EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Outcome of public consultation on 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)

Summary report of comments received during the public consultation and next steps

1. Background and consultation

The Q&A document was developed by a cross-functional implementation team formed of members of the GMP/GDP Inspectors Working Group (GMDP IWG) and Safety Working Party (SWP) of CHMP in response to feedback from regulators and industry on the 'guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'.

Feedback received at the time of the introduction of the above guide was that the guideline did not need to be applied to all products, but rather that its application should be limited to products presenting a higher hazard. For these a more stringent methodology, as compared to traditional approaches to setting maximum allowable carry-over, would need to be applied. Traditional approaches were still thought to be fit-for-purpose for products not falling into this category.

As a result, the Q&A was developed to clarify practical implementation aspects of the guideline and options available to determine the relevant aspects of the guideline that needed to be applied.

The Q&A was subject to a public consultation between January 2017 and 30 April 2017.

Following the consultation, a stakeholder workshop was conducted at EMA on 20-21 June 2017 with 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 summary of the discussions held at the workshop can be accessed at the following link:

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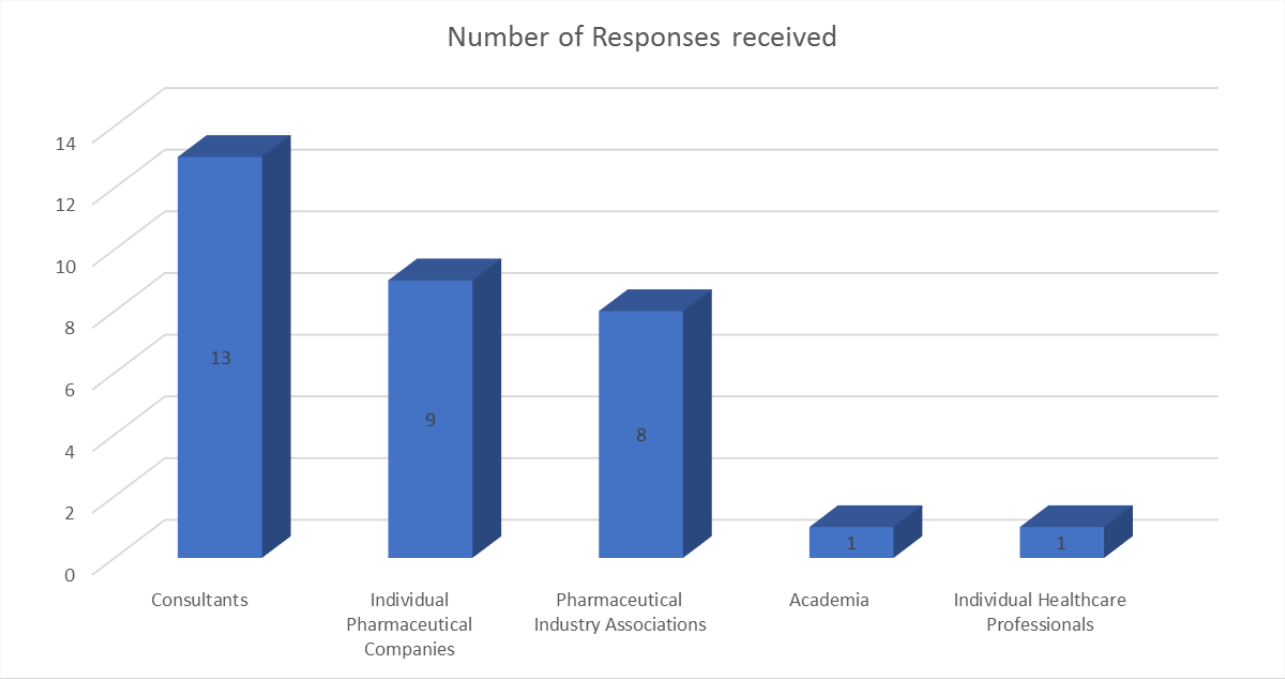
Send a question via our website www.ema.europa.eu/contact

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/08/WC500233051.pdf

2. Contributors

The predominant 'group' of contributors to comments on the Q&A was companies or individuals providing consultancy or services to the industry. This was followed by individual pharmaceutical companies and pharmaceutical industry associations, the latter representing the highest proportion of manufacturers.

The distribution of respondents is shown in the graph below:



3. Summary of main points raised during the consultation

Overall, stakeholders highlighted concerns on the proposed Q&A interpretation of the possible use of the guideline, although some supportive comments were also received. In particular, concerns were expressed on the methodology to follow in order to assess whether materials fall into the previously proposed highly hazardous category. Additionally, the reference to allowing prospective use of traditional approaches to determine exposure limits such as 1/1000th of a therapeutic dose for lower hazard products was not supported by some stakeholders as this was regarded as not being in line with the principles of the Guideline on setting Health Based Exposure Limits. These points were further explored at the workshop (see meeting output link above) where stakeholder groups accepted that applying the HBEL to all products would entail further work and expense for industry beyond that proposed in the Q&A that was subject to consultation. Following this meeting the implementation team undertook to consider the comments from stakeholders and consequently the Q&As were updated.

The implementation team accepted the stakeholders' proposal not to pursue the highly hazardous approach and traditional approaches for determining hazard and risk (e.g. 1/1000th of a dose and 10ppm) and therefore these do not appear in the finalised Q&As. As such the Q&As require manufacturers to determine HBELs assessments for all medicinal products they manufacture.

Highly-hazardous products

References to a highly hazardous category in former Q&As 1, 2 & 4 were not supported. The bases for these comments were that the categorisation was not considered scientifically rigorous in comparison to use of the full guide and many companies had already committed resource to assessing all products against the guide. Because of the weight of opinion against this approach the Q&As were modified to remove the binary system of assessment and categorisation of highly hazardous. Applicability of HBEL to all medicinal products was confirmed in new Q&A1. However, in order to give an indication of the relative hazards of products via a PDE value a hazard model was introduced as the revised Q&A 2.

Use of Occupational Exposure Limits (OEL) or Occupational Exposure Bands (OEB) to determine approximate Permitted Daily exposure (PDE)

Use of Occupational Exposure Limits (OEL) or Occupational Exposure Bands (OEB) to determine approximate Permitted Daily exposure (PDE) and allow categorisation as highly hazardous as per former Q&A 3 was not supported on the basis that additional adjustments may be required considering differences in target population. It was proposed that OEL or OEB may best be used to prioritise the application of the guide to existing products for manufacturers with very large numbers of products. As such this Q&A was removed.

Traditional dose-based calculations

The former Q&A 4 allowing for traditional dose-based calculations such as 1/1000th of a dose to be applied for non-highly hazardous products was not supported as it was considered more scientifically rigorous to consider all points of departure. In addition, this traditional approach may not be appropriate for all populations. With the highly hazardous approach not being retained it is believed by EMA that continued use of the 1/1000th dose approach is not relevant and this Q&A will not be retained. However, where cleaning validation has been completed based on these traditional values it would not be expected that manufacturers would relax cleaning standards. This was clarified in the final published document as new Q&A 6.

Use of LD_{50}

Q&A 5 of the initial draft was largely supported although the possible use of LD_{50} in assessment of materials such as API intermediates, excipients and cleaning agents resulted in different opinions. EMA acknowledged the proposals but still is of the opinion that LD_{50} should not be used as a point of departure for calculation of HBELs. The Q&A was only modified to reflect applicability to drug products and published as new Q&A10. Applicability of data sources for API intermediates, excipients and cleaning agents will be considered and may be the subject of Q&A at a later date.

Cleaning limits

Comments on Q&A 6, the application of cleaning limits, proposed that additional safety factors beyond PDE were not supported for cleaning limits as these were justified against an already safe exposure limit, while application of 1/1000th and 10ppm as cleaning limits were not scientifically justified. Several queries were submitted as to the application of cleaning limits. EMA has given this further consideration and provided clarification in the published Q&A document under new Q&A6. This Q&A refers to process capability (the capability of the process rather than necessarily a statistical approach) and retaining traditional limits where these are tighter than that supported by HBEL. Additionally, the concept that HBEL would be acceptance limits and an alert level (providing a margin of safety) within HBEL should be established as would be the case for environmental monitoring of clean rooms.

Ectoparaciticides and the use of the guideline by the veterinary sector

General support was provided for the initial Q&A 7 approach on ectoparaciticides but suggestions for clearer wording were made. EMA took this into consideration before finalising this as new Q&A 11.

Concerns were raised in relation to the practical use of the guide for the veterinary sector. It was regarded that the guideline/Q&As should include more detail for the veterinary industry especially with regards to species and veterinary products specificities. In relation to this, neither the guideline nor the former Q&A 8 was considered adequate to define a veterinary-specific approach. EMA gave further consideration to views expressed and concluded that it was not appropriate to have separate rules for veterinary products although account should be taken of specific risks related to different species. This is now outlined in new Q&A 12.

Expertise for development of HBELs

Comments on the former Q&A 9 suggested that the Q&A should focus more on the expertise needed for developing health-based exposure limits rather than how inspectors will assess this. This was incorporated into the revised document as new Q&A 4 and Q&A 5 that confirms requirements for contract provision in relation to HBELs.

Threshold of Toxicological Concern (TTC)

In relation to former Q&A10, comments noted the absence of reference to the Threshold of Toxicological Concern (TTC) as referred in the guide. EMA acknowledged this and clarifies that Q&A 10 was not intended to oppose the use of TTC as stated in the guide, but rather to provide further clarification on applicability to Investigational Medicinal Products. This was included in the published document as new Q&A13.

Use of HBELs

Comments on the former Q&A11 stated that HBEL should be conservative enough to cover all age groups and additional specific adjustment is not required. EMA gave this further consideration and removed this Q&A.

Against former Q&A12 comments acknowledge the role of HBEL in the compliance with chapter 5 of the EU GMP guide. Some rewording proposals were considered by EMA and this was included in the published Q&A as new Q&A3.

The reference to highly hazardous products in Q&A13 attracted specific comments, with clarification requested over the definition of dedicated facilities in this context. Some rewording proposals were considered by EMA before including in the published document as new Q&A9.

Concern was expressed that the wording of the original Q&A14 did not take account of substances that may have PDEs below 1.5 µg/day. EMA gave this further consideration when re-assessing the Q&As and determined that this Q&A was not needed as the matter was adequately described in the HBEL guideline.

Mindful of industry expectations that HBELs be applied to all medicinal products a new Q&A7 was introduced to allow manufacturers to exclude analytical testing post completion of cleaning validation. This would be conditional that they can show via a science-based quality risk management study that cleaning is consistent, the hazards are adequately controlled and there is clear evidence that residues can be visually detected at residue limits justified by HBEL and safely allowing for practical variables such as people variation, light, access, surface impact etc. Requirements for good practice visual inspection were stated in new Q&A 8.

4. Next steps

Following the consultation and workshop the Q&As have been revised to take account of comments received. A further public consultation is not foreseen as most comments were considered in the updated Q&A document.

5. Annexes

List of contributors and their individual comments as published on the Agency's website: http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2018/08/WC500252902.pdf