



# Mitigating Cross-Contamination in Shared Production Facilities Using Risk-Based Cleaning Validation Methods: Considerations and Case Study

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The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). Since 1992, USP has worked with USAID to support low- and middle-income countries in addressing critical issues related to medicines information and quality. The PQM program provides technical assistance to build the capacity of medicines regulatory authorities and quality assurance systems in countries with weak health systems. PQM also provides technical support to manufacturers of quality-assured priority medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal, newborn, and child health (MNCH).

## Table of Contents

<b>Acknowledgments .....</b>	<b>iv</b>
<b>Acronyms .....</b>	<b>v</b>
<b>I. Introduction .....</b>	<b>1</b>
<b>II. Evolution of Cleaning Validation.....</b>	<b>2</b>
Evolution of cleaning validation in industry .....	2
Evolution of regulatory guidance for cleaning validation .....	2
EMA questions and answers .....	5
<b>III. Employing a Risk-Based Approach for Cleaning Validation: Examples .....</b>	<b>7</b>
CV matrixing of products to select worst-case product.....	7
Demonstrating repeatability of cleaning with the cleaning method being manual, semi-automatic, or automatic (clean in place) .....	7
Cleaning limit.....	7
<b>IV. Case Study: Prevention of Cross-Contamination of Cyclosporine into an Anti- Tuberculosis (TB) Medicine in a Shared Manufacturing Facility .....</b>	<b>9</b>
Background.....	9
Risk assessment and mitigation of potential cyclosporine cross-contamination..	9
Cyclosporine cleaning validation – limit of cleaning evaluation .....	12
<b>V. Conclusion .....</b>	<b>14</b>
<b>References .....</b>	<b>15</b>

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## Acronyms

ADE	acceptable daily exposure
ADI	acceptable daily intake
AHU	air handling unit
API	active pharmaceutical ingredient
BW	body weight
CV	cleaning validation
DD	largest daily dose
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
GMP	good manufacturing practices
HBEL	health-based exposure limit
HEPA	high-efficiency particulate air
HVAC	heating, ventilation, and air conditioning
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISPE	International Society for Pharmaceutical Engineering
LD <sub>50</sub>	lethal dose 50 percent
LOAEL	lowest-observed adverse-effect level
MACO	maximum amount carryover limit
MDD	maximum daily dose
MF	modifying factor
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PDE	permitted daily exposure
PK	pharmacokinetic
PQM	Promoting the Quality of Medicines (program)
Q&A	questions and answers
QRM	quality risk management
Risk-MaPP	Risk-Based Manufacture of Pharmaceutical Products
SBS	smallest subsequent batch size
SSA	shared surface area
TB	tuberculosis
UFC	composite uncertainty factor
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization
WHO PQ	World Health Organization Prequalification (program)



## I. Introduction

This report provides an essential overview of the evolution of the regulatory expectations and industry advances in cleaning validation (CV) approaches, including recent risk assessment considerations. CV has become a regulatory requirement for preventing potential cross-contamination of products manufactured in the same equipment train in the European Union, the United States, Canada, Japan, and elsewhere. The need for CV approaches for priority essential medicines is especially important given the limited commercial value and interest of manufacturers in such products.

For priority essential medicines to be eligible for procurement by international donors, manufacturers must demonstrate their products were manufactured in compliance with international good manufacturing practice (GMP) standards such as those developed by the WHO Prequalification (WHO PQ) Program. Avoiding cross-contamination during manufacturing is a critical component of GMP; at a minimum, pharmaceutical manufacturers must generate CV data for the worst-case product to be manufactured using undedicated equipment to demonstrate that the potential for cross-contamination is minimized.

Compliance with current GMP requirements can be an expensive investment for manufacturers, sometimes requiring them to build separate facilities for products that are hazardous for contaminating other products. This is particularly true for public health essential medicines that offer small margins. However, conducting thorough risk assessments and employing effective risk mitigation strategies may help manufacturers, particularly those in low- and middle-income countries, effectively manage the potential for cross-contamination and fulfill international regulatory requirements.

