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June 30, 2020
World Health Organization
Avenue Appia 20; CH-1211 Geneva 27, Switzerland
Gigantev@who.int

Reference: WHO Working document QAS/20.849

Dear Dr Valeria Gigante (WHO Technical Officer):

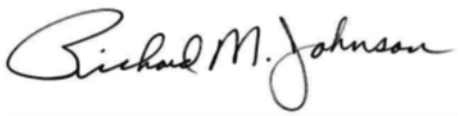
PDA appreciates the opportunity to provide comments to the WHO Working document QAS/20.849: Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities. The details included by the experts the World Health Organisation (WHO) are a welcomed directional move towards a global harmonization of requirements.

Attached is the comment table with general and specific comments, recommendations, and justification to further clarify the feedback. The comments have been developed by the PDA Technical Report 29 and 49 Cleaning Validation Task Force and other subject matter experts in our global membership who are very supportive this document. Our comments reflect recommendations to align with ASTM International Standards E3106, E3219, as well as the stated PDA Technical Reports which provide a framework for a specific element of a cleaning validation program. We are pleased that WHO is moving towards science, risk, and statistics-based approaches. In addition, cleaning validation activities should align with the cleaning validation process sequence as outlined in ASTM E3106 to further support harmonization efforts. PDA recommendations are prepared by a committee of experts in pharmaceutical manufacturing, taking into consideration comments received from other subject matter experts, our international membership, and the industry at large.

The comments were peer reviewed and approved for use by the PDA Science Advisory Board and PDA Board of Directors consisting of pharmaceutical manufacturing experts.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality.

Kind regards,



Richard Johnson
President & CEO, PDA
CC: Claire Vogel, WHO ; Jahanvi (Janie) Miller, PDA

Comments on WHO Working document QAS/20.849, May 2020
Title of the document: Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities

Comments submitted by: Parenteral Drug Association Technical Report 29 and 49 Revision Team
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Date: 24May2020

Template for comments

*Kindly complete the table **without modifying the format** of the document - thank you.*

General comment(s) if any:	**Originator of the comments**
The comments have been developed by the PDA Technical Report 29 and 49 Cleaning Validation Task Force and other subject matter experts in our global membership who are very supportive this document. Our comments reflect recommendations to align with ASTM International Standards E3106, E3219, as well as the stated PDA Technical Reports which provide a framework for a specific element of a cleaning validation program. We are pleased that WHO is moving towards science, risk, and statistics-based approaches. In addition, cleaning validation activities should align with the cleaning validation process sequence as outlined in ASTM E3106 to further support harmonization efforts. PDA recommendations are prepared by a committee of experts in pharmaceutical manufacturing, taking into consideration comments received from other subject matter experts, our international membership, and the industry at large.	PDA

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
N/A	Across Document	To harmonize with “19 April 2018 EMA/CHMP/CVMP/SWP/246844/2018 Committee for Medicinal Products for Veterinary Use (CVMP) Committee for Medicinal Products for Human Use (CHMP) “Questions and answers on implementation of risk-based prevention of cross-	Change “traditional” to “historic” throughout the document.	M	PDA

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		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)" The term "traditional" implies continuation of the previously utilized cleaning validation strategies and does not encourage cleaning validation practitioners to employ risk and science-based approach. On the other hand, the term "historic" indicates strategies that were simply employed in the past.			
2	97-98	This change is consistent with the ICH Q8-Q12 approach prevalent in current quality risk management pharmaceutical manufacturing practice, as an enabler of quality management system (ICH Q10).	Change from "the different possible approaches – including methods that account for pharmacological and toxicological data (Health-Based Exposure Limits {HBEL}) – that could…" to: "the risk-based and the science-based approach based on an identification of the residual material hazards that evaluate pharmacological and the toxicological data to establish Health-Based Exposure Limits (HBEL) – that should…"	M	PDA
2	101-102	This document provides tools for implementation, rather than points to consider	Change from "points to consider when reviewing the current status and approaches to cleaning validation" to: "tools to develop, qualify and maintain cleaning validation program"	M	PDA
2	103-104	Redundant with line 97	Remove "It further focuses on approaches where HBELs setting need to be considered in cleaning and cleaning validation approaches."	L	PDA
2	104	Typo	Change "needs" instead of "need", Change "HBELs" to "HBEL"	L	PDA

