ISPE’S GUIDES AND HOW THEY APPLY TO CLEANING AND CLEANING VALIDATION

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CLEANING VALIDATION CONFERENCE
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Objectives

> ISPE’s Risk-MaPP Guide and its impact on cleaning
  – What is Risk-MaPP?
  – Health-based limits and cleaning
  – Revision 2 Updates with respect to cleaning

> ISPE’s Cleaning Guide Status
  – Baseline® Guide Status
  – Good Practice Guide Status
HOW RISK-MAPP FITS INTO CLEANING AND CLEANING VALIDATION
Risk-MaPP

Risk-MaPP* provides a scientific risk-based approach, based on ICH Q9, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety.

Risk-MaPP
A roadmap to compliance
Risk-MaPP
Introduces Health-Based Limits

ADE
A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime. By definition the ADE is protective of all populations by all routes of administration.

$$ADE \ (mg/day) = \frac{NOAEL \ (mg/kg/day) \times BW \ (kg)}{Ufc \times MF \times PK}$$
Risk-MaPP
Threshold of Toxicological Concern

Provides guidance for relatively unstudied compounds that fall into one of three categories:

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)
Risk-MaPP  
Why Health-Based Limits Matter

## Opioid Analgesic

<table>
<thead>
<tr>
<th>Result</th>
<th>ADE</th>
<th>LCD*</th>
<th>LD50/50,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mg/day</td>
<td>1/1000</td>
<td>0.01 mg/day</td>
<td>14 mg/day</td>
</tr>
</tbody>
</table>
## Risk-MaPP
**Why Health-Based Limits Matter**

### Cytotoxic Antineoplastic Agent

<table>
<thead>
<tr>
<th></th>
<th>ADE</th>
<th>Result</th>
<th>Rationale or Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/1000 LCD</td>
<td>1 µg/day</td>
<td>Excess cancer risk 1 x 10^{-5}</td>
</tr>
<tr>
<td>LD50/50,000</td>
<td>70-960 µg/day</td>
<td>Low Clinical Dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4800 µg/day (4.8 mg/day)</td>
<td>Lethal Dose 50% test animals</td>
<td></td>
</tr>
</tbody>
</table>
## Risk-MaPP

*Why Health-Based Limits Matter*

### Hormonal Agent

<table>
<thead>
<tr>
<th>Result</th>
<th>ADE</th>
<th>LD50/50,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 µg/day</td>
<td>1/1000 LCD</td>
<td></td>
</tr>
<tr>
<td>50-75 µg/day</td>
<td></td>
<td>40,000 µg/day(40 mg/day)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rationale or Basis</th>
<th>(NHEL) no hormonal effect level in animals</th>
<th>Low Clinical Dose</th>
<th>Lethal Dose 50% test animals</th>
</tr>
</thead>
</table>

*ISPE.org*
Risk-MaPP
Why Health-Based Limits Matter

Acceptance Limit (based on ADE)

Margin of Safety

New Limit determined by adding additional safety factors

Apparent Margin of Safety

Data
Risk-MaPP
Transitioning to Health-Based Limits

> In many instances current cleaning programs including cleaning validation may be adequate when transitioning to health-based limits.

– Compare current $1/1000^{th}$, 10 ppm, or other to the ADE or PDE value

» If the ADE or PDE value is greater than the current value, cleaning and cleaning validation can adequately meet the health-based limit.

• This is the case with many products.

» If the ADE or PDE value is lower than the current value, then the cleaning program and cleaning validation need to be reviewed to confirm adequacy.
Risk-MaPP Revisions
Updates to Cleaning Aspects

> Introducing a new product into the facility
  – Cleaning process development prior to entry into facility.

  » If not possible a robust risk assessment that considers all available historical information and cleaning performance data to assess the risk from the cleaning process.

  » Verification of the cleaning should also be performed after each campaign of the new product introduced when cleaning development activities are not able to be completed.

  – Analytical methods must be sensitive enough to detect the residue limits.
Risk-MaPP Revisions
Updates to Cleaning Aspects

> Inactivation of API during Cleaning and Sterilization

– The ADE methodology is based on the assumption that the product is active after cleaning and sterilization.

– If the API degrades into pharmacologically inactive fragments, the acceptance limit for the process residue should be set based on the inactive fragments instead of the active ingredient.

– This requires studies to determine if the product can effectively be degraded and denatured into inactive fragments.

– To determine the effectiveness of the degrading and denaturing process the ADE is necessary to ensure that the API is not present in unsafe levels after degrading/denaturing.

