

## “Quality Tools for Improving a System of documentation as the basis for Good Manufacturing Practices”. Practical Case

Biunayki Reyes Díaz<sup>1\*</sup>, Andrés Tamayo Domínguez<sup>2</sup>, Mirtha Castiñeiro Díaz<sup>3</sup>, Gudelia Pérez Monras<sup>4</sup>, Cristina García Aguirre<sup>2</sup>, Gisela Calas Domínguez<sup>2</sup>, Angela Sosa Espinosa<sup>5</sup> and Rodolfo Valdés Veliz<sup>1</sup>

<sup>1</sup>Process Control Department, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba

<sup>2</sup>Monoclonal Antibody Department, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba

<sup>3</sup>Pharmacy and Food Institute, U.H. Habana, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba

<sup>4</sup>Quality Assurance Direction, U.H. Habana, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba

<sup>5</sup>Biosafety Department, U.H. Habana, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba

### Abstract

The documentation system is one of the mandatory elements reviewed during inspections of any regulatory agency. Generally, 20 to 30 percent 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 48/1/5/4, specific for the “a” determinant of the Hepatitis B surface antigen (HBsAg). This MAb is routinely used as reagents for the purification of vaccines.

The work was separated into three basic stages: *Diagnosis and Assessment of Specific and General Documentation of the System; Maintenance and improvements to the document system and New regulatory perspectives*. The effective functioning of a documentation system in which the main objective has been to guarantee stable and solid production processes for the preparation of biopharmaceutical products, allowing the release and commercialization of a considerable number of utility batches for human health.

**Keywords:** GMP; Documentation system; Quality tools; Biotechnology

### Introduction

In the different guidelines and regulations related with GMPs in general, the importance of a well structured documentation system for a biopharmaceutical company should be emphasized, since it is quintessential to evidence the quality of a product, its design, and management, thus representing a valuable tool for the company to comply with applicable regulations and to maintain itself in an advantageous position in the current competitive environment [1].

In this paper, we expect to show the approach used in the implementation of some quality tools for the establishment of GMP as well as the documents related to the compliance with the rules, regulations and international agreements. Illustrate steps that were followed for the conception, revision and approval of the documentation system and quality control strategy used to approve the sanitary registry for an antibody productive process used as reagents in the purification of vaccines, based on a careful analysis of production particularities.

### Methodology for the design

The development and evolution of any document goes through a series of stages comprising what is known as the document's lifecycle [2], 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?
- What other documents are interconnected?

Responses to these questions were carefully analyzed so as to make sure they are really needed and to avoid redundancy that would eventually cause an overload of the documentation system affecting its effective and efficient functioning.

According to the schedule and steps to follow for identifying document requirements which served as a starting point for their design and implementation, quality tools were used and work was separated in three basic stages:

Stage 1: Diagnostics and Assessment of Specific and General Documentation System

Step 2: Maintenance and improvements to the document system

Stage 3: New regulatory perspectives.

**\*Corresponding author:** Biunayki Reyes Díaz, MSc., Process Control Department, Center for Genetic Engineering and Biotechnology, P.O. Box 6162, Habana 10600, Cuba, E-mail: [biunayki.reyes@cigb.edu.cu](mailto:biunayki.reyes@cigb.edu.cu)

**Received** June 09, 2011; **Accepted** September 27, 2011; **Published** September 29, 2011

**Citation:** Díaz BR, Domínguez AT, Díaz MC, Monras GP, Aguirre CG, et al. (2011) “Quality Tools for Improving a System of documentation as the basis for Good Manufacturing Practices”. Practical Case. Pharm Anal Acta 2:136. doi:10.4172/2153-2435.1000136

**Copyright:** © 2011 Díaz BR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Materials and Methods

The production process of MAb CB.Hep-1 includes four main steps:

1. Conformation of the cell banks and inoculum
2. Ascites production
3. Immunoglobulin G (IgG) purification
4. Immobilization on Sepharose CL 4B7

In every step, several unitary operations, processes, and quality controls are carried out.