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2	106	Consider adding Cosmetics and Medical Devices to the scope as these are in the scope of both American Society for Testing and Material (ASTM) E3106 "*Standard Guide for Science Based and Risk Based Cleaning Process Development and Validation* " and ASTM E3219 "*Standard Guide for Derivation of Health Based Exposure Limits (HBELs)"*	Change “The principles” to “This guidance outlines the general principles and approaches that WHO considers appropriate elements of cleaning validation for the facilities that manufacture human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), cosmetics and medical devices, referred to in this guidance as products”.	L	PDA
3	114	Recommend changing the Definition of "*Cleaning Validation*" and using the definition found in ASTM E3106	Replace: " Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size". With " - collection and evaluation of data, from the cleaning process design stage through cleaning at commercial scale, which establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment, taking into consideration factors such as batch size, dosing, toxicology and equipment size".	H	PDA
3	125	Recommend changing the Definition of "*Margin of Safety*" and using the definition found in ASTM E3106	Replace: "The margin of safety is the distance between a calculated acceptance limit and the actual residues after cleaning. It indicates the probability that a patient has to be exposed to the API residues resulting	H	PDA

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			from cleaning. With: "difference between the cleaning acceptance limit (based on HBEL) and the process residue data"		
3	129	Recommend changing the Definition of "*maximum safe Carryover (MSC)*" and using the definition found in ASTM E3106	Replace: "Mathematically calculated quantity of residue from a previous product when carried over into a different product that can represent potential harm to the patients" With: "The maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients".	H	PDA
3	132	Recommend changing the Definition of "*maximum safe surface residue (MSSR)*" and using the definition found in ASTM E3106	Replace: The maximum safe surface residue is mathematically calculated dividing the quantity of residue on a contact surface by the total area of contact (Maximum Safe Carryover/Total Equipment Surface Area). With: The MSSR is the maximum amount of process residue that can remain on equipment surfaces and still be safe to patients. The MSSR is mathematically calculated dividing the Maximum Safe Carryover (MSC) by the total area of contact (MSC/Total	H	PDA

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			Equipment Surface Area). For example, the MSSR is not used as a limit and is only used for Risk Assessment. The comparison of process residues to MSSRs may be used for risk assessments, to understand the margin of safety for that process residue, and to demonstrate whether the process residues on equipment product contact surfaces pose significant risk to patients.		
3	134	To clarify the calculation	Change “Total Equipment Surface Area” to “Total Equipment Shared Product Contact Surface Area” Add: “Maximum surface residue that does not lead to potential harm in the patients.”	H	PDA
3	136	Monitoring is part of verification. Verification is not an “addition to monitoring”	Change to: "…verification. The application of methods, procedures, tests, and other evaluations as a single cleaning event or continued monitoring, in order to determine compliance with GMP principles."	L	PDA
4	145	To clarify historically based approach.	Change “suggested in GMP texts” to “suggested in GMP texts based on arbitrary and not risk based and scientifically based criteria.”	H	PDA
4	148	The continued use of traditional approaches should be justified by the company through a Risk Assessment. Suggest changing the text to reflect this need.	Change sentence to: "Where historical acceptance limits are *still being* used, ~~the decision should be discussed~~ ~~and~~ *this must be* justified *and documented in a Risk Assessment* inclusive of a comparison between historical data and HBEL as an alternative to new approaches in setting acceptance criteria.	H	PDA
4	150	To harmonize with “19 April 2018 EMA/CHMP/CVMP/SWP/246844/2018 Committee for Medicinal Products for Veterinary Use	Add “For existing products, manufacturer’s historically used cleaning limits could be retained and can be considered alert limits provided that when	H	PDA

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		(CVMP) Committee for Medicinal Products for Human Use (CHMP) “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)”	taking cleaning process capability into account, they provide sufficient assurance that excursions above the HBEL will be prevented.”		
5	154	Editorial, as guidance discussed specific risk base and science based approach	Change “Approaches” to “Approach”	H	PDA
5	156	First sentence implies that traditional cleaning validation was adequate, and this may not have been the case for some products. In some cases, traditional limits were set arbitrarily and may not have provided for patient safety even though they may have passed the arbitrary limit	Change sentence to: "Historic cleaning validation approaches often simply verified that an existing cleaning procedure met historic limits.	M	PDA
5	160	Sentence can be improved to align more closely with ASTM E3106 principles.	Change sentence to: Manufacturers should ensure that their cleaning *procedures are appropriately developed* and that their cleaning validation provides scientific evidence that *residues of* products manufactured in shared facilities can be *removed to safe levels providing a high margin of safety to patients.* Control measures *should be* implemented to mitigate the risks of contamination and cross-contamination	M	PDA
5	168	Typo/Recommendation to standardize terminology.	HBEL setting instead of HBELs setting. Recommend defining HBEL in the first appearance without the “S” and that it stands for Health Based Exposure Limits (plural). Therefore the "s" should not appear in any location within this document if	L	PDA

