European Federation of Pharmaceutical Industries and Associations

Case Study – Evaluation of Health-Based Exposure Limits and Potential Impact on Manufacturing Equipment Cleaning Limits

EMA Workshop on generation and use of Health Based Exposure Limits (HBEL)
Date: 21 June 2017 * Version: 2.0






Presentation

Gretchen Allison, Pfizer Global Quality Operations – Validation Team Leader

Outline

- Background/Scope
- Step By Step Example
- Industry Experience
- Considerations for Inspections/Key Messages

Scope

Primary Scope of this Case Study: Drug Product

- Commercial Drug Product
- Small Molecule
- New vs Legacy
- Product residue removal (vs micro, cleaning agent removal)
- Non-dedicated Manufacturing Equipment

Background

- Historically used drug product manufacturing equipment cleaning limits based on 1/1000 minimum therapeutic dose
- Some markets still expect 1/1000 dose limit, or lower of that and NMT 10 ppm limit
- Any cleaning must pass visual inspection
- EMA Health Based Exposure Limit (HBEL) guide published, effective 2015
- Some other markets (e.g. PICS, China) also expect HBEL assessment in establishing cleaning limits
- New active ingredients and associated drug product have documented HBEL at the time of commercialization
- ADE = PDE
- For older (legacy) products already on the market, it's a bit more complicated….

For existing/older (legacy) products already on the market, it's a bit more complicated….

Overview of Workprocess

For Legacy Products: Assess ADE based cleaning limits

Step 1: Identify and prioritize existing Active Ingredients and associated Drug Products for HBEL evaluation

Step 2: Establish ADE value: see scenarios on next slide

Step 3: Compare health based cleaning limit to existing cleaning limit

- Where existing cleaning limit (e.g. based on 1/1000 minimum therapeutic dose) is lower than health-based (ADE) derived cleaning limit, the existing cleaning limit maybe retained as an acceptable approach
- Where health based derived cleaning limit is lower than existing cleaning limit, a new health based cleaning limit is implemented for use. This may require:
  - Cleaning, sampling, and analytical test method detection level evaluation
  - Potentially lower detection limits to be established and validated

Must be done on product by product basis. For sites with many legacy products = significant time/resource

