Are We Setting Limits Correctly?

Webinar
August 19, 2008

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Agenda

- Background for ISPE efforts
- How limits currently set
- Objections to current methods
  - With critique
- Proposal for new methods
  - With critique
- Going forward

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What is RiskMaPP

- Risk Management for Pharmaceutical Production
- Containment "Community of Practice" in ISPE
- Major focus is restriction of "highly potent" or specific compounds or classes to dedicated equipment or area
  - Examples are beta-lactams and hormones
- Will produce ISPE Baseline Guide - RiskMaPP, with "science-based and risk based approach, based on ICH Q9, for setting health-based cross-contamination limits, cleaning validation limits, and operator exposure limits"

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Cleaning Baseline Guide

- Different document and team
- Major focus is cleaning limits, design of cleaning processes, analytical strategies, process control (including PAT)
- Will produce ISPE Baseline Guide - Cleaning, with "science-based and risk based approach, based on ICH Q9, for setting health based cleaning validation limits, for development of cleaning procedures, and guidance on implementing PAT for cleaning"
  - Draft of outline (one page) on ISPE web site

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Documents

- July 2007 Draft of ISPE Baseline Guide: Cleaning
- September 2007 Draft of ISPE Baseline Guide - Volume 10: Risk-MaPP
- Presentations by Andy Walsh at ISPE meeting in June 2008
  - I believe these are Walsh's presentations, and not formal documents of ISPE group
  - However, what said in these presentations is reflective of what in two ISPE documents

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RiskMaPP team members

- 20 scientists reflecting various disciplines
  - 4 Toxicologist
  - 2 QA
  - 4 EH&S
  - 2 Cleaning Validation
  - 8 Engineering/Operations
- Geographic distribution
  - 11 USA
  - 6 Europe
  - 3 Japan
- Includes FDA representation

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Cleaning guide team members

- 16 scientists reflecting various disciplines
  - API
  - CIP
  - Development
  - Biotech
  - Visual clean
  - Clinical
  - CIP/PAT
  - Statistics
  - Toxicology
  - Pharma
  - Methods
- Includes FDA representation

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Major issues for limits

- In 2 drafts and in June ISPE conference, it is stated that current methods of setting limits are:
  - Not science based
  - Not risk based
  - Arbitrary

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Current methods of setting limits

- General approach
- Dose based
- Toxicity based
- Defaults
- Additional factors

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Possible uses of "limit"

- Concentration in subsequent product (µg/mL) – L1
  - This is the limit calculation challenged
- Absolute amount in manufacturing vessel train (mg) [MAC – maximum allowable carryover] – L2
- Amount per surface area (µg/cm^2) – L3
- Amount per analytical sample (µg) – L4
- Concentration "rinse" water (µg/mL) –L4

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L1 for finished drugs

- Fourman and Mullen approach for active
  - Most stringent of dose calculation and 10 ppm (in next product)
    AND
  - Visually clean

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PIC/S limits

- PIC/S approach
  - Most stringent of...
    - Dose calculation in next product
    - 10 ppm in next product
    - Visually clean

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In subsequent product – L1

- Concentration which results in no more than 0.001 minimum dose of active in maximum dose of subsequent product

  or

- 10 ppm in subsequent product

  WHICHEVER IS LOWER!

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Why 10 ppm?

- 10 ppm in L1 applies to L1 only
- If calculated limit is higher, lower limit to level that should be "reasonably avoidable" (see Human Drug CGMP Note of 2nd Quarter 2001)
  - Limits should be reasonably achievable
  - Medically safe
  - Not affect product quality

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Other default limits?

- Some companies choose a default limit not for L1 value, but a default limit for L3 value
  - Same rationale, to prevent situations with grossly high limits
- Default for L3 typically 4 mcg/cm^2
- Based on typical value where residue should be readily visible (meaning if above that value will fail visual test)
  - Note that still may fail visual examination at 4 mcg/cm^2 or below

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Overall equation for L4

$$\frac{(0.001)(\text{min.dose act.A})\ (\text{B.S.})\ (\text{S.A.})}{(\text{max.dose Prod.B})\ (\text{S.S.A.})\ (\text{S.D.A.})}$$

For swab sample, where:

B.S. = minimum batch size Prod.B

S.A. = sampled area

S.S.A. = shared surface area

S.D.A. = solvent desorption amount

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"Non-dose" modifiers

- Effects of actives other than therapeutic effects
  - Cytotoxicity
  - Allergenicity
  - Reproductive hazards
- May require dedicated equipment, or may set limits as not detectable by best available technique
  - Confirm non-detectable value is appropriate
- Interaction of drug actives (A and B)

