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ADE’s and Their Importance

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Agenda

- What is an ADE and why are they important?
- How determined
  - NOAEL vs. LD50 vs. MSDS vs. OEL
  - Safety Factors, Uncertainty Factors, Modifying Factors
  - Contra-indications and Subpopulations
  - Adjustments to ADEs for route of administration
  - Significant digits
- How does the non-toxicologist use this information?

An ADE is:

Acceptable Daily Exposure (ADE):

A daily dose of a substance below which no adverse effects are expected by any route, even if exposure occurs for a lifetime. This value is set by toxicologist based on clinical and other in use data and is used to assess the risk of cross contamination.

EMA's PDE

- EMA's latest draft guidance for setting health-based limits uses the terms PDE or threshold value. These are defined as:

  A substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Why are ADEs important?

- ADEs provide a safe limit that can be used to assess the risk to the patient in the event of cross contamination
- ADEs are used to develop cleaning limits and to assess the risk from airborne and mechanical transfer
- By definition, ADEs are very conservative

How are ADEs determined?

Based on clinical studies, literature, etc. toxicologists determine the ADE using the following formula

$$ADE = \frac{NOAEL\ (mg/kg/day) * BW\ (kg)}{UFc * MF * PK}$$

Where:

NOAEL is No Observed Adverse Effect Level

BW is the body weight

UFc is the composite uncertainty factor

MF is the modifying factor

PK is the pharmacokinetic adjustment

} These terms may be expressed in a variety of ways

How are PDEs determined?

Based on clinical studies, literature, etc. toxicologists determine the PDE using the following formula

$$PDE = \frac{NOAEL\ (mg/kg/day) * BW\ (kg)}{F1 * F2 * F3 * F4 * F5 * PK}$$

Where:

NOAEL is No Observed Adverse Effect Level

BW is the body weight

F1 – F5 Adjustment factors as defined in ICH Q3C

PK is the pharmacokinetic adjustment

What is a NOAEL?

The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

From Wikipedia and the US EPA website

Factors – Safety, Uncertainty, Modifying

- Uses science-based adjustment factors to address areas of uncertainty
  - Interspecies Differences
  - LOAEL to NOAEL extrapolation
  - Modifying Factor- to address residual uncertainties – professional judgement

Adjustments to ADEs for Route of Administration

- Adjustments to the ADE can be made if the route of administration of the study data is of a different route than the products being assessed (study done with intravenous products and manufacturing is for OSD).
- Note FDA expressed that it is preferred that the study data route match the route for the assessed product if possible.

Contra-Indications and Subpopulations

ADE monographs should clearly state the subpopulations reviewed and addressed as well as any contra-indications that exist.

What Does LD50 Mean?

- Lethal Dose for 50% of the Population (LD50)

  represents the dose where 50% of the test population (rats, mice, dogs, etc.) experience death. This value can vary with the species of test population.

- Adverse effects would be expected long before death.
- Note animal toxicity studies do not necessarily extrapolate to humans

Which LD50?

Acute and Local Toxicity – LD_{50} values of 200, 200, 500 and 150 mg/kg were determined in the guinea pig model following intramuscular, intraperitoneal, oral and subcutaneous routes of administration, respectively.

LD_{50} values of 420, 180, 1450 and 225 mg/kg were determined in the mouse model following intraperitoneal, intravenous, oral and subcutaneous routes of administration, respectively.

LD_{50} values of 500 1000 and 300 mg/kg were determined in the rat model following intraperitoneal, oral and subcutaneous routes of administration, respectively.

In the rabbit model LD_{50} values of 350 and 500 mg/kg were determined following oral and subcutaneous administration, respectively.

How Are MSDS' Created?

- Material Safety Data Sheets (MSDS) have a suggested standardized format but the input to the MSDS' vary widely even for the same material.
- The purpose of the MSDS is to alert workers and emergency personnel with proper handling techniques and procedures.

How are these values used?

Patient Protection - ADE

- Mcg/day
- Cleaning limits
- Compare to amount of one product in another product

Operator Protection - OEL

- Mcg/m^3/8 hours
- Air monitoring/ wipe samples
- Compare to emission from systems

OEL or ADE?

Based on same data but…..

- OEL is typically based on the amount of air an operator breathes in an 8 hour shift
- OEL takes into account work force that is basically healthy and of working age
- ADE should be protective of patient population which by definition has some health issue

Tips for understanding ADE Values

- Rule of thumb ADE = 10 x OEL
  - If the ADE is lower than the OEL, ask why
- What route of exposure was used
- Where all subpopulations reviewed
  - For known sensitizers were the sensitized populations included?
- Was there sufficient data to support the value or does the value need periodic review?

Significant Digits

- Do not make the result of the calculation look more exact than it is!
- Just because 1000/900 = 1.111 does not mean the result is 1.111….by the significance of the digits the result is no more exact than 1

How does the non-toxicologist use this?

- Setting limits for cross contamination
  - Cleaning limits
  - Cross contamination
- Setting limits for operator protection
  - OEL
  - Surface limits
- Be an educated consumer!