Reference flowchart slide for workprocess

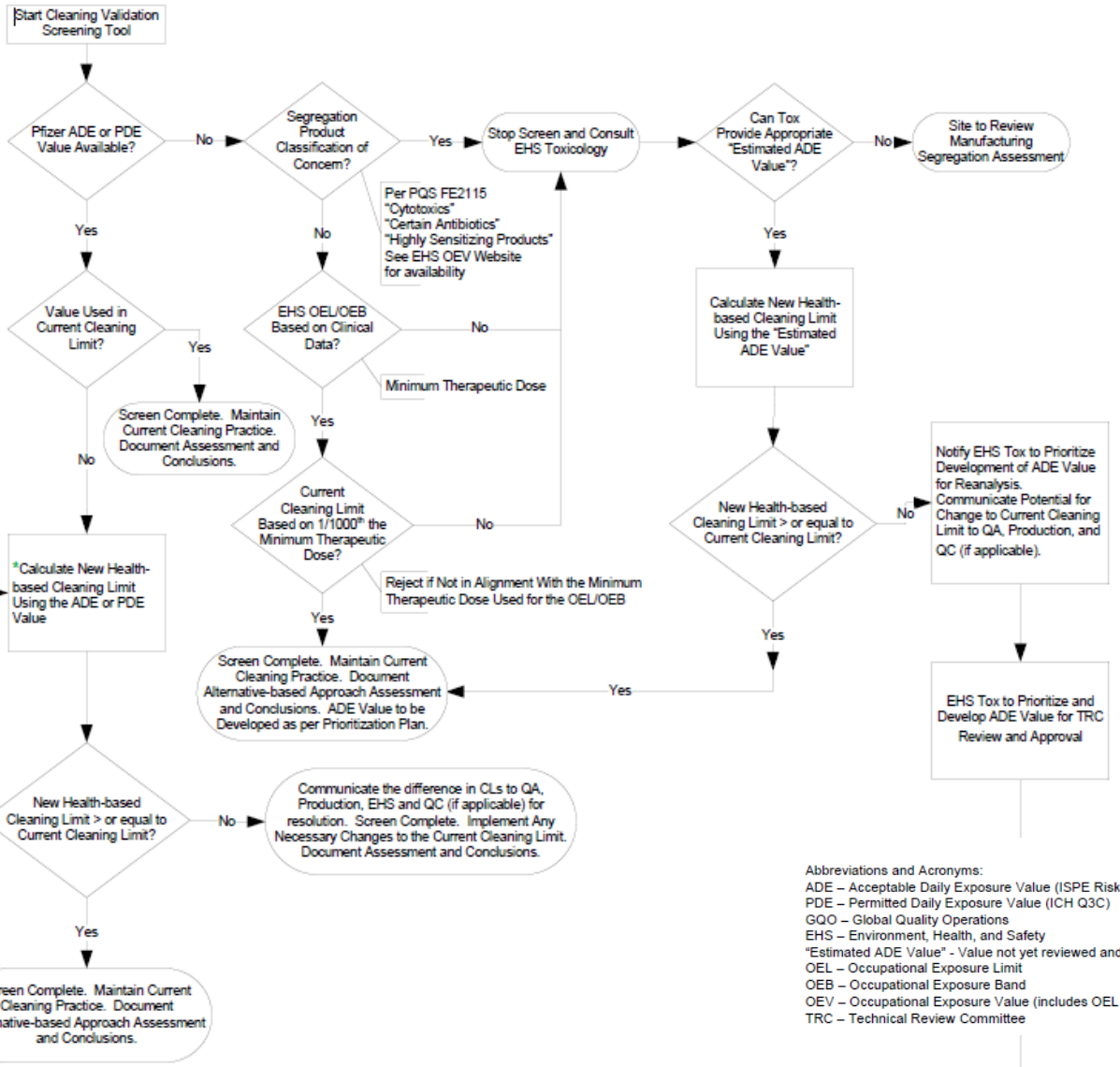
Step 2 Scenarios: Establishing ADE value

Scenario A: For new active ingredients/drug product documented HBEL in place at the time of commercialization i.e. ADE values available

Scenario B: If no ADE available:

- Screen out highly sensitizing beta lactams and review Segregation product assessment
- For all Other products with no ADE value: Check OEL/OEB monograph: is it based on clinical data?
  - If the OEL/OEB is based on the low clinical dose, then ADE development can be assigned a lower priority as 1/1000 the same minimum therapeutic dose (MTD) will be sufficiently conservative – regardless of how high or low (i.e., "potent") the MTD may be.
  - If the OEL or OEB is NOT based on the low clinical dose then the product is prioritized for Tox review and estimation of the ADE using the OEL/OEB monograph. Compare against current cleaning limit and prioritize full ADE development, as needed
- For lower priorities, ADE to be developed per prioritized plan
- Once ADE developed, calculate cleaning limit based on ADE and compare to existing cleaning limit

Flow chart (derived from PharmTech Europe Dec2015 publication)



Abbreviations and Acronyms:
ADE – Acceptable Daily Exposure Value (ISPE Risk-MaPP)
PDE – Permitted Daily Exposure Value (ICH Q3C)
GQO – Global Quality Operations
EHS – Environment, Health, and Safety
"Estimated ADE Value" - Value not yet reviewed and approved by Pfizer's Technical Review Committee (TRC)
OEL – Occupational Exposure Limit
OEB – Occupational Exposure Band
OEV – Occupational Exposure Value (includes OEL and OEB)
TRC – Technical Review Committee

(*) - See alternative approach on next page

Example of small molecule cleaning limits calculation using the ADE value and minimum therapeutic dose

Common Industry Cleaning Limit Calculations:

Step 1: Calculate Maximum Allowable Residue (MAR) as mg of Product A per kg of Product B for either:

- **A specific product changeover of Product A to Product B, or**
- **Calculate a worst case cleaning limit considering all products made in same equipment**

Minimum Therapeutic Dose MAR : For 1/1000 min. therapeutic dose, SF=0.001

$$\textbf{Dose MAR} = \frac{T_A \text{ (mg of A)} \cdot \text{conversion } (10^6 \text{ mg of B/kg of B}) \cdot (SF)}{B_B \text{ (units of product B)} \cdot C_B \text{ (mg of B/unit)}}$$

Health Based Exposure Limit (Tox) $MAR_{ADE/PDE}$

$$\textbf{TOX MAR}_{\textbf{ADE/PDE}} = \frac{\text{ADE or PDE (mg of A/day)} \bullet \text{conversion } (10^6 \text{mg of B/kg of B})}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

Example of cleaning limits calculation using the ADE value and minimum therapeutic dose

Common Industry Cleaning Limit Calculations (Continued):

Step 2: Using Calculated MAR from Step 1, convert MAR to the allowed amount per cleaning sample:

Residue Acceptance Limit (RAL) for Swabs as (mcg of A) per Swab:

$$\textbf{Swab RAL} = \frac{\text{MAR (mg of A/kg of B)} \cdot L_B \text{ (kg of B)} \cdot A_S \text{ (cm}^2\text{/swab)} \cdot \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in cm}^2\text{)}}$$

RAL for Rinsate as (mg of A) per kg of Rinse:

$$\textbf{Rinsate RAL} = \frac{\text{MAR (mg of A)/(kg of B)} \cdot L_B \text{ (kg of B)}}{W_R \text{ (kg of Rinse Used)}}$$

Example 1: Resulting Swab Cleaning Limit Grid

Product A = Drug Product being cleaned out of equipment

Product B = Next Drug Product to be made in that equipment

For a given manufacturing equipment producing 4 different Drug Products, one would have the following permutations of cleaning limits for each change-over cleaning:

Changeover from Product 1 to product 3 results in the worst case lowest cleaning limit

Product A / Product B	1 Calculated Limit mcg/swab	2 Calculated Limit mcg/swab	3 Calculated Limit mcg/swab	4 Calculated Limit mcg/swab
1		240	3000	4000
2	1200		2100	560
3	35	4500		600
4	500	2400	60	

Example 2: Establishing Worst Case Cleaning Limits for Therapeutic Compounds

Product	Input TA	Input BB	Input CB (mg dosage unit)	Result Max Daily Dosage (mg dosage unit/day)	Input LB (kg)	Result Dose MAR (mg A/Kg next drug Product1 to 3)	Input AS (cm2)	Input EW (cm2)
1	2.5	1	150	150	650	1.89	100	100,000
2	5	2	250	500	1000	--	100	
3	10	3	440	1,320	200	--	100	
4	50	5	250	1,250	750	--	100	
5	100	4	800	3,200	700	--	100	
Worst case comment	Prod 1 is lowest		Highest weight	Next product 5 is highest	Prod 3 is smallest batch	Prod 1 to 3 is lowest		100,000

Note when establishing worst case limits, the worst case Product A to Product B changeover scenario is typically used in the calculation. Resulting in overly conservative limit for most changeover scenarios.

Example 3: Spreadsheet Reflecting the Inputs for Provisional ADE Values

After screening of products for potential segregation, assess Other products made in that equipment

Drug Substance	Endpoint Used	Dose (mg)	PK/MF	UFc	ADE Value (Oral) (mg/day)	ADE Value (Parenteral) (mg/day)
Product 1	MTD	250	0.4	90	2	1
Product 2	MTD	100	0.7	30	3	2
Product 3	MTD	1	0.6	30	0.03	0.02
Product 4	MTD	20	0.5	30	0.7	0.3
Product 5	Long-term rat LOAEL	0.3 mg/kg /day	1	180	0.08	0.08
Product 6	MTD	0.5	1	30	0.02	0.02