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Limits based on LD_{50}

Used for detergents

$$\text{ADI} = \frac{LD_{50} \text{ X body weight}}{\text{(conversion factor)}}$$

$$\text{L1 (ppm)} = \frac{\text{ADI of chemical X } 10^6}{\text{max. dose of next product}}$$

Notes: Conversion factors like 5 X 10^4 are not appropriate; should be 10^5 to 10^6

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Two approaches

- LD_{50} converted to NOEL, then NOEL to ADI
  - Once "conversion" factor and one "safety" factor
- LD_{50} converted directly to ADI
  - One conversion factor

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Conversion factor references

D L Conine, B D Naumann, and L H Hecker, Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices, *Quality Assurance: Good Practice, Regulation, and Law*, Vol. 1, No. 3, pp. 171-180 (1992).

H J Kramer, W A van den Ham, W Slob, and M N Pieters, Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short-Term Toxicity Data, *Regulatory Toxicology and Pharmacology*, vol. 23, pp 249-255 (1996).

D.B. Layton, B J Mallon, D H Rosenblatt and M J Small, Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data, *Regulatory Toxicology and Pharmacology*, Vol. 7, pp. 96-112 (1987).

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Toxicity calculations

- Most companies use a dose calculation if a dose is available
- Only use a toxicity calculation if a dose is not available
  - Cleaning agents
  - Degradants or by-products
  - Intermediates (in API manufacture)
- Some companies will use the lower of a dose calculation and a toxicity calculation if both are available

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Summary of current status

- Dose-based calculation
- Default value
- Toxicity calculation if no dose
- Other "non-dose" concerns (cytotoxicity, allergenicity, reproductive hazards, etc.)

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First Presentation

- "Cleaning Validation Acceptance Limits – Past, Present and Future", Andy Walsh, Clean6Sigma LLC, presented at ISPE conference on Engineering Regulatory Compliance, 2-5 June 2008, Arlington, VA.

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Pre-1993 Limits

- 1992 PMA survey
- 44 approaches
- Inconsistent from company to company
  - Probably true
- Arbitrary
  - On what basis say they are arbitrary without seeing rationale or justification
  - Just because different, does that make them arbitrary

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Lilly approach and variants

- Fourman and Mullen paper
- PDA Technical Report No. 29
- PIC/S 2001
- CEFIC/APIC 2000
- TPP 2000 CV Guidelines
- Note: Also referenced in FDA document.

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2006 PDA Survey

- Types of limits
  - Dose only 49%
  - Dose & default 22%
  - Dose, default & visual 45
  - Default 4%
  - Process capability 10%
  - LOD 6%
  - Other 16%
- Note total is more than 100%

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2006 PDA Survey (2)

- Dose "Safety Factor"
  - 0.01 13%
  - 0.001 85%
  - 0.0005 2%
  - 0.0001 6%
- Defaults
  - 10 ppm 89%
  - 1 ppm 6%
  - <15 ppm 6%
  - <1 ppm 3%

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2008 Status

- Claim made that limits are *still*:
  - Inconsistent
  - Arbitrary (10 ppm)
  - Not science-based or risk-based

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Inconsistent?

- 85% used 0.001 factor & 89% used 10 ppm as default
  - This is amazing consistency for industry
- But consistency is not point. In a risk-based and science-based program, companies may set limit differently based on their situations
  - Example: Vaccine dosed once, antibiotic dosed for limited time (week), cholesterol drug dosed for lifetime

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Arbitrary?

- If issue is limited to 10 ppm, the majority of companies set limits using default of 10 ppm only if default is below dose based limit
- In one sense is arbitrary (default could be different as long as it is below safety calculation)
  - Addresses reasonable avoidance

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Arbitrary? (2)

- Does arbitrary refers to safety factor? (unclear from presentation)
- However, it *is* arbitrary in that most people use 0.001 and not 0.0011 or 0.0009
- Safety factors by their nature are a consensus
  - Why 10^{-6} as SAL for sterilization?
  - Why 3 log reduction for endotoxin reduction in washing vials?

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Not science & risk based?

- I think there is reasonable science behind 0.001 of dose being safe level.
  - May be overkill, but generally is safe (with exception of non-dose issues)
- Default level is based on practicality
- Basis of risk is adjusting the program to a specific situation
  - Not surprising that all companies use different details in their approaches
  - But fundamental approach is the same

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Other problems?

