

# Using Health-Based Exposure Limits to Assess Risk in Cleaning Validation



**Ester Lovsin Barle, PhD,  
MScTox, ERT**  
*Corporate Occupational  
Toxicologist*  
**Lonza**

Setting data-driven, scientific cleaning validation limits reduces inconsistencies and risk with pharmaceutical dosage form product carryover.

## Background

In December 2016, the European Medicines Agency (EMA) released for public review a questions-and-answers document focused on the risk-based prevention of cross contamination in pharmaceutical manufacturing and setting health-based exposure limits (HBELs) (1). EMA made clear that HBELs should be established for all products. EMA also noted that limits for cleaning purposes should continue to be based on risk assessments including the concept of safety margins to help account for variability in cleaning processes and analytical methods (2).

Since HBELs were introduced in the European Union in 2015, inspections have shown that manufacturers have been slow to adopt EMA guidelines and many do not have the expertise within their organizations to create good-quality HBELs. A few companies that have developed HBELs have not been using them other than to determine cleaning limits. This has revealed limited use in cross-contamination and risk assessment.

## The History of HBELs

The term *HBEL* was first introduced in EMEA guidelines in 2014 with the intention of establishing health-based exposure limits when identifying cross-contamination risks while manufacturing different medicinal products in shared facilities. Occupational exposure limits (OELs) are based on the same data and the same scientific principles as the HBEL limits used in carryover limits.

In 2010, an International Society for Pharmaceutical Engineering (ISPE) guidance was published describing the use of acceptable daily exposure (ADE) limits in cleaning validation and risk assessment. The EMA followed with a regulatory document in 2015 that detailed permitted daily exposure (PDE) limits.

HBELs, PDEs, and ADEs are defined as doses that are unlikely to pose an adverse effect if an individual is exposed by any route of administration at or below the dose every day for their entire lives. A lifetime for a patient is considered to be approximately 80 years; a working lifetime, considered in the OEL, is approximately 40 years.

## Reliability of Limits Used in Product Carryover

The risk of product carryover in pharmaceutical manufacturing came to light in 1988 with the recall of cholestyramine USP. The API used to make this drug had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The contamination

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was traced to inadequate cleaning and cleaning validation of drums that were previously used to recover solvents during pesticide manufacturing at another facility.

Five years later, Gary Fourman and Michael Mullen of Eli Lilly suggested a combination of limits for product carryover, including 10 ppm as the maximum amount of drug that could appear in another product (3). This amount was considered to be the threshold beyond which dose could potentially create an effect in individuals.

Another criteria for limiting product carryover is LD<sub>50</sub>, which is a dose that is used in animal studies via oral administration and is lethal in 50% of the population. This endpoint is unreliable for human toxicity and is considered less accurate in assessing patient risk. Thus, the use of LD<sub>50</sub> for determining cleaning limit is not appropriate.

Third is the widely used 1/1,000 minimum daily dose (MinDD) criteria. Also proposed by Fourman and Mullen (3), this exposure limit suggests that no more than 1/1000 of a drug's therapeutic dose can be present in another product or as residual product on a piece of equipment.

And last are HBELs, which, in contrast to the aforementioned criteria, address who can be exposed and how they can be exposed. HBELs take into account all the relevant data that are important for determining a scientifically justified limit for the target population, including sensitive patients such as children, pregnant women, and the elderly. In addition, they address the route by which the exposure may occur.

In summary, many criteria have been used in the past to determine a safe cleaning limit. Limits have been interpreted individually, perhaps even subjectively. Due to difficulties and inconsistencies in the application of these approaches to the wide variety of pharmaceutical dosage forms across entire industry, no single, consistent approach exists for establishing limits for cleaning validation.

## The Beauty of HBELs

So, how do we identify a reliable, scientific limit? HBELs are an important part of the solution because there are consistent, harmonized, and set by experts. HBELs are relevant for the manufacture of specific products or routes of administration, and they are adequate for risk assessment. They also eliminate the need to use undefined terms such as "certain cytotoxic" or "certain hormone."

Creating a good HBEL and monograph is based on evaluating all relevant available pharmacological and toxicological data including both non-clinical and clinical data. Data collection inspection must identify:

- The chemical and its mechanism or mode of action;
- Any health hazards found in the preclinical studies;
- Any health hazards and effects found in clinical studies, unless a drug is not yet in the clinic;
- The pharmacokinetic and pharmacodynamic aspects of the drug; and

- The routes of patient exposure that were not intended originally.

