PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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AIDE-MEMOIRE

INSPECTION OF HEALTH BASED EXPOSURE LIMIT (HBEL) ASSESSMENTS AND USE IN QUALITY RISK MANAGEMENT

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1. DOCUMENT HISTORY

Adoption by Committee of PI 052-1	22 May 2020
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2. INTRODUCTION

2.1 The establishment of Health Based Exposure Limits (HBEL) when different medicinal products are produced in shared facilities are detailed in the PIC/S PI 046 Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities (HBEL Guide).

2.2 The guideline is supplemented by PI 053-1 "PICS 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'" (HBEL Q&A).

2.3 This document describes an approach to assessing HBEL that can be conducted by inspectors without specialised toxicology knowledge.

2.4 Inspectors should be aware that HBEL assessments are an interpretation of available data and application of adjustment factors assigned through expert analysis. However, there can be differences in the use of data that can result in variation in HBEL values between assessments of the same substance by different experts. Variations up to 3-fold are typically present and may extend beyond this at times. If variation between different HBEL values is seen at levels at or above 10-fold, then this should be investigated to determine if one or more HBELs has been inappropriately processed. For example, if an HBEL for a substance is set at 8 µg/day by one expert and 120 µg/day by another then this would be worthy of further investigation.

2.5 The continuum diagram seen in the Q&A document (PI 053-1) reflects the fact that there is no hard cut off between hazard levels, and no high risk/low risk bands. As such the absolute HBEL in µg/day should be taken as an indicator of where the substance

sits on the continuum. It is important to note, the action that the site takes via Quality Risk Management (QRM) to control the hazard and reduce the risk is of significant importance with the µg/day value being an indicator of the hazard level that needs to be addressed.

2.6 Permitted Daily Exposure (PDE) is a form of HBEL and is the model defined in the HBEL guide. As such this may be the most common HBEL that inspectors encounter. However other similar terms such as Acceptable Daily Exposure (ADE) may also be seen and may be considered equivalent.

2.7 As with all aspects of Good Manufacturing Practices (GMP), the category of deficiencies recorded should relate to the significance of the finding and the threat to patient safety. A critical deficiency would only be recorded where there was an immediate and obvious threat to patient safety. Major deficiencies are more likely where manufacturers handle lower HBEL products and have significant gaps with the expectations of PIC/S GMP and supporting guides.

3. PURPOSE

3.1 The purpose of this aide-memoire is to define an approach that inspectors may consider when inspecting HBEL documents. Prompts to consider, expectations and PIC/S GMP references to use are recorded (as well as references to the Q&A for information). The aide-memoire can be used as a supporting document for inspection of cross contamination risk in shared facilities.

4. SCOPE

4.1 This aide-memoire incorporates inspection of the HBEL assessment report as well as the Quality Risk Management (QRM) assessment for cross contamination control. The two topics are incorporated as the use of the HBEL reports µg/day value in the QRM study is as important as the generation of the value.

5. Aide-memoire for Inspection of Health Based Exposure Limit (HBEL) Assessments and Use in Quality Risk Management

No.	Prompt	Expectation	GMP Reference & (information reference)
Section 1 – The Health Based Exposure Limit Assessment			
1	Is the HBEL assessment report a comprehensive document?	An HBEL assessment report should have: • A summary of the decisions, justification and final HBEL figure. • Be signed and dated by the person(s) conducting the assessment and include or reference their Curriculum Vitae (CV). • Comprehensive literature search consulted as part of the assessment. • Clearly documented search strategy • Results of the search and commentary on findings. • Identification of critical effects and points of departure that will be used in HBEL calculations – nonclinical data and clinical experience. Clear rationale for assignment of adjustment factors.	Chapter 4 principle, 4.3, HBEL Guide section 6
2	Is the summary supported by data in the report?	The conclusions recorded in the summary should be drawn from specific points made in the text of the document and should not have excluded any points made without clear justification.	Chapter 4 principle, HBEL Guide Annex
3	Review the CV for the person(s) completing the HBEL.	A CV should provide evidence of the qualifications (typically pharmacy, pharmacology or other relevant pharmaceutical science degree), background in toxicology with reasonable previous experience in determination of health-based exposure assessments such as: • Occupational Exposure Limit (OEL) • residual solvent • elemental impurities (by establishing PDE). Self-taught experience in HBEL since the HBEL guide was introduced in 2014 may not be adequate without other relevant qualifications and experience.	Chapter 2; 2.1, (HBEL Q&A 4)

