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Quality Tools for Improving a System of Documentation as the Basis for Good Manufacturing Practices - Mini-Review

Biunayki Reyes Díaz[1*] and Angela Sosa Espinosa[2]

*[*1]Process Control Department, Centre for Genetic Engineering and Biotechnology, Habana, Cuba*
[2]Biosafety Department Center for Genetic Engineering and Biotechnology, Cuba

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ABSTRACT

The documentation system is one of the mandatory elements reviewed during inspections of any regulatory agency. Generally, more than 20% of the deviations detected in a pharmaceutical inspection, are directly related to the documentation of quality system in each of the components or systems inspected. Given that no regulation on GMP will tell us in detail how the documentation system should be, we aimed to show in this work an approach used to implement some of the quality tools for establishment and maintenance of GMP and inherent Documentation in order to comply with the normative, national and international regulations typical of a productive process monoclonal antibody (MAb) which is secreted by the hybridoma.

Keywords: GMP, Documentation system, Quality tools and Biotechnology

INTRODUCTION

The development and evolution of any document goes through a series of stages comprising what is known as the document's lifecycle [1], it begins with the conceptual definition of its purpose, followed by an archiving step and final destruction, and depending on the case, a new cycle may begin with a new edition of the document. In order to decide on the creation of a specific document, we asked ourselves the following questions: What is the purpose of the document? What information should the document contain to achieve its purpose? Who participate in its preparation? Who will implement it? Whom will the information contained in it be addressed to? And what other documents are interconnected?

MATERIALS & METHODS

Quality tools

WORK IN A TEAM: Work in a team is the integration of a group of people related to each other, sharing a common goal and working hard to achieve their goals who regularly meet to identify and solve problems related to the proposed objectives.

FLOW CHARTS: They trace the various steps of the process and all inter-relationship, allowing us to identify critical points in the process, sequence of events, external and internal relationships, inspection points, entries and exits, thus facilitating their analysis.

RESULTS & DISCUSSION

Stage 1: Diagnostics and Evaluation of Specific and General Documentation of the System

A set of observations obtained by the Head of Production, Documentation Specialist, and the specialist in validation from a data collection process of regulatory standards and guidelines, evidenced the need to prepare documents after the following structure. We analyzed each step of the process and the requirements demanded by the guidelines defined aforementioned: For Standard Pattern Operation Procedures, in which operations should be documented, for the quality specifications as standardized system by the quality assurance department and their classification, we identify which our critical and non-critical PNs were, and for the batch master files, once former documents have been

Corresponding author: Biunayki Reyes Diaz, M.sc, Process Control Department, Centre for Genetic Engineering and Biotechnology, Habana, Cuba, E-mail: biunayki.reyes@cigb.edu.cu

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identified we define the RML. For the whole production system, common operations general to all stages were documented, performing and approving SOPs which were related to basic activities of compliance with Good Manufacturing Practices, such as: Personnel Flow and Flow of Materials into the clean area, Use of Personnel Transfer and Change of Clothes, Cleaning and Sanitation of the Areas, Coding System and Storage of Samples, among many others. Documents, along their life cycle, go through a series of stages, each of which must be carefully defined and implemented in daily practice. In the process of implementation of the documentation system it was necessary to determine the responsibilities and activities in line so as to meet the life cycle of documents: generation, reviewing, approval, new editions, obsolescence and destruction.

Stage 2: Maintenance and improvements to the document system

After each document has been discussed, approved and set up, we proceeded to check their handling and use mainly through self-inspections. Just the same way as the handling and use of documents had been verified in inspections performed by the Direction of Quality Assurance and National Regulatory Center.

The number of deficiencies in year 2000 were up to 25, all mostly related to documentation of the process, this was due to we yet had not enough experience, nor with a section exclusively addressed to this activity, and as has been presented elsewhere [2], although we were organizing ourselves to go into a truly quality system, to the extent that our system was improving from deficiencies found by the national regulatory agency which decreased over eight times, and in spite of the fact that in all cases they were overcome in the follow-up inspection, with a few remarks, which were associated with changes to improve the process.