This report provides important financial rationale and regulatory justification for manufacturers of priority essential medicines to maintain a robust CV program and conduct a risk mitigation strategy for minimizing cross-contamination. It includes a case study and examples that demonstrate how to (1) successfully mitigate risks of handling a product (in this case, cyclosporine) in a multiple product manufacturing facility, and (2) leverage existing CV approaches toward the recent health-based CV limit regulatory requirements. The methodology outlined in this report should serve as a guide for manufacturers endeavoring to manage the risk of cross-contamination, and thereby potentially save millions of dollars in new equipment and labor costs and reduce the time-to-market of critical medicines.

## II. Evolution of Cleaning Validation

### Evolution of cleaning validation in industry

In the early 1980s, the pharmaceutical industry was struggling with the concept of validation. In 1984, Harder published an article, “The Validation of Cleaning Procedures,” which introduced concepts for establishing a cleaning limit, stating that it must be practical and achievable by a reasonable cleaning procedure and must be verifiable by analytical methodology that exists in the company.<sup>1</sup> Harder’s paper referenced 21 Code of Federal Register §193, “Tolerances for Pesticides in Food Administered by the Environmental Protection Agency,” and included a table of limits for a variety of hazardous pesticides and herbicides. Harder pointed out that the amount of drug products ingested by an individual is much lower than the amount of food ingested. Therefore, he suggested that acceptance limits for drug substances—comparable to those used for pesticides—would be reasonable.

In 1989, Mendenhall of Abbott Laboratories expanded upon the ideas presented by Harder, adding such concepts as using a matrix approach for CV in a multiproduct facility, testing for cleaning agents, and using placebo batches.<sup>2</sup> In addition, he suggested cleaning acceptance limits that became the risk assessment-derived health-based exposure limits.<sup>3</sup>

From 1989 to 1992, the U.S. Food and Drug Administration (FDA) and Barr Laboratories, Inc., had issues concerning the interpretation of the GMPs,<sup>4</sup> which resulted in FDA suing Barr Labs in June 1992. FDA’s process validation requirement was upheld in court, and although CV was required under the court ruling, it had not yet become a direct regulation.

In 1993, Fourman and Mullen of Eli Lilly published an article in which they proposed the use of a combination of acceptance limits for active pharmaceutical ingredients (APIs).<sup>5</sup> They suggested that any carryover of product residue should meet the following criteria:

- No more than 0.001 dose of any product will appear in the maximum daily dose of another product.
- No more than 10 ppm of a product will appear in another product.
- No quantity of residue will be visible on the equipment after cleaning procedures are performed.

### Evolution of regulatory guidance for cleaning validation

In 1993, FDA issued its “Guide To Inspections Validation Of Cleaning Processes” for FDA mid-Atlantic region inspectors.<sup>6</sup> The guide provided regulatory justification for inspection expectations by referencing 21 CFR § 211.67, “Equipment Cleaning and Maintenance,” and was adopted for use by all domestic and foreign FDA inspectors 1 year later. Although the guide contained content that could be traced back to the articles by Harder, Mendenhall, Fourman, and Mullin, it does not endorse any of the limits. Instead, it advises the companies to ensure that the basis for any limits is scientifically justifiable.

In 1998, FDA issued its “Draft Guidance for Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients”<sup>7</sup> after determining that the regulations in 21 CFR, Parts 210 & 211 applied



only to finished dosage form drugs and not to the APIs. The guidance recommended that residue limits be practical, achievable, verifiable, and based on the most deleterious residue based on pharmacological or physiological activity of the API, and left up to the industry to justify actual limits.

In 2001, FDA participated with the International Conference on Harmonisation (ICH) in developing its Q7A Good Manufacturing Practice Guidance for APIs and, in 2016, its Q7 Revision. The CV GMP requirements were identical to those in the 1998 FDA draft guidance for APIs.