4	If an HBEL assessment was contracted out or procured, review the contract agreement.	A contract should be in place stipulating relevant GMP requirements of the service provision. Evidence should be available of an assessment of the legality (no conflicts of interest), suitability and competence of the contract acceptor.	Chapter 7; 7.1, 7.5, 7.7, 7.14, 7.15, 7.16, 7.17.
5	Has the manufacturer (typically Quality department) recorded an assessment of the HBEL document received from the toxicologist?	The manufacturer's assessment should be at a similar level to an inspector and consider the same prompts as in this document. Additionally, the manufacturer should consider the practical elements related to manufacture (nature of the hazard in relation to other products manufactured and whether a detailed QRM study is viable – or if dedicated facilities are required). This assessment may be recorded as a stand-alone assessment or included in other documents such as cleaning validation master plan (CVMP), wider QRM study etc.	Chapter 7; 7.5
6	Is the literature search well documented and does it appear to include a breadth of references?	If the manufacturer is the innovator (or under contract from the innovator): Source pharmacological and toxicological data, should have been used/provided. If the manufacturer is not the innovator, multiple data sources should have been consulted, such as: European Public Assessment Reports: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%25253Aname_field/Human/ema_group_types/ema_medicine_en Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/ Toxnet: https://toxnet.nlm.nih.gov/ Toxicity Reference Database (ToxRefDB) https://catalog.data.gov/dataset/toxicity-reference-database-bcf19 Aggregated Computational Toxicology Online Resource (ACToR) https://www.epa.gov/chemical-research/actor Integrated Risk Information System (IRIS) https://www.toxnet.nlm.nih.gov/newtoxnet/iris.htm	HBEL Guide section 6

		Occupational Exposure levels (OELs) derived by competent authorities or originator to ensure workers safety (WHO, OSHA, MAK) ECHA database of registered compound data (https://echa.europa.eu/information-on-chemicals/registered-substances) Note: During inspection be aware of challenges in identifying deliberate exclusion of data sources. If concerned about the risk from the product, refer the HBEL for expert assessment.	
7	Is the literature search strategy documented?	Is there a plausible explanation of why the search used was considered most appropriate?	Chapter 4 principle
8	Are the results of the search recorded, with appropriate commentary on findings?	Does the report account for the data found through the search? Are aspects searched, where no information was found related to the product, also recorded e.g. carcinogenicity?	Chapter 4 principle
9	Does the assessor justify the relevant critical end point(s) (lowest dose that causes a toxic effect) used in the HBEL calculation(s)?	Typically, the lowest HBEL value obtained will be used. If not, this should be justified. If concerned about this, you may wish to seek an expert opinion should the control of the product in shared facilities be high risk.	Chapter 4 principle, HBEL Guide section 6
10	Have all the adjustment factors (AF) used been explained/justified?	A rationale for the selection of AFs should be recorded in support of the HBEL calculation. An explanation should be provided for the effect on HBEL for different routes of administration (of potentially contaminated products) and for Veterinary Medicinal Products, any susceptibility for specific species.	HBEL Guide section 4.1, 6.
11	Consider how the HBEL value differs to other HBEL values you have previously seen for the same product?	HBEL values may vary due to interpretation of data and use of adjustment factors by toxicologists. The following guidance should be considered: • Differences of a factor of 3 are normal and should not raise concern. • Differences between 3-fold and 10-fold need more attention but may be justified. • Differences >10-fold are generally not justifiable, this may be due to: ○ use of wrong starting point ○ disregard of clinical data ○ false application of safety factors ○ incomplete data search ○ wrong weighting of data	PIC/S Annex 20; QRM section 3.

