IPEC Europe Observations and Recommendations on
"Guidelines On The Formalised Risk Assessment For Ascertaining The Appropriate Good Manufacturing Practice For Excipients Of Medicinal Products For Human Use"
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Original Text	IPEC Europe Suggested Alternative (if none then original text is clear and needs no alteration)	Commentary
	Purpose and Scope	
	This document provides guidelines for the Manufacturing Authorisation Holder so that they can comply with the requirements to perform the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients intended to be used in medicinal products for human use.	We propose a Purpose and Scope to make it explicit to whom the document applies.
1. INTRODUCTION		
1. Directive 2011/83/EC provides, in Article 46(f), as follows: "*The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The holder of the manufacturing authorisation shall ensure that the appropriate good manufacturing practice so ascertained, is applied. The holder of the manufacturing authorisation shall document the measures taken under this paragraph*"		

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2. The fifth paragraph of Article 47 of Directive 2001/83/EC provides that : "*The Commission shall adopt guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in the second paragraph of point (f) of Article 46.*"		
3. These guidelines are presented below: • Section 2: "Determination of appropriate GMP based on type of excipient" provides guidance on how to assess and rank the risk presented by the excipient. • Section 3: "Determination of Excipient Manufacturer´s Risk Profile" covers identification of appropriate GMP and assessment, ranking and control of the risk profile of the excipient manufacturer. • Section 4: "Confirmation of Application of Appropriate GMP" presents guidance on how to manage the risks of use of the excipient on an on-going basis.	3. These guidelines are presented below: • Section 2: "Determination of appropriate GMP based on type of excipient" provides guidance on how to assess the risk presented by the excipient. • Section 3: "Determination of Excipient Manufacturer´s Risk Profile" covers identification of appropriate GMP and assessment and control of the risk profile of the excipient manufacturer. • Section 4: "Confirmation of Application of Appropriate GMP" presents guidance on how to manage the risks of use of the excipient on an on-going basis.	"Ranking" actually serves no useful purpose in this process. Both material and suppliers are assigned a "ranking" but this does not reflect their subsequent control via determination of GMP. It should be removed.
4. The excipient risk assessment/risk management procedure should be incorporated in the Quality Management System of the Manufacturing Authorisation Holder.		
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.	This is the only instance of must – everywhere else uses "should".

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2. DETERMINATION OF APPROPRIATE GMP BASED ON TYPE OF EXCIPIENT		
6. The Quality Risk Management guidelines (ICHQ9) in Part III of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 (*EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* – hereafter 'EU-GMP') provide principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include excipients.	6. The Quality Risk Management guidelines in Part III of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 (*EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*) (ICHQ9) can be applied to the use of excipients in pharmaceutical products.	This is NOT how "EU-GMP" is used in the remainder of the document, - i.e. limited only to ICH Q9 in Part III – e.g. Art 15 "EU-GMP" is not a suitable acronym for this part of EU-GMP and it was felt confusing. Indeed the rest of the document does not use "EU-GMP" to mean Quality Risk Management rather the expected use as the GMPs for Drug products and APIs. Hence calling it ICH Q9 and elsewhere as a reference in the document. The final sentence is too terse and it is not clear what "aspects" are and how they would be applied to excipients
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. Quality risk management and assessment tools such as those listed in ICH Q9 should be used for this purpose.	The guidance document tells you how to do the risk assessment – HACCP is only one tool and is not considered to be a good example to use in this kind of risk assessment. Only documenting the material as a high, medium or low risk achieves nothing. The real reason for performing the assessment is to determine the risk profile and then balancing the level of GMP required against it.

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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:	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, its use and nature would determine the factors to consider in the risk assessment. For example:	This is a closed list and users may limit their risk assessment to just these factors and not consider other relevant ones.
• 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) • Sterility assurance (for excipients claimed to be sterile) • Use of dedicated equipment and/or facilities • Environmental control and storage conditions	• 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) • Sterility assurance (for excipients claimed to be sterile) • Use of dedicated equipment and/or facilities • Environmental control and storage conditions • Starting Point of the application of GMP in the manufacture of the excipient • Other factors as identified or known to be relevant to assuring patient safety	

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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 Critical Quality Attributes of the medicinal product	9. Additionally, with respect to the use and function of each excipient the Manufacturing Authorisation Holder should also consider the following factors such as: • The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion, paediatric use 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	Closed list again, hence final bullet points What is a "composite" excipient and why is this a specific risk? All excipients have the "potential" to impact the quality of the medicinal product (critical or not) - the role of the excipient in assuring medicinal product quality should be known through development and validation activities.

