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Summary of discussions at the workshop on the generation and use of health-based exposure limits (HBEL) held on 20-21 June 2017 at the European Medicines Agency (EMA)

The aim of the workshop was to develop understanding of the use and application of Health-Based Exposure Limits (HBEL) in the context of quality risk management of cross contamination during the manufacture of different products in the same manufacturing facilities. Invitations to participate in this workshop were extended to experts in toxicology and in manufacturing quality representing a number of industry or professional associations known to the GMP/GDP Inspectors' Working Group ("Interested Parties"), GMP inspectors and Safety Working Party (human and veterinary sectors) experts. The regulatory participants were comprised mostly of the team established to oversee implementation of recent guidance on this topic.

Generation of HBEL

The main theme on the first day of the workshop was sharing of experience on the generation of HBEL and on the second day it was the use of HBEL in risk management, i.e. the selection of appropriate technical and organisational measures to control cross-contamination. Significant time was also set aside in the workshop for a discussion on the Q&A related to the topic that had recently been published by EMA for public consultation. In fact the workshop started with presentations from the regulators explaining the reasons why the implementation team decided to publish these Q&A. The opening session also included sharing of some common inspection findings connected with cross contamination control and HBEL.

While the industry associations present recognised the scientific value of HBEL in risk identification in the context of cross contamination control, as expected by EU authorities, it was pointed out that some non-EU regulators have explicit requirements that cleaning validation limits are set at 1/1000th of the minimum therapeutic dose. It was confirmed that PIC/S GMP guidelines are formally aligned with those of EU and therefore also include the need for a toxicological evaluation. To date the topic of HBEL has not been extensively discussed at PIC/S itself but it is understood that an "Expert Circle" on cross contamination control will be formed soon.



Presentations from the industry stakeholders also started with key points on the Q&A for EMA consideration. The first two main industry presentations covered the establishment of HBEL throughout the product lifecycle, prioritising risk assessments and illustrating techniques that can be used to set provisional HBEL. This was followed by a presentation strongly advocating that a rigorous HBEL approach, utilising appropriate toxicological expertise to characterise the hazard that a compound presents, should be carried out for all compounds and arguing that levels based on clinical dose alone for compounds defined as non-hazardous was not an appropriate approach. The experience of one particular company with a wide range of products is that approximately 10% of its compounds had an HBEL lower than 1/1000th of the minimum daily dose. Some useful material was presented on what GMP inspectors could expect to see which might help to evaluate the suitability of HBEL monographs without necessarily possessing particular toxicological expertise themselves.

Draft Q&A published by EMA

As evident from the opening presentations, the most contentious Q&A appear to be numbers 2 and 4. These Q&A reflect a desire on the part of the regulators to avoid manufacturers without available in-house toxicological expertise, having to outsource full HBEL evaluations when it is clear that only low hazard products are involved. For many legacy products, for which clinical safety profiles are well-established, an HBEL based on the 1/1000th minimum therapeutic dose would normally be considered as a sufficiently conservative approach and conventional cleaning validation limits are likely to be safe. These Q&A attempt to identify compounds for which this approach would not be suitable by defining characteristics that would categorise them as “Highly Hazardous” and thereby in need of a full HBEL evaluation. It was not intended that those products evaluated as not highly hazardous would be excluded from the need for risk management determination of suitable organisational and technical controls. Industry stakeholders felt that this flexibility was a retrogressive step and this was also reflected in much, although not all, of the public feedback that EMA had received during the consultation period for the Q&A. Many manufacturers have already complied with the new guidance and it was also suggested that toxicological expertise would still be necessary, albeit to a lesser extent, with the flexibility proposed in order to ensure that the determination as to whether products handled are highly hazardous or not is scientifically sound.

