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Fecc comments to Part 1 Chapter 5: Production – EU Guidelines GMP

Via email

To,

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Brussels, 28 June 2013

Subject: Fecc comments to the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part 1 Chapter 5: Production.

The European Association of Chemical Distributors (Fecc) welcomes the opportunity to comment on EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part 1 Chapter 5: Production.

Fecc represents the chemical distribution industry in Europe and supports any initiative that strengthens the supply chain and increases the safety of medicinal products. As part of the supply chain Fecc members support Guidelines on Production that lay out clearly defined procedures, comply with the principles of Good Manufacturing Practice (GMP) and are in accordance with the relevant manufacturing and marketing authorizations. Fecc appreciates the intended modifications in this chapter as they generally represent the principles of traceability in

the starting materials supply chain and clarify regulatory requirements not precisely described in the current version of the guideline. We have reviewed the draft document and have the following comments.

PARAGRAPH	TEXT AS PROPOSED	PROPOSED REWORDING BY FECC	COMMENTS
Starting materials			
5.26	The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. **Where possible starting materials should be purchased directly from the manufacturer of the starting material.**	**Where possible marketing authorization holder (MAH) should consider purchasing starting materials directly from the manufacturer or from a suitably qualified and approved distributor.**	Depending on the level of support and service and understanding of pharmaceutical requirements provided by the

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	The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a quality agreement or specification.		manufacturers of starting materials it may be advantageous and have benefits to procure starting materials from a distributor familiar with both parties. These distributors can contribute with traceability and regulatory services. Since risk assessment principles should be applied to control the supply chain this should ensure proper qualification of the entire supply chain including distributors.
5.27	For the approval and maintenance of suppliers of active substances and excipients, the following is required: **<u>Active substances</u>** Supply chain traceability should be established and the associated risks, from active substance		

	starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.		
	The supply chain and traceability records for each active substance **(including active substance starting materials)** should be available and be retained by the EEA based manufacturer or importer of the medicinal product.	The supply chain and traceability records for each active substance ~~**(including active substance starting materials)**~~ should be available and be retained by the EEA based manufacturer or importer of the medicinal product.	Records of the API starting materials defined by EU GMP Part 2 Guidelines are available at the API manufacturer. To provide these records to the medicinal product manufacturer would not increase safety and quality of APIs. Further to provide that information to the importer of the medicinal product is also not a requirement in EU GMP Part 2 Guidelines. Part 1 and Part 2 Guidelines should be consistent.
	Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. **The holder of the manufacturing authorization shall verify such compliance either by himself or**	**The holder of the manufacturing authorization should verify such compliance either by himself or through**	Independence, qualification and approval of such entities are more important to ensure quality of such audits than a formal contract between the parties. Furthermore, "should" would be

	through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk. Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross- contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Corrective and preventive actions should be implemented. Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain. **Excipients**	**an entity acting on his behalf which is independent, qualified and approved by the MAH.**	appropriate in place of "shall" as used in general Guidance language.
	Excipients which are considered to pose a particular risk to the quality of the medicinal product, based on formalised quality risk management, should be given similar attention to those for active substances.	**Excipients and excipient suppliers should be controlled appropriately based on the results of the formalised quality risk assessment required by article 46(f) of Directive 2011/62/EU**.	All excipients and excipient suppliers should be controlled appropriately, not only those that pose a "particular risk". This is also required by article 46(f) of Directive 2011/62/EU. Therefore, we propose alignment with the directive and the related risk assessment guideline for

			excipients. Further, it is not clear what is meant by "particular risk".
5.33	Manufacturers of finished products are responsible for any testing of starting materials as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing of each batch themselves according to annex 8. The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled: a) A formal agreement should be signed, **according to chapter 7**, between the finished product manufacturer and the starting material manufacturer. Among the respective responsibilities described in the formal agreement, special attention should be paid to those related to the distribution conditions (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material. b) The finished product manufacturer should perform audits at appropriate intervals at the site(s) carrying out the testing (including	**A formal agreement should be signed, between the finished product manufacturer and the starting material manufacturer or supplier as applicable.**	In case of utilization of suppliers test results, a formal agreement should be in place but this must not be similar to the one with contract laboratories because the suppliers are providing the starting materials **and** the analytical service. In such a case the analytical services can and should be included in the general quality agreement covering also the delivery of the starting materials. A separate contract according to chapter

	sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the Marketing Authorisation dossier.		7 would add additional administrative burden without additional benefit. Furthermore, "supplier" should be added to extend the scope to entities other than the original manufacturer, of the starting material, which may provide test results.
	c) **The certificate of analysis provided by the starting material manufacturer should be signed by a designated person** with appropriate qualifications and experience. This person should ensure that each batch has been manufactured and checked for compliance with the requirements of the formal agreement.	**The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person**…….	Certificates of analysis may be provided by entities other than the starting material manufacturer. Therefore, "supplier" should be added.
	d) **The finished product manufacturer should have a significant experience in dealing with the starting material manufacturer** including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered.	**The finished product manufacturer should have a significant experience in dealing with the starting material manufacturer/supplier...**	See comment above and consider consistency with the wording in e) where the term "supplier" is used.

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	e) The finished product manufacturer should also perform a full analysis at appropriate intervals and compare the results with the supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificate of analysis from the supplier should be discontinued until these measures are completed. Notes: 1. A similar approach should apply to packaging materials as stated in GMP part I, 5.41. 2. Identity testing of starting materials should be performed according to the methods and the specifications of the relevant Marketing Authorisation dossier.		

About Fecc

The European Association of Chemical Distributors (Fecc) is the voice of the chemical distribution industry in Europe. With a growing membership of companies and national associations, Fecc represents around 1,700 companies of which many are small and medium sized enterprises (SMEs). Members service a very wide range of industries and meet the manufacturing requirements of sectors as diverse as paints and textiles to cosmetics and pharmaceuticals each with their own diverse demands and purchase volumes.

The chemical distribution industry in Europe employs around 30,000 people and has an annual sales leverage of approximately €26 billion.

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