METROLOGY for DRUG DELIVERY

MEDD II

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GOOD PRACTICE GUIDE:

Calibration of Medical Infusion Pumps

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This good practice guide was written as part of activity A5.3.1 from the EMPIR Metrology for Drug Delivery (MeDD II) project. The three-year European project commenced on 1st June 2019 and focused on providing traceable measurements of volume, flow and pressure of existing drug delivery devices and mixing behaviour and occlusion phenomena in multi-infusion systems. For more details about this project, please visit www.drugmetrology.com

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The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

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Why is Calibration Important?

There have been numerous injuries, deaths and adverse health effects associated with the use of infusion pumps which have highlighted significant safety issues [1]. For example, approximately 80-90 % of hospitalised patients in the UK receive intravenous (IV) therapy using infusion devices to deliver medication, fluids and nutrients into patients [2,3]. It is extremely important that the delivery of medication and other fluids is precisely controlled over time, and the delivered dose is accurately known, especially for critical drugs at high concentration. Regular calibration and maintenance of infusion pumps enables the identification of any issues with equipment and ensures correct dosage to patients, minimising potential safety risks.

Syringe infusion pumps and incubator for new-borns in hospital

Typical infusion pumps include:

- Syringe
- Peristaltic pump delivery
- Gravity controlled delivery
- Insulin
- Patient controlled analgesia (PCA)
- Elastomeric piping
- Pain killing drugs
- Enteric nutrition

Although there are many different types of infusion pump, this guidance document focuses on critical drug delivery applications which require a high degree of accuracy. Such applications include drugs with a narrow therapeutic margin, drugs with a short half-life, high concentration drugs and any infusions given to neonates, which normally occurs at very low flow rates. