TRANSLATION PROBLEMS IN THE CONSTRUCTION PROJECT OF A PHARMACEUTICAL PRODUCTION ENTERPRISE BASED ON GMP STANDARDS

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Annotation. WHO defines Good Manufacturing Practices (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization."

Key words: GMP, procedure, facility system, bioassays, categories

Aim. GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch records and distribution records; and systems for recall and investigation of complaints.

The guiding principle of GMP is that quality is built in to a product, and not just tested in to a product. Therefore, the assurance is that the product not only meets the final specifications, but that it has been made by the same procedures under the same conditions each and every time it is made. There are many ways this is controlled - validation is that part of GMP that ensures that facility systems, equipment, processes, and tests procedures are in control and therefore consistently produce quality product. Validation is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes. Validation studies are performed for analytical tests, equipment, facility systems such as air, water, steam, and for processes such as the manufacturing processes, cleaning, sterilization, sterile filling, lyophilization, etc. There will be a separate validation for the lyophilizer as an equipment item and for the lyophilization process; for the cleaning of glassware and the cleaning of the facility; and for the sterilization process and for the sterility test. Every

step of the process of manufacture of a drug product must be shown to perform as intended. Validation studies verify the system under test under the extremes expected during the process to prove that the system remains in control. Once the system or process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications are made, or problems occur, or equipment is replaced or relocated, revalidation is performed. Critical equipment and processes are routinely revalidated at appropriate intervals to demonstrate that the process remains in control.

A protocol is a written set of instructions broader in scope than a Standard Operating Procedure (SOP). SOPs are the detailed written instructions for procedures routinely performed in the course of any of the activities associated with pharmaceutical manufacturing. A protocol describes the details of a comprehensive planned study to investigate the consistent operation of new system/equipment, a new procedure, or the acceptability of a new process before it is implemented. Protocols include significant background information, explain the rationale for and the objective of the study, give a full description of the procedures to be followed, set out the parameters to be measured, describe how the results will be analyzed, and provide pre-determined acceptance criteria for making conclusions. Validation studies, stability studies, and clinical studies are examples of written protocols for pharmaceutical manufacturers. Validation protocols are important in ensuring that documented evidence is taken which demonstrates that an equipment item, a system, a process or a method consistently performs at a specified level. Validation of analytical assays is the process of establishing one or more of: accuracy, precision, linearity, range, limit of detection, limits of quantitation, specificity, and ruggedness as appropriate to the type of assay. For physico-chemical methods there are accepted defined limits for these test parameters. Bioassays are much more variable in outcome and also often use animals and cells in the assay which in themselves are variable, and can have broad acceptance limits. The discussion in this guide is limited to bioassays. Bioassays. There are three broad categories of bioassays which are commonly used for biological products: binding assays, cell-based assays, and whole animal assays. Some complex assays are in more than one of these categories. Binding assays are those that involve the binding of two or more molecules. Immunoassays are an example of this type. Binding assays are used for monitoring a molecule during purification steps and for cleaning validations. Binding assays are not generally considered acceptable for potency assays because the presence of a molecule as determined by a binding

interaction is not necessarily an indication of the activity of the molecule. Cell assays are those where the product evokes a measurable response in specific cells: clumping, cell lysis, cell fusion, or generation of a specific detectable chemical. These assays can be more variable than binding assays and must be performed carefully to ensure consistent results. Cell-based assays are often used for potency assays.

Conclusion. Whole animal assays are more difficult and involve the care, maintenance and handling of animals. They are time consuming and highly variable. The biological response of an appropriate species to an active drug is compared to the response to a reference product or to uninoculated controls as a measure of activity. These assays are used for pyrogen assays, general safety assays, and potency assays. Because of their expense, the large number of animals used, the time spent, and their variability, whole animal assays for potency are usually only performed for the final product release.

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