THE EUROPEAN COMMISSION LAUNCHES A CONSULTATION PROCESS IN RELATION TO THE MANUFACTURING PRACTICES FOR MEDICINAL PRODUCTS

To Our Clients and Friends:

On 17 January 2013, the European Commission (the "Commission") initiated a public consultation in relation to the revision of its Good Manufacturing Practice Guidelines (the "GMP Guidelines").[1]

In addition to demonstrating the safety and efficacy of the medicinal product, manufacturing authorisation holders are obliged to guarantee the consistent quality of the product by complying with the "Good Manufacturing Practices" ("GMP") for medicinal products and to use as start materials only active substances that have been manufactured in accordance with the detailed GMP Guidelines.[2] The GMP Guidelines contain guidance for the interpretation of the EU Directive on good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (the "Directive on Good Manufacturing").[3] In order to interpret the provisions of Directive on Good Manufacturing account should be taken of a collection of rules and regulations governing medicinal products in the European Union known as "EudraLex", of which the GMP Guidelines are but one constituent.[4] Compliance with these principles and guidelines is mandatory within the EEA.[5]

The proposed revisions will affect the chapters of the GMP Guidelines governing (i) the premises and equipment where the medicinal products for human use are produced (refer to chapter 3 of the GMP Guidelines); (ii) the production of these products (refer to chapter 5); (iii) quality control (refer to chapter 6) and (iv) complaints, quality defects and product recalls (refer to chapter 8).

With its revision, the Commission is considering addressing, in particular, the following points:

1. Providing more detailed guidance regarding the prevention of cross-contamination, including the provision of guidance regarding a new complementary toxicological assessment procedure (refer to chapter 3 and 5 of the GMP Guidelines, entitled, respectively "Premises and Equipment", and "Production").

2. Enhancing the qualification of suppliers in order to reflect the legal obligation of manufacturing authorization holders to ensure that active substances are produced in accordance with worldwide and EU GMP, (i) introducing requirements such as, inter alia, establishing supply chain traceability and (ii) clarifying and harmonizing the expectations of manufacturers regarding the testing of starting materials (refer to chapter 5 of the GMP Guidelines, entitled "Production").

3. Introducing a new section regarding the technical transfer of testing methods (refer to chapter 6 of the GMP Guidelines, entitled "Quality Control").
4. Modifying the rules applicable to the investigation of quality defects / complaints and to the adoption of decisions in relation to product recalls or other risk-mitigating actions, in particular reflecting the so-called "Quality Risk Management" principles. The modification would, on the one hand, emphasize the need for (i) investigating the cause(s) of quality defects/complaints; and (ii) for adopting appropriate preventative actions in order to guard against a recurrence of the issue. On the other hand, the revision would clarify the rules applicable in relation to the reporting of quality defects to the competent authorities (refer to chapter 8 of the GMP Guidelines, entitled "Complaints, Quality Defects and Product Recalls").

Interested parties may submit their comments before **18 July 2013** by email to: ADM-GMDP@ema.europa.eu and SANCO-pharmaceuticals-D6@ec.europa.eu

In particular, the Commission's revision would include, among others, the following changes:

**I. Revision of Chapter 3: Premises and Equipment**

The current text of section 3(6) does not provide any guidance on how to assess the risk of cross-contamination. The revised section 3(6) suggests appropriate measures concerning the design and operation of the manufacturing facilities including a toxicological evaluation to establish threshold values for risk identification. The EU Medicine Agency’s draft Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities[6] provides additional guidance.

**II. Revision of Chapter 5: Production**

**II.1 Prevention of Cross-Contamination**

The revision of sections 5(17) and following of the GMP Guidelines have a close connection to revised chapter 3 and are also aiming at improving the guidelines on the prevention of cross-contamination. More specifically, pursuant to the revised section 5(18), manufacturers of medicinal products would, e.g., be required to adopt "appropriate technical or organizational measures" in order to prevent cross-contamination, including a more robust design of the premises, equipment and processes. This may ultimately even result in the entire separation of the facilities used in the manufacture of products.

**II.2 Qualifications of suppliers and excipients of starting materials**

The current wording of sections 5(26) and following, regarding the qualifications of suppliers, would be revised in order to reflect the legal obligation of holders of a manufacturing authorization to ensure that active substances are produced in accordance with the GMP Guidelines and by only resorting to suppliers of active substances which meet the requirements provided for in the Guidelines.

The revised Sections 5(26) and 5(27) are of particular relevance, requiring the holders of manufacturing authorisations to document how they select and approve their suppliers of starting materials. This would include, e.g., the establishment of supply chain traceability and of periodic audits, proportionate to the risks of the materials and their sources.
The revision would furthermore introduce requirements for the approval and maintenance of *excipients* of active substances which pose particular risks to the quality of the products.