– If residual API is found after the degrading/denaturing process, the acceptance limit should be determined based on the ADE value of the API.
Risk-MaPP Revisions
Updates to Cleaning Aspects

> Why not use the lowest of all methodologies to set the limits?
  – The health-based limit represents a level that is safe for all patient populations and reducing this further does not increase patient safety
  – Actually lowers the apparent margin-of-safety. Lower than necessary cleaning acceptance limits increase the risk of a cleaning failure.

> It is expected that companies will have robust cleaning processes that provide as large a safety margin as possible especially where existing data indicates the ability to clean to very low residue levels.
Risk-MaPP Revisions
Updates to Cleaning Aspects

> Cleaning validation in the product lifecycle

Following completion and approval of cleaning validation runs, a risk-based program of ongoing monitoring should be established to assure the cleaning process remains consistent and effective.
Statistical measures of cleaning process capability should be utilized where they are both feasible and meaningful.

- It is possible, but not likely, that there will be sufficient data generated during Process Design (or “stage 1”) of a new product/new cleaning process to assess process capability prior to validation and routine use.

- More commonly however, there is insufficient or inadequate pre-validation cleaning data so as to be useful in constructing the science and data based case for cleaning procedure efficacy.

- In most situations, “real-world” shop-floor data must be collected and analyzed for this purpose. The collection, analysis and reporting of cleaning process output data is the function and purpose of the two subsequent lifecycle stages.
Risk-MaPP Revisions
Updates to Cleaning Aspects

> It is important that the residue data is as far below the health-based residue level as possible. Comparing these data to the residue level derived from the ADE provides a measure of the “True Margin of Safety” for the cleaning process.

> If risks are high (where the residue data is near or above the health-based residue level), then additional measures, such as improving the cleaning procedure and/or increasing monitoring frequency, should be pursued and documented.

> If risks cannot be reduced to acceptable levels or are considered too difficult to implement, then the equipment being cleaned should be either dedicated or made disposable.
Risk-MaPP Revisions
New Product Introduction

> The introduction of new products may be significantly accelerated by using existing data IF such data captures both performance of the cleaning process developed and the understood nature of any residuals to be removed.

– Evaluate against the existing worst-case product(s) for acceptable residual limits and “cleanability”. If new product is new worst case, cleaning validation is necessary, otherwise may not need cleaning validation.

– Caution must be used in interpreting pass/fail results for existing (validated) procedures as quantitative and objective indications of the capability of any new, “similar” procedures.

– Only actual data is data.

– If suitable analytical results for existing cleaning procedures are not available, new ones must be generated to determine acceptability.
Risk-MaPP Revisions
Cleanability at Small Scale

> It is not necessary to simulate the entire cleaning process at small scale; instead, it is sufficient to simulate the worst-case location from the standpoint of cleanability. If the process residue can be adequately removed from the worst-case location, it follows that it can also be adequately removed from other locations in the equipment.

> Another important consideration in the development of experimental models for evaluating cleanability is to determine the worst-case mechanism or means of cleaning.

– For clean-in-place systems, the worst-case mechanism of cleaning is typically through diffusion-controlled mass transfer in a gravity-induced falling film

– For manual processes the worst-case means of cleaning is determined by physical limitations associated with manually cleaning the worst-case location
Risk-MaPP Revisions

Visual Inspection

> Unlike analytical sampling and testing, visual inspection can and must be done (to whatever degree possible) with every cleaning process execution.

> Prior to initiation of manufacturing of the subsequent batch, equipment is routinely inspected for visual cleanliness by manufacturing personnel and documented in the manufacturing batch record.

> Any failure of the visual inspection is also recorded so that a true assessment of the cleaning program can be made.

> Establish visual detection levels of residues generally visible to operating personnel, given the site-specific variables such as equipment configurations and light conditions on the shop floor.
Risk-MaPP Revisions
Cleaning Validation Program

> Base on science and risk-based understanding of the hazards and cleaning agents

> Use Quality unit preapproved protocols containing sampling sites, methods and rationale for selection, details of cleaning procedure, and both visual and analytical criteria for acceptance

> Include multiple test repetitions to demonstrate consistency and reproducibility

  – There is no current expectation to formally justify the number of validation runs, that is, a three-run cleaning validation is still typical and generally acceptable.

  – Science and process knowledge should always be the first consideration, and an evaluation of run-to-run variability should still be a factor to determine the actual number of runs required to provide sufficient assurance prior to commercial use of a new cleaning procedure.
Risk-MaPP Revisions
Continued Process Verification for Validated Cleaning Processes

> Monitor post-validation in a justified and effective manner to assure ongoing cleaning procedure effectiveness.

– “Stage 3” or continued process verification (CPV) monitoring for a validated cleaning process can include analytical and/or visual components, applied in a risk-based manner that is dependent on very specific and contextual aspects of a given product and its cleaning processes.

