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Application Note

March 11, 2020

Keywords or phrases:
GMP, Good Manufacturing Practice, GLP, Good Laboratory Practice, Quality system, compliance, pipetting

Are You Compliant When it Comes to Pipetting?

Guidelines to Ensure Compliance with Good Laboratory and Manufacturing Practices

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Introduction

When developing or testing your medical device, there is always the question: are you following methods for current Good Laboratory Practice (cGLP) or current Good Manufacturing Practice (cGMP)? In this practical guide, we've compiled a list that you can follow to give you peace-of-mind on the topic of compliance.

Quality systems and standards regulating product development and manufacturing of pharmaceuticals, medical devices, and the way clinical studies are conducted, such as GLP, GMP and ISO 9000 series, require that appropriate and technically valid standard operating procedures (SOPs) are followed and a regular, documented maintenance and calibration process is in place for all instruments.

In this guide, we'll look into some tools and principles that can help with these demanding requirements, especially when it comes to your pipetting practices.

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Section II
Good Laboratory Practuice Principles
1. Test Facility Organisation and Personnel
1.1 Test Facility Management's Responsibilities
1. At a minimum it should:
(e) Ensure that appropriate and technically valid standard operating procedures are established and followed, - -

Fig 1. Picus® NxT password protection option on display

Ensure That Standard Operating Procedures Are Followed

Ensuring that appropriate and technically valid SOPs are followed is a core requirement for GLP and GMP compliance. In practice in the laboratory, this means repeating the set work instructions, without deviations.

Many other processes at the workplace are already fully or semi-automated, and this kind of assistance is also available for laboratory work. Electronic pipettes, such as the Sartorius Picus® NxT, can be used to simplify and speed up workflows by allowing integration of SOPs to programmable pipetting protocols. Once activated, the program automatically adjusts the parameters after each completed step.

This reduces the possibility of human error that is apparent when manually adjusting the pipette parameters. The programs can be password protected (Fig. 1) to add an extra layer of security to ensure proper protocol is followed.
The use of electronic pipettes has ergonomic benefits, and also raises the pipetting performance and repeatability of dispensing of inexperienced and moderately experienced personnel to the level of experts (Fig. 2).

User-dependent sources of pipetting errors can accumulate up to a 2% increase in the standard deviation, according to ISO8655. So, use of electronic pipettes eliminates these errors, because the electronic piston movement ensures consistency.

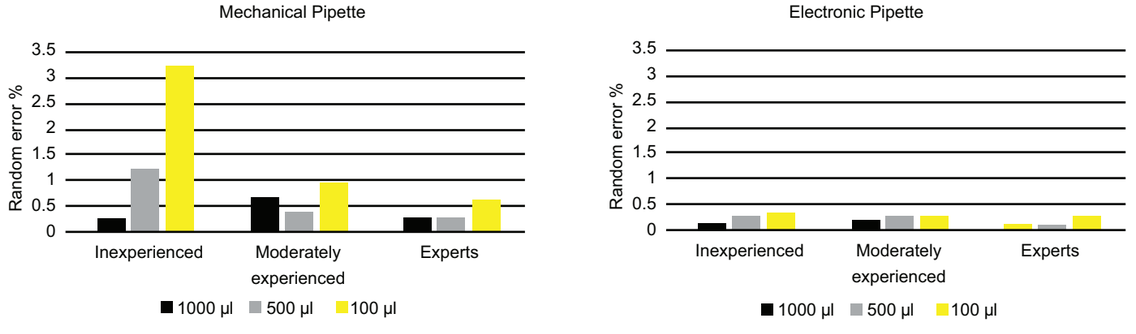

Fig 2. The random error of dispensing 1000 µl, 500 µl and 100 µl using a 1000 µl mechanical or electronic pipette by inexperienced, moderately experienced, and expert users from testing conducted by Sartorius. The standard ISO 8655 recognizes the major error sources and sources of variation to be operator derived. Dispensing with mechanical pipettes is more likely to have operator derived variance compared to electronic pipettes, where the system operates the piston consistently. Uneven piston movement and rhythm when manually operating the piston of the mechanical pipette is known as the pipetting "handwriting". Lab personnel may feel like an expert in pipetting, but when working according to GLP, an electronic pipette is the best tool to eliminate these differences between users.