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10. Having established and documented the risk profile of the excipient, the Manufacturing Authorisation Holder should establish and document the elements of EU-GMP that he believes are needed to be in place in order to control and maintain the quality of the excipient (e.g. EU-GMP, Part I, Annex 1 and Annex 2, Part II etc.).	10. Having established and documented the risk profile of the excipient, the Manufacturing Authorisation Holder should establish and document the appropriate GMP (see #11) that he believes are needed to be in place in order to control and maintain the quality of the excipient	The "EU-GMP" is defined in #6 as ICH Q9. This is not what is intended in this clause. This document defines the elements of GMP for excipients so why not use those in this clause? Otherwise the clause requires Part I and Part II to be the only acceptable GMPs to be used. Having gone to the extent of defining the elements of GMP for excipients in #11 why not then refer to those instead?
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:	11. The determination of appropriate GMP 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 elements should be considered where critical to excipient quality:	We were not sure what "This" referred to. Only instance of "will" in text – "should" inserted. Prefer to use GMP "elements" as mentioned in #10 rather than principles.
a) Establishment and implementation of an effective Quality Assurance system		
b) Sufficient competent and appropriately qualified personnel	b) Availability of competent and appropriately qualified staff	
c) Defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities	c) Defined job descriptions for personnel responsible for critical manufacturing and quality activities	The original text is more proscriptive than Part II which only requires this for personnel engaged in manufacturing of intermediates and APIs.

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d) Training programmes for all staff involved in manufacturing and quality activities	d) Training programmes for staff involved in critical manufacturing and quality activities	"all" is too encompassing
e) Training programmes related to health, hygiene and clothing	e) Training programmes related to health, hygiene and clothing as identified as necessary to the intended operations	This mandates these training programmes in all circumstances when a risk based approach would indicate that these may not be needed. This is also more proscriptive than Part II.
f) Provision and maintenance of premises and equipment appropriate to the intended operations	f) Provision and maintenance of premises and equipment as identified as necessary to the intended operations	As point e)
g) Documentation system(s) covering all processes and 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	g) Documentation system(s) covering processes and specifications for critical manufacturing and quality operations including retention of batch/lot documentation, and other quality records for a defined period.	"all" is too encompassing The key element here is only "critical" activities. There is also a requirement for all excipients to have an expiry date which exceeds the requirements in Part II GMPs for APIs. Few excipients have expiry dates.
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 needs of continuous processes.	Full traceability is not possible in continuous plants or where bulk tanks are used and alternative systems need 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) Provision and maintenance of an independent quality control function.	Not all excipient manufacturers have an independent quality department and these successfully supply excipients

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j) Retention of records for starting materials and excipients and retention of samples of excipients for the periods required by EU GMP	j) Retention samples of excipients for a defined period.	Record retention is covered in bullet g)
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 agreement	"any" is too encompassing Contract is too specific
l) Maintenance of an effective system whereby complaints are reviewed and products may be recalled		
m) Regular self-inspection programmes		
n) Any other (non-GMP) measures required to manage or control the identified risk.	Delete this bullet	This is not an element of GMP. This clause belongs elsewhere maybe a separate clause on its own or in Section 3 below
3. DETERMINATION OF EXCIPIENT MANUFACTURER´S RISK PROFILE		
12. A gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should then be performed.		
13. Data/evidence to support this should be obtained through audit or from information received from the excipient manufacturer.		
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 Good Manufacturing Practices.	14. Certification of quality systems and / or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered as these may fulfil the requirements.	"accreditation" is only for those organisations certifying organisations as compliant to a management system standard

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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 for that excipient manufacturer.	Ranking in high medium and low and then have a risk control strategy for these buckets that would meet the needs of all types of pharmaceutical product might be too simplistic. A supplier may provide excipients used for parenterals and dry products - one control strategy would not be appropriate to both. It is better to develop the control strategy by considering both the material characteristics, what it is used for , and the control processes employed by the supplier. Just ICH Q9 in other clauses based on the definition in #6
16. The Manufacturing Authorisation Holder should have a series of risk mitigation strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy (e.g. audit, document retrieval and testing) should be established.	16. The Manufacturing Authorisation Holder should have a series of risk mitigation strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy (e.g. audit, document retrieval and testing) should be established. The Manufacturing Authorisation Holder may use the outcome of the risk assessment as a starting point of dialogue with the supplier.	
4 CONFIRMATION OF APPLICATION OF APPROPRIATE GMP		

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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	a) Number of defects on received batches/lots of excipients	
b) Type/severity of defects on excipients		
c) Loss of relevant quality system accreditation by excipient manufacturer	c) Loss of relevant quality system and or GMP certification 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.		
	Based upon this evidence the applicability of the level of GMP required and the control strategy should be reviewed and revised as appropriate.	