Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Health Based Exposure Limits (HBEL) and Q&As

The EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) & EMA/CHMP/CVMP/SWP/463311/2016

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Content

- Intent of HBEL
- Post Implementation Observations.
- Explanation of key Q&As.
- Consultation feedback and consideration.

HBEL

- A process to allow assessment of the hazards posed by a pharmaceutical including toxicological considerations.
- A process to support a move away from GMP chapter 3 & 5 requiring certain types of products to be manufactured in dedicated facilities.
- A tool to support more flexibility for manufacturers to justify controls that may be effective short of full dedicated facilities.
- Draft agreed by Safety Working Party in 2012.
- Adopted in 2014 following consultation that concluded in 2013.
- Implemented in phased approach from June 2015

Consultation prior to implementation of EMA/CHMP/ CVMP/ SWP/169430/2012

- Consultation brought out several points including:
  - General support for the concept of Health based exposure limits.
  - Need for alternative approaches.
  - Desire by some to retain option of traditional approaches.
    - For low hazard products
    - For existing products with historically adequate control.
  - Suggestion that the guide be applied for highly hazardous products only.

Post implementation observations

- Following implementation of the guide (EMA/CHMP/ CVMP/ SWP/169430/2012) a number of factors were apparent to regulators:
  - Most manufacturers were slow to adopt the guide approach and few were working with or towards established PDEs.
  - Many did not have the expertise within their organisations to deliver HBEL (PDE). Many who had PDEs had outsourced the work.
  - Feedback to inspectors from some sites was that determining PDEs on low hazard products was unnecessary and disproportionate regulation.
  - To differentiate those ‘few’ with specific toxicological concerns a system was introduced that required assessment of all products, even those that were known low hazard.
  - Although the guide allowed for other justified approaches, sites were not considering this but rather taking no action.

Post implementation observations

- PDE calculations for many products resulted in values that would be in excess of visual thresholds and thus were not discerning from a cleaning validation perspective.
- Thus not supportive of EU Directive 2003/94 Article 8 paragraph 2; *"…..in order to avoid contamination, cross contamination……"*
- Some EU Competent Authorities (CAs) felt unable to inspect against the HBEL guide as Inspectors did not have the skills and knowledge to challenge data that would be presented on inspection.
- Inspectors referring PDEs for subsequent 'expert' assessment where support was available. This would delay conclusion of deficiencies and categorization of such on inspection.
- In most cases those sites that had developed PDEs did nothing with them other than determine a cleaning limit.

Q&As

- A sub group of the Inspectors Working Group and Safety Working Party first met in Q1 2016 to consider how the HBEL was being implemented and what it expected.
- The group believed they had adequate experience of the issues seen and further consultation with industry was not considered at this point.
- Questions were drafted based on the recorded issues.
- Answers were developed with toxicological input from the Safety Working Party.
- The Q&As were regarded as providing interpretation of the HBEL guide but also offered an *alternative option* to application of Health Based Exposure Limits where detailed toxicological assessment was not proportionate to the hazard.
- As such the Q&As were not intended to be mandatory but rather to offer an optional alternative (as allowed by the guide).
- Q&As published for consultation in January 2017.

Q&As – so called highly hazardous category

- Reference to products as highly hazardous and non highly hazardous was developed. This provided an opportunity for the latter not to be applied through the full HBEL guide process thus supporting proportionate regulation.
- This however was not intended to be mandated and those companies already with PDEs or who preferred this approach could continue down this route.
- As a result an option to retain the (universally and historically used) 1/1000th of a dose was provided for non highly hazardous products. This could be used for setting cleaning limits (the purpose for which this has traditionally been used).
- It was not intended to suggest that a product categorised as non-highly hazardous should not be handled and controlled safely via risk assessment.
- It was believed that the Q&A #2 approach to identifying highly hazardous products could be utilised with less toxicological expertise. Thus helping small, medium manufacturers and/or those only manufacturing lower hazard products.
- It was also considered that 1/1000th of a dose(Q&A #4) was equivalent to the PDE approach determined from human clinical data but with an additional safety factor of 10 to set cleaning limits within the Permitted Daily Exposure. This would ensure PDE is not exceeded as a result of variability in cleaning and inspection.
    - Low compliance manufacturers often react best to fixed limits/expectations

Q&As, some further points of explanation

- Q&A1 was intended to clarify that a health based exposure limit is required although this may not necessarily be via the EMA guide route.
- Q&A6 intended to provide guidance on setting cleaning limits;
  - Highlighting that the guide (PDE) approach was not expected to set cleaning limits as these would have to be tighter than the exposure limit.
  - Highlighting that traditional cleaning limits would still be effective for lower hazard products.
- Q&As 7 & 8 on veterinary aspects were developed.

Q&As

- Q&A12 was intended to highlight a key issue seen on inspection;
  - Even where PDEs have been generated, most companies use them to set cleaning limits but do not use them as input to meaningful risk assessments to develop organisational and technical control measures.
- Q&A13 was intended to highlight a commonly seen strategy by manufacturers (even following implementation of the HBEL guide);
  - Where products are manufactured that may not be suitable in common shared facilities they are grouped into a separate facility without always considering the cross contamination risk between the products grouped.

Consultation and comments received

- Comments have been received related to all the Q&As with some conflict of opinion between stakeholders.
- 32 Stakeholders submitted comments.
- Q&As drawing most comments were 2, 3, 4, 6.
- Key comments have been compiled and reviewed by the working group.

Key topic areas on Q&As for discussion

- Q&A 2 - Use and applicability of Highly Hazardous categories
  - As a core means of assessing need for full use of ‘the guide’.
  - As a means of prioritising use of the guide.
  - Suitability of factors included such as sensitisers and highly potent.
  - Roles and responsibilities for developing PDEs
- Q&A3 – Use of OEL/OEB to determine if products Highly Hazardous
  - Suitability of generating PDE from OEL/banding – adjustment factors and basis of OEL.
  - As a means of prioritising use of the guide.
  - As a means of estimating highly hazardous products
- Q&A 4 - Continued availability of 1/1000th of a dose approach
  - Challenge over scientific basis

Key topic areas on Q&As for discussion

- Q&A 6 - Setting cleaning limits
  - Process capability for existing products
  - Approach for new products to sites – basis of cleaning process development
  - From PDE or other suitable routes/ Additional safety factor from PDE route
- Q&A 7, 8 & General comment - Further specific guidance required for veterinary manufacturers
- Q&A 14 Use of TTC in establishing HBEL – concerns over applicability
- Any other specific points for discussion that stakeholders wish to raise.

Further issues to be addressed

Identification of points requiring further clarification (including EFPIA points submitted with comments) e.g.:

- Options for Health based approach on APIs & Intermediates
- Options for Advanced Therapy Medicinal Products
- Position on very low hazard products, acceptable approaches
- Different hazard limits in various regulations, clarification required
- High sensitising potential definition.
- &????

In Summary

- The Q&As were designed to provide practical benefit to both industry and regulators.
- 32 stakeholders have submitted comments to EMA on the Q&As.
- The implementation team are committed to engagement with stakeholders and welcome this workshop.
- Finding an appropriate way forward to ensure that 2003/94, chapters 3, 5 and health based exposure limits can be implemented in an effective and practical manner is the goal of the implementation team.

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