In 2005, the International Society for Pharmaceutical Engineering (ISPE) translated a concept paper from the European Medicines Evaluation Agency on the need for updated GMP guidance concerning dedicated manufacturing facilities in the manufacture of certain medicinal products.<sup>8</sup>

In 2006, ICH Q9 Quality Risk Management (QRM) Guidance was introduced to offer a systematic approach to the assessment, control, communication, and review of risks to the quality of the drug across its lifecycle.

In 2009, ISPE issued its Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP). The guide provides a scientific risk-based approach based on ICH Q9 for setting health-based cross-contamination and CV limits based on the acceptable daily intake (ADI) and not a fraction of the therapeutic dose, 10 ppm carryover, on the Lethal Dose 50 percent ( $LD_{50}$ ), or on any other toxicity criteria.

The ADI is the amount of a chemical or API (mg/kg body weight) in food, drinking water, or product-to-product cross-contamination that can be safely ingested by humans each day over a lifetime without appreciable adverse health effect.

Occupational exposure limit (OEL) is designed to be an 8-hour a day, 40-hour a week airborne concentration, which nearly all workers may be repeatedly exposed to day after day without effects, based on currently available information. It does not take into account persons with hypersensitivity to the compound in question. An average worker would breathe approximately  $10 \text{ m}^3$  of air over an 8-hour day.

The following abbreviations are used in the calculations, below: ADI (acceptable daily intake); BW (body weight); MDD (maximum daily dose); MF (modifying factor); NOAEL (no observed adverse effect level); OEL (occupational exposure limit); PK (pharmacokinetic adjustment); SSA (shared surface area); UFC (composite uncertainty factor).

*Calculation of the ADI:*

$$\text{ADI (mg/day)} = \frac{\text{NOAEL} \left( \frac{\text{mg}}{\text{kg}} \right) \times \text{BW (kg)}}{\text{UFC} \times \text{MF} \times \text{PK}}$$

*Calculation of Health-Based Cleaning Limits:*

$$\begin{aligned} \text{Swab Limit (Product Contact Surfaces) (mg/swab)} &= \frac{ADI \left( \frac{mg}{day} \right) \times \text{Batch size (mg)} \times \text{Test Area (cm}^2\text{)} \times \text{Recovery Factor}}{MDD (mg) \times SSA(\text{cm}^2)} \\ \\ \text{Rinse concentration (mg/L)} &= \frac{ADI \left( \frac{mg}{day} \right) \times SB(\text{mg}) \times \text{Rinsed Area (cm}^2\text{)}}{\text{Volume of Rinse (L)} \times MDD(\text{mg}) \times SSA(\text{cm}^2)} \end{aligned}$$

*Calculation of OELs:*

$$\text{OEL (mg/ m}^3\text{)} = \text{ADI (mg/day)} / (10 \text{ m}^3 \text{ /day)}$$

In 2014, the European Medicines Agency (EMA) incorporated the Health-based Exposure Limits (HBEL) for use in risk identification in the manufacture of different medicinal products in shared facilities. Chapters 3 and 5 of the EMA GMP guideline were revised to promote a science and risk-based approach using a “Toxicological Evaluation” for establishing threshold values for risk identification.

The EMA recommendations include the review and evaluation of pharmacological and toxicological data for individual active substances and determination of threshold levels as referred to in the GMP guideline. These levels can then be used as a risk identification tool to carry over limits used in CV. All available animal and human data for hazard identification would include nonclinical pharmacodynamic data, repeat-dose toxicity studies, carcinogenicity studies, in vitro and in vivo genotoxicity studies, reproductive and developmental toxicity studies, and clinical data on therapeutic and adverse effects, according to EMA. The threshold level for cross-contamination by the EMA is the permitted daily exposure (PDE), which represents 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 (similar to acceptable daily exposure (ADE) defined in the Risk-MaPP Guide). Appendix 3 of the ICH Q3C and VICH GL 18 Guidelines present the following equation for the derivation of the PDE:

$$PDE = \frac{NOAEL \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

NOAEL is the highest tested dose at which no “critical” effect is observed. If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value.

