METHODS OF CALIBRATION AND CHARACTERIZATION OF TEMPERATURE CONTROLLED ENVIRONMENTS

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Una din problemele importante ale utilizatorilor de medii termostatate este aceea de a stabili cat mai exact caracteristicile metrologice ale acestora. Multe ramuri ale industriei solicita aceasta capabilitate, fiind astfel necesara o dezvoltare a unor metode de etalonare si caracterizare metrologica a mediilor termostatate in functie de aplicatiile utilizatorului. In acest articol se dezvolta patru tipuri de metode de etalonare si caracterizare metrologica a mediilor termostatate. Aceste metode sunt comparate din punct de vedere tehnic si economic luand in considerare numarul de traductoare, volumul util si incertitudinea de masurare astfel incat utilizatorul mediului termostatat sa poata alege metoda optima pentru aplicatiile sale.

One of the important problems of today's temperature-controlled environments users is to establish with accuracy the metrological characteristics of those temperature-controlled environments. Many industries requires this capability, so it is necessary to develop methods for calibration and metrological characterization of temperature-controlled environments according to user applications. In this article are developed four types of calibration and metrological characterization methods of temperature-controlled environments.

These methods are compared in terms of technical and economical aspects considering the number of transducers, useful volume of the temperature-controlled environment and measurement uncertainty, so that the temperature-controlled environments users can chose the optimal method for its applications.

Keywords: interior volume, useful volume, set temperature, deviation of set temperature, temperature indicator, uniformity, stability, measurement point

1. Introduction

A temperature-controlled environment refers to closed premises with or without forced air circulation (forced convection) or with saturated steam circulation, which allows temperature tests.

For ten years, no one had doubts about the temperature indicator of a climatic test chambers.

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In the past, climatic test chambers were loaded to maximum, so there was no place to put a thermometer inside the precincts. Nobody cared if there was a movement of air. Most temperature-controlled environments with thermostat (incubators, refrigerators) were not equipped with ventilation system. When this temperature-controlled environment were provided with a temperature indicator, no one questioned the value displayed on it.

Temperature indicator is an indicator device wich belongs to temperature-controlled environment and displays the temperature measured by temperature transducer of temperature-controlled environment.

Today, industry standards have become so stringent that it is necessary to resort to specialized service providers in order to validate this type of equipment (temperature-controlled environments).

Requirements and standards regarding various production activities have encouraged the development of this new methods of metrological characterization of temperatutre-controlled environments.

In october 2002 was created NF X 15-140 AFNOR (Association française de normalization) standard, which provides a set of specifications for metrological characterization and verification of climatic test chambers.

In 2007 was published the international standard IEC 60068-3-11, which gradually replaced the NF X 15-140 french standard.

In the category of temperature-controlled environments, the following equipments are included: autoclaves, stability testing chambers, temperature controlled incubators, refrigerators, freezers, hot rooms, dry freezers and depyrogenation tunnels.

Premises whose conditions are controlled in temperature and humidity are usually used for preservation, storage, pharmaceuticals, and to define the so-called "cold chain" in the production and distribution of food products and pharmaceuticals.

In the pharmaceutical industry for products and active substances, climatic test chambers are used for long-term stability testing and conducting trials of accelerated stability conditions, before they be put on the market.

Temperature-controlled environments can have any size. Interior volume of the temperature-controlled environment is defined by the internal dimensions of height, width and depth of enclosure.

The calibration and metrological characterization of a temperature-controlled environment consists in evaluating its operating characteristics [1].

This allows manufacturer to communicate the performances defined in accordance with conventional and reproducible conditions, users to acknowledge the actual environmental performances, and by periodic measurements, to determine if the temperature-controlled environment preserves its performances over time.

The main objectives of metrological characterization methods are to determine at least the uniformity and stability of air or saturated steam temperature [2], the deviation of set temperature or indication error (if applicable) and measurement uncertainty [3]. Uniformity characterizing in steady conditions, the maximum difference between values measured between two points in the workspace at a time. Stability characterizing in steady conditions temperature variations in a section of the workspace.