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			concurred with that definition and acronym as first referenced.		
5	164-169	The bullet points should be re-ordered to follow the ICH Q9 and ASTM E3106 processes and give a more organized flow. Most importantly, Risk Assessment must come before any other activity. Suggested wording changes: In addition, change “points” to “elements” To better describe elements of the program.	Change sentence to: This approach should include at least the following elements which are further described in the text below: • Risk Assessment *to identify hazards and analyse risks including derivation of* HBELs; • *Cleaning process development studies* including cleanability studies; • *Determination* of technical and organizational controls; • *Risk-based selection* of Analytical procedures; • Cleaning *process qualification* with *process* capability *demonstrated* through statistical evaluation. • *Cleaning process* control *strategy*;	H	PDA
5	172	The Master Plan should be developed based on the outcomes of the Risk Assessment.	Change sentence to: Manufacturers should describe their policy and approaches, including the points mentioned above, in *the Risk Assessment*. A master plan *for cleaning validation should be developed based on the outcomes of the Risk Assessment*	H	PDA
5	175	Clarify what is meant by appropriateness of cleaning validation.	Change sentence to: It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness	H	PDA

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			of *existing* cleaning validation *studies*.		
5.1	183	Suggest adding ASTM E3106 as a reference.	Change sentence to: Risk management principles, as described in *ASTM E3106 (10) and* other WHO guidelines on quality risk management (*11*), should be applied to assist in identifying risks and controls to mitigate contamination and cross-contamination	H	PDA
5.2	199	Clarify that non-contact surfaces are included in scope if identified as a risk during the Risk Assessment.	Change sentence to: Consideration for cleaning validation should cover contact surfaces, as well as non-contact surfaces, *if* the latter have been identified as areas of *risk in the Risk Assessment.*	H	PDA
5.2	206/207	The principle that all equipment must be included in cleaning validation should be stated up front.	All equipment including equipment and components that are difficult to clean…	M	PDA
5.2	207	To clarify shared surface area calculation.	Change "also be included in the cleaning validation and calculations" to "as well as tools such as scoops, spatulas also be included in the cleaning validation and calculations if they are not dedicated."	M	PDA
5.3	211	State that solvents/detergents should be selected based on a scientific evaluation and risk analysis. Suggest including references to ASTM Standards: G121 "Standard Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents" G122 "Standard Method for Evaluating the Effectiveness of Cleaning Agents"	Change sentences to: "Solvents and detergents used in cleaning processes should be selected based on cleaning process development studies including cleanability studies (ASTM E3106). They should also be appropriate for their intended use. The selection of the relevant solvent and detergent should be scientifically justified."	H	PDA

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		G121 and G122 were developed originally for oxygen service but have been used in the industry for many years and have been recently updated to include pharmaceutical, biotech and medical devices in their scope.			
5.3	215-216	If recommendation for line 211 is adopted these lines become redundant.	Recommend removal of these lines if line 211 is adopted.	H	PDA
5.3	219	Language logic: removal of detergent residues is not *after* cleaning.	Either say “removal by cleaning” or “assurance after cleaning that removal has been successful” change detergent to cleaning agent	L	PDA
5.4	227	More clarity	… mainly on product contact surfaces”	L	PDA
5.4	230	Update guidance to reflect accepted practices on sampling.	Change sentences to: “Swab sampling is the preferred method that should be used. Rinse samples are acceptable for surfaces inaccessible for swab sampling. Visual inspection must always be performed in the locations where it is possible.”	M	PDA
5.4	234	To assure statistical significance of sampling.	Change “The location” to “The number and locations (swab samples) and the manner…”	H	PDA
5.4	241	Editorial, as “are” does not grammatically fit.	Change “are” to “and”	H	PDA
5.5	N/A	To capture logical sequence of the process.	This section should be moved after Section 5.8		PDA
5.5	248	A cleanability study is not performed for effectiveness against microorganisms. While some microorganisms may be inherently removed by detergents/cleaners, this is not the intent of these products, which is more suited for DET/AET tests.	remove "microorganisms" as it is misleading.	H	PDA
5.5	250	The term concentration should not be used here. Concentration typically concerns volume, but surface	Change sentences to:	H	PDA