If no NOAEL is obtained, the lowest-observed adverse-effect level (LOAEL) may be used.

Factors F1 to F5 address the following sources of uncertainty:

- F1: a factor (values between 2 and 12) to account for extrapolation between species.
- F2: a factor of 10 to account for variability between individuals.

- F3: a factor of 10 to account for repeat-dose toxicity studies of short duration (i.e., less than 4-weeks).
- F4: a factor of 1–10 that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity, or teratogenicity.
- F5: A variable factor that may be applied if the no-effect level was not established. When only a LOAEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

## EMA questions and answers

In January 2017, EMA published a questions and answers (Q&A) document on (1) implementation of risk-based prevention of cross contamination in production and (2) the Guideline on Setting Health-based Exposure Limits (HBELs) for Use in Risk Identification in The Manufacture of Different Medicinal Products in Shared Facilities.<sup>9</sup> The Q&A document focused on the HBEL applicable to more hazardous drugs. The significant Q&As are summarized below:

### **Question 1: What products or active substances are considered highly hazardous?**

Answer: Highly hazardous products are those that can cause serious adverse effects at low doses and that therefore would benefit from a full toxicological assessment in order to derive a safe HBEL. Evidence indicating that a product or active substance falls within any of the following categories should result in a product being considered highly hazardous:

- Genotoxic (specifically mutagenic) compounds that are known to be, or highly likely to be, carcinogenic to humans
- Compounds that can produce reproductive and/or developmental effects at low dosages
- Compounds that can produce serious target organ toxicity or other significant adverse effects at low doses
- Compounds with a high pharmacological potency (i.e., recommended daily dose of <1 mg [veterinary dose equivalent 0.02 mg/kg])
- Compounds with a high sensitizing potential

### **Question 2: Could OELs or Occupational Exposure Bands be used to support assessment of products to determine whether they may be highly hazardous?**

Answer: Extrapolation of an OEL: a preliminary PDE can be simply done by using the following formula:

$$\text{PDE } (\mu\text{g}/\text{day}) = \text{OEL } (\mu\text{g}/\text{m}^3) \times 10 \text{ m}^3 \text{ (the volume of air breathed by a worker in 8 hours).}$$

If the resulting PDE Value is 10 mg/day or lower, the product should be considered highly hazardous.

### **Question 3: Can calculation of HBELs be based on clinical data only (e.g., to establish the HBEL on 1/1000<sup>th</sup> of the Minimum Therapeutic Dose)?**

Answer: For products that have a favorable Therapeutic Index, the therapeutic dose information could be used as the point of departure for calculation of the HBEL (e.g., the PDE). Under these circumstances, HBEL based on the 1/1000th of the minimum therapeutic dose approach would be

considered as sufficiently conservative and could be utilized for risk assessment and cleaning limit computation purposes.

**Question 4: Is the use of LD<sub>50</sub> to determine health-based limits acceptable?**

Answer: LD<sub>50</sub> is not an adequate Point of Departure to determine an HBEL.

**Question 5: How can limits for cleaning purposes be established?**

Answer: Although the EMA Guideline may be used to justify cleaning limits, traditional cleaning limits used by industry, such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products.

This EMA draft position is an improvement over the Risk-MaPP Guide. This leeway allowed by EMA to justify using traditional cleaning limit approaches could allow manufacturers to leverage their existing CV work to meet the recent HBEL requirements. For products classed as highly hazardous, such as sensitizing, teratogenic, and mutagenic compounds where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach.