- Limits may be impossible to meet
- Question whether this is based on analytical method or cleaning process
- Just because you can't measure, does this mean the limit should be set higher
- Also, consider deactivation or degradation as option in cleaning
- Note that proposed replacement will raise some limits and lower others, leaving this objection moot

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"Safety Margin"

- Example
  - Limit is 1 ppm
    - Data is 0.32, 0.61, .79 and 0.89
    - Mean = 0.65, 2σ = 0.43, mean + 2σ = 1.1
  - Limit is 10 ppm
    - Same data
    - Mean = 0.65, 3σ = 0.43, mean + 3σ = 1.3
  - "Margin of safety" is distance between actual data and acceptance limit
- For same product manufactured, in first case is there less of a "margin of safety" (meaning *patient* safety)?

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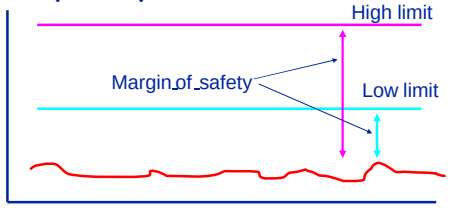
"Safety Margin" (2)

- Graphical presentation



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"Safety margin" (3)

- Question: Is safety "to patient" as claimed by Walsh really different just because I changed my limits?
- Risk is based on what is there (absolute amount), not on difference.
- "Safety margin" *for manufacturer* in achieving validation is different
  - More likely to pass with higher limit

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"Safety margin" (4)

- Question to consider
  - If limits are set higher, will manufacturers continue to clean to same levels, or will cleaning suffer (and actual values go up)
- Clarification: Manufacturers generally want to be significantly below the established limit.
  - If limit is 1 ppm, I would not design a cleaning process to produce data at 0.65 ppm; I would try for data below 0.3 ppm
  - If limit is changed to 10 ppm, then data at 3 ppm might be seen as acceptable

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"Safety margin" (5)

- Claim is made that cleaning better (lower actual data) increases safety margin
  - True either by Walsh definition or by a science-based approach
- Claim made that 10 ppm default reduces "margin of safety"
  - By Walsh definition is true
  - But with same data, does not change patient risk
  - And, may allow higher actual data, thus posing higher risk to patient

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"Safety margin" (6)

- Need to be careful in use of term like safety margin
- If limit is X ppm (whatever criteria), is there a difference in safety between
  - Data of 0.3X ppm
  - Data of 0.1X ppm
- If limit properly justified and controlled, both have an insignificant risk to patient

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Default values

- Claim is made that use of default values makes concern similar for low potency and high potency drugs
  - High potency: Dose limit = 9 ppm, that limit is used
  - Low potency: Dose limit is 1000 ppm, use default of 10 ppm
  - With same data of 3.2, 6.1, 7.9 and 8.9 ppm, why is concern the same?
- That claim is valid, but why is allowing 1000 ppm (0.1%) of an active in another drug product acceptable
  - Would also expect at 1000 ppm for equipment to visually dirty

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Implementation

- Calculation confusing and time consuming
  - Training and education is solution
  - Approach suggested by Walsh could be just as confusing and time consuming
- Limits cannot be met
  - Already addressed – dedicate or improve cleaning

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Topical

- Questions why topical treated the same as injectables
- Walsh slide gives PDA TR 29 ranges for safety factors:
  - Topical being 0.1-0.01
  - Injectables being 0.001 – 0.0001

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Topicals (2)

- PDA TR is "points to consider"
- I am not aware of any topical manufacturer who sets limits at 0.1 of a dose
- His example of a topical leaving a gross amount behind (using 0.1 of a dose) is a perfect illustration of why default values are used
- Cannot criticize setting limits by considering each element in isolation

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Teratogens/sensitizers

- How dose calculation takes these into consideration?
- I agree here. This is something that "trumps" the dose based calculation, but is done on a case by case basis (and is currently being done)

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Teratogen data

- Data presented

Active	0.001 dose	lowest teratogen dose
Difenoxin HCl	0.001 mg	<61 times lowest dose
Coumadin	0.001 mg	4 mg/kg
Diethystilbestrol	0.001 mg	0.4 mg/kg
Ribavirin	0.6 mg	0.12 to 0.14 mg/kg

- Assuming 60 kg adult, in all cases 0.001 dose is below lowest teratogen dose
- Assuming 60 kg adult, in all cases except Ribavrin, 0.001 dose is below 0.01 X lowest teratogen dose
- Unclear about the significance of this data for illustration (if teratogen effects were below 0.001 dose, then would certainly have concerns)

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Reflect back

- If a holistic view is taken of how we currently set limits, it is reasonable to assert that they are:
  - Science based (in their principles)
  - Risk based (in their implementation)
  - Not arbitrary (in that they are not just picked out of the air)
- Can they be implemented more consistently? YES
- Can they be achieved? YES, in most cases
- Can they be improved? YES

