a whitepaper from

NSF Health Sciences Pharma Biotech

Regulatory **Update**

by Pete Gough, Executive Director, NSF Health Sciences Pharma Biotech

EU News

EU GMP Chapter 3 (Premises and Equipment)

The final version of the revised chapter, dated August 13, 2014, was published in September along with the final versions of Chapters 5 and 8. All three revised chapters become effective on March 1, 2015. This revision, together with the revised Chapter 5, is part of a move to adopt a risk-based approach to cross-contamination control using a toxicological evaluation to determine appropriate residue limits.

The draft chapter adds the following new requirement in section 3.6:

> *"Cross-contamination should be avoided 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.*
>
> *Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:*
>
> *i. the risk cannot be adequately controlled by operational and/or technical measures,*
>
> *ii. scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or*
>
> *iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method."*

EU GMP Chapter 5 (Production)

The final version of the revised Chapter 5, also dated August 13, 2014, was published in September. It contains the following changes:

- Sections 17 to 21 were updated to include a new section and to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment
- Sections 27 to 30 were updated to include a new section on the qualification of suppliers in order to reflect the legal obligations introduced by Directive 2011/62/EU, the FMD and supply chain traceability
- Sections 35 and 36 were inserted to clarify and harmonize expectations of manufacturers regarding the testing of starting materials
- Section 71 introduces guidance on notification of restrictions in supply

Section 5.20 requires that *"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".*

This section then states that the outcome of the quality risk management *"should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family".*

Section 5.21 provides a long list of technical and organizational measures that can be taken to mitigate the risk of cross-contamination.

In late November 2014 the CHMP/CVMP published the final version of the "Guideline on setting health based

exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities". This new guideline, effective from June 1, 2015, is to be used for the toxicological evaluation required by the revised Chapters 3 and 5 and the draft Annex 15 when conducting a risk assessment to determine the need for dedicated facilities and to determine cleaning validation limits in shared facilities.

The main features of the Chapter 5 changes relating to **starting materials** are a series of requirements to implement the legal changes in Directive 2011/62/EU, the Falsified Medicines Directive.

A new Section 71 has been added to provide guidance regarding **"Product shortage due to manufacturing constraints".** This adds obligation for the marketing authorization (MA) holder to promptly notify the competent authority of "*any constraints in manufacturing operations which may result in abnormal restriction in the supply".*

EU GMP Chapter 8 (Complaints and Product Recall)

The final version of the revised Chapter 8, dated August 13, 2014, was published in September along with the final versions of Chapters 3 and 5. All three revised chapters will become effective on March 1, 2015.

This is a comprehensive change and the principal reasons for the changes are:

- To reflect quality risk management principles to be applied when investigating quality defects/complaints and when making decisions in relation to product recalls or other risk-mitigating actions
- To emphasize the need for the cause(s) of quality defects/complaints to be investigated and determined, and that appropriate preventative actions are put in place to guard against a recurrence of the issue
- To clarify expectations and responsibilities in relation to the reporting of quality defects to the supervisory authority

The new requirements include the following:

- The need for appropriately trained and experienced personnel to be responsible for managing complaint and quality defect investigations
- The need for sufficient personnel and resources to be available for the handling, reviewing and investigation of complaints and quality defects
- Central management of complaints that does not result in delays to the investigation and management of the issue
- A detailed list of items to be included in a quality defect investigation

There are new sections giving details of expectations for investigation and decision making and root cause analysis and corrective and preventative action.

In the recall section, the new requirements include:

- Any retrieval of product from the distribution network as a result of a quality defect should be regarded and managed as a recall
- For investigational medicinal products, all trial sites should be identified and the countries of destination should be indicated. The sponsor should implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall
- It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities
- The risk of shortage of an essential medicinal product which has no authorized alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action (eg a recall) which would otherwise be required should be agreed to with the competent authority in advance
- Both within-office-hour situations and out-of-office hour situations need to be considered when evaluating the effectiveness of recall arrangements and the need for mock recalls

NSF Health Sciences Pharma Biotech

2001 Pennsylvania Avenue NW, Suite 950, Washington, DC 20006 USA
Tel: +1 (202) 822-1850 | USpharma@nsf.org | www.nsf.org/info/pharmabiotech

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF
Tel: +44(0)1751 432999 | Fax: +44(0)1751 432450 | EUpharma@nsf.org

UK News

Guidance for UK IMP MIA Holders on the Use of UK Stand Alone Contract Laboratories

This guidance was issued in August 2014 and is applicable to all manufacturing/import authorization (MIA) holders manufacturing investigational medicinal products (IMPs) in the UK. It updates and changes the previous guidance published in June 2010.