### **III. Employing a Risk-Based Approach for Cleaning Validation: Examples**

A risk-based approach is to be applied to any validation and change control quality system related to validation of any manufacturing process, equipment, cleaning, and analytical method. Tools for risk assessment (e.g., Failure Mode and Effect Analysis) can be applied for each requirement of the CV study protocol to identify the risk for each requirement. A risk mitigation strategy can then be developed, and the risk score can be evaluated before and after execution of the risk mitigation strategy. The strategy should be documented in the CV protocol and the results reported in the CV report.

Examples of the CV requirements and use of the risk-based approach are discussed below.

#### **CV matrixing of products to select worst-case product**

- Create a grouping of products or APIs manufactured on the same equipment train.
- Risk identification: The intent is to minimize CV study to one product or API for each equipment train. Score the risk as high before the mitigation strategy in the protocol.
- Mitigation strategy: Identify the “worst case” product/API considering the solubility, hardest to clean product/API, and the most toxic candidate. Develop a detailed cleaning procedure for that product/API to be validated. Score the risk as theoretically low in the protocol if your CV strategy would be successful with the worst-case product/API. If the CV strategy meets the acceptance criteria, you have successfully used the risk-based approach.

#### **Demonstrating repeatability of cleaning with the cleaning method being manual, semi-automatic, or automatic (clean in place)**

- Risk: The hardest to validate would be a manual cleaning method. Score the risk as high before the mitigation strategy in the CV protocol.
- Mitigation strategy: Develop a detailed step-by-step standard operating procedure/work instruction for the manual cleaning with operating training and testing requirements, train the operators, and document the training. Score the risk as theoretically low if your CV study is successful with the procedure-trained operators conducting the manual cleaning for typically three consecutive successful CV batches. If the CV study meets the acceptance criteria, you have successfully used the risk-based approach.

#### **Cleaning limit**

- Risk: The CV study will need to demonstrate that the cleaning method employed for the equipment train to be studied for CV consistently controls potential carryover of the product, cleaning agents, and extraneous material into a subsequent product to a level that is below predetermined levels. The cleaning limit will need to be justified as the most stringent criteria from industry current standards.
- Mitigation strategy: For the compound(s) under the CV study, calculate the cleaning limit for

the contaminant product into the subsequent product of the smallest batch size by a general limit method (i.e., 10 ppm carryover), an HBEL toxicology-based (ADI/PDE) method (especially if the product is hazardous), and a therapeutic dose-based (i.e., 1/1000th of the smallest dose) method. Select the lowest limit for the CV study, thus minimizing health-based risk. If the CV study meets the acceptance criteria, the risk-based approach was successfully used.

**A word of caution:** Use a balanced approach to achieve the most conservative cleaning limit. If the compound is not hazardous—and using the HBEL approach is too cumbersome in terms of barrier technology and advanced analytical instruments—then settling for one of the traditional cleaning limits, such as 10 ppm carry over, may be justified as long as the risk-based approach is still employed and cross-contamination failure modes have been mitigated. The case study for CV of cyclosporine in a multi product manufacturing facility, below, illustrates this point.

## **IV. Case Study: Prevention of Cross-Contamination of Cyclosporine into an Anti-Tuberculosis (TB) Medicine in a Shared Manufacturing Facility**

This case study aims to highlight the establishment of cleaning limits by traditional approaches vs. current health-based exposure limits, and how existing data can be used to support risk assessment efforts for cleaning validation.

### **Background**

The PQM program, in an effort to support WHO PQ of an anti-TB drug, works with a manufacturer to assess production of TBX capsules from a shared soft-gelatin capsules manufacturing facility (ABC) that also produces cyclosporine capsules. Cyclosporine is defined as a hazardous compound, and the risk of cross-contamination of this material into TBX capsules must be demonstrably minimized to an acceptable level. This case study describes the risk assessment and implementation of a risk mitigation strategy to successfully minimize the potential of cross-contamination of cyclosporine into any other products being manufactured in the same ABC site.