In addition, HBEL monographs must contain an expert assessment to identify:

- Any critical effects on the patient and the worker. *Critical effect* is defined as the most sensitive adverse effect that is considered relevant to the target population.
- The assignment of adjustment factors. These values provide a margin of safety between an unwanted effect and the HBEL.
- Several calculations of HBEL, if data allows. However, the selected HBEL must be clearly explained and justified.

A good HBEL monograph can be lengthy and may take up to 40 hours of expert work. However, for the purposes of cleaning validation experts, a summary page should be designed to quickly identify the parameters for setting cleaning validation limits, as well as for industrial hygiene exposure assessments. An important aspect of HBELs is that all its parameters are looked at for each drug individually.

## Regulatory Requirements

With regard to exposure limits and associated data, the Rules Governing Medicinal Products in the European Union chapter on good manufacturing practices (GMPs) state that manufacturing authorization holders must ensure that active substances are produced in accordance with GMPs (4). Audits should be carried out at the manufacturer and distributor of active substances to confirm that they comply with the relevant GMP practice. Finally, consideration should be given to potential cross-contamination from other materials on site.

The owner of the data used for HBELs must clearly communicate it to the manufacturer, whether it is internal or external. The manufacturer should ensure that the quality of the incoming data is sufficient to provide safe manufacturing of all products produced in the shared facility for patients and workers alike.

## Good Practices in the Use of HBELs

OELs, as well as PDEs and ADEs, are mathematical representations (as ranges) of potential biologic effects. This is similar to the number of calories that individuals are recommended to eat in a given day, which is based on age, height, weight, and activity level, but it is not an absolute number. OELs are conservatively set for a daily lifetime exposure via inhalation.

OELs are often the basis for banding in the pharmaceutical industry. In a recent survey of pharmaceutical companies, most firms applied some sort of hazard or exposure banding with various numbers of bands and categories in their systems. These banding concepts are largely linked to historical processes within companies and are unlikely to be harmonized across the industry. OELs—like PDs and ADEs—do not require additional banding by a toxicologist. Banding or defaulting OELs to a safe limit is appropriate for drugs in early-stage development.

After an OEL is calculated, it can be directly compared to industrial hygiene in monitoring and the risk for workers can be identified and mitigated. Many times, the attractiveness of easy banding and categorization concepts is so appealing to end users that they disregard the need for a proper risk assessment. Banding based on hazards or OEL should never be a substitute for industrial hygiene expertise or define engineering solutions.

A high-quality HBEL can be compared to the previously used method for deriving maximum safe carry-over based in 1/1000 minimum daily dose (MinDD). If the comparison shows that the PDE is higher than 1/1000 MinDD, cleaning is sufficient and no action is required. However, if the HBEL or PDE is lower than 1/1000 MinDD, a retrospective check of previous cleaning is in order (see **Figure 1**).

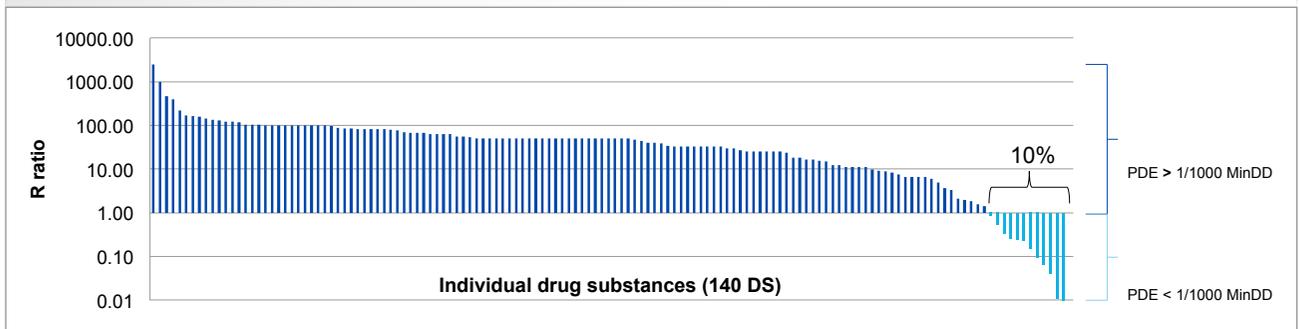
A recently published study of 140 reported drug substances from a typical pharma portfolio was compared to the minimum daily dose criteria with calculated PDE. Approximately 10% of the substances had PDE lower than 1/1000, which could be

a potential risk for patients if 1/1000 MinDD criteria was used previously (5).