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		residues are typically expressed by areas.	The lowest *residue level per unit surface area* of a substance that can be removed by following the cleaning procedure should be established for different materials, intermediates and products on different materials of construction. The *amount of residue remaining should* be expressed in mg/m2, or mcg/cm2.		
5.5	255, 256	Include references to ASTM Standards: G121 "Standard Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents" G122 "Standard Method for Evaluating the Effectiveness of Cleaning Agents"	Change sentences to: The method should be scientific and may include spiking on coupons made from different materials of construction (*Ref G121*) . *ASTM G122*, or other appropriate methods, may be used.	H	PDA
5.5	260	To add completeness and granularity.	Add at the end of the sentence “and associated recovery factors.”	M	PDA
5.5	262	Clarify terminology.	Change sentence to: The results should be documented in authorized reports and used in further determinations, such as Maximum Safe *Surface* Residue (*MSSR*).	M	PDA
5.6	267	To reflect ICH Q9 steps	Change “assessment of risks” to “identification, evaluation, assessment and control.”	H	PDA
5.6	271	To add essential source of risk.	Add “product” just before “premises.”	H	PDA
5.7	287	To correct proper attribution of measures.	Move “dedicated equipment” to “technical controls”	H	PDA
5.8	293	Typo/Recommendation to standardize terminology.	HBEL setting instead of HBELs setting. Recommend defining HBEL in the first appearance	L	PDA

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			without the “S” and that it stands for Health Based Exposure Limits (plural). Therefore the "s" should not appear in any location within this document if concurred with that definition and acronym as first referenced.		
5.8	313-328	Order of this table is not logical and there are duplications.	Per ASTM E3219: • substance identification • chemical structure • clinical indication • mode of action • route of administration • preclinical/nonclinical data, for example o acute and repetitive dose studies o genotoxicity data o reproductive toxicity data o carcinogenicity data • clinical data • pharmacodynamics and pharmacokinetics • identification of the critical effect(s) • point of departure for the HBEL calculation(s) • adjustment factors • justification of the selected lead rationale (if calculations with different PODs were made)	H	PDA
5.8	337	More clarity. Selected adjustment factors must be justified (explained) not only justifiable.	F represents various adjustment factors. The value selected should be justified.	H	PDA
5.8	339	Based on a current manufacturing practice many manufacturers are CMOs who have no toxicological knowledge in-house. Often the assessment is not performed by the manufacturer but by contracted experts or the client of the manufacturer.	Change to “The report should be reviewed by an individual with in depth-knowledge on the substance or a peer PDE document author with appropriate qualifications.”	M	PDA

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		The report should be reviewed by an individual with in depth-knowledge on the substance or a peer PDE document author with appropriate qualifications.	An alternative change Delete the terms “manufacturer” and “in-house”.		
5.8	341/342	The report must give enough detail to explain the PDE derivation to an independent expert. The term “summary” may be interpreted as suggesting something very short. Misleading to put special emphasis on genotoxicity and carcinogenicity. These effects and all others must be discussed in the report (see bullet list above). In the new system, the HBEL is the measure for the toxicity of the compound, and qualitative descriptors such as “genotoxicity” or “carcinogenicity” are only used by the expert to derive an HBEL but are no longer mentioned in the outcome of the assessment. The HBEL is protective of any effect, and the downstream user does not need to care about what the lead effect of the compound is and what family it belongs to. The HBEL is a safe limit. An HBEL with a “carcinogenicity” notation is not more critical than one without it. In addition, if a cleaning agent may enter a drug as a cross-contaminant or a synthesis intermediate is made on the equipment before the final API, these cleaning agents and intermediates also need to have an HBEL to determine how much carry-over is acceptable.	Change “product” to “substance, cleaning agent and degradant”. Change “genotoxicity and carcinogenicity” to “toxicity”.	M	PDA
5.8.	344	Additional clarity to support the statement.	“establishing” (or “defining”) the protocol measures instead of “considering”.	H	PDA
5.9	351	To clarify and to reflect FDA Guidance for Inspection of Cleaning Procedures (1993)	Change “justifiable” to “scientifically based, practical, achievable, and verifiable”	H	PDA
5.10	379	Suggest using established references to existing regulatory guidance such as EMA's Guideline with	"The higher the PDE value, the lower the hazard. The products and therapeutic groups considered for	H	PDA