ABC had identified cyclosporine as a worst-case product to clean (based on solubility and toxicity) and carried out a CV study using an empirical cleaning limit of 10 ppm carryover into the next smallest batch produced using the same manufacturing equipment. This next smallest batch could be of TBX. During the risk assessment by PQM, it was determined that this CV approach was inadequate and that the CV study data should be evaluated against the current EU GMP recommended HBEL for risk mitigation of cross-contamination. Follow-up visits were carried out by PQM staff to the ABC site to reassess the historical CV work and evaluate the cyclosporine HBEL-based limits compared to the empirical cleaning limit employed by ABC.

### **Risk assessment and mitigation of potential cyclosporine cross-contamination**

An audit tour of the ABC facility was conducted to identify the risks (failure modes) of the potential for cross-contamination of cyclosporine in TBX, the product of interest for WHO PQ. In all instances, the risks were assessed and shared with the ABC staff. A joint strategy to mitigate the risks identified was agreed upon, with the corrective actions defined, and timelines established. A failure mode and effect analysis was drafted, and the risk scoring was done for the observations before mitigation and after the potential corrective actions. The overall risk of manufacturing TBX and cyclosporine soft gelatin capsules in the same facility would be mitigated and reduced to an acceptable level, provided ABC successfully carried out all the corrective actions as discussed and agreed upon. Individual risks assessed and the strategy to mitigate the same are briefly described below:

## Sampling the API

Assessed risk	Corrective action for risk mitigation
The sampling room has the required negative pressure, but there are no sink/bubble sequence airlocks at its entry. Any spillage or aerosolized cyclosporine API could potentially contaminate the next product being sampled, and the powder could be carried by the operator to other parts of the warehouse and manufacturing operation.	ABC management suggested not sampling the cyclosporine API. ABC would obtain a pre-sample from the API vendor for the lot received. It was suggested that the quality agreement with the vendor should spell out the commitment by the supplier to accurately perform the sampling and certify that the sample was from the same lot it is purported to represent.

## Heating, ventilation, and air conditioning (HVAC) return air control for the sampling room in the warehouse

Assessed risk	Corrective action for risk mitigation
There is no high-efficiency particulate air (HEPA) filter in the return air duct or at the intake of the air handling unit (AHU). Any spillage or aerosolized cyclosporine API could potentially contaminate the next product being sampled, and the powder could be carried by the operator to other parts of the warehouse and manufacturing operation.	The decision not to perform the sampling operation by obtaining a pre-sample of every lot from the API manufacturer of cyclosporine API would also mitigate this particular risk.

## API dispensing room

Assessed risk	Corrective action for risk mitigation
The API dispensing room has the required negative pressure, but there are no sink/bubble sequence airlocks. Any spillage or aerosolized cyclosporine API could potentially contaminate the next product being sampled, and the powder could be carried by the operator to other parts of the warehouse and manufacturing operation.	ABC management agreed not to weigh out or dispense the cyclosporine API. ABC would obtain a pre-dispensed exact quantity required for manufacturing a dosage form batch from the API vendor for the lot received. It was suggested that the quality agreement with the vendor should spell out the commitment by the supplier to accurately perform the dispensing and certify that the quantity of the API was from the same lot it is purported to represent.

## HVAC return air control for the API dispensing room

Assessed risk	Corrective action for risk mitigation
There is no HEPA filter in the return air duct or at the intake of AHU. Any spillage or aerosolized cyclosporine API could potentially contaminate the next product being sampled, and the powder could be carried by the operator to other parts of the manufacturing operation.	The decision not to perform any weighing or dispensing of the API operation and instead obtain a pre-weighed quantity for every batch of cyclosporine capsules manufactured at ABC from the API manufacturer of cyclosporine API would also mitigate this particular risk.