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ADI approach

- "ADI" is daily dose "below which no adverse effects are anticipated"
- Most clinically significant health effect helps define the NOEL/NOAEL or LOEL/LOAEL
- Use "safety factor(s)" to account for "sources of uncertainty"

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ADI approach (2)

- Health effects include (but not limited to):
  - Pharmacology
  - Acute toxicity
  - Sensitization
  - Subchronic/chronic toxicity
  - Reproductive toxicity
  - Mutagenicity /Genotoxicity/ Carcinogenicity

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ADI approach (3)

- Uncertainty factor
  - Individual variability
  - Interspecies extrapolation
  - LOAEL to NOAEL extrapolation
  - Subchronic to chronic extrapolation
  - Route extrapolation
  - Database quality and completeness
  - Modifying factor "used for Additional Uncertainties"

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ADI approach (4)

- ADI = $\frac{\text{NOAEL X BW}}{UF_c \text{ X MF}}$
- Where
  - ADI is in mg/day
  - NOAEL is in mg/kg/day
  - BW is body weight in kg
  - UF_c is uncertainty Factor(s)
  - MF is Modifying Factor

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ADI approach (5)

- In MAC calculations, ADI replaces 0.001 of a dose
- Once calculate L1 value using ADI, other calculations (L2, L3,L4) are exactly the same as before

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ADI approach (6)

- LeBlanc critique
- ADI approach is perfectly acceptable, and is consistent with what currently should be done
- However, it is subject to the same issues that that are advanced against current approach
  - Is complex and difficult to implement to same extent dose calculation is
  - What "uncertainty factor" and modifying factors" will be used
    - Not one set of factors applies to all

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ADI approach (7)

- LeBlanc critique
- Without default value (either L1 or L3), will not prevent situations in which gross contamination is allowed (and that default value will always be subject to being called arbitrary)

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ADI approach (8)

- LeBlanc critique
- In "Using 6 Sigma…" presentation, Walsh presents an example of an NSAID with a daily dose of 80 mg having an ADI of 40 mg (Is pharmacologic effect an adverse effect?).
- It would seem *unacceptable* to have 40 mg per day of that NSAID active in a drug product (50% of dose).
  - Would have to apply a dose criterion (or default) to bring it to an acceptable level

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ADI approach (9)

- LeBlanc critique
- Factors to use?
- ICH Q3C uses five factors to evaluate in considering PDE (permitted daily exposure) of residual solvents in drug products
  - F1 = between species
  - F2 = variability among individuals
  - F3 = accounts for short term studies
  - F4 = cases of severe toxicity
  - F5 = factor for when LOEL used

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ADI approach (10)

- LeBlanc critique
- 0.001 dose calculation, with separate consideration of cytotoxics, genotoxic, reproductive hazards, allergenics, etc. still seems to be a reasonable, implementable approach for commercial manufacture, if implemented correctly
- Use of ADI approach is possible, if implemented correctly
- ADI approach certainly appropriate where there is no dose

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TTC approach

- "Thresholds of Toxicological Concern"
- "Safe value" for any chemical species
- Reference

  Dolan, D. G. et al. "Application Of The Threshold Of Toxicological Concern Concept to Pharmaceutical Manufacturing Operations", *Regulatory Toxicology and Pharmacology* 43, 1-9 (2005).
  - Carcinogens: safe at 1 mcg/day
  - Likely to be potent: safe at 10 mcg/day
  - Others: Safe at 100 mcg/day

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TTC approach (2)

- Critiqued by LeBlanc
- Reference
  - LeBlanc, D.A. "Applicability of the 'Threshold of Toxicological Concern' Concept to Residue Limits for Cleaning Validation", American Pharmaceutical Review, Vol 5:1, pp 93-97 (Jan-Feb 2008).
- Concerns: Probably more conservative than ADI toxicity calculation, but significantly above dose limit

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TTC approach (3)

- Example of simvastatin (not carcinogenic and not highly potent or toxic) for L1
  - Dose-based limit: 14 ppm
  - TTC-based limit: 286 ppm
  - Toxicity based limit: 651 ppm
- Something doesn't compute, and I am not convinced that it is the dose-based limit that is wrong
- Note that all three above default limit of 10 ppm

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SPC Approach

- Walsh summary slide refers to "Statistically based Risk Assessment of cleaning data (Cpk/Ppk)" and to "Acceptance Limits based on Statistical Process Control (SPC)"
- These concepts are discussed in the next presentation, "Using 6 Sigma / FMEA Approaches for Determining Cleaning Validation Requirements", by Andy Walsh of Clean6Sigma, presented at presented at ISPE conference on Engineering Regulatory Compliance, 2-5 June 2008, Arlington, VA.

