Cross Contamination & the EU GMP Guide

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Outline

- PICs GMP (v13) and Cross Contamination (CC)
- EU GMP Guide changes to Chapters 3 & 5
- Other related EU regulatory changes
- Regulatory differences – meaning and intent of changes
- What are EU inspectors expectations?
- Some questions asked by industry
- Examples of cross contamination deficiencies in EU?
- EU Guide Q & As - some details and the latest thinking
- How different will the PIC/S GMP Guide and EU regulatory expectations be?

Cross Contamination & PICs GMP (v13)

Principle Ch 3 – "…Their *layout and design* must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products… "

3.6 ".. to minimise the risk of a serious medical hazard due to cross- contamination, *dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms).* The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. *For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken*

Chapter 5

5.18 – "…Contamination of a starting material or of a product by another material or product must be avoided. *This risk of accidental cross-contamination arises from*…."

5.19 – "…Cross-contamination should be *avoided by appropriate technical or organisational measures,…"*

5.20 – "…*Measures* to prevent cross-contamination and their effectiveness should be *checked periodically* according to set procedures."

Other aspects of PICs GMP(v13)

QUALITY RISK MANAGEMENT

1.12 Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.

1.13 The principles of Quality Risk Management are that:

The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(ii) The level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.

Changes to Chapters 3 & 5 of EU GMP Guide

3.6 Cross-contamination should be prevented for all products by *appropriate design and operation* of manufacturing facilities.

The measures to prevent cross-contamination should be commensurate with the risks. *Quality Risk Management principles should be used to assess and control the risks.*

Depending of the level of risk, it *may* be necessary to *dedicate premises and equipment* for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

- the risk cannot be adequately controlled by operational and/ or technical measures,
- scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or
- relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Changes to Chapter 3 & 5

5.21 "The *outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organizational measures* required to control risks for cross-contamination. *These could include,….*"

5.20 "A Quality Risk Management process, which *includes a potency and toxicological evaluation,* should be used to assess and control the cross-contamination risks presented by the products manufactured"……

Other Regulatory Changes
The EMA "Tox Model"

"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"

"document aims to recommend an approach for deriving a scientifically based threshold value for individual active substances to be applied for risk identification. The guideline outlines how the data on which the threshold value is derived should be presented in order to achieve a clear and harmonious approach across pharmaceutical industry."

"An approach to review and evaluate *pharmacological and toxicological data* of individual active substances and thus enable determination of threshold levels as referred to in the GMP guideline. These levels can be used as a risk identification tool and can also be used to justify carry over limits used in cleaning validation."

Calculating a PDE

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

Where;

PDE- Permitted daily exposure

NOAEL = No observed adverse effect level

F# = adjustment/uncertainty factors for species, variation in response, duration of exposure, specific known hazards, data availability etc.

From Appendix 3 ICH Q3C (R4) "Impurities: Guidelines for residual solvents"

Also specifics considerations for: actives with genotoxic potential, actives with a highly sensitising potential, Therapeutic macromolecules and peptides..

Regulatory Differences

- What do the differences mean in practice ?
  - Some key points
- What is the intent of the regulatory change?
  - Scientific approach
  - Contextualises technical and organisational measures
- What about implementation dates ?
  - EMA GMP
  - PIC/S

Expectations
Control of Cross Contamination using HBEL – Quality System

- There will be a process for assessing and controlling new and existing molecules in the facility
- Systems in place will be subject to regular review
- Systems will be run and controlled by appropriately qualified (trained) staff who are subject to documented assessments

Expectations
Control of Cross Contamination using HBEL – Risk Management

- Be able to demonstrate robust QRM techniques
- QRM process and compliance will be recorded in a clear and concise manner and show scientific justification for patent safety limits.
- Cleaning to be validated. There will be an ongoing control strategy based on risk with appropriate technical and organisational controls. The control strategy will be subject to regular review
- Have an understanding of failure opportunities and residual risk.