### Bulk product suspension manufacturing room

Assessed risk	Corrective action for risk mitigation
<p>The bulk product suspension manufacturing room has the required negative pressure, but there are no sink/bubble sequence airlocks. The cyclosporine API powder is handled here. There could be a spillage resulting in the aerosolized API powder potentially contaminating the next product being compounded, and the powder could be carried by the operator to other parts of the operation.</p>	<p>ABC agreed to use an isolator over the manhole of the compounding tank during the cyclosporine API powder addition to contain the material. This was the highest risk unit operation, once the sampling and dispensing operations risks of handling the cyclosporine API powder material were addressed.</p>

### HVAC return air control for the bulk product suspension manufacturing room

Assessed risk	Corrective action for risk mitigation
<p>In the bulk product suspension manufacturing room, the return air duct does not have a HEPA filter. Even after installation of the isolator to cover the addition of the API powder into the compounding tank, there is still an element of risk due to potential spillage of the powder and failure of the isolator. Any spillage or aerosolized API could potentially contaminate the next product being dispensed in that room as well as other rooms supplied by the same AHU.</p>	<p>ABC agreed with the suggestion to add a HEPA filter in the return air duct and made a commitment to do so. This addition may need more than just adding a filter in the return air duct; an increase in the AHU capacity may be required upon addition of the HEPA filter.</p>

### Soft-gel capsule filling, drying, and aging line

Assessed risk	Corrective action for risk mitigation
<p>In the soft-gel capsule filling room, there is free entry and exit without additional gowning. The cyclosporine capsule-filling line is next to the line that fills the TBX capsules. There are no entry airlocks or additional gowning requirements for entering or exiting the filling line. The operator on the cyclosporine line could potentially cross-contaminate other products on any of the other filling lines by carrying dried cyclosporine line residues on his or her gloves and/or gowning fabric.</p> <p>Soft-gel capsule drying room and aging area: Each area is a big, open space with the drying lines for all the fill lines in this common space. Any broken capsule residues can cross-contaminate other capsules in the porous drying lines. Operators on the cyclosporine line could potentially cross-contaminate other products on any of the other drying lines and the aging room by carrying dried cyclosporine line residues on their gloves and gowning fabric in the drying and aging storage areas.</p>	<p>ABC management agreed to physically separate each of the filling, drying, and aging lines, with a separate HVAC unit for each line to minimize the cyclosporine cross-contamination potential.</p>

## Cyclosporine cleaning validation – limit of cleaning evaluation

### Existing Cleaning Validation Data

ABC had established a CV program based on the worst-case compound selected on solubility and toxicity (based on LD<sub>50</sub>). ABC identified cyclosporine as the worst-case compound among the products they manufacture and carried out a CV study using an empirical cleaning limit of 10 ppm carry over into the next smallest batch produced using the same manufacturing equipment. This next smallest batch could be TBX.

**Corrective action for risk mitigation – applying current HBEL regulatory expectations:** To evaluate the cleaning limit of cyclosporine on the HBEL approach, a commercially available toxicological assessment Fastrac document was acquired.<sup>10</sup> This document reported the OEL value of cyclosporine to 5 µg/ m<sup>3</sup>. The PDE can be calculated with the formula (also provided in Question 2 of the EMA Q&A, above):

$PDE (\mu\text{g}/\text{day}) = OEL (\mu\text{g}/\text{m}^3) \times 10 \text{ m}^3$  (the volume of air breathed by a worker in 8 hours).

Cyclosporine PDE = 5 µg/ m<sup>3</sup> x 10 m<sup>3</sup> = 50 µg, which is greater than 10 µg, the threshold value established by EMA to be classified as a highly hazardous compound. As allowed by EMA (also provided in Question 5 of the EMA Q&A, above), limits for cleaning purposes can be established by following the approaches of traditional cleaning limits used by the industry such as 1/1000<sup>th</sup> of minimum therapeutic dose or 10 ppm of one product in another product, for non-highly hazardous products.

The Fastrac monograph document [9] provides ADE value, calculated by the ISPE Risk MaPP Guide, as 40 µg, which is more conservative than the PDE estimate of 50 µg derived above.