### Inoculum preparation

Inoculum preparation includes maintaining the Master and Working Cell Banks (MCB/MWCB) and growing the suspended or stationary methods in spinner flasks. Each production batch is originated from a fresh ampoule of the seed. Subsequently, 106 hybridoma cells are inoculated intraperitoneally in each mineral oil primed BALB/c mice [3].

Purification consists of several chromatography gel filtration cycles in Sephadex G-25 coarse (Amershan- Pharmacia, Uppsala, Sweden) Protein an affinity. After this chromatography, incubation in 0.1 molar (M) citric acid pH 3.0 for an hour at 4°C was carried out. The ultra

filtration and sterile filtration steps complete the basic diagram of the purification process [4].

The purified antibody is stored at 4°C for further use as immunoligand to purify the rHBsAg.

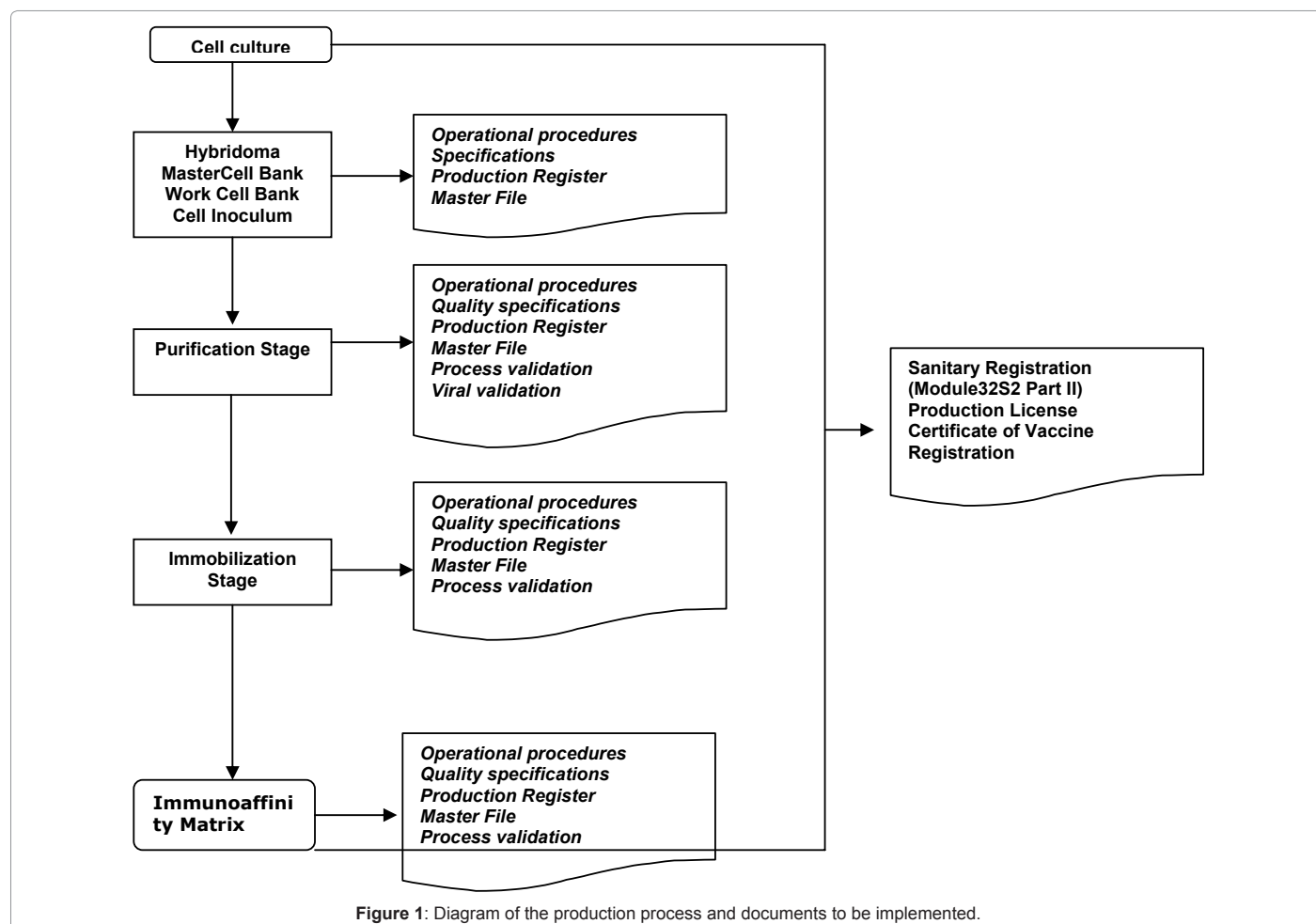
### Quality tools

**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. All revision of national and international regulations and documents related to the quality policy was performed by a team.

**Flow charts:** These diagrams constitute a graphical representation the sequence of all process operations. 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 and Discussion

Pharmaceutical regulations such as GMP for drugs and medical devices, GMP (Good Manufacture Practices), as well as quality system standards like ISO (International Standard Operations), require a strong documentation system. This includes quality and policy manuals, work instructions, operation flowcharts, SOPs, plans, and various types of



**Figure 1:** Diagram of the production process and documents to be implemented.

records and validation protocols within other documents. These serve to provide evidences that the manufacturing process followed the established specifications. Such regulations, however, do not provide guidelines on how to set up and manage documentation systems. Therefore, it is left to companies to design and implement their own internal documentation systems.

We illustrated the establishment of a documentation system and quality control strategy designed to support the production

Stage no 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 identified which were our critical and non-critical *Part Numbers* (PN) were, and for the batch master files, once former documents have been identified we define the *Batch Master Record* (BMR), taking into account that the process consists of three basic stages as shown in the diagram of the process.

For the whole production system, common operations general to all stages were documented, performing and approving a total of 20 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, in [Figure 2](#) shown an example of SOP).