PK/MF = Pharmacokinetic Adjustment Factor or Modifying Factor
UFc = Composite Uncertainty Factor
MTD = Minimum Therapeutic Dose
"Other" = Segregation not required per Segregation Quality Standard

Step by Step Example

Prioritizing Development of Health-Based Exposure Values and Evaluating Effectiveness of Current Cleaning Limits

Follow the decision tree tool in Flowchart

1. Identify the product: ‘Capzone’
2. Check if the ADE value for Capzone is available.

Step 3: If an **ADE value is available**

- If an **ADE value is available**, perform the cleaning limit (CL) calculation. Or, compare the ADE value directly to the 1/1000 minimum therapeutic dose value used in the cleaning limit calculation, since the rest of the variables of the cleaning calculation are identical whether performing a dose based limit or an ADE based limit calculation.
- Compare if the CL using ADE is greater than, or less than the current limit. Document the assessment and conclusions, including effect on the Cleaning Validation (CV) Program:
  - If the new health-based CL > or equal to Current CL, can maintain current CL.
  - If the new health-based CL is <current CL, evaluate the difference between the two CLs with site Quality Assurance, Production, EHS, Quality Control (if applicable) for further discussion and resolution.

Step 3: If an **ADE value is not available for Capzone**

- Determine if Capzone has been assessed for segregation (e.g. highly sensitizing beta lactam). If it does not require segregation:
- Verify if the OEL or OEB monograph is available
- Verify if the monograph is based on the minimum therapeutic dose:
  - Refer to the abstract on the first page of the monograph i.e. the monograph is based on the minimum therapeutic dose when the monograph states that it is based on clinical data, or both clinical and nonclinical data
  - If it is not clear in the monograph that this was based on the minimum therapeutic dose then further toxicologist analysis is required (step 6)
- Verify if current cleaning limit (CL) was calculated using 1/1000th of the same minimum therapeutic dose used to calculate the OEL or OEB.
- If so, then current CL is considered appropriate. Document the assessment and conclusions.

Further toxicological analysis

- Further toxicological analysis is required when:
  - An ADE is not available and the product requires segregation assessment
  - The OEL or OEB is not based on the minimum therapeutic dose or is not available
  - If current CL was not calculated using 1/1000 of the same minimum therapeutic dose used to calculate the OEL/OEB (e.g., it was calculated using NMT 10ppm, or used a SF of 1/100, etc.)
- The toxicologist determines if a provisional ADE value can be defined. If so, the site may utilize it in the comparison to existing cleaning limits.
- The site will calculate a health based CL
- If the new health-based CL is lower than current CL, notify the toxicologist to prioritize the development of ADE value for re-analysis. Communicate to site Quality Assurance, Production, EHS, Quality Control (if applicable) the potential for change to the current CL for further discussion and resolution.

Finalize the assessment

- Once the ADE has been determined and approved, the site will verify that the provisional and approved ADE values are the same. If not the same perform step 4 – recalculate the health based CL and compare to existing CL.

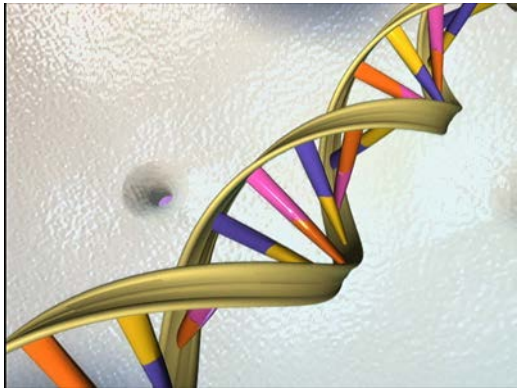
- If an ADE value cannot be determined (e.g. highly sensitizer Beta lactam products) then the site will review the manufacturing segregation assessment

Note Steps need to be repeated for each product

Large Molecule Considerations

- Biological products often degrade and denature during cleaning, rendering them inactive

