24/11/2015

To whom it may concern

"IA on GMP for MP for human use".

In response to the public consultation seeking stakeholders views on the content of the detailed Commission Implementing Act on Principles and guidelines on good manufacturing practices for medicinal products for human use, pursuant to the first paragraph of Article 47 of Directive 2001/83/EC (herein referred to as the Delegated Act on GMP), MHRA wishes to express the following views and proposals to help the Commission develop its thinking and preparation of the required implementing act.

There are no definitions included, these are needed and should include a definition of ‘manufacture’ which will provide legal certainty as to what is within and what is outside GMP control. This is particularly relevant to the new section (2.13) for ATMPs and where the cut off is between mainstream manufacture and reconstitution (sometimes referred to as ‘finishing’ activities):

1. ‘medicinal product’ means any product as defined in Article 1(2) of Directive 2001/83/EC;

2. ‘manufacturer’ means any person engaged in activities for which the authorisation referred to in Article 40(1) and (3) of Directive 2001/83/EC or the authorisation referred to in Article 13(1) of Directive 2001/20/EC is required;

3. ‘qualified person’ means the person referred to in Article 48 of Directive 2001/83/EC or in Article 13(2) of Directive 2001/20/EC;

4. ‘pharmaceutical quality assurance’ means the total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use;

5. ‘good manufacturing practice’ means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use;

Lines 28 to 31

Manufacturers have to comply with the principles and guidelines of good manufacturing practice for medicinal products for human use. Compliance with good manufacturing practice for medicinal products for human use is instrumental in ensuring the quality of the products.
This should refer to the relevant references in 2001/83/EC for example:

“This Regulation lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 40 of Directive 2001/83/EC.”

Lines 41 to 44

By means of the repeated inspections referred to in Article 111(1a), the Member States shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by the new Implementing Directive concerned by this consultation.

This paragraph should end with a reference to the Regulation and not “the consultation”.

Line 46

Member States shall also take into account the compilation, published by the Commission, of Union procedures in inspections and exchange of information.

Please consider amending to “….of Union procedures on inspection…”.

Lines 63 to 66

The manufacturer shall ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as granted by the competent authorities.

This section would benefit from being reworded for example:

“The manufacturer shall ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for the grant of that marketing authorisation.”

Lines 69 to 70

If a variation to the marketing authorisation dossier is necessary, the application for modification shall be submitted to the competent authorities.

It is unclear whether this includes the newer types of variations (do and tell etc).

Lines 108 to 109

That set of documents shall enable the history of the manufacture of each batch

We think that this sentence should end with: “to be traced.”

Lines 110 to 113

For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

Further consideration should be given to long term retention of documentation (batch records
process and analytical validation) which is pivotal to the marketing authorisation application.

Lines 114 to 121

When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer to another storage system, against loss or damage or data, and audit trails shall be maintained.

Due to the change to electronic ways of working, a new first paragraph is proposed;

All data, irrespective of the format in which it is recorded, should be generated, used and stored in a manner which ensures that it is complete, consistent and accurate. Measures should be in place to protect the data from unauthorised loss or amendment. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer to another storage system, against loss or damage or data, and audit trails shall be maintained.

Lines 130 to 132

Any new manufacturing or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated.

In order to be better aligned with the recent new revision of Annex 15 revision the following text is suggest:

Critical manufacturing processes shall be subject to ongoing process verification, including re-validation where appropriate.

Line 161

2.10. Work contracted out

It is proposed that this should be changed to ‘Outsourced activities’ to align with the revised Chapter 7 title.

Line 173

2.11. Complaints and product recall

This should align with the revision of Chapter 8 revision.

Lines 189 to 191 and 192 to 196

The requirements provided for in the Directive shall be adapted to the specific characteristics of advanced therapy medicinal products in accordance with a risk- based approach.

The adaptation to the specific characteristics of those products will be elaborated in a Commission guideline. On 23 July 2015, a targeted stakeholder consultation on the
Consideration should be given to amending to refer to “in accordance with the principles of Quality Risk Management”. This was included in GMP in 2008, is well established across EU inspectorates and was based on the International Conference on Harmonisation’s Q9 document.

The term ‘risk based approach’ should be avoided since it will be confused with that in Annex 1 Part IV of 2001/83/EC for ATMPs which is specific for data to be included in the marketing authorisation application.

This is further clarified in the CAT guideline (EMA/CAT/CPWP/686637/2011) which defines a risk based approach “as a strategy aiming to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC.”

In section 4, the CAT guideline provides further text to differentiate the ‘risk based approach’ from approaches used in GMP and medical devices – “It should also be differentiated from risk analysis such as it is used for medical devices or as part of quality management of ATMP production as described in ICHQ9/Annex 20 GMP guideline.”

Yours sincerely

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