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Date
April 24, 2012

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Comments on open consultation.

To whom it may concern:

Please find enclosed comments from DSM Nutritional Products Ltd. on

Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use
Concept Pater submitted for public consultation

DSM Nutritional Products Ltd. Comments:

General comment(s):

The concept paper "Delegated Act on the Principles and Guidelines of Good Manufacturing Practice for Active Substances in Medicinal Products for Human Use" is open for public consultation. Purpose of the delegated act is to facilitate the implementation Directive 2011/62/EU ("Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products."). Main purpose is to prevent the entry into European Union of falsified drug.

We would like to draw the attention of EU commission to the following:

As of today, EU regulatory framework, in accordance with ICH guidelines and PIC/S guidelines recognize today the need for a graduated application of the GMP requirements. More specifically, EU has adopted in 2000 the ICHQ7 (GOOD MANUFACTURING PRACTICE FOR ACTIVE PHARMACEUTICAL INGREDIENTS) as note for guidance CPMP/ICH/4106/00. This lead to the publication of the guideline referred to as EudraLex Volume 4 Part II: Basic Requirements for Active Substances used as Starting Materials.

Paragraph 10 of the concept paper reads as follow "the principles and guidelines for GMP would be the same during the manufacturing of active substances as well as medicinal products". We understand that the term 'principles and guidelines" should refer to commission directive 2003/94/EC of 8 October 2003. It is unclear however if it is the intention of commission to suppress Part II of the GMP guidelines, and apply the requirements of Part I to APIs. We would strongly oppose to such a change, as this would

1. *create a disharmony between the ICH regions*
2. *increase the manufacturing cost for API*
3. *As a consequence of 2, provide more incentive to unscrupulous manufacturers to avoid the higher costs of compliance, and penetrate aggressively into a higher cost market*

We would therefore appreciate to see clearly stated that the guidelines from EudraLex Volume 4 Part II: Basic Requirements for Active Substances used as Starting Materials will remain the framework of good manufacturing practice for active pharmaceutical ingredients.

Specific Comments:

1. Extension of the Directive on GMP for medicinal products to active substances

Consultation item n°1: Do you agree with this appraisal and approach? Please comment.

We agree on the possible extension of scope of Directive 2003/94/EC to active substances. However, the paragraph 10 remains too ambiguous with respect to detailed guidance. It should be clarified that while the principles for GMP will be the same during manufacturing of active substances as well as medicinal products, the detailed guidance will remain specific, in accordance to the ICH principles. Please refer also to the general comments section (see above).

2. Adaptation of regulatory requirements of Directive 2003/94/EC to active substances

Consultation item n°2: Are there other aspects which should be considered? Please comment.

Yes, other aspects have to be considered:
Article 3(1). Requirements for inspections for APIs are defined in 2001/83/EC as amended in Article 46b(2)(b)(ii) are only defined in case APIs are imported.
Article 10(3): Provision for re-validation should not apply to active pharmaceutical ingredients, see 12.60 of EudraLex Vol4 Part II (Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specification, there is normally no need for revalidation)

Consultation item n°3: Do you consider this list complete? Please comment.

We do not consider this list complete:
Article 6 should be amended to reflect wording of EudraLex Vol4 Part II: Something like: "The API manufacturer shall establish document and implement an effective system for managing quality

that involves the active participation of management and appropriate manufacturing personnel. The manufacturer of drug product shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different department". The term 'pharmaceutical quality assurance", as defined in Article 2(5) should be restricted to application to medicinal products manufacturing.

Article 7(1) should be amended to reflect wording of EudraLex Vol 4 Part II (3.10). Something like "At each API manufacturing site, there should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs".. The term 'pharmaceutical quality assurance", as defined in Article 2(5) should be restricted to application to medicinal products manufacturing.

Article 11(4, third paragraph) should be amended to reflect the guidelines of EudraLex Vol4 Part II (11.7). Concerning APIs, it is not today required to retain sample of starting materials

Consultation item n°4: Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?

We don't agree with this specific point. The paragraph 7.14 of EudraLex Vol.4 part II reads "Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control." and is sufficient for the purpose of good manufacturing practice.

It should be clarified that specific detailed guidance documents should be issued by commission concerning active pharmaceutical ingredients. This would guarantee to keep in force the EudraLex Vol.4 part II. For this, Article 3, paragraph 2 should be amended and should make reference to 'Guide to good manufacturing practice for medicinal products, for active pharmaceutical ingredients and for investigational medicinal products'

Consultation item No 5: Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.

So far, all delegated acts in force took the form of regulation (Eurlex search on March 26). This ensures direct application by all member states and simplifies implementation of the measure. We would recommend that the delegated act should take the form of regulation.