The guidance provides information on when a contract lab should, and should not, be named on an IMP manufacturer's MIA. Most importantly, the guidance provides the MHRA's expectations of the MIA holder's responsibilities when using contract laboratories, which are:

- Have a system to assess the suitability, competency and GMP compliance of proposed contract laboratories prior to their use
- Ensure that the contract laboratories used are visible within the manufacturer's quality management system and listed in its site master file
- Update their respective licenses/authorizations to name the contract laboratory if the contract laboratory meets the criteria for an MHRA GMP inspection
- Ensure that a written technical agreement which describes the GMP responsibilities of each party, and also refers to the scope of testing and type of tests covered by the agreement, has been put in place
- Have a system of ongoing supervision for contract laboratories, including arrangements to periodically formally reassess compliance, based on risk
- Ensure that contract laboratories meeting the criteria for inspection have a valid GMP certificate prior to data generated by the laboratory being used by the contract giver for batch disposition decisions

Note: The MHRA publishes a list of inspected stand-alone contract laboratories on its website. This list is updated at least annually.

Freight Consolidation Depots and Short-Term Storage of Medicinal Products

In August 2014, the MHRA published its position on freight consolidation depots (freight forwarders) and on short-term storage of ambient and refrigerated medicinal products in the Hot Topics section of its website.

This position makes it clear that since the UK implementation of the Falsified Medicines Directive 2011/62/EU, both the act of export of a human medicine and the holding of a human medicine intended for export, by way of wholesale distribution, now requires authorization. This means that a number of companies and their sites that were not previously regulated now require a wholesale distribution authorization (WDA(H)).

The MHRA's GDP Inspectorate is raising awareness of the impact of the new regulations to those parties that are either directly or indirectly affected and any freight consolidator or freight forwarder in the air, sea or road transport sector that is either holding ambient medicinal products on site for more than 36 hours or has cold room facilities will require a wholesale distribution authorization WDA(H).

ICH News

ICH M7 – Genotoxic Impurities

At the June 2014 meeting, the guideline Assessment and Control of DND Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk received Step 4 approval.

This guideline offers guidance on analysis of structure activity relationships (SAR) for genotoxicity. Furthermore, it is intended to resolve questions such as whether impurities with similar alerts that potentially have similar mechanism of action should not be combined in calculating a threshold of toxicological concern (TTC) and whether the TTC may differ based on differences in the approved duration of use.

NSF Health Sciences Pharma Biotech

2001 Pennsylvania Avenue NW, Suite 950, Washington, DC 20006 USA
Tel: +1 (202) 822-1850 | USpharma@nsf.org | www.nsf.org/info/pharmabiotech

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF
Tel: +44(0)1751 432999 | Fax: +44(0)1751 432450 | EUpharma@nsf.org

ICH Q12 – Product Lifecycle Management

A concept paper has been completed for a new guideline to address the technical and regulatory considerations for pharmaceutical product lifecycle management and was endorsed by the ICH Steering Committee on September 9, 2014. An EWG will start work on the topic at the ICH meeting in Lisbon in November 2014.

The proposed guideline will apply to pharmaceutical products, including currently marketed chemical, biotechnological and biological products. However, each regulatory authority will decide whether generic medicines can be included in the scope of this guideline.

This guideline is intended to work with ICH Q8 to Q11 Guidelines and will provide a framework to facilitate the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more predictable and efficient manner across the product lifecycle. The specific change management issues that will be addressed by this guidance are proposed to be:

- The regulatory dossier:
  - ♦ Developing a harmonized approach to regulatory commitments
  - ♦ Delineating the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier
- Quality system:
  - ♦ Establishing criteria for a harmonized risk-based change management system
  - ♦ Clarifying expectations and reinforcing the need to maintain a knowledge management system
- Post-approval change management plans and protocols
  - ♦ Introducing the concept of a post-approval management plan
  - ♦ Establishing criteria for post-approval change management protocols
  - ♦ Encouraging enhanced product development and control strategy approaches (QbD)

Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. It will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in, a firm's pharmaceutical quality system (PQS) for management of post-approval CMC changes.

Cite as: NSF International. December 2014. Regulatory Update – Journal 31. NSF: Ann Arbor, MI.

NSF Health Sciences Pharma Biotech

2001 Pennsylvania Avenue NW, Suite 950, Washington, DC 20006 USA
Tel: +1 (202) 822-1850 | USpharma@nsf.org | www.nsf.org/info/pharmabiotech

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF
Tel: +44(0)1751 432999 | Fax: +44(0)1751 432450 | EUpharma@nsf.org