Expectations Control of Cross Contamination using HBEL – Expertise

Staff need to have:

- Expert knowledge not least about the toxicity and pharmacological data relating to products
- A sound understanding about how to avoid cross contamination
- Sufficient knowledge and understanding about the design of the facilities, equipment and processes of manufacture

Control of Cross Contamination using HBEL – Industry Questions

- There has not been a problem up to now so why change?
- What if the Toxicity data does not exist?
- What if the maximum permitted carry over is much higher than we allow now?
- We meet the limit so presumably this means risk of cross contamination is acceptable?
- What are the concerns around the QRM process?
- Is "visually clean" an acceptable limit ?
- Do we need a dedicated facility for each product?

Deficiency findings

- Process for introducing new products did not include a toxicological understanding and evaluation.
- Risk assessment did not challenge/determine the effectiveness of risk reduction measures attributed.
- Development of secure organisational and technical measures to prevent cross contamination were not adequately aligned with the Permitted Daily Exposure (PDE) limits.
- Cleaning and control was not adequately thorough for the nature of high risk products manufactured.
- Cleaning procedures …did not contain adequate instruction to allow the dismantling, cleaning and inspection to be conducted in a consistent manner.
- The process for development of cleaning methods on process equipment did not require that an adequate understanding of the design and construction of the equipment was required

Ref – MHRA GMP Symposium 2015 Graeme McKilligan & Christine Gray

See MHRA Deficiencies 2015 & 2016 in MHRA Blog

Recent Regulatory Q & As

- Fourteen Q & As published FOR COMMENT final version not published yet
- These highlight the fact that a HBEL is required for all products
- That the use of HBEL is of most benefit for highly hazardous products.
- Also highlight that EMA Tox Model states:

"Deviation from the main approach highlighted in this guideline to derive such safe threshold levels could be accepted if adequately justified."

That a HBEL does not need to be applied in full to all products. Traditional approach of 1/1000 dose can still be applied if product not classed as highly hazardous.

Recent regulatory updates – Q & As

- For non highly hazardous products 1/1000 of dose can be taken as HBEL and used as cleaning limits i.e. these limits can be used to develop and assess Organizational and Technical control measures
- Guidance is provided in Q & As on how to determine if your product is categorized as HH
- Points out that HH products require more extensive Organizational and Technical Measures to ensure patient safety e.g. dedicated parts / facilities
- Also highlights that it is not envisaged that cleaning limits established & validated prior to 2015 should be relaxed

Deficiencies associated with use of HBEL and on-going discussions

- Deficiencies are available on MHRA Blog – what the deficiency findings are is important not just for industry but also for regulators

- Recent EMA workshop on generation and use of Health Based Exposure Limits (HBEL) – June 21st 2017
  - Industry point of view and questions
  - Regulatory point of view and questions
  - Discussion Outcomes

PIC/S Position

The PIC/S Working Group on Controlling Cross-Contamination in Shared Facilities (CCCISF), chaired by UK / MHRA, has finalized a **draft PIC/S Aide-Memoire on Cross Contamination in Shared Facilities**, currently under internal consultation. The Committee also endorsed a new mandate for this Working Group for it to become an Expert Circle in order to develop specific training for inspectors in this field.

PIC/S Press release following Geneva meeting Feb 2017

Conclusion

1. The implemented EU changes represent a scientific approach to cross contamination by relating risk to patients to a toxicological and pharmacological action evaluation
2. A similar scientific approach has yet to be fully implemented by PIC/S but QRM approach is in the PIC/S Guideline….
3. Recent EMA discussions demonstrate there is still some way to go to achieve agreement on the correct scientific approach for all products

Glossary

- HH – Highly Hazardous
- QRM – Quality Risk Management
- PDE – Permitted Daily Exposure
- MACO – Maximum Acceptable Carry Over
- HBEL – Health based exposure limits

Useful links

PICs Guide

https://www.picscheme.org/layout/document.php?id=975

PIC/S Press Release

https://www.picscheme.org/layout/document.php?id=1044

EU GMP Guide & Changes to Chapters 3 & 5 & Tox Model

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Recent Q & As for HBEL

www.ema.europa.eu/docs/en_GB/document_library/Other/.../WC500219500.pdf

MHRA Blog

https://mhrainspectorate.blog.gov.uk/2017/03/15/prevention-of-cross-contamination-in-shared-facilities-chapter-3-5-and-the-guideline-on-setting-health-based-exposure-limits/

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Thank you for your time.

Questions?

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