The HBEL ADE-based approach was used to calculate the cleaning limit for manufacturer ABC's CV scenario described earlier for the worst-case equipment and smallest batch size of the subsequent product, as illustrated below:

The cleaning limit (µg/cm<sup>2</sup>) for the swab method =  $ADE \times (1000 \mu\text{g}/\text{mg}) \times (\text{SBS}/\text{DD}) / \text{SSA}$ , in which the following abbreviations are used:

- Product to be cleaned = Product A
- Next product to be manufactured = Product B
- ADE = acceptable daily exposure of Product A (mg/day); 40 µg/Day = 0.04 mg/day
- 1000 = unit conversion factor from mg to µg
- SBS = smallest subsequent batch size of Product B (mg); 250 kg = 250,000,000 mg
- DD = largest daily dose of Product B (mg/day); 3.87 g = 3870 mg
- SSA = shared product contact surface area between Product A and Product B (cm<sup>2</sup>); 46,051 cm<sup>2</sup>

The calculation below yields the answer for the HBEL-based cleaning limit for swab method as equal to 48.26  $\mu\text{g}/\text{cm}^2$ .

$$\frac{0.04 \text{ mg} \times 1000 \frac{\mu\text{g}}{\text{mg}} \times \frac{215,000,000 \text{ mg}}{3870 \text{ mg}}}{46,051 \text{ cm}^2 \text{ (surface area of agi homo mixer for cyclosporine batch)}}$$

**Corrective action for risk mitigation – leveraging existing 10 ppm-based cleaning limit:** Company ABC’s CV study employed a 10 ppm maximum amount carry over limit (MACO). The cleaning limit based on the 10 ppm MACO approach in ABC’s study was calculated to be  $10 \text{ ppm} \times \text{SBS} = 0.00001 \text{ mg}/\text{mg} \times 215,000,000 \text{ mg} = 2,150 \text{ mg}$ .

The calculation for cleaning limit for the swab testing method –  $\text{MACO amount}/\text{surface area of the mixer} = 2,150 \text{ mg}/46,051 \text{ cm}^2 = 46.69 \mu\text{g} / \text{cm}^2$ .

In this case study, the cleaning limit value, calculated based on the 10 ppm MACO into the next smallest batch, was lower than the HBEL ADE-based cleaning limit.

The existing CV study and the historical data developed at ABC for cyclosporine were justified against the current HBEL ADE-based cleaning limit regulatory expectations. ABC could stand on its historical CV work by writing an addendum to its CV study report for the comparison of the HBEL-based cleaning limit to the 10 ppm MACO approach. This saved ABC millions of dollars in equipment, labor costs, and product development time.

## V. Conclusion

This paper has provided a broad overview of the evolution of cleaning validation from the 1980s to today's risk assessment considerations. Risk assessment concepts began to take hold in the mid-1980s, with Harder's work establishing a practical, achievable, and verifiable cleaning limit for industry. By the end of the decade, concepts by Mendenhall and others gave rise to the approaches for CV in multiproduct facilities, testing for cleaning agents, and acceptance limits—including those for APIs—now used in calculating risk assessment-derived health-based exposure limits. Beginning in the 1990s, FDA began to issue guidance for inspections and residue limits. These were followed by FDA and ICH guidance on GMPs and systematic approaches to risk assessment of the quality of medicines across the lifecycle.

Building on that knowledge, we have shown that there is a way to mitigate risks for the manufacture of some medicines in multiple product facilities that does not involve extreme and costly measures. For example, medicine manufacturers in low- and middle-income countries and elsewhere that comply with the GMP upgrades and CV requirements can reduce cross-contamination risks to acceptable levels without having to construct or dedicate new facilities. This is especially critical for companies that manufacture critical essential medicines with small economic margins. A carefully implemented risk-based cleaning validation approach can prevent product cross-contamination while also minimizing the cost of producing and improving access to critical medicines.

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