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Typical GMP Deficiencies at Manufacturers of Chemical APIs - An Overview

Excerpt from the GMP Compliance Adviser, Chapter 20.F.5.14

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Figure 20.F-24 provides an overview of the GMP deficiencies that, in the author's experience, are frequently encountered during audits of active substance manufacturers.

At a glance: the most common GMP deficiencies at active substance manufacturers	
Deviations	Insufficient documentation of deviations Inadequate root cause analyses Lack of risk assessment with regard to further potentially impacted batches Insufficient qualification/training of the employees
Quality Risk Management	No systematic approach Superficial risk assessments Insufficient follow-up of actions from risk analyses
Product Quality Review	No in-depth assessment of the available data Lack of evaluation of the effectiveness of corrective actions Insufficient evaluation of returns PQRs are prepared too late.
Personnel	Insufficient compliance with hygiene regulations Inadequate training of external service providers
Water	Insufficient monitoring Lack of rationale for setting warning and action limits Insufficient actions taken when limits are exceeded
Documentation and protocols	Violations of ALCOA rules and data integrity requirements for electronic systems.

Materials management	Inadequate pest control measures Insufficient sampling conditions Insufficient qualification suppliers of raw materials, active substance starting materials and intermediates
Production	Measures to prevent contamination at different stages of production are inconsistent. Lack of definition of the maximum campaign length Lack of definition of holding times of uncleaned or cleaned equipment
Packaging and labelling	Insufficient controls before starting the packaging process
Laboratory controls	Shortcomings in the examination of OOS results Stability samples not stored in containers that mimic market containers.
Cleaning validation	Insufficient consideration of possible microbiological or endotoxin contamination Insufficient care in the identification of worst case products and the selection of sampling points
Returns	Inadequate procedures for handling returns

Figure 20.F-24 Common GMP deficiencies at active substance manufacturers

Thematically, there is thus a striking overlap here with the deficiencies found during GMP inspections of medicinal product manufacturers. From the author's point of view, the production of active substances generally takes place at a high level; with regard to the fulfillment of the respective GMP requirements, active substance manufacturers are not necessarily in a worse position than medicinal product manufacturers.

Due to the increasing use of electronic systems, it is to be expected that deficiencies in the area of documentation or, for example, the handling of deviations and OOS results will be identified and avoided more quickly in the future. However, this will also result in new sources of errors and requirements, especially with regard to the validation of electronic systems and the maintenance of data integrity. From the author's point of view, the focus of audits at active ingredient manufacturers will certainly continue to shift in the direction of checking these requirements.

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