Stage 3: New regulatory perspectives

As biotechnology and the development of monoclonal antibodies are rapidly evolving fields, the information contained in these guidelines may become obsolete or be subjected to rapid changes making them new and susceptibly with better information attained. In an evaluation conducted in production, starting from continuing improvements desired to be implemented to the process, and taking into account new regulations, which are more specific for this type of product, we started to implement a new regulatory kind of self-inspection.

As a result of brainstorming done, found that further aspects required to go deeper into them, those related to (Compliance with; new regulations issued by FDA [3], WHO [4] and EMA [5]; quality specifications and process operation procedures). Each of these ideas generated were expanded in various stages of research, using the techniques of the 6 M's, cause-effect diagrams and weighting of experts by the Borda method, risk analysis of each system, among others. Based on the outcome diagnosis, we developed the cause-effect diagram **(Figure 1)**.

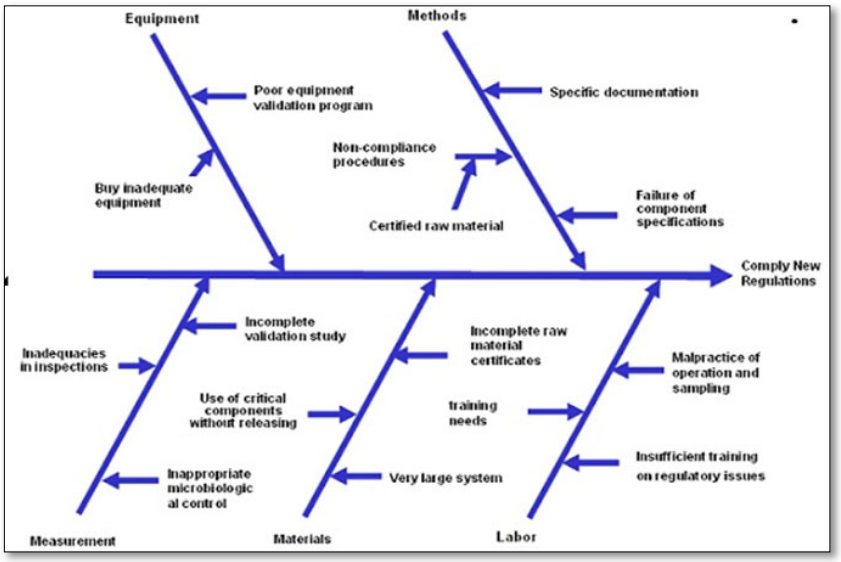

Figure 1. Cause and effect diagram of the analysis used by the 6 M (s) to the production process.

METHYLATION AND TOMOURIGENESIS

Considering new data in the field of DNA methylation, it is now possible to propose a model for how this modification can influence to mourigenesis. The findings on DNA methylation in cancer can be interpreted in two different ways. On the one hand, it is possible that normal cells

become transformed through the occurrence of driver mutations and then undergo de novo and demethylation as a result of this event, setting in motion a series of programmed changes in gene expression [10]. Alternatively, a subpopulation of normal cells that have already undergone changes in methylation, perhaps as a result of aging, may represent preferred targets for oncogenic transformation. According to this, the presence of abnormal methylation in cancer actually comes about through selection of pre-existing normal cells characterized by a methylator phenotype. Once this is formed, it would, of course, be preserved in progeny cells, much in the same manner as mutations [11] **(Figure 1)**.

CONCLUSION

The effective functioning of documentation system has been the basis for implementation of the Good Practices during the development of different production process steps taken place in department, allowing the release and commercialization of a considerable number of utility batches for human health. It also served as the basis to implement the same system in the second productive alternative with regard to the product.

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