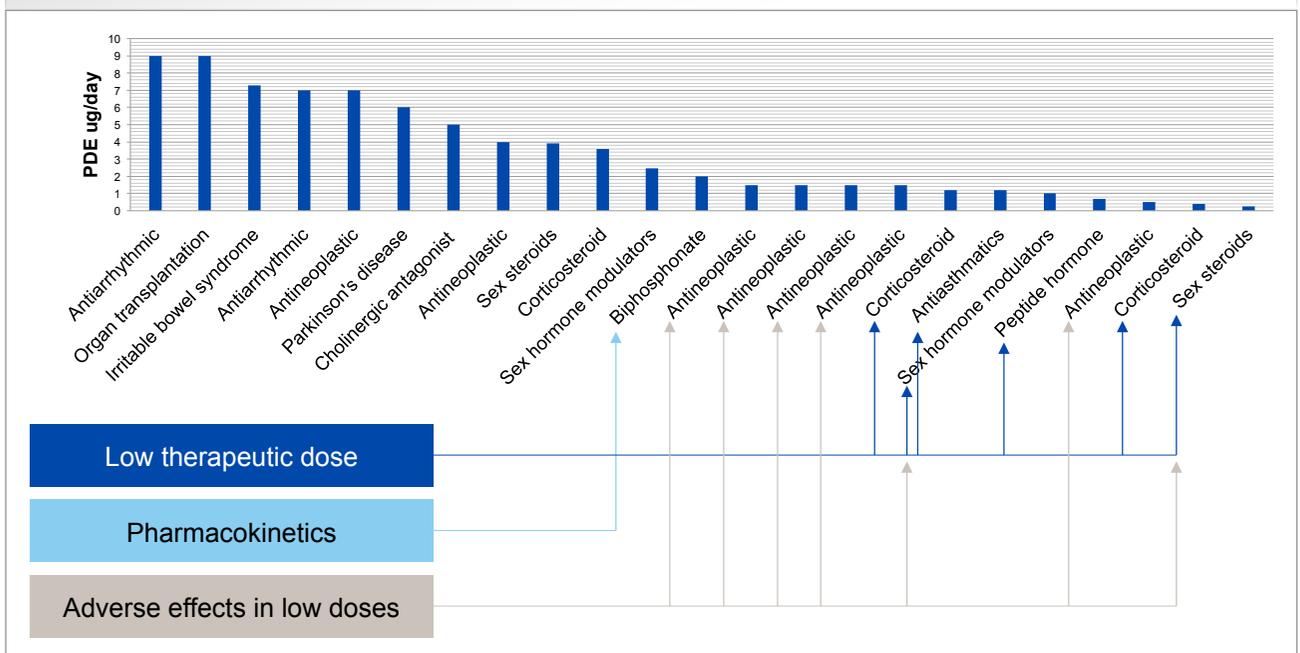
PDEs can be less than 10 ug per day for several reasons. For example, it may stem from low therapeutic dose, pharmacokinetic factors such as accumulation in the tissues, adverse effects in low doses, or a combination of those factors. PDE calculation is, however, only the first step in assessing the risks for cross-contamination in a multi-purpose manufacturing facility (see **Figure 2**). Other criteria that are included in determining risk is batch size, maximum daily dose of the next product, as well as criteria associated with cleaning that are not related to toxicology.

PDE of the previous product, batch size, and the maximum daily dose of the next product are used to calculate the maximum safe carryover (MSC) from the previous product. The MSC value for each possible changeover in the facility is then calculated with the shared surface of the equipment between the previous and the next product, and plotted in a table

**Figure 1:** Permitted daily exposure (PDE) by the route/0.001 MinDD (R ratio).



**Figure 2:** Reasons for “low” permitted daily exposure (PDE) (under 10 ug/day).



(see **Figure 3**). The lower table identifies products at potential risk for contamination because their surface residue is below the cleaning capability in this facility, which was determined to be 20 mg/m<sup>2</sup>. Such risks must be mitigated by developing cleaning procedures, avoiding difficult changeovers, and careful campaign scheduling (6).

**Margin of Safety**

After an HBEL is established, should the 10 ppm and 1/1,000 MinDD criteria still be applied? The margin of safety is the distance between the analytical data and the HBEL base limit, which is indicated by a green arrow on **Figure 4**. This margin of safety indicates the probability of patient exposure to the API residues resulting from ineffective cleaning (7).

If there is a low margin of safety, the process cleaning capability is poor because of the risk that the drug will contain a contaminant above the HBEL may be high. As seen in **Figure 4**, the true margin of safety cannot be measured when imposing the 10 ppm or 1/1000 MinDD criteria in addition to the HBEL.

**Summary**

HBELs are scientifically justified limits, and other criteria such as 10 ppm and 1/1000 MinDD are not needed in addition to show the level of the cleaning process capability. As a consequence, cleaning validation efforts should be focused on where the risks are high with the science behind the HBEL pointing companies toward products that have the greatest risk.