Set temperature is the selected value on the temperature regulator to obtain the desired or specified value of temperature. The deviation of the temperature is the difference between set temperature and temperature measured inside the temperature-controlled environment.

Four main metrological characterization methods of temperature-controlled environments were determined, namely: loaded/empty environment characterization method, loaded environment characterization method, characterization method of the environment upon testing and characterization method in indivisible isolated points of the environment [3].

The uncertainty components in the case of metrological characterization methods, the number of transducers used depending on the useful volume and metrological characterization procedures were determined. Useful volume is that part of the volume inside of temperature-controlled environment where the temperature is kept within the maximum permissible errors.

2. Scope of metrological characterization

Calibration and metrological characterization of a temperature-controlled environment consists in the evaluation of its operating conditions. This allows manufacturer to communicate the performances defined in accordance with conventional and reproducible conditions, users to determine the actual performances of the used environment and by using periodic measurements, to determine whether their environment preserves its performances in time.

3. Metrological characterization objectives

The main objectives of metrological characterization are to determine at least the performance in terms of uniformity and stability of air or saturated steam temperature.

This allows determining if the temperature-controlled environment is appropriate to be used in accordance with the needs of the user. Characterization and calibration may include conformity evaluation [7], it can be performed only in individual measurement points or it can be performed during tests. These parameters are determined by using reference measurement instruments [3]. A measurement point is a place inside the temperature-controled environment in which is placed a temperature transducer.

4. Calibration methods

Have been developed four basic methods for the calibration and characterization of a temperature-controlled environment: U Method (unloaded/empty environment calibration method), L Method (loaded environment calibration method), T Method (environment calibration method during tests) and IP Method (method of calibration in individual isolated points within the environment).

Furthermore, the four methods of calibration shall be each analyzed.

4.1. Unloaded/empty environment calibration method (U method)

The method is used to characterize the temperature-controlled environment before use and during the periodical performance verifications. This provides a global image of the temperature-controlled environment. In this stage the cold and/or hot spots can be determined, and depending on the needed application, the temperature-controlled environment can be properly used by the user. The extreme spots (hot and/or cold) can be isolated if they cause changes in the applications of the user. Unless specific provisions are stipulated, temperature transducers are placed at equal distances from walls, namely 1/10 of each of the sizes of the internal volume (Figure 1).

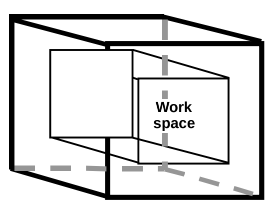

Fig. 1. Workspace

There are 10 temperature transducers for a workspace smaller than 2 m^3, 15 for a workspace between 2 m^3 and 20 m^3, other volumes being determined by agreement between the involved parties.

When a set of 10 temperature transducers is used, 8 transducers shall be placed in the corners of the workspace, one transducer shall be placed in the center and the tenth transducer shall be placed in the center of the area which defines the access to the workspace (Figure 2).

The area which defines the access to the workspace has an important contribution to the characteristics of the environment and to the correct assessment of measurement uncertainty.

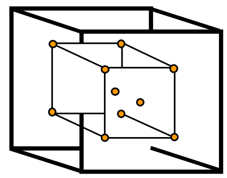

Fig. 2. Position of transducers for a volume smaller or equal to 2 m^3

For a volume between 2 m^3 and 20 m^3, calibration is carried out with 15 transducers. Nine transducers shall be placed as the previously described nine and six transducers shall be distributed in the center of the areas which define the workspace (Figure 3).

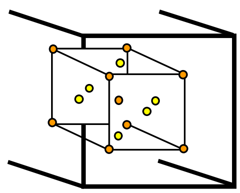

Fig 3. Position of transducers for a volume between 2 m^3 and 20 m^3

For workspaces greater than 20 m^3, the measurement points should determine a cubic network with a network constant value of max. 1 m.

The method is used when performing the operation qualification for a temperature-controlled environment, when it is mandatory to establish an acceptance criteria which to define the maximum allowed temperature variation inside the useful volume and to determine if the temperature-controlled environment maintains its characteristics.