Thresholds of Toxicological Concern

1) compounds that are likely to be carcinogenic.
(ADE = 1 µg/day)

2) compounds that are likely to be potent or highly toxic. (ADE = 10 µg/day)

3) compounds that are not likely to be potent, highly toxic, or genotoxic. (ADE = 100 ug/day)

Dolan DG, Naumann BD, Sargent EV, Maier A, Dourson M Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. *Regul. Tox. Pharm.* 43:1-9 (2005)

Regulatory View of ADEs

- Whichever of these criteria resulted in the lowest carryover, constituted the limit applied for cleaning validation. However, these limits do not take account of the available pharmacological and toxicological data and may be too restrictive or not restrictive enough. Hence, a more scientific case by case approach is warranted for all classes of pharmaceutical substances. – EMA
- Check the manner in which limits are established. … The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable. - FDA

How ADEs are used for Cleaning Limits

Use this:

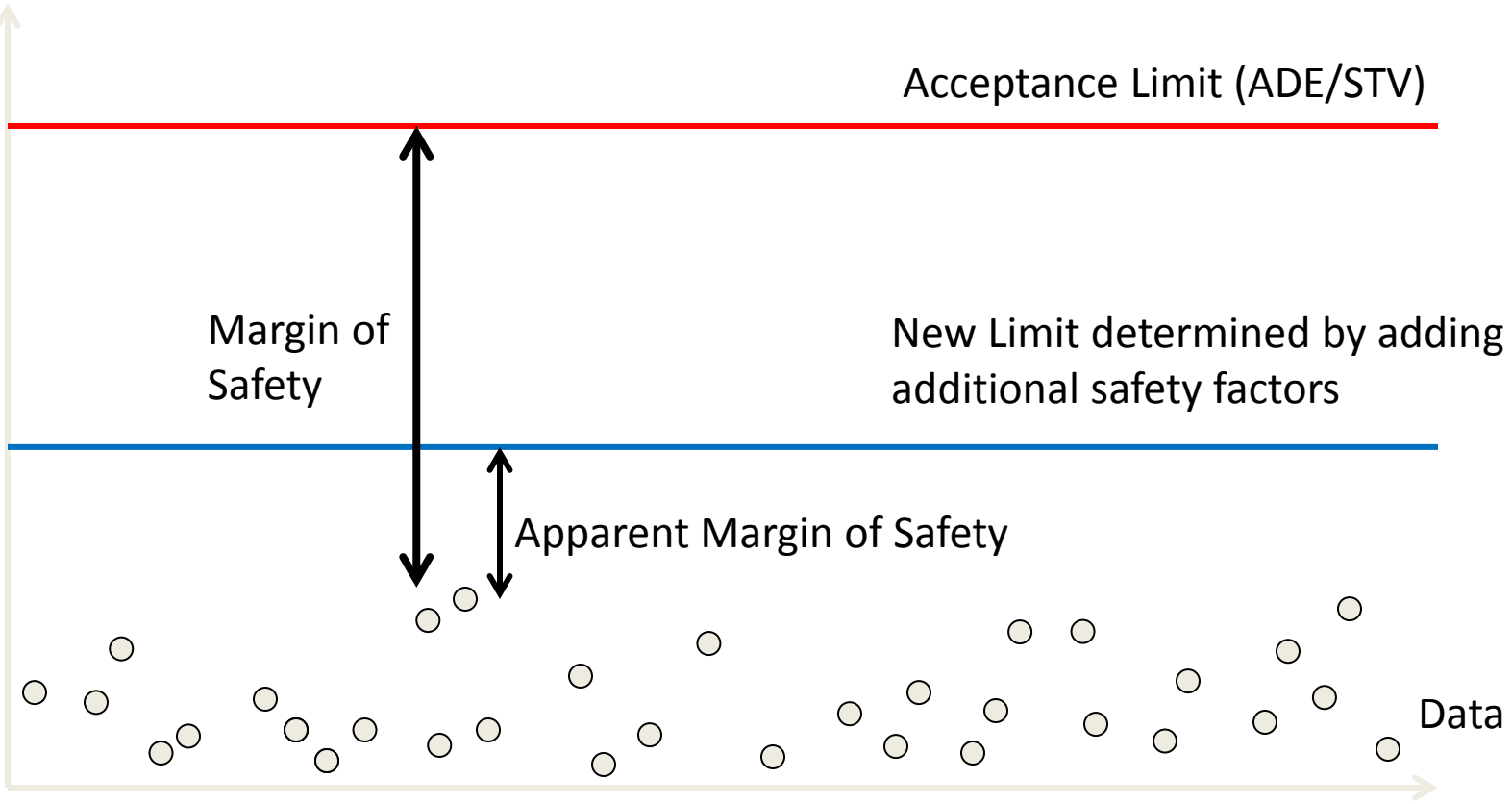
$$\text{Health Based} = \frac{\text{ADE}}{\text{Value}} \times \frac{\text{Batch Size}}{\text{Max Daily Dose}}^{*}$$

Instead of this:

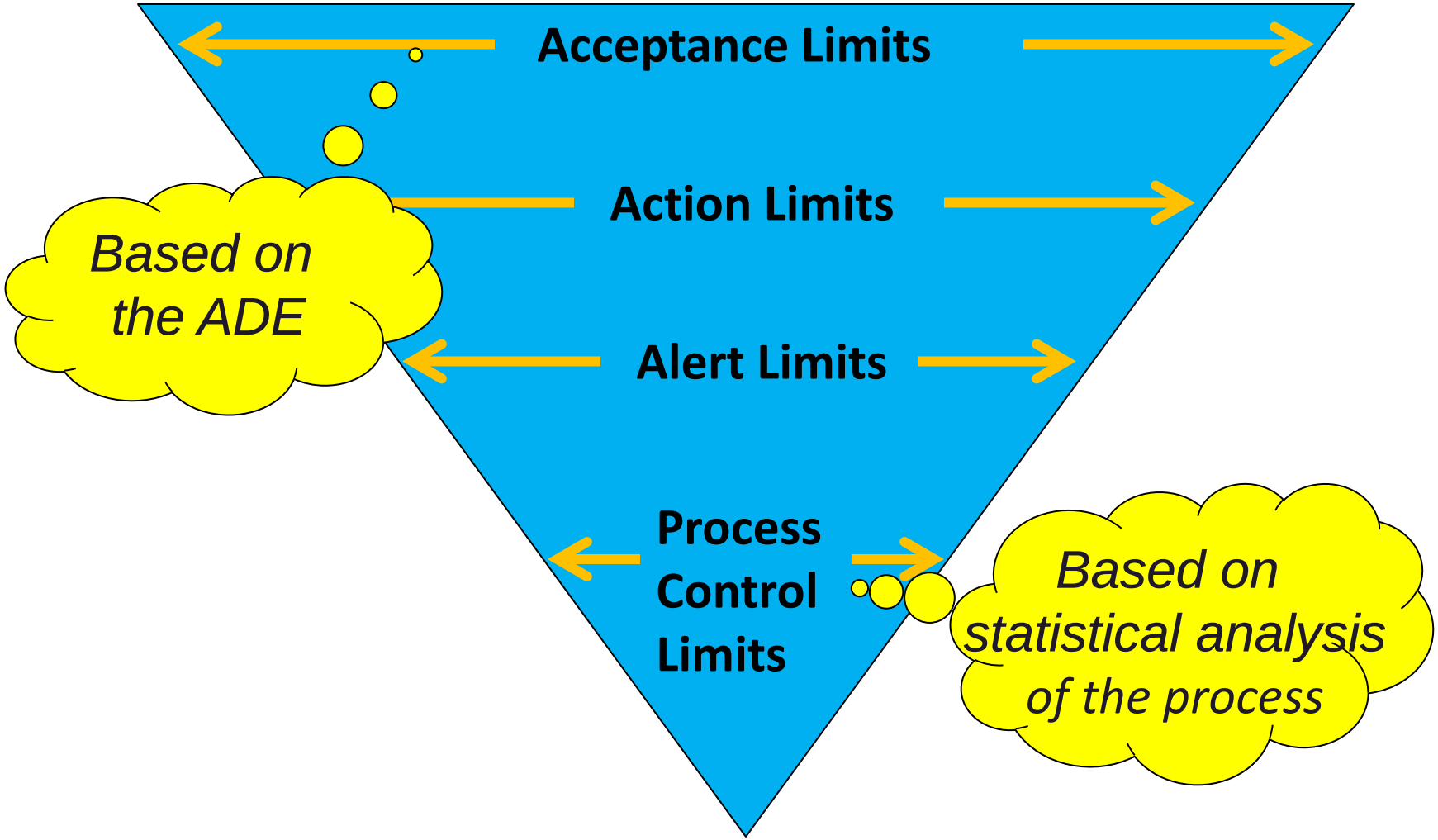
$$\text{Dose Based} = \frac{\text{Lowest Marketed Dose}}{\text{MACO}} \times \frac{\text{Batch Size}}{1000} \Big/ \text{Max Daily Dose}^{*}$$

***Of next product**

What is the effect of adding safety factors?



Hierarchy of Limits



Visual Residue Limits

- Fourman and Mullen determined a visible limit of ~100 µg per 2 X 2-in. swab area or ~4 µg/cm^2 .
- Jenkins and Vanderwielen observed residues as low as 1.0 µg/cm^2 with a light source.
- Forsyth *et al.* determined <0.4- to >10-µg/cm^2 VRLs for active pharmaceutical ingredients (APIs) and excipients.

AC (based on 1/1000th LCD)	AC (based on ADE)
7.9	157.7
0.5	15.8
0.5	15.8
0.4	11.3
0.3	2.8
7.5	15.1
15.7	3497.0
10.5	35.0
5.2	3497.0
0.1	0.5
0.2	5.5
3.3	6.6

- AC = Acceptance Criteria in mcg/cm^2
- Why not go with the lowest value?
- Visual Limit = 1 – 4 mcg/cm^2

How ADEs Are Used to Assess the Risk of Cross Contamination

- Cleaning Limit calculations
- Assess airborne and mechanical transfer potential
- Drug in drug assessment