**References**

(1) European Medicines Agency, *Questions and Answers on Implementation of Risk Based Prevention of Cross Contamination in Production* and “*Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities*” (EMA/CHMP/CVMP/SWP/169430/2012),

**Figure 3:** The MSC value for each possible changeover in the facility is calculated.

Example of a shared facility with 11 APIs by using cleaning capability of 20 mg/m<sup>2</sup> (6)

$$MSC_{\alpha} [g] = \frac{PDE_{\alpha} [\mu g] \times Batch\ size_{\alpha} [kg]}{Maximum\ Daily\ Dose_{\alpha} [mg]}$$

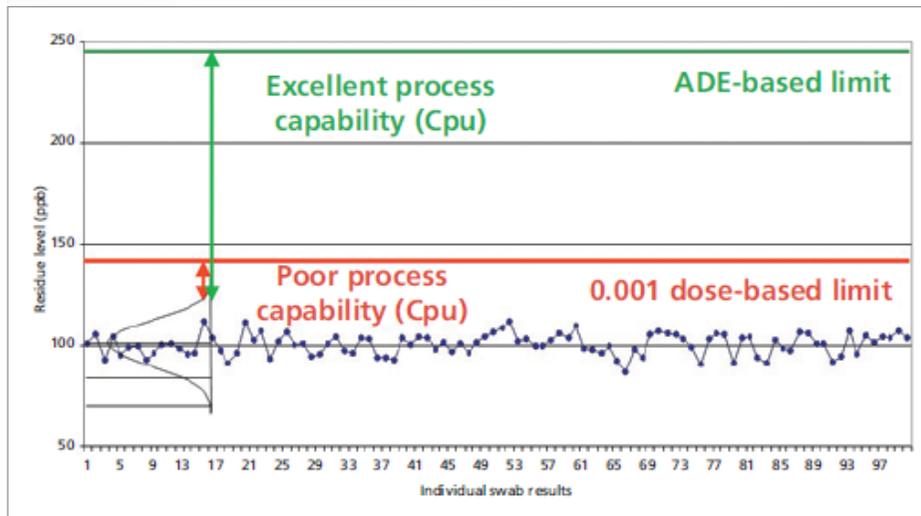
$$M\ S\ S\ R_{\alpha} [mg/m^2] = \frac{MSC_{\alpha} [g] \times 1000}{Surface\ for\ \beta [m^2]}$$

Risks are identified when surface residue is under the cleaning capability of 20 mg/m<sup>2</sup>

API	PDE [µg/day]	Maximum daily dose [mg/day]	Batch size [kg]	Equipment surface [m <sup>2</sup> ]
1	7	40	580	100
2	65	200	690	125
3	200	2000	180	100
4	85	300	330	180
5	85	100	470	188
6	30	300	1075	188
7	10	1440	216	60
8	330	100	310	78
9	15	750	207	220
10	1000	3000	335	100
11	5	450	120	100

MSRR	Following Product (B)										
	1	2	3	4	5	6	7	8	9	10	11
1		195	6	43	175	133	18	278	9	8	19
2	9850		60	410	1675	1276	170	2665	84	76	180
3	29400	5530		1222	5000	3809	510	7949	250	226	540
4	12200	2295	75		2075	1581	211	3300	104	94	225
5	12200	2295	75	507		1581	211	3300	104	94	225
6	4850	910	30	202	825		85	1310	41	35	90
7	1470	276	10	61	250	190		397	13	11	27
8	48941	9204	300	2035	8325	6341	847		418	376	897
9	2205	415	15	90	375	286	38	596		15	40
10	146970	27640	904	6110	25000	19043	2542	39744	1255		2695
11	735	140	5	30	125	95	13	199	6	6	

**Figure 4:** Improved process capability moving from 0.001 dose to acceptable daily exposure (ADE) limits.



Dec. 15, 2016, [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2017/01/WC500219500.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/01/WC500219500.pdf)  
 (2) Z. Brennan, “EMA Releases Q&A on Exposure Limits and Hazardous Compounds,” Jan. 9, 2017, <http://raps.org/Regulatory-Focus/News/2017/01/09/26523/EMA-Releases-QA-on-Exposure-Limits-and-Hazardous-Compounds>  
 (3) G.L. Fourman and M.V. Mullen, *Pharm. Technol.* 17(4), 54–60 (1993).  
 (4) EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/chapter\\_5.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/chapter_5.pdf)  
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 (6) M Crevoisier et al., *Pharm. Technol.* 40(8), 52–56 (2016).  
 (7) A. Walsh et al., *Pharm. Technol.* 40(8), 45–55 (2016).