Draft Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate GMG for Excipients of Medicinal Products for Human Use

General remark

Most of the additives (including the colouring materials) intended for use in foodstuff are widely used in medicinal products as well and vice verse. This practice is formally implemented in Directive 2009/35/EC (on the colouring matters which may be added to medicinal products clearly stating that experience has shown that there is no reason, on health grounds, why the colouring matters authorised for use in foodstuffs (including supplements) should not also be authorised for use in medicinal products. This principle can be applied for all types if excipients (not only for colouring matters). As a consequence of this approach any GMP to be applied for excipients of medicinal products should be in harmony with the Global Guide to Good Manufacturing Practice for Supplements published by IADSA (http://www.iadsa.org/page.php?key=publications,84bba31b9915f0afc36c2fdba119c1895fcc297e,168,1).

Accordingly the guideline should discuss this issue in detail at least in section 1. ("Introduction") in order to clarify the similarities to and differences (if any) in the risk assessment on food d additives and excipients of medicinal products. It worth mentioning the legislations on food additive (133/208/EU and 231/2012/EU) are very detailed and based on safety evaluations.

According to our pinion the risk assessment of novel excipents (as defined in the common technical documentation /section 3.2.P.4.6/) should be discussed separately from the other known excipients due to the possible huge difference in the risk levels.

On the other hand we don't understand the requirement for implementation, by which date the manufacturer is required to make the excipient RA? Is the deadline the same on which date the guideline takes effect? Our suggestion is to allow an approx 6 months transitory period to meet the risk assessment requirement.

Our comments:

Point of draft guideline to be modified	**Current description**	**Our suggestion**	**Comment/explanation**
Point 1	Directive 2011/83/EC provides, in	*Here the scope of these guidelines*	There is no meaning to cite here the

	Article 46(f), as follows: "*The holder of the manufacturing authorisation…*	*should be defined*	exact wording of the Directive 2011/83/EC Concerning the scope the question is whether the widely used composits (Prosolv, Ludipress, Opadry etc.) are subjects to these guidelines or their individual components as well. Is there any category (for example excipients which do not appear in the final drug product i.e water, solvents) which is exempted from this formalised risk assessment?
Point 2	The fifth paragraph of Article 47 of Directive 2001/83/EC provides that : "*The Commission shall adopt*	As above	
Point 7	These Quality Risk Management principles should be used to assess the risks presented to the quality, safety and function of **each** excipient		Clarification is needed, what does it mean each excipient (see above comments)
Point 8-9.		Several aspects (such as TSE risk, impurities, storage condition, function, quantity, pharmaceutical form of excipients etc.) listed in paragraph 8 and 9. are almost the same as the aspects to be discussed in detail in the Common Technical Documentation/CTD) (section "Pharmaceutical Development") therfore we recommend to delete these aspects. There is no reason to duplicate of assessments	

		which are already included in the CTD. It is not clear, what is the correlation between the daily patient intake of excipients and good manufacturing practise. Even in the case of active substance the safety issues are discussed separately from the GMP (clinical and non-clinical assessment) therefore we suggest from this section where the appropriate GMP for the manufacturing sites of the excipients are discussed. The safety of the excipients should be described separately in the CTD (section "*3.2.P.4.6 Novel Excipients For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).*")	
Point 8	For each excipient , the MAH should identify the risks presented to the quality, safety... Areas for consideration would include: .... • use of dedicated equipment and/or facilities • environmental control and	For each excipient , the MAH should identify the risks presented to the quality, safety... Areas for consideration would include: .... *(the last two items indicated in blue should be moved to Point 11)*	These items belong to the GMP environment of the manufacturer, not to the quality and safety aspects.

	storage conditions		
Point 9	Additionally, with respect to the use and function of each excipient the Manufacturing Authorisation Holder should also consider… - Daily patient intake of the excipient - Whether the excipient is a composite	Daily patient intake of the excipient at least the worst case. We do not have data on this and we found no such data available on the Internet either. The quantity used of the excipient for the manufacture of medicinal products at least the worst case.	Clarification is needed, how should it consider (see above comments)
Point 10	... MAH should establish and document the elements of EU-GMP that he belives are needed to be in place...	... MAH should establish and document the elements of EU-GMP that he belives are needed to be in place... Manufacturers of substances commonly used as foodstaffs (e.g. sugar) and minerals (e.g. kaolin, magnesium oxide) are out of scope of such evaluation. Requiring certified quality management system from suppliers.	Such materials which are used in large quantity as food can be considered as safe. Mining companies sell their minerals in large quantities for other industries. The small quantity taken by the pharma industry is not enough to ask successfully for implementation of expensive GMP procedures. Due to the fact that these suppliers are mainly involved in food industry or in certain cases in mining industry.
Point 11		Not clear to us what is the purpose with this list. How to consider these points?	