4.2. Loaded environment calibration method (L method)

The environment can be loaded in accordance with the user application or by loading at least 40 % of the workspace with standard samples. While testing this method, we determine that at least 40 % of the loaded workspace influenced the characteristics of the temperature-controlled environment. The effect of the load has been determined by an additional measurement of unloaded environment.

For a typical load, 10 temperature transducers are used. The number of temperature transducers is 10 for a workspace smaller than 2 m^3, 15 for a workspace between 2 m^3 and 20 m^3 and for other volumes, the number of transducers is determined by agreement between the involved parties. For very small objects, one must use at least five temperature transducers. For large objects or with unusual form, one must use additional temperature transducers. If a temperature transducer can not be placed in the center of the workspace, it shall be placed at 2 cm from one side of the load and it must be exposed to the air flow.

The method is used when carrying out the performance qualification for a temperature-controlled environment and when it is mandatory to establish the maximum temperature variation inside the loaded temperature-controlled environment.

A metrological characterization of a test climatic chamber was performed at a set temperature value of 23 °C using a set of ten thermocouples in order to have a clear picture of the loading effect.

In this case the effect of radiation is almost nonexistent, having no influence on the determinations that were made.

Eight thermocouples were placed in the corners of the workspace (1/10 of each of the sizes of the internal volume), one thermocouple was placed in the center and the tenth thermocouple was placed in the center of the area which defines the access to the workspace (1/10 of the size of the area which defines the access to the workspace) (Figure 4).

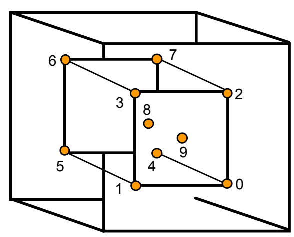

Fig 4. Position of thermocouples inside the temperature-controlled environment

Temperature variations inside the workspace were determined for each thermocouple as the difference between the maximum and minimum temperatures recorded values (the same measurement conditions without humidity control).

Temperature values were recorded using a one minute sample interval.

The number of values that were recorded are 30 for each thermocouple after obtaining a stabilize temperature.

To highlight the value of at least 40 % that influenced the metrological characteristics of the temperature-controlled environment, to determine the effect of loading, metrological characterization were conducted using three configurations of the climatic test chamber useful volume, namely: empty climatic test chamber (configuration I), climatic test chamber with a load of 25 % of the workspace (configuration II), having a climatic test chamber load 50 % of the workspace (configuration III).

Temperature value variations recorded on each thermocouple for each of the three configurations are described in table 1.

Temperature differences between configurations, on each thermocouple, are described in table 2.

Tabel 1

Differences between configurations

Thermocouple number	Thermocouple variation Configuration I (^{0}C)	Thermocouple variation Configuration II (^{0}C)	Thermocouple variation Configuration III (^{0}C)
0	0.06	0.08	0.01
1	0.06	0.07	0.03
2	0.03	0.04	0.02
3	0.04	0.04	0.02
4	0.08	0.11	0.06
5	0.03	0.06	0.03
6	0.04	0.05	0.02
7	0.04	0.05	0.03
8	0.06	0.05	0.03
9	0.05	0.06	0.03

Values obtained in table 2 represent the differences between maximum values for each thermocouple for each configuration separately and differences between minimum values recorded for each thermocouple for each configuration separately.

Tabel 2

Loading effect

Thermocouple number	0	1	2	3	4	5	6	7	8	9
Difference between maximum values recorded by thermocouples										
Temperature difference between configurations I and II (°C)	-0.03	-0.04	-0.07	-0.12	-0.01	-0.02	-0.14	-0.04	0.04	-0.02
Temperature difference between configurations I and III (°C)	0.03	0.01	0.10	0.07	0.14	0.27	0.02	0.03	0.01	0.02
Difference between minimum values recorded by thermocouples										
Temperature difference between configurations I and II (°C)	-0.02	-0.01	-0.01	0.00	-0.03	-0.03	-0.01	-0.01	0.01	-0.01
Temperature difference between configurations I and III (°C)	0.09	0.10	0.10	0.16	0.09	0.05	0.18	0.08	0.03	0.13

The loading effect in this case is 0,16 °C (maximum average value).

