QUALITY MANAGEMENT SYSTEMS IN DRUG DEVELOPMENT

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Preclinical research and development are of major importance in the development of a pharmaceutical. Based on the gathering of pharmaceutical, pharmacological and toxicological data, test substances for further development have to be selected. In consequence it is essential particularly during these very early development phases to avoid wrong strategic decisions. This underscores the necessity to ensure the validity of preclinical data by means of appropriate quality management systems (QMS). Therefore different QMS are described and discussed with regard to their suitability for use in preclinical research and development. The QMS presented can be divided into three categories concerning formal and content-related aspects: certifiable QMS, accreditable QMS and QMS, which are subjected to authorization and monitoring by the responsible authorities. The QMS relevant in this case are, for the certifiable QMS ISO 9001, for the accreditable QMS ISO 17025 and ISO 15189 respectively and for the QMS subjected to authorization by the responsible authorities GMP, GCP and GLP. ISO 17025 deals with general requirements for the competence of testing and calibration laboratories. Though its objective is the reliability and comparability of measuring results, an accreditation according to ISO 17025 is not required by the applicable regulations. Regardless of regulatory obligation the Central Institute of the Bundeswehr Medical Service has achieved an accreditation according to ISO 17025 which includes the field of pharmaceutical research and development. This way pharmaceutical research and development is embedded to the QMS of the whole institute and results from this particular area accomplish the unique quality standards of the Institute. This is of eminent importance as far reaching decisions might depend on results from this field.

DRUG CONTROL BY THE AUTHORITIES: HOW TO ASSURE QUALITY WITH A FEDERAL PATCHWORK

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Our authority is one of currently nine Official Medicinal Control Labs (OMCL's) which are responsible for the handling of all drug samples taken by authorities in the particular federal state. Samples are taken regularly according to a plan as well as irregularly because of suspicion. Formerly the samples were mostly taken directly from the manufacturer in the course of regular inspections. Nowadays more and more samples are taken from sales and distribution in order to find transport related quality problems and counterfeits. The general analytical strategy is a screening for non-compliance. The structures of the authorities vary from one federal state to another. Therefore it is important that the German OMCL's work together in an expert group under the auspices of the Zentralstelle der Länder für Gesundheitsschutz (ZLG). Agreements on standards of the analytical spectrum have been achieved. Samples can be exchanged in case of special demands. Moreover, a European OMCL network has been established coordinated by the European Directorate for the Quality of Medicines (EDQM). Preparing expert reports on the classification of borderline products becomes increasingly important, whether or not these are medicinal products, medical devices, dietary supplements, cosmetic products, or food. The parallel import of drug products from other European countries has become a big business. However, the regulations are currently insufficient to ensure that these products meet the same quality standards as the original products. In particular, it is difficult and sometimes impossible for the local authorities to obtain the respective quality documents. A future challenge will be the increasing importance of biopharmaceuticals. A state-of-the-art analytical examination requires remarkable improvements in equipment and personnel. German OMCL's work hard to prepare for the challenges of an ever-changing market and keep the local competence in the interest of drug safety.

“OUT-OF-SPECIFICATION“ (OOS) RESULTS: FDA GUIDANCE AND EUROPEAN EXPECTATIONS

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Countless conferences, workshops, continued-education programs and publications have dealt with the topic of Out-of-Specification (OOS) Test Results after the Barr decision of February, 1993, and the following issuing of the FDA “Guide to the Inspection of Quality Control Laboratories“.
Surprisingly, inadequate workflows or procedures used during the investigation of deviations and, especially, out-of-specification (OOS) results are still main triggers for the issuing of warning letters or “483 Findings“ by the FDA.
In October 2006 the FDA has published its long-awaited Guidance for Industry “Investigating Out-of-Specification Test Results for Pharmaceutical Production”, which contains a few new approaches and some clarifications compared to the Draft Guidance from 1998. The agencies´ requirements are compared to the European expectations. A general workflow how to perform an investigation following an OOS test result is proposed and the most important points of the final FDA OOS Guidance are presented.

(1) FDA, Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production; (final) October 2006; www.fda.gov/cder/guidance/3634fnl.pdf
(2) Renger, B. “Handling Out-of-Specification (OOS) Results in the Laboratory”, in **GMP Report Vol. 1**, “FDA Requirements for cGMP Compliance”, Editio Cantor Verlag, Aulendorf, (2007) pages 97 - 119

QUANTITATIVE GEL ELECTROPHORESIS SOURCES OF VARIABILITY

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Gel electrophoresis is known for its often unsatisfactory precision. Standard deviations (RSD%) in a range of 13 – 40% and in some particular cases even up to about 60% RSD% have been reported. Potential major sources of variability for this technique include the staining or rather detection of separated proteins, the transfer between first and second dimension and the training in 2-DE performance of the analyst. Two groups of gels of the same sample were compared, the first group was prepared by a trained person, the second group by an untrained one. Comparison of both groups shows a significant difference. By preventing oxidation, aggregation and precipitation at the equilibration step the transfer between the first and second dimension and consequently precision in 2-DE can be improved. Staining with dyes such as Coomassie or Fluorescence staining has become most popular. However, a common big drawback of these methods is the high background staining which results in a limitation of sensitivity and finally in a low reproducibility. A direct detection of separated proteins by native fluorescence offers many advantages. A threefold better signal-to-noise ratio was found, although the sample was used in an 800-fold lower concentration. This improvement together with well-defined peaks resulted in a better quantitative spot reproducibility of approximately 12 – 16% RSD%. Possibly the variabilities due to detection and evaluation were already reduced to minor error components. However, according to the law of error propagation, the major error sources dominate the total error. In order to really prove the good detection and evaluation, these other sources of variability have to be reduced next.

MEDICINAL PLANTS: FROM HARVESTING TO CULTIVATION – CONSEQUENCES FOR QUALITY AND PRODUCTION OF HERBAL REMEDIES

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Over a long time medicinal plants were only harvesting on their natural origin (1). Unfortunately this plant material has a low quality by a general reduced homogeneity and also by differing contents of their for the efficacy responsible constituents. In addition the collectors can harvest also material from other plants, if there are only small or no differences in the constitution between the medicinal plant and the other plants. For that the specifications limit the content of foreign matter and include special purity tests. After the successful cultivation programs of the last decades the main herbal drugs can be obtained without the described problems and consequently their specifications should be reviewed. So for example special purity tests of similar plant material should be eliminated. Now after the implementation of the current guidelines of GAP and GMP some important points for the quality check should be transferred to the time of harvesting. Then at best a conformity should be given over the absence of other plant material. The representative samples for the total release check should be generated directly after drying and to proof the correct particle size for extraction sampling should be carried out during cutting. Therefore the classic inspection of incoming plant material can be reduced like the current test procedure for synthetic active pharmaceutical ingredients.

(1) Tegtmeier M et Harnischfeger G (2005) Phytogalenik: Plädoyer für die moderne Mischextraktion. Pharmazeutische Zeitung 150 (44): 18-25