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Section II
Good Laboratory Practuice Principles
4. Apparatus, Material, and Reagents
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement

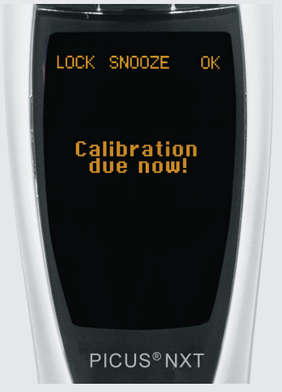

Fig 3. Picus® NxT calibration reminder on display.

How to Ensure That Instruments Are Calibrated?

Has someone in your lab ever forgotten to calibrate their pipettes before the calibration due date set in your SOPs? Most laboratories use sticker labels on pipettes, but they are far inferior in helping you remember than the calendar notifications you use for your other important dates.

Some electronic pipettes, such as Sartorius Picus® NxT, can be set to enforce proper calibration interval by using the calibration reminder option (Fig. 3). With the help of the reminder, you will be aware of pipettes in the lab with expired calibration, thus saving you from frustration you experience when your work must be delayed to find a calibrated pipette.

The last calibration date can be set into the pipette software by trained service personnel and you can set a calibration interval, after which the pipette notifies you of an upcoming calibration.

Forget about the sticker labels, as there is a more reliable way to make sure calibrations are performed on time

What is the Correct Calibration and Maintenance Interval?

This is one of the most frequently asked questions, but is not all there is to it. Laboratories need a documented pipette quality control program to meet regulatory and quality system requirements.

The user is responsible for setting up the program, according to ISO 8655, a standard for piston-operated volumetric apparatuses.. The program should describe an in-lab cleaning and testing routine, the calibration and maintenance interval, and how to ensure continuous education of your lab personnel.

Our suggestion for a two-tier program, that will ensure continuous monitoring of pipetting deviations, is created by adhering to the following guidelines:

- In-lab cleaning and testing routines, with pipette performance checked in-lab regularly, for instance, daily, weekly, or monthly
- Regular calibration and maintenance of pipettes performed at an accredited service laboratory, annually, biannually, or even every 3 – 4 months.

Anyone who has set up a Quality Program knows that the first steps can be challenging, but to get you started, we have added guidance in the supplemental material.

Are You Sure About the Volume?

– a Human Factor

To be certain that your measurements are in accordance with the study plan and relevant SOPs, your pipette should have a simple and unambiguous volume display with clear digits (Fig. 4). This way, volume setting is effortless and a quick glance is all it takes to affirm that you are using the intended volume setting, thus keeping your mind on your experiment.

If you choose a mechanical pipette, make sure that the volume display clearly shows all digits to ensure that volume setting and checking doesn't take your mind off of your work.

Fig 4. From left to right: Sartorius Picus® NxT electronic pipette display, Sartorius Tacta mechanical pipette four digit volume display, Manufacturer A mechanical pipette three digit volume display and Manufacturer B three digit volume display. The Sartorius pipettes unambiguously display the selected volume. The Manufacturer A and B pipettes' volume display use a red-black color code to indicate the decimal separator and an analog line indicator for the last value.

Summary

A pipette is a precision measuring apparatus that has a significant influence on your lab results, but it can also be your companion in ensuring compliance.

Compliant pipetting can be achieved easily by creating a Pipetting Quality Control Program, according to industry best practices and by equipping laboratories with Picus® NxT electronic pipettes that can be programmed according to SOPs and work instructions and remind users to perform periodical maintenance and calibration.

To implement, the quality program should be documented and controlled with SOPs for laboratory personnel. SOPs should cover all aspects of the program, including the continuous training of personnel to pipettes and pipetting.

Supplement 1

In-Lab Testing Routine
An in-lab testing routine includes a regular check of all pipettes in the laboratory for systematic and random error..

1. What Should Be Done?
Pipettes are checked using a balance or a photometer, the systematic and random errors are calculated from the results, compared against acceptance limits, and recorded.

This testing can be done by the actual users of the pipettes, but the results should be checked and documented by an independent party, such as quality management personnel.

2. How Often?
The testing frequency is based on the risks associated with the use of the pipettes – the testing interval should be in proportion with the amount of work you can afford to lose if you find the pipettes are out of specifications.

Practices used in various labs differ greatly, but a common testing routine is monthly or weekly, sometimes even daily.

Pipettes should also be checked each time after autoclaving pipettes or pipette parts. A performance check is also needed if pipette is dropped or if physical damage is suspected.