There is another reason why being able to categorise compounds as highly hazardous is advantageous that most industry participants were unlikely to be aware of. It is helpful for EU authorities to flag sites that are handling highly hazardous products in respective manufacturing authorisations. This information about on-site activities is often of value to other authorities and also to potential contract givers and a way of defining these product types in a consistent manner is needed. The current system, based on the superseded chapter 3 of the GMP guidelines, is recognised as unsuitable.

No conclusion was reached on this particular discussion during the workshop but the regulators remain keen on the idea of flexibility in some cases. A large number of manufacturers, although contributing to a small portion of the pharmaceuticals market, are small companies with limited product ranges often handling products that intuitively present a low hazard and it may be disproportionate to force such manufacturers to conduct full HBEL evaluations. Many of these companies have not adequately responded to the new guidance but inspectorates are generally taking a light-handed enforcement approach at this time. Stakeholders indicated that they would not object to opportunities for a flexible approach but were not in favour of what they saw as a binary hazardous and non-hazardous approach. Stakeholders also pointed out that the terms “hazardous” and “highly hazardous” may be misleading as they may have a different meaning in toxicology and manufacturing. The aim of the Q&A is to distinguish products with a high risk of causing adverse health effects at low doses from those of lower risk. On the other hand the workshop discussions have helped regulators to recognise the dangers of

over-simplification and that often, a reasonable HBEL can be easily derived from readily available data although some toxicological expertise may be needed. The workshop discussions will help regulators find an appropriate way forward.

Q&A 6 was also the subject of significant discussion. This Q&A concerns the relationship between HBEL and limits used for cleaning validation or verification. EU regulators never intended that HBEL be equated to limits for this purpose. Neither did they intend to endorse 1/1000th of the minimum therapeutic dose nor 10ppm, common traditionally used limits in the industry although not mentioned in official GMP guidelines. Q&A 6 was intended to clarify that a margin of safety is required below the HBEL to account for variability, for example in the cleaning process or analytical methods, but not that an additional factor be included within the HBEL itself. In many cases, retaining the traditional limits would automatically provide this margin of safety. Discussions also clarified that there is a concept of “Pharmaceutically Clean”, partly accepted as visually clean. All parties agreed that visible residues are unacceptable even if quantified and shown to be lower than the HBEL.

Q&A 14 concerns whether the Threshold of Toxicological Concern (TTC) for mutagenic products of 1.5 µg/person/day is an acceptable default approach to establish an HBEL. Following brief discussion regulators agreed in principle that where data is actually available that this should be used instead, noting that for some high potency substances the calculated PDE may be lower than the TTC. In such cases a full toxicological assessment would be required to derive a HBEL.

There was some discussion as to whether the term “Dedicated Facilities” needed definition. It is acknowledged that this can be misinterpreted and although the regulators felt that sufficient clarification is given in Chapter 5 of the GMP Guide on technical and organisational arrangements to control cross-contamination risks, clarification may be necessary on the extent of measures that could result in a facility being considered as fully dedicated.

A question was posed on whether the draft Q&A will be withdrawn. It was explained that publishing Q&A for public consultation is not normal practice so it should be understood that these Q&A are not necessarily the EU regulators’ final position. The regulators are nevertheless sensitive to the fact that if there is a prolonged delay before their finalisation (or replacement) they could be understood as defining a final position. The workshop discussions will be of great value in better understanding the public comments and in deciding the future of these Q&A.

Use of HBEL

The session started with presentations from three inspectorates on current expectations supplemented by observations from the other inspectorates present. From the ensuing discussions it was clear that experience in the field concerning the use of HBEL is variable at present. Inspectors are not necessarily focussing on how HBEL are being calculated but are expecting them to be generated and used. Many of the problems seen by inspectors relate to the poor application of long-standing GMP expectations in cross-contamination control rather than specific issues on HBEL. It was also noted that observing operations taking place plays an important part for inspectors to assess controls in operation including cleaning practices.

