LOGFILE Feature 13/2022

# 13 GMP Requirements for Excipient Manufacturers

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Based on the risk assessment documented in the excipient dossier and the risk profile of the excipient, the risk team defines the necessary GMP requirements in the next step.

At this point, the EU excipient guideline[1] stipulates that the medicinal product manufacturer specifies those GMP elements from EudraLex, Volume 4, which in his opinion are necessary to control and maintain the quality of the excipient. Specifically, according to the guideline, Annexes 1 and 2 of the EU GMP Guide and Part II of the EU GMP Guide are available for selection.

As helpful as the excipient guideline is in principle in the risk assessment of excipients - this restriction to EudraLex Volume 4 is clearly a weak point. If drug manufacturers strictly implemented this requirement, drug production would have come to a standstill on 21 March 2016 (the deadline from which the guideline had to be implemented). This is because most excipient manufacturers have not implemented an EudraLex-compliant quality management system.

Fortunately, the guideline itself provides two possible ways out of the dilemma. Firstly, the excipient manufacturer does not have to implement the entire Part II of the EU GMP Guideline. Instead, the guideline specifies those elements (see below) that must be taken into account as a minimum and otherwise leaves it up to the pharmaceutical manufacturer to define any further elements he considers necessary (always based on the risk profile of the excipient). In addition, the guideline points out in section 3.3 that any existing certifications of the excipient manufacturer should be taken into account, as they may already fulfil the quality management requirements.

On this basis, Maas & Peither Pharma GmbH has decided on the procedure described below.

The following **general GMP elements** are to be established by each excipient manufacturer regardless of the risk profile of the excipient:

- Implementation of a quality system
- Staff
    - In sufficient numbers
    - Competent and appropriately qualified
    - Job descriptions for managers in manufacturing and quality unit
    - Training programmes for all production and quality unit staff (technical, health, hygiene and protective clothing)

[1] Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (Text with EEA relevance) (2015/C 95/02)

- Appropriate facilities and equipment and their regular maintenance
- Documentation system for procedures and specifications of all activities in manufacturing and quality unit (e.g. SOPs, manufacturing and testing instructions, specifications)
- Unique article and batch numbers for starting materials, intermediate products and auxiliary materials for complete traceability
- Qualification programme for suppliers
- Quality control of the excipient; the person responsible for the batch release must be independent of production
- Retention of records of starting materials and the excipient itself, and retention of samples of the excipient for the periods required by EU GMP Guide, Part II
- Written contracts for quality-related activities outsourced to third parties
- Complaints and recall management system
- System for managing changes and deviations as well as CAPAs
- Self-inspection programme
- Monitoring of environmental and storage conditions (if required according to the storage requirements of the excipient)

For all excipients with medium or high risk, the risk team checks the necessity of further **specific GMP elements** according to EudraLex, Volume 4. Thereby, specific GMP elements are not necessary in every case! Corresponding guidelines for the decision can be found directly in the excipient dossier.

It is by no means mandatory to define further specific GMP elements for excipients with medium or high risk. Depending on the specific risks, they may be sufficiently controlled by the general GMP elements. Specific GMP elements should therefore only be defined if this really seems necessary to control certain risks.

The risk team documents the result of the assessment and the general and, if applicable, specific GMP elements required at the excipient manufacturer in the excipient dossier. After completion of the assessment, the excipient dossier is dated and signed by the members of the risk team.

For the sake of completeness, it should be mentioned that the procedure described above is not sufficient for sterile or biotechnologically produced excipients. In these cases, it seems to make sense to use Annex 1 or Annex 2 of the EU GMP Guide as a basis, as specified in the excipient guideline.

*The text is a translated and shortened extract from the German* ***sample SOP-641-02 Risk assessment of excipients****.*

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