Therefore the minimum value of 40 % of the loaded workspace is considered an appropriate value for determining the loading effect for a temperature-controlled environment.

4.3. Environment calibration method during tests (T method)

Loading is carried out in accordance with the typical user application. The method of calibration of the environment during testing consists in: determination of correction, which must be applied to the indication of the indicator during the test, determination of temperature uniformity within the loaded workspace, temperature instability in the load and also the determination of the radiation effect.

This method is frequently used for characterization of autoclaves and depyrogenation tunnels. These type of temperature-controlled environments are critical for the manufacture of sterile drugs and to maintaining the initial qualified status. This is the reason why this type of characterization method plays an important role in the pharmaceutical industry.

This method was developed using autoclaves. Autoclaves are temperature-controlled environments wich use saturated steam to perform sterilization.

Metrological characterization of an autoclave, having a useful volume of 47 litres, was performed using 12 thermocouples (Figure 5).

Set points for sterilization process were 122 ºC and 15 minutes for sterilization time. The sterilization process is controlled by two resistance temperature detectors. First is placed outside the load (inside useful volume) and the other one inside the autoclave drain line.

Ten thermocouples were inserted in packages so as the measuring junction of thermocouple lie inside the packages (sterilization bags) where the steam penetrates more difficult. The last two thermocouples were placed in the same positions as the resistance temperature detectors wich control the process.

Fig 5. Position of transducers inside the autoclave

Using this method for metrological characterization was noted an increase in uniformity value from 0.68 °C in 2004 to a value of 0.94 °C in 2008, having a peak in 2006 of 1.16 °C (table 3). Although the value of the temperature uniformity increased in four years the stability (fluctuation) had a different evolution.

The autoclave drain line was determined as the coldest spot during sterilization cycles.

Tabel 3

Uniformity inside metrological caharaterized autoclave

Year	Uniformity (°C)
2004	0.68
2004	0.63
2004	0.68
2005	0.47
2005	0.70
2006	1.16
2006	0.88
2006	0.67
2008	0.89
2008	0.94
2008	0.94

Evolution of temperature values inside autoclave during sterilization cycles are shown in figures 6 and 7.

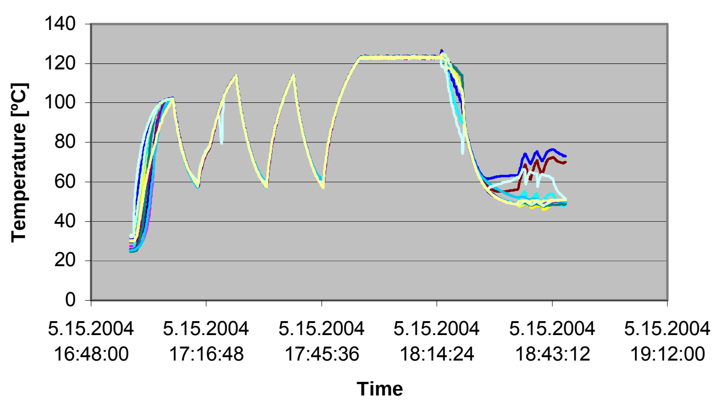

Fig 6. Evolution of temperature inside autoclave

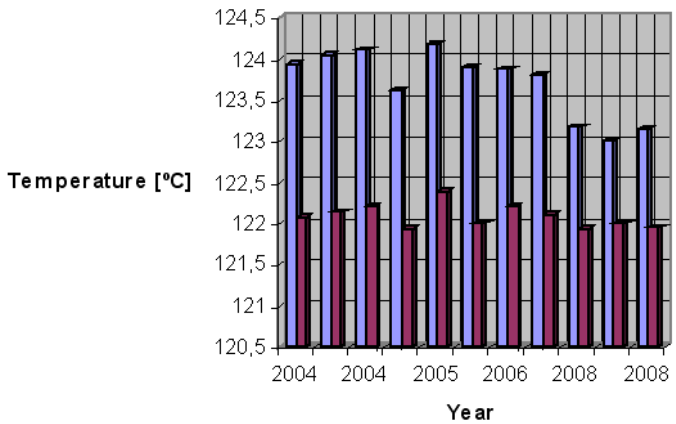

Fig 7. Maximum and minimum values of temperature during sterilization cycles

Maximum values are marked with blue and the minimum values are marked with purple.