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 ([Figure 3](#)).

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. Completion of each inspection, the deficiencies was discussed in a committee with the participation of Production Head, documentation specialist, responsible for the area involved and the auditor. To eliminate the cause of deficiencies were defined to implement corrective action; some of the deficiencies list below.

- The sampling procedure does not indicate what to do after the operation.
- There is no documented evidence of homogeneity of study samples
- The activation procedure does not specify the number of sub lots that can be processed
- Flowchart not clear checkpoints

These measures were adopted and implemented, the nature of corrective action was focused primarily remedial education staff, growing the staff in the handling and proper use of different types of documents, in their importance and the need for meet regulatory requirements established for compliance with Good Manufacturing Practices. The improvement of the system in this second period (2003-

PROCEDURE FOR CLEANING AND DISINFECTION OF CLEAN ROOM.		
SOP 2.22.002.92	edition 03	Sheet 4 to 4
Effective : ____/____/____		Amendment 00
<b>A) PURPOSE / PRINCIPLE</b> This document establish a sequence of steps to ensure the cleaning and disinfecting the areas of production of monoclonal antibodies.		
<b>B) APPLIES TO</b> Clean rooms of monoclonal antibodies production.		
<b>C) RESPONSIBILITY</b> The strict enforcement is the responsibility of the operators designated for cleaning and disinfection of areas. The heads of each one checked that the procedure is fulfilled.		
<b>D) SECURITY CONSIDERATIONS</b> • Staff must be trained for this activity and meet the special requirements of Good Manufacturing Practice for work in clean areas with aseptic processes.		
<b><u>Walls cleaning:</u></b> Run wet cleaning using wet cloths or mops in sterile solution of sanitizing agent. Do this with short, straight vertical, overlapping starting from the ceiling to the floor. Perform cleaning of occasional furniture and floors as indicated in CLEANING AND DISINFECTION		
<b>Made by:</b> <b>Position:</b> Documentation Specialist. <b>Reviewed by:</b> <b>Position:</b> Production department Head <b>Approved by:</b> <b>Position:</b> Production Director	<b>Signature</b> _____ <b>Date:</b> ____/____/____ <b>Signature</b> _____ <b>Date:</b> ____/____/____ <b>Signature</b> _____ <b>Date:</b> ____/____/____	

Figure 2:

2008) was a reduction in the number of documents after meetings with several other productions and the Quality Assurance Department of the institution.