		• If the difference is >10-fold and there is a potential risk to patient safety as a result of the HBEL used and reference to an expert within the Competent Authorities is recommended. • Assess the margin of safety that has been established between the HBEL value and cleaning limits. A factor of 10 may be reasonable to provide confidence that permitted exposure is not breached. • The difference could be related to the dosage form of the potentially contaminated product, check what route of administration used in determining the HBEL.	
Section 2 - The QRM Study for Organisational and Technical Control measures based on the HBEL			
12	Examine the procedure related to cross contamination controls to see how the manufacturer uses HBEL within the context of a risk-based study on cross contamination control.	The procedure should explain how the manufacturer uses HBEL as an input to the QRM study. What sets aside one QRM study from another is: 1. How they consider the risk associated with the hazard (defined by HBEL as the quantity that can be considered as a safe permitted contaminant per daily dose of another product). 2. How they then use the level of the hazard (quantitative HBEL) to assess the risks of cross contamination and develop risk reduction measures (organisational and technical controls). 3. How they establish suitability of, and monitor, the risk reduction measures adopted.	Chapter 4; 4.3, Chapter 5; 5.20
13	Review the QRM study, it should be aligned with the level of the HBEL.	The QRM study is typically supported by a tool such as Hazard Analysis and Critical Control Points (HACCP) or Failure Modes and Effects Analysis (FMEA). Both can be effective tools and others may be relevant also such as Failure mode, effects and criticality analysis (FMECA). Gauge how well the HBEL value is used within the QRM study to identify and remove potential cross contamination opportunities. This is as important as establishing the HBEL value. The company should have considered the level of permitted exposure they are trying to control by considering the HBEL value in the context of controls required.	Chapter 5; 5.20, 5.21, (HBEL Q&A 3)

		The multidisciplinary team responsible for the QRM study should have considered where and how within the facility, contamination at the HBEL level could be transferred into a subsequent product batch. This should have been considered at batch level where a contaminant may be homogenously mixed within a batch (e.g. prior to blending) but also where it may be partially mixed (e.g. at the end of blending, such as a contaminated outlet valve) or at unit dose level (e.g. at compression, encapsulation, primary packaging). Considering opposite ends of the continuum and with regard to a sliding scale in between: • 1µg/day is much easier to cross contaminate at a significant level to the next product than 10000µg/day and so the level of detail of the assessment and the resultant controls will be significantly different. • 1µg could be transferred to unit dose level much easier than 10000µg. The level of controls required would be completely different and dedicated parts may be needed to consistently prevent 1µg contamination. • With 1µg a detailed practical, well informed investigation of hold up points is essential to identify points that may hold up contamination. • With 10000µg a thorough investigation for hold up may still be needed but hold up would have to be more significant and thus less likely to remain undetected. Dedicated parts may not be required. Take careful note of manufacturers (particularly with low HBEL products) that simply convert an HBEL into a cleaning limit and demonstrate their swab method can detect to the required level. This is not a QRM approach. Also take careful note of manufacturers (particularly with low HBEL products) who justify low risk based on current controls without practically assessing if these are actually effective. Reference to historical performance may also be inappropriate if the controls were not adequate. Remember cross contamination above HBEL levels may not always have been detectable.	

14	Consider the structure and general content of the HBEL QRM assessment report.	A 100-page document without structure is very difficult to inspect (and for the company to use effectively) and should in itself be a deficiency. The QRM should be structured with the usual sections of a report such as: Title, approvals, content, executive summary, overview of the equipment/facility, specific assessments, summary, conclusions, references etc. Beware of manufacturers presenting a large QRM study to deliberately make inspection of the detail difficult.	Chapter 4; 4.3. PIC/S Annex 20; QRM section 3.
15	Challenge aspects of the HBEL QRM assessment.	Where controls appear poor, poorly justified (and risk seems significant) or where low HBEL products (red/dark amber section of the continuum) are manufactured in shared facilities, select examples of more complex equipment or the facility (walk through the facility/equipment firstly) and consider the manufacturers risk assessment against actual practice. Actual practice should reflect the controls defined in the assessment and these should offer the control suggested. Consider asking for demonstrations of controls, review cleaned equipment (ask for it to be fully dismantled) to look for signs of visual contamination. Request evidence for effectiveness of critical local extracts and air handling systems.	Chapter 4; 4.1

6. REFERENCES

PIC/S PE 009 Guide to Good Manufacturing Practice for Medicinal Products, Part I; Basic Requirements for Medicinal Products

PIC/S PE 009 Guide to Good Manufacturing Practice for Medicinal Products, Annexes including PIC/S Annex 20 Quality Risk Management

PIC/S PI 043 Aide-Memoire Cross-Contamination in Shared facilities

PIC/S PI 046 Guideline on Setting Health Based Exposure Limits for use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities

PIC/S PI 053 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

7. REVISION HISTORY

Date	Version Number	Reasons for revision