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Fecc response to draft guidelines on the formalised risk assessment for ascertaining appropriate GMP for Excipients of Medicinal Products

Via email

To,

European Commission - DG SANCO

sanco-pharmaceuticals-d6@ec.europa.eu

Brussels, 29 April 2013

Subject: Fecc response to public consultation on guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice (GMP) for excipients of medicinal products for human use.

The European Association of Chemical Distributors (Fecc) welcomes the opportunity to comment on the draft consultation document on guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice (GMP) for excipients for human use.

Fecc represents the chemical distribution industry in Europe and supports any initiative to strengthen the quality and safety of medicinal products and pharmaceutical excipients. In this context we support the application of appropriate GMPs for pharmaceutical excipients.

As part of the pharmaceutical supply chain Fecc members work with excipient manufacturers as well as with pharmaceutical companies. We have reviewed the draft consultation document and have the following comments.

ORIGINAL TEXT	PROPOSED REWORDING BY FECC	COMMENTS
1. INTRODUCTION		
5. Importers of medicinal products must have the risk assessment/management documentation for appropriate GMP for excipients available on site.	5. Importers of medicinal products **should** have the risk assessment/management documentation for appropriate GMP for excipients available on site.	Replacing 'must' with 'should' would be appropriate since this is a guidance document.
	6. It is recommended that the Manufacturing Authorisation Holder share information and discuss the outcome of the risk assessment with the supplier to enable cooperation with the	We are of the opinion that good communication between MAH and supplier is necessary to successfully access risk and implement risk mitigation strategies.

	excipient supplier.	
2. DETERMINATION OF APPROPRIATE GMP BASED ON TYPE OF EXCIPIENT		
7. These Quality Risk Management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the excipient in question as "low risk", "medium risk" or "high risk". Quality risk management tools such as those listed in ICH Q9 (for example, hazard analysis and critical control points – HACCP, etc.) should be used for this purpose.	7. These Quality Risk Management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the excipient in question as "low risk", "medium risk" or "high risk". **Quality risk management and assessment tools such as those listed in ICH Q9 should be used for this purpose.**	We propose to keep open which tool may be used. None of them should be specifically highlighted
8. For each excipient used, the Manufacturing Authorisation Holder should identify the risks presented to the quality, safety and function of each excipient from its source (be that animal, mineral, vegetable, synthetic etc.) through to its incorporation in the finished pharmaceutical dose form. Areas for consideration would include: • Transmissible Spongiform Encephalopathy • Potential for viral contamination • Potential for microbiological or endotoxin/pyrogen contamination • Potential, in general, for any impurity originating from the	8. For each excipient **from each supplier used**, the Manufacturing Authorisation Holder should identify the risks presented to the quality, safety and function of each excipient from its source (be that animal, mineral, vegetable, synthetic etc.) through to its incorporation in the finished pharmaceutical dose form. **The type of excipient and its use should determine the areas for consideration, for example:** • Transmissible Spongiform Encephalopathy • Potential for viral contamination • Potential for microbiological or endotoxin/pyrogen contamination • Potential, in general, for any impurity originating from the raw materials (e.g. aflatoxins, pesticides) or generated as part of the process and carried over (e.g. residual solvents and catalysts)	Otherwise this list may be considered a closed list. Other areas of consideration may have to be included.

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raw materials (e.g. aflatoxins, pesticides) or generated as part of the process and carried over (e.g. residual solvents and catalysts) • Sterility assurance (for excipients claimed to be sterile) • Use of dedicated equipment and/or facilities • Environmental control and storage conditions	• Sterility assurance (for excipients claimed to be sterile) • Use of dedicated or **other appropriate equipment** and/or facilities • Environmental control and storage conditions • **Starting Point of GMP in the manufacturing process of the excipient** • **Other items which may be relevant for excipient safety and quality**	Dedicated equipment is not always used. This should be recognised.
9. Additionally, with respect to the use and function of each excipient the Manufacturing Authorisation Holder should also consider: • The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion etc.) • The function of the excipient in the formulation (e.g. lubricant in a tablet product or preservative material in a liquid formulation etc.) • The quantity used of the excipient for the manufacture of medicinal products • Daily patient intake of the excipient • Any known quality defects both globally and at a local company level related to the excipient • Whether the excipient is a composite • Potential impact on the	9. Additionally, with respect to the use and function of each excipient the Manufacturing Authorisation Holder should also consider **the following items, for example:** • The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion etc.) • The function of the excipient in the formulation (e.g. lubricant in a tablet product or preservative material in a liquid formulation etc.) • The quantity used of the excipient for the manufacture of medicinal products • Daily patient intake of the excipient • ~~**Any**~~ Known quality defects both globally and at a local company level related to the excipient • **Known impact on the Critical Quality Attributes of the medicinal product** • **Other factors as identified or known to be relevant to assuring patient safety**	Otherwise this list may be considered a closed list. Other areas of consideration may have to be included. We recommend deleting ‘any’ as not all quality defects may be know and indentified by the MAH