The reports resulting from inspections carried out mainly in 2000, 2004 and 2006 were analyzed prior to the three inspections conducted by the WHO. The results are shown in Figure 4. As he gained experience in quality management, deficiencies identified by internal audits by the Department of Quality Assurance IGBC and national regulatory agency CECMED decreased.

The correspondence which took the deficiencies in the documentation for each year was: for 2000 to 46% in 2004 to 17% and in 2006 with 11% in all cases the deficiencies were overcome in the follow-up inspection, to a greater extent in 2006 year reaching 100% compliance with corrective measures proposed, there were signs was associated with changes to improve process.

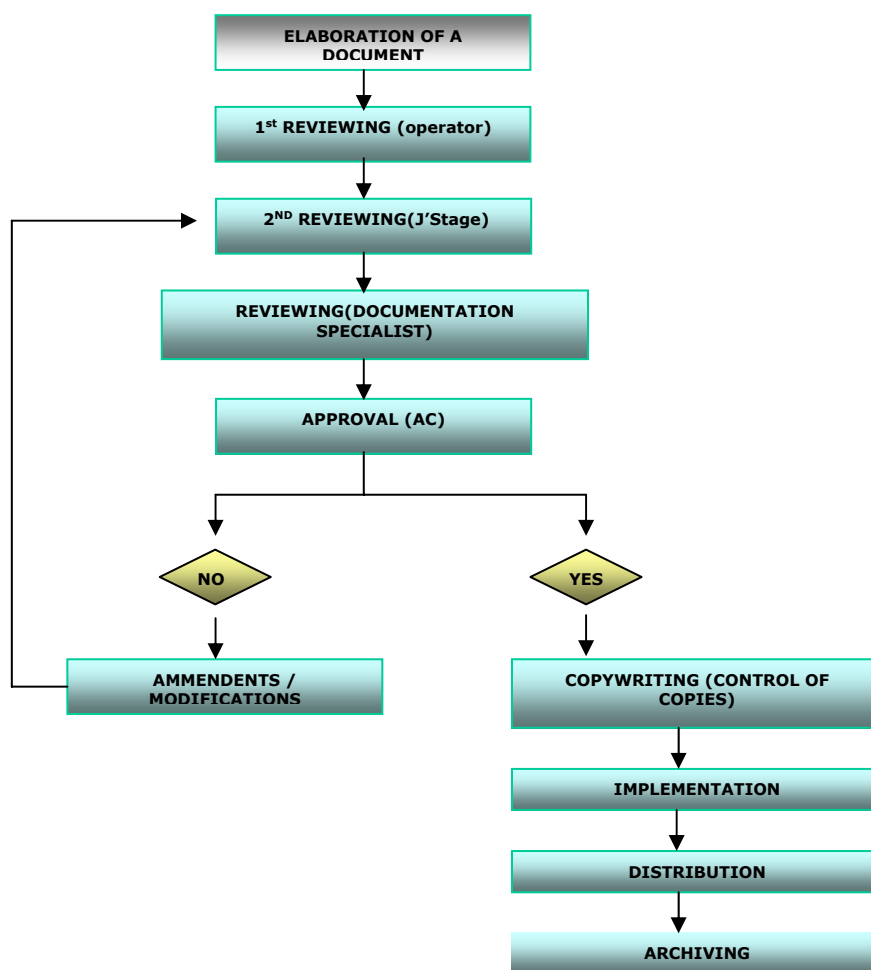
Stage 3 new regulatory perspectives:

The main characteristic of these products is that they are produced by mammalian cells in culture or are taken directly from an animal. In both cases, the starting material is capable of harboring adventitious agents - generally viruses that can result in significant harm to humans.

