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FREQUENCY OF CALIBRATION: A CRITICAL ISSUE FOR QUALITY CONTROL IN THE PHARMACEUTICAL INDUSTRY

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Abstract:

A methodology which defines the frequency of calibration of measuring instruments that control key processes in the pharmaceutical industry is described. In accordance with international standards and best laboratory practices (ISO/IEC 17025), the methodology incorporates the experience of renowned laboratories of the Brazilian pharmaceutical industry. These laboratories accepted to participate in a survey to analyze the current practices and procedures regarding the choice of the periodicity of calibration. Given the uncertainty associated with the master standard as stated in the calibration certificate of the instrument to be used in the manufacturing process, the concept of maximum error assessment was introduced. In this sense, the acceptable error in the manufacturing process and the impact of non-compliance in calibration led to a general criterion for establishing the frequency of calibration.

Keywords: Industrial metrology, pharmaceutical industry, process measuring instruments, calibration management, frequency of calibration.

1. INTRODUCTION

The adjustment of the periodicity of calibration of measuring instruments is a topic extensively discussed in the specialized literature and in major measurement-related technical events. This is an important issue in industrial metrology management as an incorrect choice of the frequency of calibration may incur in faulty measuring results. And this is particularly critical in the pharmaceutical industry –a key industry related to human health– where measurement errors may eventually lead to undesirable recalls. But if a universal method for selection of the (initial) frequency of calibration for all types of instruments under different operating conditions cannot be implemented, a general procedure may certainly be devised and tested in the manufacturing of pharmaceutical products.

Based on a comprehensive survey involving well known quality control laboratories in the pharmaceutical industry [1], the present work reviews the best practices used to select the frequency of calibration of process measuring instruments and proposes an alternative methodology.

2. CALIBRATION FREQUENCY: SURVEY TO IDENTIFY PHARMACEUTICAL LABORATORIES BEST PRACTICES

In the Rio de Janeiro - São Paulo industrial axis, where 80% of the Brazilian pharmaceutical industry is located, 76% of the pharmaceutical laboratories declared to adopt a fixed period for the initial frequency of calibration. The best laboratory practices are summarized in Table 1 according to the status —critical and non-critical— of each process measuring instruments [1].

Table 1 – Best laboratory practices declared by the participants

	Critical instrument	Non-critical instrument
Biannual	5%	30%
Annual	55%	55%
Twice a year	40%	15%

It is important to note that laboratory practices are often confidential as they reveal critical elements of their quality management system. And this certainly restrains the study. Despite such limitations, it was possible to develop a scheme to define the calibration frequency interval based upon relevant attributes which reflect the best laboratory practices (expounded in section 4, Proposed Practices).

3. STANDARD PRACTICES REPORTED IN THE LITERATURE

The review of the most common practices specifically applicable to set up the frequency of calibration of process measuring instruments used in the pharmaceutical industry, is summarized below:

3.1- Reference #1 – GAMP (2002) [2]

Criteria:

a) The calibration frequency shall be defined for each individual measuring instrument.

b) A critical assessment team[2] shall be responsible for the definition and approval of the frequency of calibration.

[1] Instrument can be considered critical or non critial for the pharmaceutical manufacturing processes. Critical are thoses which assert quality end non-critical those used to control the process.

[2] Criticality Assessement Team (CAT) is usually composed of experts with interest in the use of equipment/systems, quality control and maintenance.

c) The basic criterion adopted for establishing the frequency of calibration shall incorporate the following conditions:
- manufacturer's recommendations;
- standards and relevant procedures;
- instrument record (instrument past behavior);
- overall impact of non-compliances in the calibration process and
- previous experience of the laboratory technical staff.

d) The critical process measuring instruments shall be calibrated at least twice a year.

3.2 - Reference #2 – Dills (2000) [3]

Criteria:

a) Process measuring instruments stability;

b) Major function of the instrument in the manufacturing process;

c) Intensity of the use of the measuring instrument.

3.3 - Reference #3 – Lira (2001) [4]

Criteria:

a) Type of instrument;

b) Manufacturer's recommendation for the periodicity of calibration;

c) Critical analysis of the behavior of similar instruments;

d) Accuracy required by the manufacturing process.

3.4 - Reference #4 – Gates (2003) [5]

Criteria:

The standard periodicity of calibration of the measuring instrument is annual, except for the most critical instruments which, under normal operating conditions, should be recalibrated at least twice a year.

3.5 - Reference #5 – Internet

The "Yahoo calibration internet Group" (www.grupocalibracao.com) suggests two alternatives:

3.5.1 – Quantitative method

In this method, the initial frequency of calibration (time interval recommended to recalibrate the equipment after it was put in use) is determined by the product of the three impact factors described through the equation:

$$OF = WF \times FF \times LF \quad (1)$$

where:

WF – Wear factor.
FF – frequency of use factor.
LF – localization condition factor.
OF – overall factor.

