The European Industrial Pharmacists Group has closely examined the proposed revision of Chapter 5: Production of Volume 4 of the Rules Governing Medicinal Products in the European Union, and is pleased to offer the following recommendations.

The EIPG notes that the revised document only aims at addressing Problem Statements outlined in the EMA's Concept Paper on Changes to Chapter 5 of the GMP Guide issued in May 2007[1], particularly the obligation for manufacturing authorization holders to use as starting materials active substances that have been manufactured in accordance with GMP guidelines, and the harmonization of practices and expectations concerning the testing of starting materials. Despite the recommendation of this same document to phase in these changes at the same time as existing work concerning updated GMP guidance for dedicated facilities in the manufacture of certain medicinal products, in line with a concept paper issued in 2005, this work is still ongoing. Thus, the introduction of this revised document is almost premature, a consideration that becomes all the more evident when guidelines on certain issues, such as the criteria to be implemented in the decision process of classifying an excipient as a high risk material or otherwise, have yet to be drafted.

Moreover, despite a third recommendation of the May 2007 Concept Paper being that of the clarification of the term "starting materials" as utilized in Chapter 5 vis-à-vis its applicability to active ingredients and/or excipients, the EIPG is of the opinion that, sadly, this objective has not been achieved through the current draft. Indeed, if anything, the draft as presented lends to greater inconsistency in this regard, inconsistencies that, regrettably, are not limited to this particular issue, but also extend to other concepts within the document.

As mentioned in the Concept Paper, Article 46f of Directive 2001/83/EC, as amended, limits the need to use starting materials which have been manufactured in accordance with GMP guidelines to active substances. However, albeit that the Concept Paper recognizes the fact that it is understood that the term "starting materials" includes excipients, this article as drafted proceeds to limit the term "starting materials" to active substances. On the other hand, one cannot ignore the latest legislative resolution of European Parliament on the proposal for a directive amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source.[2] This document proposes to solve the inconsistency in limiting the term "starting material" to active substances, by amending Article 46f to specifically state that holders of a manufacturing authorization should use only active substances which have been manufactured in accordance with GMP guidelines, i.e. the term "starting material" will be eliminated. The second paragraph of the proposed version, however, then proceeds to specify that holders of a manufacturing authorization shall ensure that excipients are suitable for use in medicinal products by verifying the appropriate good manufacturing practices. This dual specification in the Directives confirms the importance of considering both active substances and excipients as starting materials.

[1] Doc. Ref. EMEA/INS/GMP/128505/2007
[2] Document Reference P7_TA-PROV(2011)0056

The EIPG then makes the following specific recommendations:

Paragraph 5.24

5.24 Processes and procedures should undergo periodic critical ~~*re-validation*~~ **evaluation** [3] to ensure that they remain capable of achieving the intended results.

Paragraph 5.25

5.25 Starting materials should only be purchased from manufacturers, importers or distributors of ~~*active substances*~~ **starting materials**[4] approved by the manufacturers of medicinal products, ~~*named in the relevant specification*~~ and, where possible, directly from the manufacturer of the starting material. Purchase of starting materials should be controlled by written procedures. ~~*The supply chain of each starting materials should be known and be documented.*~~ [5]

It is recommended that the specifications established by the manufacturer for the starting materials ~~*be discussed*~~ **are agreed upon**[6] with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling, packaging and distribution requirements, as well as complaints and rejection procedures are ~~*discussed*~~ **agreed upon**[6] with the manufacturer and supplier, and ~~*that the outcome of these discussions are*~~ documented.

Paragraph 5.26

5.26 The selection, including qualification and approval of suppliers, and the purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers and the associated risks involved in that starting material's supply chain. Procedures for the assessment and purchase and acceptance of starting materials, including critical packaging materials should be documented as part of the quality management system. The approval of suppliers of starting materials should be controlled by ~~*QC and production*~~ **the quality unit**[7]. Suppliers of active substances and, ~~*certain*~~ excipients ~~*considered to be high risk materials*~~[8] used as starting materials, should be

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[3] Par. 45 of Annex 15: Qualification and Validation of Volume 4 of the EudraLex states, in dealing with revalidation, that "Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation." It is not clear why an attempt is being made to prescribe for stricter practices in Chapter 5 than are permitted in other parts of the Volume.

[4] Starting materials include both active substances and excipients, and it is therefore inappropriate to limit good practices to active substances.

[5] This requirement is specifically stated in Par. 5.26 and therefore its repetition here is superfluous.

[6] Both the current and the proposed Chapter 7 of Volume 4 of the EudraLex clearly state that outsourced activities "must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product ….. of unsatisfactory quality". It is therefore essential the specifications established by the manufacturer for the starting materials, and all aspects of their production and control, are not only discussed, but agreed upon, with the supplier.

[7] The responsibility for approval of suppliers is that of the quality unit, which includes the quality assurance and quality control divisions, but that is independent of production. This is specifically stated in Par. 7.12 of Part II of Volume 4, governing the manufacture of active substances, and can be extended, *inter alia*, to Part I.

[8] It is not clear why these obligations are being extended only to **some** excipients, particularly in the absence of guidelines to indicate on what basis excipients are to be evaluated as high risk or otherwise. The proposed directive to amend Directive 2001/83/EC states, in the proposed change to Article 46f "The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by

periodically audited to confirm that they comply with current GMP requirements and that supply chain traceability[1] of the starting material is being maintained. The findings from each audit should be documented~~, *and audit reports should be available for review by Inspectors*~~[9].

Footnote to Paragraph 5.26

[1] A record of where each ~~*active substance*~~ **starting material**[10] ~~*(including its critical starting materials)*~~[11] is manufactured, propagated, processed and handled prior to its use in the manufacture of a medicinal product. The record should include the names and addresses (including reference to the DUNS number) of each manufacturer, distributor, trader/broker and shipper involved in this part of the supply chain.

Notes to Paragraph 5.31

Notes:

1. The same requirements apply to packaging materials as stated in GMP part I, ~~*5.40*~~ **5.41**.[12]

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verifying the appropriate good manufacturing practice..". No mention is made of limiting this obligation to critical excipients.

[9] In the process of audits, the holder of a manufacturing authorization may be given access to certain supplier-sensitive information. Revealing this information in an audit report may cause considerable problems with regards to supplier confidentiality and non-disclosure agreements. Moreover, a supplier audit is, ultimately, an extension of one's own internal audit procedures. EMA Document EMA/INS/GMP/313513/2006 Rev 1 on the Conduct of Inspections of Pharmaceutical Manufacturers or Importers states that "the system for performing self-inspections in the company should be examined, although the reports themselves should not normally be read by the inspector." This principle should also apply here.

[10] The main paragraph (5.26) makes reference to both active substances and excipients, i.e. starting materials, but the footnote restricts the provision to active substances, and is therefore inconsistent with the main text.

[11] There is sufficient confusion over the term "starting material". Adding to that confusion by referring to starting materials of starting materials is not recommended.

[12] The correct reference is Paragraph 5.41, rather than 5.40.