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Overall Approach

- Presents case of multiproduct facility
- Approach is
  - Define: cleaning problem
  - Measure: TOC database
  - Analyze: statistically, FMEA
  - Improve: optimize, post-FMEA
  - Control: continuous verification/PAT

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Statistical approach?

- Purpose of statistical analysis?
- Setting limits?
  - Question is asked but not answered in slides
- Determination of process control?
  - Yes, if used correctly

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For limits for CV?

- Generally are not appropriate
  - Example: mean + 3σ
- SPC only tells you if operating consistently
- Does not tell that data is at safe level
- Could have *well controlled* process at levels 10 times any safety limit (based on dose or ADI)
- Other issue is whether I will have enough data at beginning of a new product to analyze statistically and set limits

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For process control?

- Statistical analysis may be used
- I prefer not to refer to the control range as limits
  - Exceeding limit suggests failure
- I prefer to call them alert levels
- Analogy to cleanroom action/alert levels
  - Exceeding level may not be a safety failure
  - Exceeding level suggests possibility of loss of control
  - Exceeding level requires investigation

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Statistics for swabs?

- Example given involves swabbing equipment
- Is it appropriate to average or analyze swab data from different locations?
- Averaging or analysis is usually done based on same population
- Example: I take water sample from my WFI loop daily – makes sense to look at averages and treat them by statistical analysis

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Statistics for swabs? (2)

- If I sample under the agitator blade (a worst case) and a sidewall location (not at the air/liquid interface), are those the same population?
- They are data points in my cleaning validation
- But rationale for treating by statistical analysis is problematic

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Statistics for swabs? (3)

- Possible approach
- Do SPC for *equivalent* locations, such as swab sampling under agitator blade only
- Issue is collecting adequate data for SPC analysis
- If need >20 data points, will I collect swab data under the agitator blade for 20 runs, and *then* set limits
- More likely to do it for 3 runs (validation) and then perform only rinse water sampling for routine monitoring
  - Could eventually do SPC on rinse water sampling with enough runs

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Statistics for swabs? (4)

- Can use TOC and analyze data over several different products?
- Even more problematic
- In what sense is statistically analyzing samples from different cleaned products justified, even though cleaning process and swab locations are same
  - Only possible reason is to demonstrate equivalence, but cannot assume equivalence upfront
- Walsh suggests that TOC database be developed by facility, by area, by cleaning process and by equipment (?)

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"Level of risk"

- Walsh presents case of equipment train, and compares actual data against "USL" (which is limit based on ADI) to determine "Margin of safety"
- In example presented, an ADI amount is allowable *in each individual equipment item* in the train
  - Limits much higher for lower surface area items – therefore margin of safety is greater
  - Conclusion is that certain equipment items (like utensils) are lower risk
  - But, for train with 4 items allows 4 X ADI value in next product
- Be careful with this example!

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Bulk biotech limits

- Interestingly, area where argument can best be made about limits not being science-based is bulk biotech
- Not mentioned in ISPE documents and Walsh presentations at all
- Note that manufacturers are starting to address issues:
  - Degradation studies
  - Clearance studies
  - Safety limits based on actual residues (degraded actives)

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Going forward

- Always valuable to evaluate what we are doing
- Not necessary or appropriate to trash what we have done
- ADI approach can be valuable if approach is modified
- 0.001 dose is (in a way) a determination of an acceptable daily amount

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Going forward (2)

- In ADI determination, include
  - Dose calculation
  - NOEL or NOAEL (includes cytotoxicity, etc.) or LD_{50} calculation
- Also include a default value, such as L1 = 10 ppm or L3 = 4 mcg/cm^2
- Include equipment is visually clean
- Avoid term "ADI" – pick something unique (without food connotations)

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Going forward (3)

- Develop database of limits on well established actives with non-dose effects comparing
  - 0.001 dose
  - TTC
  - ADI (based on NOEL or LD50)
- Perhaps do the same with cytotoxics, allergenics, etc.
- With L1 and L3 limits, this would paint a picture of what we are doing in changing the way we set limits

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Going forward (4)

- In RiskMaPP document, consider separating out issue of restriction of hazardous compounds from *changing* cleaning validation limits
- Make sure RiskMaPP and Cleaning Guide are consistent
  - Are related, but not absolutely joined together

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Q&A

- Questions
- Answers
- Your opinions

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Thank you for attending the webinar "Are We Setting Limits Correctly?"

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