Values of temperature (minimum and maximum) inside autoclave are dropping in time. Uniformity has worsened during the last four years. This evolution indicate a worse control of temperature inside the autoclave.

User needs a minimum value of temperature of 121 ºC at least 15 minutes [8] inside the autoclave during the sterilization cycles to be sure that the sterilization of the load was performed correctly [9].

T method of calibration and metrology characterization highlights the need for knowledge at any time of measurement the characteristics of temperature-controlled environment.

Given this overview it is possible to correct any deviations from the process to which temperature-controlled environment belongs.

4.4. Method of calibration in individual isolated points within the environment (IP method)

Calibration refers to individual measurement locations inside the thermostat precinct, which do not delimitate a workspace.

Therefore, the calibration method involves: determination of correction which applies to the indication of the indicator, determination of temperature instability at measurement point, determination of radiation effect at measurement point and determination of loading influence at the measurement point.

5. Calibration procedures

5.1. Temperature transducers

The main types of temperature transducers, which are used for the calibration of the thermostat precincts, are platinum resistance thermometers (resistance temperature detectors) and thermocouples.

Due to the fact that the sizes of transducers influence their time of response, the transducers must be small (< 5 mm). In still air, for a transducer with the diameter of 3 mm, the time of response is between 45 seconds and 75 seconds.

The most frequently used thermometers with platinum resistance are those of 'Pt 100' type [4].

The connection of the resistance temperature detectors to the system of measurement of the electrical resistance should be adequate, in order to minimize the effects caused by the connection wires (3 or 4 wires).

The most widely used types of thermocouples are: type K (Nickel-Chrome /Nickel-Aluminum), whose characteristics are in accordance with EN European standard 60584-1, type J (Iron/Copper-Nickel) and type T (copper/copper-nickel)[5].

The measurement system of thermoelectric voltage of thermocouples allows the correction of the temperature of the reference junction [6].

5.2. Data recording procedure

During calibration, at least 30 values from each temperature transducer must be recorded for each set temperature. Records must be made over a period of at least half hour. Values must be recorded at intervals of maximum one minute, after the stabilization of the precinct at each set temperature. For autoclaves, the values must be recorded at intervals of maximum five seconds during sterilization cycle and for depyrogenation tunnels the values must be recorded at intervals of maximum fifteen seconds during the depyrogenation cycle. For precincts without air circulation, the measurements will begin 30 minutes after obtaining the stabilization of temperature.

5.3. Utilization and interpretation of results

In case of calibration using L, U or T method, calibration result is valid only for the volume comprised between the points of measurement. Spatial interpolation of the determined values is permissible only for the workspace. The extrapolation of the measurement results outside the workspace is not allowed. In case of calibration carried out using IP method, the calibration result is valid only for the individual measurement points.

Local non-uniformity must be determined by using two thermometers placed at a distance of 2 cm from each other. Where the emissivity of the two thermometers is significantly different, the measurement may also serve to determine the radiation effect.

In case of calibration using several measurement points, local non-uniformity can be estimated based on the indications of the thermometers placed in various measurement points.

6. Uncertainty evaluation

The first step in assessing the measurement uncertainty is to establish the functional relation between the measure and the input sizes which depends on [10]. We will review the most frequently used case, the calibration of a thermostat precinct without loading. In this case, the measure is the correction which must be applied to the temperature indicator of the precinct and, if this is not available, to the temperature regulator.

Generally, the uncertainty of measurement includes several components. Some of these components can be evaluated starting from the statistical distribution of the measurement results and they can be characterized by standard experimental deviations [10]. The other components, which can also be characterized by standard deviations, are evaluated by the admission of probability distributions based on experience or other information.

