

METROLOGY IN PHARMACEUTICAL INDUSTRY – A CASE STUDY

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Abstract: Metrology is recognized by improving production process, increasing the productivity, giving more reliability to the measurements and consequently, it impacts in the economy of a country. Pharmaceutical area developed GMP (Good Manufacture Practice) requirements, with no introduction of metrological concepts. However, due to Nanomedicines, it is expected this approach and the consequent positive results. The aim of this work is to verify the level of metrology implementation in a Brazilian pharmaceutical industry, using a case study. The purpose is a better mutual comprehension by both areas, acting together and governmental support to robustness of Brazilian pharmaceutical area.

Keywords: Pharmaceutical industry, Metrology, Nanomedicines

1. INTRODUCTION

The importance of Metrology is concerning to provide reliability in the measurements. This occurs in standardizing some practices, demonstration of measurements uncertainties and expression of trend results to take decisions. This information is used to process control and verification of quality requirements of a product [1]. Correct measurements also contributes to the economy (it is estimated around 2.7% of GNP – gross national product - in European Union), because they avoid to rework, and consequently, reduce costs and increase productivity, besides more equitable commercial relations [2].

In pharmaceutical industry, several requirements were developed to regulate this area, as the "Good Manufacture Practices" (GMP), searching for quality, security and effectiveness. However, metrological concepts like traceability, uncertainties, were not introduced at that time.

Metrology emerged firstly in calibration of physical elements, as mass, dimension, temperature, and others. Afterwards, this concept was applied in chemistry, originating the CRMs (certified reference materials). Its importance for several sectors of chemical industry (pharmaceutical, petroleum, foodstuff) is expanding, the investments of certification, human resources, equipment and others can reach

5 to 10% of the total production costs [3].

Besides the improvement of process (Productivity, more reliability in analytical results in Quality Control), metrology in Research and Development can also contribute for new drugs, as nanomedicines for example [4]. It is essential for robustness of a company, and Brazilian pharmaceutical industry is characterized by low international insertion, negative trade balance and development of generic drugs for the national market [5].

So, the purpose of this study is to know about the level of implementation of metrology in Brazilian pharmaceutical industries, using a case study. It is expected that this study contributes to public policies, helps to orient investments and joint actions by both areas, Metrology and Pharmaceutical industries.

2. METHODS

Use of scientific references in database as SciELO, Google Scholar, "Periódicos Capes", in Portuguese and English languages during all the study.

A questionnaire was made using *SurveyMonkey*® and was sent to a national pharmaceutical company. The identification is not mentioned because of confidentiality policy. The purpose of this case study was confirms the data from published articles and updates the level of implementation of metrology in this area.

3. RESULTS AND DISCUSSION

A questionnaire was sent to a Brazilian pharmaceutical industry, whose content was about the implementation of metrology.

This is a national company and there is no affiliate in another country, confirming the low international insertion. It exports just some raw materials, mainly for European Union. According to them, the more difficult activity in exporting is the tariff. There were options like importer requirements, transportation, reliability of Brazilian product and metrological subjects – all of them characterized by low level of difficulty. So, the REACH (Registration, Evaluation, Authorization and restriction of Chemicals) - an European Union regulation, published in 2006 and before questioned if a probable technical barrier to commerce (TBT), was complied by this company. But certainly it contributed to influence negatively in trade balance of this area [6].

Most part of the sale revenues of this company is from national market, constituted by similar and generic drugs, and 5 to 6% of this is invested in Research and Development. They have patents in Brazil, but there is no nanomedicine produced by this company, justified by the difficulties to manufacture it. Nowadays there is no regulation and the risks are unknown. However, the approach among international entities, like ISO, ASTM and FDA is happening to concentrate efforts to regulate it [4].

One of the questions was about the rules or regulation used in Management System. There were options relating to ISO rules, as ISO 9001, ISO 17025, ISO 14001, GAMP (Good Practice Guide: Calibration Management), RDC ANVISA 17/2010 and there was the possibility to choose more than one answer. The result was just the national Good Manufacture Product or known as RDC 17/2010, regulated by ANVISA and required use. This question was searching to know some approach or familiarity with ISO rules that mention about metrology, but there is no contact with it.

This answer can be reinforced with the following question: Is there any human resources that have specific knowledge about metrology? The answer was no, and there is no qualification requirement in this area. It can be explained by historically, not only national but also international pharmaceutical industry, adopted the GMPs and not the metrological system.

And this absence of specific human resources in metrology can also justify the next answer. The company uses non accredited laboratories to calibrate the equipment, confirming that when there is no obligation, it is difficult to implement and invest on it. However, the consequences of non use or an inadequate use of metrological standards during a calibration can produce false results. A false disapproval can impact loss in productivity and a false approval can impact negatively in the quality of a medicine.

It was asked which was the level of difficulty in calibration in the following activities:

- For comprehension of calibration certified, the answer was low. It should consider the difficulties of a metrological standard and the amount of data of an accredited calibration certified. As reported before, this company do not use accredited calibration laboratories.
- For establishing the frequency of calibration, there is no difficulty. If there is no human resource to analyze it, maybe the frequency is established by the equipment producer.
- The difficulty to establish the frequency of intermediary verifications was considered intermediate level of difficulty, and it is explained by no published rule about it, even for accredited laboratories. A study evolving several influences has to be considered.
- And low level of difficulty to qualification of calibration service. And this answer is explained by no metrological requirements. For this company, it is not necessary that the laboratory be accredited.

The following question: During the root cause analyze, with is the frequency of the item Measurement in the Ishikawa diagram? The answer was Low. There are two possibilities to interpret it: one, that all the management system is functioning well or other, "Measurement" can not be analyzed so deeply, with all the involved factors.

Among the non conformities there is more incidence on analytical measurement instruments than in process measurement instruments. The metrological traceability can be damaged in this case, without use of CRMs and calibrated equipment.

There was a question about the frequency of using CRM and PT schemes, and the answer was: The company uses reference materials, but no certified reference materials. They do not participate of PT schemes and have no intention to do it. It is missing to know about the benefits of metrology system, Accreditation, “Exporter Alert System from Enquiry Point to TBT”, because although the company affirmed that know them, these tools are not used.

The last question was about the Nanomedicines, if the company has it in its portfolio. The answer was no. And when asked about the challenges, the answer was the manufacture of nanomedicines. And to produce an innovative product, it is necessary a constant improvement, invest in research and development and robustness in quality and productivity.

4. CONCLUSION

The national pharmaceutical industry focused on competitiveness based on quality and productivity, following the good manufacture practices, however, the calibration management and metrological insertion has not been accomplished. It is necessary to train human

resources, disseminate the benefits of the insertion of metrological concepts.

Although some technical barriers can damage some markets, as REACH, Brazilian companies like this case study have robustness enough to continue to export to them its raw materials.

However, it is necessary to notice about the importance of metrology to innovation, quality and productivity. And these three elements are essentials to keep in the market and also increase the exportation, also with innovative goods, as Nanomedicines, for example. It is essential the governmental participation and public policies to promote joint actions.

5. REFERENCES

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