This is particularly important when the production of monoclonal antibodies involves large scale use of animals which have been reported by various regulatory agencies, which have issued guidelines for the manufacture, identification and validation of monoclonal antibodies for use in humans or for purification of biologics (FDA 2001; WHO, 1992). This not only encompasses endogenous and adventitious viruses, but also the residual cellular DNA and other proteins or factors transformants. The guidelines issued by regulatory agencies FDA and WHO for the development of monoclonal antibodies are updated periodically. These guidelines serve as prototypes to establish standards that take into account in making safety and efficacy in laboratory trials to demonstrate the quality of the antibodies. This rapid evolution in a short time ago that regulatory information may become obsolete or subject to rapid changes makes them new and significant information available that determines the dynamics of the documentation system to be established.

One of these changes as new regulations was:

"Guidance for Industry Monoclonal Antibodies Used as Reagents in Drug Manufacturing" (FDA, 2001) "Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances, (subchapter 4.8. Used as Reagents Monoclonal antibodies)" (EMA, 2007), which include a specific section for this type of product



**Figure 3:** Diagram showing the flow followed by documents in their life cycle.

For the implementation of new regulatory documents was a new self-regulatory inspection where the system underwent a reassessment Documentary and applied quality tools known. Was performed with a meeting chaired by the Head of Department and Head of Documentation.

For the specialists explained the key issues related to the finding during the analysis thus beginning the investigation of root cause through brainstorming.

As a result we found that it required deeper aspects:

- Regulatory Compliance.
- Compliance with quality specifications.
- Procedures for process operation.

Each of these ideas generated were amplified in various stages of research, we apply the Plan, done, check and action (PDCA), and used the technique of the 6 M's, which satisfied the cause-effect diagram or Ishikawa (Figure 5).

These 4 steps PDCA, they said:

- The logical organization of work,
- The successful completion of the tasks required and planned

- Checking the achievements and the ability to leverage and extend learning and experiences to other cases

**Personnel training:** The establishment and maintenance of a System of Quality Assurance, manufacture and control of pharmaceuticals and biotechnological products depend greatly on the personnel [1]. It is the most important factor in production processes of medication so special care has to be taken in selecting it, as well as in capacitating and evaluating all its members.

In order to select and implement the training in order to close the gap between the required aptitude

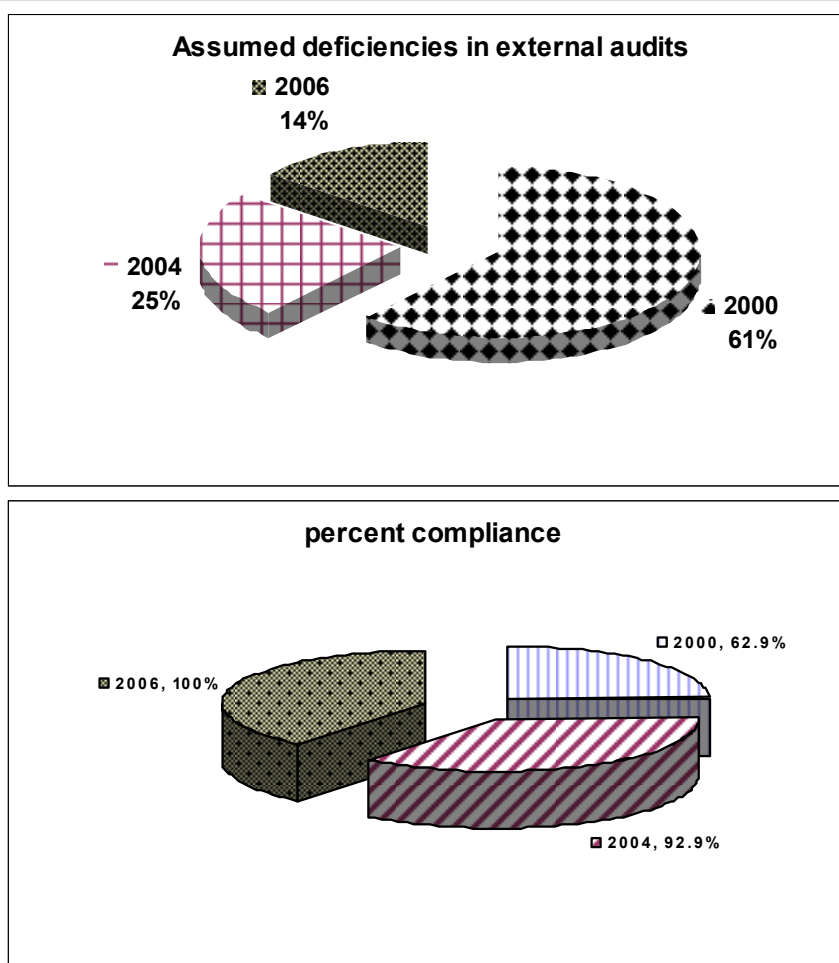
and the existing skills, the following stages were considered:

- Training needs were defined
- Training was designed and planned
- The results of training were assessed.

Discussion of the importance of regulations and procedures was within the aspects of personnel training included an assessment test to ensure that the employee has understood the information received [6].

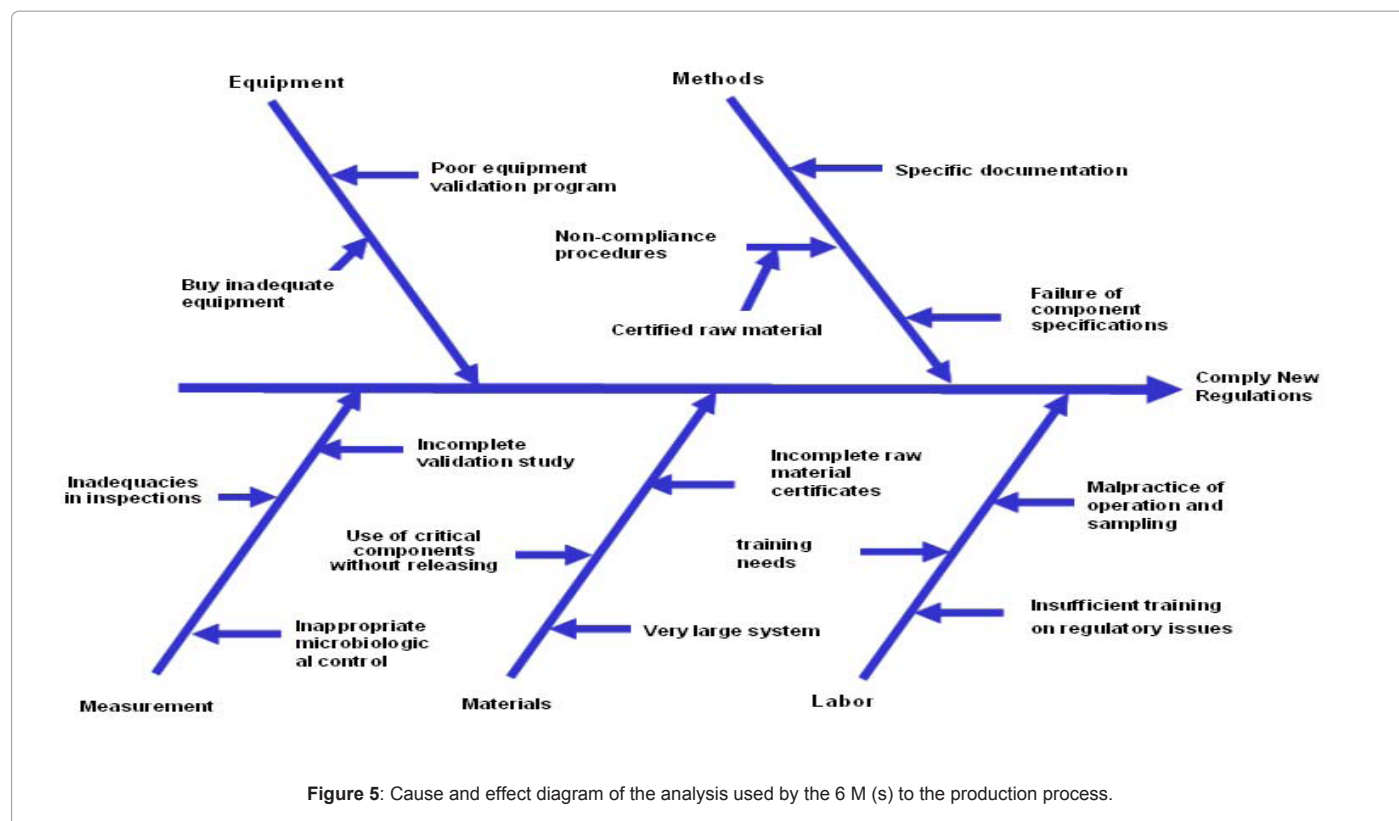
Staff training was performed through three main ways:

1. Basic courses established and scheduled by the Human Resources Direction.



**Figure 4:** Status of implementation of the nonconformities encountered by the national regulatory body CECMED in the 3 years prior to the inspection WHO.





2. Courses aimed primarily at staff training in the acquisition of knowledge of Good Manufacturing Practices, Good Laboratory Practices, Bio-security and basic knowledge for production, training is included in the qualifying record of each person and whom follow up courses were also delivered until full compliance.

## Conclusion

As a result of this work we have seen that the effective functioning of the documentation system formed the quintessence basis for the implementation and maintenance of Good Practice for the development of the different steps of the production process, allowing the release and commercialization of a considerable number of batches useful for human health. It also served as the basis to implement the same system in a second productive alternative (plant-derived antibody [7,8]).

The implementation of the documentation system enabled a set of concrete results, such as: Compliance with the requirements for documentation system for this type of industry, as reflected in the rules and regulations issued by national and international agencies. This aspect is fundamental to achieve a competitive position in the current regulatory environment

The culture of the staff with respect to compliance with Good Manufacturing Practices are being implemented has increased systematically a set of actions with direct impact on the training and motivation for proper handling of documents associated with your job.

## References

1. WHO (2003) World Health Organization Technical Report Series No. 908, p.47-79 Annex 4. Good Manufacturing Practices for pharmaceutical products: main principles.

2. Garret M (2006) Does it really have to be this difficult? Contract Pharma 8: 46-48.
3. Cosme K (1999) Producción de Anticuerpos Monoclonales por el Método de Ascitis en la Cepa Endogámica BALB/c y Ratones Híbridos F1, Animales de experimentación. Revista hispanoamericana 4:13-15.
4. Valdés R (2002) Chromatography Removal Combined with Heat, Acid and Chaotropic Inactivation of Four Model Viruses, Journal of Biotechnology 96: 251-258.
5. Pérez G (2000) Establishment of a documentation system based on the CIGB Quality System. Master Thesis ISPJAE 2000.
6. FDA (2001) Code of Federal Regulations, Guidance for monoclonal antibody Used as reagent in drug manufacturing: 1-11.
7. EMEA (2007) European Medicines Agency: Guideline on production and Quality Control of Monoclonal Antibodies and related substances. Point 4.8 Monoclonal Antibodies used as reagents p 13.
8. Bringslimark V (2004) If Training Is So Easy, Why Isn't Everyone in Compliance? BioPharm Internacional 17: 3.
9. Ramírez N, Rodríguez M, Ayala M, Cremata J, Pérez M, et al. (2003) Biochem Biophys Res Commun 308: 94.