3. What Is Needed?
For In-lab testing you will need the following items:
- 4- or 5-decimal balance with pipette calibration setup, such as evaporation trap, or a photometer system
- Software for calculating and recording results
- Disposable tips, the same type as used with the pipettes when in use
- De-ionized water or dye solutions if photometric measurement is used
- Thermometer and barometer
- Standard Operating Procedure document describing the in-lab testing routine and the procedure for dealing with pipettes that do not meet the acceptance criteria

4. What Acceptance Criteria Should Be Used?
The pipettes should be checked at 1 – 2 volumes, with 4 – 10 measurements each. The systematic and random error should be compared against the limits defined either by pipette manufacturer or ISO 8655.

5. What Are the Outcomes of the Testing?
The In-house testing routine should provide the following deliverables:
- Documented history of all your lab's pipettes, showing their testing interval, testing dates, and at minimum, the result if they met the acceptance criteria or not.
- The pipettes not meeting acceptance criteria should be clearly marked and removed from use and forwarded to maintenance and calibration for resolving the issue.

Supplement 2

Calbration and Maintenance Program
Most laboratory quality systems require a regular calibration and maintenance program for pipettes.

Today, laboratories commonly use external service providers for this labor-intensive work that require highly sophisticated quality systems.

1. What Should Be Done?
The pipettes should regularly be maintained according to the manufacturer's instructions. The maintenance consists of cleaning and greasing of pipettes, as well as replacement of wearable parts.

Alongside maintenance, the pipettes should have their performance verified by calibration – measurement of systematic and random error along with any necessary adjustments.

2. How Often?
The testing frequency is based on the risks associated with the use of the pipettes. The maintenance interval is affected by such factors as pipetting frequency, liquids dispensed, and the age and model of pipette.

A minimum maintenance interval of one year is suggested, with calibration done annually or more often, such as every 3 – 6 months. If, for example, volatile liquids or solvents are dispensed, maintenance should be done more often.

3. What Is Needed?
For a full maintenance and calibration of pipettes, the used calibration laboratory should have at minimum:

- Full ISO 8655 compliance, including controlled environment in terms of temperature, vibration, and humidity
- Accreditation according to ISO 17025 standard with traceability of measurements to international standards
- Balances with a minimum of 5- and 6-decimals, along with evaporation traps or draft shields
- Software for recording results
- Professionally trained technicians | engineers understanding pipette technology and good pipetting practices, as well as requirements set by regulatory and quality systems.

4. What Acceptance Criteria Should Be Used:
The pipettes should be measured at 2 – 3 volumes, with 4 – 10 measurements each, with systematic and random error calculated and compared against the acceptance limits. Use of limits defined in ISO 8655 or by the manufacturer of the pipettes are suggested.

5. What Are the Outcomes of the Calibration?
The Maintenance and Calibration program should provide at minimum

- Documented records of all maintenance and repair activities done to the pipettes
- Calibration certificates showing the identification of pipettes, such as serial numbers and time of calibration, tips used, measurement conditions, measurement equipment, and personnel
- Random error and systematic error should be calculated and documented, along with acceptance criteria, such as pass | fail limits.

Supplement 3

Best Practices for Setting up The Pipetting Quality Control Program
To work according to Good Laboratory Practice, a Standard Operating Procedure (SOP) for Pipette Quality Control should be defined. Below are areas that should be described at minimum in the SOP to guide laboratory personnel through the process:

1. For In-Lab Testing Routine, Define:
a. Testing frequency
b. Testing equipment and environment
c. Personnel qualifications to conduct testing
d. Measured volumes and aliquot quantities
e. Acceptance criteria
f. How to record and store the results
g. Actions of isolating and marking pipettes not meeting acceptance criteria
h. Procedures for evaluating the effect of failure on the work performed with the pipette in question

2. For Maintenance and Calibration Program, Define:
a. Requirements for a calibration laboratory, ISO 8655 and ISO 17205 at minimum
    i. Testing equipment, environment and procedures
    ii. Qualifications for maintenance and calibration personnel
b. Maintenance and Calibration frequency
c. Decontamination procedures for the pipettes before maintenance
d. Volumes tested and number of measurements
e. Acceptance criteria
f. Recording and documentation systems
g. Actions of isolating and marking pipettes not meeting acceptance criteria
h. Procedures for evaluating the effect of failure on the work performed with the pipette in question

3. For Continuous Education of Laboratory Personnel, Define:
a. Training program for personnel on correct pipetting techniques and ergonomics
b. Training on quality systems and standards related to pipettes and pipetting
c. Documentation and qualification plans for personnel training

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Status: 04 | 2020