Industry presentations during this session started with a veterinary case study highlighting additional complexities of shared equipment used for human-use and veterinary products, topical products (no clear dose) and variable target species with different body weights. Nevertheless, the case study showed how this complexity can be addressed.

ISPE presented a case study which illustrated how the topic of cross contamination control is an integrated part of the Pharmaceutical Quality System and gave examples of the use of risk

management tools. The presentation included a rationale for the setting of a hierarchy of limits below acceptance limits based on HBEL, such as process control limits, alert limits and action limits. Finally, the presentation also showed how the HBEL has uses beyond the setting of cleaning acceptance limits.

A final case study examined the situation for a company with a large legacy product portfolio, illustrating prioritisation approaches, establishing HBEL, confirming or re-establishing cleaning limits, controls and methods. The presentation included some reflections on large molecule products although this was not a focus for the workshop. Regarding large molecule products, HBEL are applicable but assuming equipment is amenable to effective cleaning risk is often diminished because the product readily degrades and non-specific analytical methods can play a useful role. There needs to be awareness however of the possibility in some cases that degradants might be pharmacologically active.

Next Steps

The final session of the workshop was used for looking forward. The industry would like a better understanding of what to expect from inspectors. It was clarified that detailed examination of how HBEL have been calculated is not anticipated although this may happen in rare cases. Inspectors do not necessarily possess the relevant expertise although over time they will develop some knowledge and a greater awareness of fundamental aspects to be able to challenge what is seen during inspections. There was some discussion about how industry can help with training and education of inspectors and ISPE, which does offer training on RiskMAPP and has already been involved with some non-EU regulator training, expressed willingness to help. As ISPE is a long-standing "Interested Party" of GMP/GDP Inspectors Working Group and is a non-profit-making organisation, there does appear to be potential opportunities and therefore scope for active follow up. It is also recognised that smaller manufacturers would benefit from education. Even if the setting of HBEL is outsourced, sufficient knowledge of the topic would enable proper qualification of vendors and a means of assuring the outsourced work is appropriately done.

It was suggested that publishing some examples showing the correct way of calculating a valid PDE could be useful.

Other topics briefly discussed included active substances. It is noted that the same approaches are applicable to active substances, as described in the introduction of the guideline. During the meeting it was recognised that there is the additional challenge of pharmacologically active intermediates. It was noted that intermediates should be subject to occupational health assessment so this can provide a potential basis for going forward. This topic would require full further consideration with appropriate stakeholders.

Another topic raised during the public consultation was the approach for "Advanced Therapy Medicinal Products" (ATMPs). These are low hazard products in this particular context and are usually processed using dedicated, often disposable, equipment. It was also noted that stand-alone GMP guidelines are being developed for ATMPs and at present these do not refer to the need for toxicological evaluation in the context of cross-contamination control.

One of the most challenging topics that the EMA Implementation Team is facing is a way of defining "Highly Sensitising products". Existing GMP guidance requires these to be manufactured in dedicated facilities although beta-lactam antibiotics are the only example referred to and even this can be questioned scientifically. Academic expertise is being sought and even if it proves possible to make progress on this topic it was stressed that EMA will not implement anything unilaterally without prior consultation with industry stakeholders and other international regulators. Stakeholders advised that they did not feel that further clarification via Q&A was required.

Finally, the regulators were keen to understand what steps could be taken to help veterinary manufacturers implement the new guidance. It is clear that there are unique challenges (e.g. different body weights intra species and across species, the particular case of parasiticides and species specific toxicity) but it has been shown in the workshop that these can be addressed. Veterinary industry stakeholders appealed for flexibility in the approach to apply in relation to their products, with the possibility of continuing to apply the traditional approach in certain cases. IFAH-Europe has suggested that Annex 4 of the GMP Guide should be updated. While it is acknowledged that this Annex has not been updated for many years, there has not been a strong case to do so to date. The regulators are open to details that could be added to the existing guidance, including Annex 4 to support appropriate implementation in the veterinary sector.