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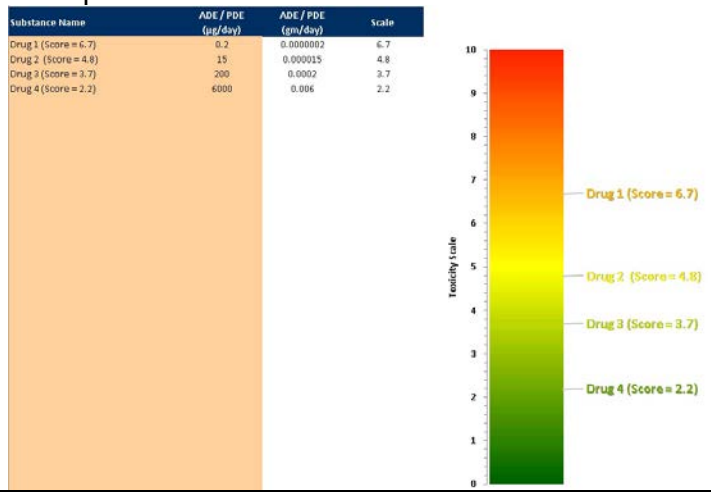
		ASTM E3106 versus a risk-MaPP.	manufacturing should be plotted based on an identified scale of risk (14)" 14 - ASTM E3106 Refer to - Walsh, Andrew, Ester Lovsin Barle, Michel Crevoisier, David G. Dolan, Andreas Flueckiger, Mohammad Ovais, Osamu Shirokizawa, and Kelly Waldron. "*An ADE-Derived Scale for Assessing Product Cross-Contamination Risk in Shared Facilities*" Pharmaceutical Online May 2017		
5.10	382	Suggest replacing Figure 1 with an example of the ADE-derived scale as described in the article cited above. The location of a compound on the scale is calculated directly from the HBEL and is a specific number instead of an approximate location.	Example of the HBEL-derived Scale 	H	PDA
5.11	391-392	Specific methods should only be compulsory where necessary based on risk. In well assessed low risk situations, less sophisticated methods should be acceptable.	Add the following “Required analytical methods should commensurate with the risk (i.e. if the maximum safe carry-over is very high, non-specific methods (or even visual inspection alone based on data driven risk assessment) may be acceptable”	H	PDA
5.11	401	To add completeness and granularity.	Add the following statement after line 401:	M	PDA

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			"Analytical methods should be able to quantify or detect residue levels at the maximum safe surface residue (MSSR)."		
5.13	413-420	To add completeness and granularity to the bullet points in this section.	Recommend adding to this section statements to the effect that: • Cleaning procedures should define critical parameters (e.g. temperatures, volumes/rinsing, cleaning agents/quantities, monitoring of control points for CIP systems, etc.), hardest to clean areas etc. as appropriate. • Manual cleaning procedures need sufficient detail to assure repeatability	M	PDA
5.13	433	To harmonize with "19 April 2018 EMA/CHMP/CVMP/SWP/246844/2018 Committee for Medicinal Products for Veterinary Use (CVMP) Committee for Medicinal Products for Human Use (CHMP) "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)"	Add to this line "and process capability" to provide practitioners with a clear path forward following principals of FDA Process Validation Guidance.	H	PDA
5.15	455-456	Clarity to avoid misinterpretation.	The presentation of individual results and data used in the calculation, should be attributable, legible, contemporaneous, original and accurate (ALCOA)."	H	PDA
5.15	456	Clarity to avoid misinterpretation.	Dispel abbreviation "ALCOA" – "attributable, legible (permanent), contemporaneous, original and accurate"	M	PDA
5.16	465	Personnel first and foremost should be trained on cleaning.	Before "cleaning validation" add the term "cleaning"	H	PDA
5.16	467	Recommend adding specificity for training in each	Add "based on their responsibilities" to the end of the	M	PDA

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		subject.	sentence.		
N/A	482	Risk MaPP is out of place amongst regulatory and consensus guidance and standards. ASTM is an international consensus standard organization. The Risk MaPP is addressing subject of containment rather than specifically cleaning validation. Although being a valuable reference on containment, the team recommends replacing it with and ASTM E3106 which has been reviewed and balloted on by regulatory agency (FDA) and ASTM E3219 which provides a more accurate information on derivation of HBEL.	Consider adding ASTM E3106 and ASTM E3219.	H	PDA