		Questionnaire or audit? Or can we decide? It is impossible to meet the requirements in Section 11 unless we perform an audit with the excipient manufacturer. When we requested them to fill a questionnaire we found that manufacturers maintaining quality systems have their own IT package in place for the customers. For this reason we get this IT package instead of filling the questionnaire. These IT packages don't include all information listed in Section 11 (job description, qualification of staff, training program). In point 11 starting materials and intermediates are mentioned together with excipients. It would be important to clarify the meaning of these phrases since the words "starting materials" and "intermediates" are generally used in connection of active substances. This will vary depending on the source, the supply chain and the subsequent use of the excipient, ~~but as minimum~~ in the risk assessment the following high level GMP principles should be considered:	
	This will vary depending on the source, the supply chain and the subsequent use of the excipient, but as minimum the following high level GMP principles should be considered:		
Point 11 paragraph a)	a) Establishment and implementation of an effective Quality Assurance system	In point 11 should be reworded, because a customer has no proper tools to measure the effectiveness of the quality	

		system of a supplier. Effectiveness can be deduced from the lack of complaints and constant supply of good quality product. The guide should be amended with: "The risk assessment should be extended to define the minimal level of the required GMP of the excipient manufacturer as well." A minimum level of GMP has to be determined, because small or medium size companies with food or cosmetic industry profile cannot be suppliers of a pharma companies even though they are producing high quality excipients. It does not worth adapting GMP of pharmaceutical industry for these kind of companies, because their major customers are coming from food and cosmetic industry".	
Point 11 paragraph f)	f) Provision and maintenance of premises and equipment appropriate to the intended operations	Provision and maintenance of premises and equipment appropriate to the intended operations. Use of dedicated equipment and/or facilities.	As above
Point 11 paragraph n)	n) Any other (non-GMP) measures required to manage or control the identified risk	n) Environmental control and storage conditions o) Any other (non-GMP) measures required to manage or control the identified risk	As above

Point of draft guideline to be modified	Current description	Our suggestion	Comment/explanation
Point 14	Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required GMP.	Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required GMP. If there is documented evidence of a successful health authority audit/ inspection performed on the site, it can be accepted as evidence of GMP without further evaluations. The manufacturers'risk profile is key issue, therefore it would be practical to nominate (at least as examples) in point 14. the quality system certifications (e.g. HACCP, ISO or other standards) which are considered to meet the required GMP. If HACCP (as mentioned in paragraph 165.) is an appropriate quality risk management tool then the interchangeability of the appropriate GMP for excipients and HACCP certification should	

		be clearly stated.	
Point 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: Audit (re-audit) of excipient manufacturer	Besides the audit(reaudit) of excipient manufacturers the use of alternate tools such as application of GMP questionnaires should be emphasised considering that the number of excipients (used in medicinal products) is much higher than the number of active substances consequently the requirement to periodically audit the manufacturers of the excipients manufacturers is not realistic.	It should be refine in line with the appropriate risk category, it should be mandatory only in case of high risk excipients. 3rd party audit report should be acceptable.
Point 17 paragraph e)		In point 17 should be reconsidered or removed: “e) Audit (re-audit) of excipient manufacturer”, audit is a very good tool when a pharmaceutical manufacturer has 2-3 suppliers, and the vendors have 2-3	

		customers. But a large company having 2-3 or more alternative excipient supplier for each item, and having huge variety of products with many different excipients has to perform approx. 300 audits yearly. And the excipients manufacturers with many customers have to support also incredible big number of customer audits. Therefore audit should not be compulsory element of the guideline, but only an alternative option of the on-going risk review. It should be much more evident that audits (re-audits) can be replaced with several information gained about the excipient manufacturers (e.g.: quality history, third party audit, authority information) or outcome of the risk assessment. Or e) should be supplemented: "e) Audit (re-audit) of excipient manufacturer upon discretion/decision of the MAH."	

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Additional item		Date of implementation (*should be precised*)	Please take into consideration that this is a huge work to perform. To implement these requirements, DP QA management needs additional resources (staff). To establish a new group for this task within QA, to perform the preliminary evaluations, to complete the action plan would take at least 6 months. Afterwards, all the data have to be collected, all the audits have to be performed. It is not possible to say that everything should be finalized within a couple of months and only drug products manufactured with "appropriate GMP excipients" can be marketed e.g. from July 1st, 2013...
General remark	„This shall be ascertained on the basis of a formalised risk assessment”	We would suggest including further means of evaluation of the risks listed in the draft guide other than formal risk assessment (e.g. GMP questionnaire, supplier evaluation/approval process)	The supplier evaluation / risk management is already incorporated in a general Quality Management System