IPEC Europe Observations and Recommendations on
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 5: Production

Original Text	IPEC Europe Suggested Alternative (if none then original text is clear and needs no alteration)	Commentary
Starting Materials		
Paragraph 5.26		
[…] Where possible starting materials should be purchased directly from the manufacturer of the starting material. […]	[…] Where possible manufacturing 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 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.

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Paragraph 5.27 - Excipients		
For the approval and maintenance of suppliers of active substances and excipients, the following is required: […] Excipients 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.	For the approval and maintenance of suppliers of active substances and excipients, the following is required: […] Excipients 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.	We are uncomfortable with the cross reference to active substances. 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 '***Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use***'. Furthermore, it is not clear what is meant by "particular risk".
Paragraph 5.32		
Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.	Only starting materials which have been released by the Quality Control Department and which *are within their retest period* should be used	This then aligns with the terminology of paragraph 5.30
Paragraph 5.33 a)		

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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.	a) A formal agreement should be signed, ~~according to chapter 7~~, between the finished product manufacturer and the starting material manufacturer *or supplier as applicable*.	In case of utilisation 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 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 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.
Paragraph 5.33 b)		
b) The finished product manufacturer should perform audits at appropriate intervals at the site(s) carrying out the testing (including 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.	b) The finished product manufacturer should *ensure that audits have been performed by appropriately trained personnel* at appropriate intervals at the site(s) carrying out the testing (including 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	We would recommend minor changes to allow audits to be performed by authorised third party organisations and certification bodies, (eg EXCiPACT). In line with the requirements for active substances (5.27)
Paragraph 5.33 c)		

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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.	c) The certificate of analysis provided by the starting material manufacturer*/supplier* should be signed by a designated person with appropriate qualifications and experience. ~~This person should~~ *The signature* ensure*s* that each batch has been manufactured and checked for compliance with *the product specification elements* of the requirements of the formal agreement.	Certificates of analysis (CoA) may be provided by entities other than the starting material manufacturer. Therefore "supplier" should be added. Signature of a CoA normally means confirmation that a batch of product meets an agreed specification. The formal quality agreement may include elements beyond the material specification. It is not practical that the CoA acts as confirmation of meeting all the requirements of the formal specification.
Paragraph 5.33 d)		
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.