### II.3 Testing of starting material

A new section 5(33) would clarify and harmonize manufacturers' responsibilities for the testing of starting materials. Manufacturers of finished products would be allowed to use test results from approved starting material manufacturers, provided that the former meet certain requirements, the most relevant of which include:

i. Identification testing of each batch of products.

ii. Formal agreements with the starting material manufacturer.

iii. Periodic audits at the starting material testing site.

iv. Performing a full analysis at appropriate intervals to compare results with the supplier's certificate.

### II.4 Product shortage

An obligation of the marketing authorization holder to notify the competent authority about product shortage due to GMP issues / manufacturing constraints would be introduced by the new section 5(68). Such notification would be due no less than 2 months before an interruption of supply (either temporarily or permanently) occurs. This notification requirement would be rounded out by an obligation of the manufacturer to inform the marketing authorization holder timely in advance of any constraints in manufacturing operations which may result in an abnormal restriction of supply.

### III. Revision of Chapter 6: Quality Control

Chapter 6 of the *GMP Guidelines* would be updated in order to include a new section concerning "the technical transfer of testing methods and other items such as out of specification results", subjecting the said transfer to stringent requirements which should be described in a written protocol which would identify at least (i) the relevant test methods; (ii) the additional training requirements; (iii) the standards and samples to be tested by both laboratories; (iv) the testing to be performed (v) the identification of any special transport and storage conditions applicable to the test items; and (vi) the acceptance criteria.

### IV. Revision of Chapter 8: Complaints, Quality Defects and Product Recalls

The current text of chapter 8 of the *GMP Guidelines* on complaints, defects and product recalls is relatively basic and concise. The Commission suggests expanding it in order to apply Quality Risk Management principles to (i) the investigation of quality defects or quality complaints and (ii) decisions on product recalls and other risk-mitigating actions including revised requirements as to when and how quality defects must be reported to the competent authorities.
The revised sections 8(1) to 8(4) of the *GMP Guidelines* require the manufacturer of medicinal products to devote sufficient resources and appropriately trained and experienced personnel in order to (i) investigate complaints and quality defects, (ii) implement risk-reducing actions, and (iii) interact with the competent authorities.

The revised sections 8(5) to 8(9) and 8(14) expand the current guidelines regarding the procedures for handling and investigating complaints and quality defects in order to include, among others:

i. A simplification of procedures to obtain product batches from the manufacturer.

ii. The implementation of a root cause analysis.

iii. Tightened reporting obligations of the manufacturer to the market authorization holder/sponsor and to the competent authorities.

The revised sections 8(20) to 8(31) expand the current guidance regarding product recalls and other potential risk-reducing actions, to include, amongst others:

i. Procedures to identify, in the case of investigational medicinal products, all trial sites and countries of destination.

ii. Information by the manufacturer and his sponsor of the marketing authorisation holder of any quality defect that could be related to the authorised product.

iii. Procedures, implemented by the sponsor of investigational medicinal products, for the rapid un-blinding of blinded products, only in so far as necessary for a prompt recall.

iv. Procedures to consult with competent authorities and to consider the extent of the recall.

v. Procedures to consider whether recall actions may affect different markets in different manners, including the risk of shortage of an essential medicinal product for which there is no authorised legal alternative. Were that the case, appropriate market-specific actions should be developed and discussed with the concerned authorities.

vi. Periodical evaluation of the effectiveness of established procedures.

V. Conclusion

The Commission's initiative to reform its GMP Guidelines should be understood as a part of a wider effort by the Commission to revise its guidance regarding the manufacture of medicinal products. The Commission subsequently issued, on 6 February 2012, the following draft documents, also for consultation:

i. A draft *Template for the qualified person's declaration concerning GMP compliance of investigational medicinal products manufactured in non-EU countries* - Stakeholders are invited to comment on this draft by 2 April 2013 at the latest.
ii. **Draft Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use** - stakeholders are invited to comment on this draft by 30 April 2013 at the latest.

iii. **Draft Guidelines on the principles of good distribution practices for active substances for medicinal products for human use** - Stakeholders are invited to comment on this draft by 30 April 2013 at the latest.

The Commission's attempts to provide enhanced legal certainty in this domain will certainly be welcome by stakeholders. That said, given that the resulting Guidelines will have a crucial impact on companies manufacturing products for sale in the EU, these might want to have a close look at the Commission's suggestions and, if necessary submit comments in order to ensure the proportionality of the resulting guidance.

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[2] Refer to the Introduction GMP Guide, available at [http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm). Needless to say, products intended to be marketed outside the European Union may also need to comply with additional requirements imposed by the jurisdiction in which the products will be marketed. E.g., products sold in the US would also need to comply with all the relevant US Food and Drug Administration requirements (which include good product manufacturing practice requirements).


Gibson, Dunn & Crutcher lawyers are available to assist in addressing any questions you may have regarding these issues. For more information on this topic or regarding Gibson Dunn’s pharmaceutical and medical device regulatory compliance practice for products for sale in the EU, please contact the Gibson Dunn lawyer with whom you regularly work or the authors of this alert:

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