The values that should be use for each factor are the following:

WF – Wear Factor.
a. high ➔ 9 or 10;
b. moderate ➔ 6, 7 or 8;
c. low ➔ 3, 4, or 5;
d. very low ➔ 1 or 2.

FF – Frequency of Use Factor.
a. high ➔ 9 or 10;
b. moderate ➔ 6, 7 or 8;
c. low ➔ 3, 4, or 5;
d. very low ➔ 1 or 2.

LF – Localization condition factor.
e. Every day ➔ 9 or 10;
f. Every week ➔ 6, 7 or 8;
g. Every month ➔ 3, 4, or 5;
h. Every year or twice a year ➔ 1 or 2.

Once the **OF** (overall factor) is calculated, the initial frequency of calibration can be obtained from Table 2.

Table 2 – Initial frequency of calibration

Range of OF values	Recommended frequency
800 < OF < 1000	4 weeks
525 < OF < 800	13 weeks
320 < OF < 525	26 weeks
160 < OF < 320	39 weeks
100 < OF < 160	52 weeks
63 < OF < 100	65 weeks
38 < OF < 63	78 weeks
18 < OF < 38	91 weeks
10 < OF < 18	104 weeks
OF < 10	156 weeks

3.5.2 – Qualitative method

Here, the initial frequency of calibration is selected according to the following attributes:

Characteristic: Degree of importance of the variable to be controlled to ensure the quality of the product to be manufactured. And it can be designated as critical, significant, important or not special.

Intensity of use: rare, often and quite often.

Environment: Loss of calibration due to different operating conditions is a critical factor to be considered in the definition of the frequency of calibration. This attribute can be classified as under control, moderated and aggressive.

4. PROPOSED PRACTICE

In accordance with the applicable international standards and best practices, the proposed method (tailor made to meet the requirements of the quality control pharmaceutical laboratories) shall consider:

- Attribute #1: a multidisciplinary decision
- Attribute #2: individual definition
- Attribute #3: manufacturing recommendations
- Attribute #4: applicable standards and specific procedures
- Attribute #5: instrument record (instrument past behavior);
- Attribute #6: impact of the non-compliance in the calibration process
- Attribute #7: rate of use
- Attribute #8: required accuracy (this attribute is based on the ratio described in equation 2:

$$\varphi = \frac{Emav1 + EDF}{Emad} \qquad (2)$$

Where:

Emav1 is the maximum error evaluated during the first calibration of the measuring instrument (Fig. 1);

EDF is the stability declared by the manufacturer, and

Emad is the maximum acceptable error in the manufacturing process.

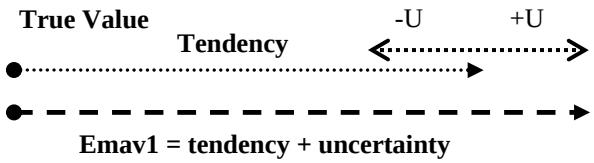

Fig. 1. Graphical procedure for evaluating Emav1

The spread sheet depicted in Annex 1 is the user's guide to select the initial frequency of calibration. Once the defined attributes have been taken into account, should be selected at least the smaller one for the first interval and approval for user, quality assurance and engineering departments.

5. CONCLUSIONS

This study involving major laboratories of the Brazilian pharmaceutical industry revealed that there is no universal solution to define the frequency of calibration of process measuring instruments. Frequency of calibration continues to be a subject of intensive investigation of industrial interest. The metrological parameter Emav1 not only proved to be of practical interest to define the frequency of calibration but also to identify the actual status of the measuring instrument.

The metrological parameter φ as defined by equation (2) gauges the maximum time use of the measuring instrument before the first re-calibration is made. The greater the value of φ the higher the probability of the current calibration to be degraded. In this sense, φ helps to double check the manufacturer's recommendation regarding calibration.

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Annex 1. Example of a typical spread-sheet data processing for calculating the initial frequency of the calibration of critical measuring instruments

TAG (individual identification)	φ Required Accuracy (Emav1 + EDF)/ Emad	Rate of Use	Impact of Non-compliance in calibration	Historical	Manufacturing Recommendations	Applicable External Standards	Time Recommended for the First Recalibration
TE-001	0,9	High	High	12 weeks	26 weeks	Not applicable	**8 weeks**
PI-003	0,5	Low	Low	30 weeks	52 weeks	52 weeks	**30 weeks**
LT-003	0,3	Moderate	Low	52 weeks	52 weeks	Not applicable	**52 weeks**