6.1. Mathematical measurement template

For physical and mathematical understanding of these four types of calibration methods, the correction of the temperature from temperature-controlled environment is described using formulas no. 1, 2 and 3.

$$\Delta t_{precinct} = t_{indicated} - t_{ref} + \delta_{ref-coeff} + \delta t_{vol} \quad (1)$$

$$\delta t_{ref-coeff} = \delta t_{ref} + \delta t_{dev} + \delta t_{ref-res} + \delta t_{env} + \delta t_{non-linearity} + \delta t_{auto-heating} \quad (2)$$

$$\delta t_{vol} = \delta t_{non-uniformity} + \delta t_{instability} + \delta t_{radiaton} + \delta t_{loading} + \delta t_{precinct-res} \quad (3)$$

All these components are described, with their own definitions, as follows:

$\Delta t_{\text{precinct}}$ – correction of the temperature of the precinct, indicated by the display of the indicator or regulator, as appropriate;

$t_{\text{indicated}}$ - temperature indicated by the display of the indicator or regulator, as appropriate;

t_{ref} - temperature indicated by the reference thermometer;

δt_{ref} – correction of the temperature indicated by the reference thermometer;

δt_{dev} – correction of deviation in time of the reference thermometer;
$\delta t_{ref\text{-}res}$ - correction of temperature due to the limited resolution of the reference thermometer;
δt_{env} - correction of the influence of the environmental temperature on the indications of the reference thermometer;
$\delta t_{non\text{-}linearity}$ - correction of non-linearity of the reference thermometer;
$\delta t_{auto\text{-}heating}$ - correction of automatic heating effect, in case the reference thermometer is a platinum resistance thermometer;
$\delta t_{non\text{-}uniformity}$ - correction of temperature non-uniformity within the workspace;
$\delta t_{instability}$ – correction of temperature instability within the workspace;
$\delta t_{radiation}$ - correction of radiation effect;
$\delta t_{loading}$ - correction of loading effect;
$\delta t_{precinct\text{-}res}$ - correction of temperature due to the finite resolution of the precinct indicator [7].

7. Conclusions

These four methods represent the basis for the development of the methods for calibration and characterization of temperature-controlled environments. Each one of these methods plays an important roll in certain fields of the manufacture industries.

All these calibration and characterization methods were developed during the last five years.

The transducers used for calibration and characterizations of temperature-controlled environment are not limited to those described in this paper. For example, to characterize a stability testing chamber, temperature data loggers can be used. These types of transducers are suitable because the acceptance criteria for stability testing chambers, regarding the fluctuation of temperature, are between ±1 °C and ±2 °C.

U and L methods are used when performing the operation qualification of temperature-controlled equipments and T method is used when carrying out the performance qualification of temperature-controlled equipments.

The developed mathematical measurement template applies to all described methods.

Advantages and disadvantages of the methods are described in table 4.

Table 4

Advantages and disadvantages of the methods

Method of calibration	Method advantages	Method disadvantages
U method	Relatively low costs, the entire work space is calibrated, it is not necessary to recalibrate when changing the sample	It is difficult to quantify the loading effect
L method	Relatively low costs, loading effect over the control of the precinct can be accurately assessed and it allows the selection of the smallest thermostat precinct that produces the necessary conditions	It is necessary to recalibrate the precinct, if the tested object significantly differs from that object for which the calibration has already been made
T method	Provides the best estimate of the temperature which the object is subjected too, it is ideal when different types of objects are used and different types of loadings are carried out, it allows accurate assessment of the loading effect on the precinct control, the precinct is not calibrated for unnecessary conditions.	It may be the most expensive method because the measuring equipment is permanently necessary and calculation of uncertainty must be made for each testing
IP method	Low costs, one set of calibrated measurement instruments is sufficient for several precincts, recalibration is not necessary when the object subjected to testing is changed	The effect of the tested object is difficult to quantify, although it may be negligible for objects which are very small compared to the volume of the precinct

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