S=13
A ADE 15 µg/day	**8500 0.026** **0.061**

- Most Potent
- Followed by most Dose Uptake
- Smallest Batch
  - Dose units
  - Kg
- Largest surface area

Dose A>B: (0.001)I/J x K/L x M

10 ppm A>B: 10 x S/L x M

Risk-Based Surface Residue Acceptance Levels-
A pragmatic approach

- Whenever it fits the situation and is practical, achievable and verifiable, we will use accepted industry approach to setting surface residue limits including ADE, ARL, VRL…
- However, there will be exceptions and variations including different surface or sample criteria for different equipment, different criteria for different sample locations,…..

A pragmatic approach to residue acceptance critera

- In all cases, residue levels will be based on a thorough risk assessment that assures potential residue carryover will not adversely affect the user of the product or affect product quality.
- Use ADE, LOD, ARL/MSSC as reference points.
- ***Actual process capability ultimately determines process acceptance criteria for cleaning validation***