Critical Quality Attributes of the medicinal product		
11. This will vary depending on the source, the supply chain and the subsequent use of the excipient, but as a minimum the following high level GMP principles should be considered: a) Establishment and implementation of an effective Quality Assurance system b) Sufficient competent and appropriately qualified personnel c) Defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities d) Training programmes for all staff involved in manufacturing and quality activities		
e) Training programmes related to health, hygiene and clothing	e) Training programmes related to health, hygiene and clothing **when necessary for the operations**	There may be operations in excipient manufacturing which are not critical to hygiene. In these cases specific training may not be needed. A risk assessment should determine the need for such training.
f) Provision and maintenance of premises and equipment appropriate to the intended operations	f) Provision and maintenance of premises and equipment **when necessary for the operations**	See comment to e)
g) Documentation system(s) covering all processes and	g) Documentation system(s) covering all processes and	Many excipients are accompanied by a "retest date" specified by the

specifications for the various manufacturing and quality operations including retention of batch documentation, which should be for at least one year after the expiry date of the excipient batch to which it relates	specifications for the various manufacturing and quality operations including retention of batch documentation, which should be for at least one year after the expiry date **or in case of given retest recommendations at least one year after the last successful retest of the excipient batch** of the excipient batch to which it relates	manufacturer. This should be taken into consideration.
h) Systems for coding and identifying starting materials, intermediates and excipients to allow full traceability	h) Systems for coding and identifying starting materials, intermediates and excipients to allow **traceability and consider the specific conditions of continuous manufacturing processes.**	Full traceability is not always feasible in continuous process plants. This needs to be considered.
i) Provision and maintenance of an independent quality control department under the authority of the person nominated as responsible for overall Quality Control	**i) A system for quality control of the excipients and a responsible person independent from production to release the batches.**	Not all excipient manufacturers have an independent quality department but should have an independent function for batch release.
j) Retention of records for starting materials and excipients and retention of samples of excipients for the periods required by EU GMP	j) Retention of records for starting materials and excipients and retention of samples of excipients for the periods **as defined**.	In the sense of this guidance reference to other than EU-GMP should be allowed but this should be defined in the quality system.
k) Systems to ensure that any activity contracted out is subject to a written contract	k) Systems to ensure **that quality critical** manufacturing activities contracted out is subject to a written contract	"any" is too prescriptive. This may encompass services not relevant to ensure excipient safety and quality.
3. DETERMINATION OF EXCIPIENT MANUFACTURER´S RISK PROFILE		
14. Quality system certification or accreditation held by the excipient manufacturer and the	14. Quality system **and GMP** certification held by the excipient manufacturer and the standards against which this has been granted	"Accreditation" is only applicable for certification bodies but not for manufacturing companies. GMP

standards against which this has been granted should be considered as this may meet the required Good Manufacturing Practices.	should be considered as this may meet the required GMP.	certification should be considered.
15. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, the Manufacturing Authorisation Holder should perform a further risk assessment to determine the risk profile (i.e. low risk, medium risk or high risk, for that excipient manufacturer). It is recommended that the Quality Risk Management guidelines (ICHQ9) in Part III of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 are used to classify the risk profile of the excipient manufacturer. Quality risk management tools such as those listed in there (HACCP etc.) should be used for this.	15. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, the Manufacturing Authorisation Holder should perform a further risk assessment to determine the risk profile (i.e. low risk, medium risk or high risk, for that excipient manufacturer). **It is recommended that the Quality Risk Management guidelines ICHQ9 are used to classify the risk profile of the excipient manufacturer. Quality risk assessment tools such as those listed in ICHQ9 should be used for this.**	We propose to keep open which tool may be used. None of them should be specifically highlighted. Therefore, HACCP should not be mentioned here.
4. CONFIRMATION OF APPLICATION OF APPROPRIATE GMP		
17. Once the "appropriate GMP" for the excipient and the risk profile of the manufacturer has been defined on-going risk review should be performed through mechanisms such as: a) Number of defects on received batches of excipients		

b) Type/severity of defects on excipients c) Loss of relevant quality system accreditation by excipient manufacturer d) Observation of trends in drug product quality attributes (this will depend on the nature and role of excipient) e) Audit (re-audit) of excipient manufacturer.	c) Loss of relevant quality system **and or GMP** certification by excipient manufacturer	

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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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