- EMA HBEL guide Sect 5.3: using ADE value of the active and intact product may not be required for macromolecules



Industry Experience

At Pfizer: based on internal survey

- Assessment outcomes vary by manufacturing site: e.g. dependant on their equipment use (e.g. dedicated or multi-product), type of products (e.g. small or large molecules)

- Generally in > 85% of cases, dose cleaning limit is lower than health based cleaning limit using ADE, often by an order of magnitude or more

- Performing the assessment for legacy products consumes significant resources (e.g. time)

In industry: based on prior EfPIA survey: Generally in > 85% of cases, dose cleaning limit is lower than health based cleaning limit using ADE

Industry Experience

At Pfizer: Why are sites reluctant to use/change to less stringent health based cleaning limits?

- Most sites have cleaning validation complete (or ongoing for new products, other changes)
- Changing the cleaning limits requires re-assessment of:
  - The analytical test and sampling methods used to detect the product residue (e.g. have they been validated in a range to include the new higher limit?)
  - The equipment cleaning validated status: does validation need to be re-executed?
- There is risk of failing visual inspection after cleaning when using health based cleaning limits, which are often significantly higher than dose based cleaning limits
- If site experience is that they can consistently clean to the lower dose limits, there is often little motivation to consume resources to assess using less conservative cleaning limits
- Some markets still expect dose based cleaning limits

Considerations for Inspections

- Developing HBELs for legacy products is time consuming, especially for sites with hundreds of products
- For legacy processes, assessing current cleaning limits vs HBEL derived cleaning limits can take significant time and effort, depending on the number of products at a manufacturing site
- In majority of cases (>85%), dose based cleaning limits used historically in industry are more conservative than use of HBEL cleaning limits
- Risked based approach to prioritization and assessment is wise use of resources
- Do manufacturing sites have a documented risked based plan/approach, especially for legacy products, with established timelines?
- Are qualified toxicologists intimately involved with the process per that documented plan/approach?

Concluding remarks from the Associations

- **All express their thanks for the opportunity to engage in dialogue at this workshop, and offer their resources for future discussion**
- **For us, a successful outcome will ensure:**
  - **The difference between risk and hazard is well understood**
    - **Regulators will have confidence in the processes used by industry to derive HBELs**
  - **It's not just about the numbers**
  - **There is a lot of scholarship associated with deriving HBELs**
    - **It is understood that many, especially smaller, companies may not have site-based or in-house expertise and resources and may have to outsource the work**
    - **Extensive discussion about the derivation of HBELs during an inspection may not be possible**

Next Steps

- **We recommend a substantial revision of the Q&A document**
  - **Or revision to the SWP guideline**
    - **We would appreciate an opportunity to comment on any future Q&A, reflection paper or revised guideline prior to release**
- **There are also topics of importance that remain to be resolved e.g.,**
  - **Relating to animal health products**
  - **Responsibilities of the manufacturer vs MAH**
- **Given the complexity of the subject matter, future timelines should be carefully considered**
  - **It may be that the recent implementation timelines were too short and resulted in some companies being unable to make sufficient investment in HBEL determinations**
- **Similar to the increased collaboration between assessors and inspectors, we support the greater involvement of safety experts with the inspectors**

efpia

European Federation of Pharmaceutical Industries and Associations

Questions?






European Federation of Pharmaceutical Industries and Associations

Backup






Approach 2: How can I use the existing OEB to estimate a default ADE band for comparison against the current cleaning limit for investigational product?

- OEB paradigm closely aligns with ADE value methodology so bottom of band can be read to a default ADE value
- Same value as derived using Threshold of Toxicological Concern (TTC) outlined by Dolan et al 2005
- Where existing cleaning limit is lower than the calculated HBEL cleaning limit, development of a full ADE maybe lower priority

Pfizer OEB	Default ADE Value (default TTC per Dolan et al)
OEB 1	10,000 ug/day
OEB 2	1,000 ug/day
OEB 3	100 ug/day
OEB 4	10 ug/day
OEB 5	1 ug/day