– On-line TOC to directly measure (or correlate with) residual levels

– Swab or rinse of “worst-case” monitoring locations, a risk assessment informed by the cleaning validation run results can aid in determining the most challenging and failure-indicating sample locations

– In cases where the acceptance limits are well above visual detection and the cleaning process is robust, analytical sampling may be reduced as justified by risk assessments.
Risk-MaPP Revisions

Visual Inspection

> When health-based residual limits are at or below the limits of visual detection, visual inspection is of only indirect value in determining an absence of active ingredient residue.

> A qualification criterion for visual inspection of cleaned equipment by personnel should be considered.

> Following the precepts of ICH Q9, the level of effort and formality should be commensurate with the patient risk, and therefore the degree of formality around a visual inspection qualification program is best established by site and product specific risk assessment.
Risk-MaPP Revisions

Dectability

> Where the method of detection is visual only

  – it is important to understand the visual acuity of the staff and what level of residue is considered safe.

  – If the safe level is below the visual acuity of the staff then the risk of failure not being detected may be considered high whereas if the safe level is well above (several orders of magnitude) the visual acuity of the staff the risk of failure not being detected may be considered low.

> The degree of variability in product contact equipment cleaning processes should be understood and considered as a primary factor in ongoing monitoring decisions.

  – As an example, automated CIP processes present less risk from a variability perspective than manual cleaning methods, and may therefore justify less ongoing monitoring (once mechanical reliability is proven) than a manual process.
The Guide was a spin off from the Risk-MaPP Baseline® Guide to more adequately address the cleaning aspects of pharmaceutical equipment.

- The guide’s focus was on science, statistical and risk-based approaches – a future state - not the current baseline for GMP compliance

Baseline® Guides generally include regulatory review prior to publication

- The Cleaning Baseline® Guide only received input by one regulator
- The input from one regulator was not considered adequate to support use of the category. There has been a substantial discord on the need for this further review, and especially in regard to making subsequent amendments to the guide content.
In the spring of 2015, ISPE’s Guidance Documents Committee (GDC) requested an additional SME review to ensure that the scope of the Cleaning Validation Baseline® Guide draft was appropriate in parallel with a review by regulators, in order to allow use of the “Baseline” document category.

The guide content was originally maintained on the ASTM website, with whom ISPE had an amicable agreement regarding shared copyright.

- The situation regarding the existing writing team became significantly more complex with their unauthorized and unprecedented copywriting of the text.

Because of this lack of clarity and confirmation of the “Baseline® Guide” standard of the Guide content, ISPE has decided not to further develop or to publish the existing Cleaning Validation Baseline® Guide draft.
Cleaning Baseline® Guide Status

> ISPE has stated its ownership of well-known marks such as trademarks, logos and repeatedly offered its disposition to resolve the matter.

– However these overtures have been met with the current writing team’s unwillingness to consider any changes to the text and its ownership thereof.

> In its place and with a view to providing a work of knowledge that adds value to the entire ISPE community, ISPE is planning a new Guide on cleaning.
ISPE is forming a team to develop a Good Practice Guide on Cleaning.

- A Good Practice Guide (GPG) focuses on the “how to”
- A Baseline® Guide focuses on the “what needs to be done”

Current status

- Co-Leads on board
  » Joseph Payne, QA, Alcamí formerly AAI Pharma
  » Rob Walker, GMP Consultancy Ltd

- GDC mentors on board
  » Nick Haycock, Amgen
  » Stephanie Wilkins, PharmaConsult Us
Cleaning Guide Status

How will this guide be different to the myriad of others available?

- Provide specific “how to” advice
- For example some guides state:
  
  » “operators should be qualified for visual inspection”
    - This guide will provide information on issues to consider and methods to qualify operators for visual inspection
  
  » “use risk assessment or risk management techniques”
    - This guide will provide practice advice on what to consider when assessing and managing risk as well as some examples
Cleaning Guide Status

> This document would provide a single source of information, in respect of how to clean and the validation of different cleaning practices

> For who? Regulations associated with cleaning and validation; Different types of cleaning; acceptance criteria, Sterile dosage forms; oral solid dose, biotech, APIs, Analytical techniques?
Cleaning Guide Status

> Tentative topics to be included:
  – Regulations and applications to cleaning and cleaning validation
  – Cleaning methodologies
  – Equipment issues and challenges
  – Dedicated equipment and campaign manufacture issues
  – Sampling techniques and locations
  – Acceptance criteria
  – Examples of assay methods and validation
  – Change Control and impact on Validation status
Q&A

> Questions, comments?

> Thank you!

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  – +1 908-575-7745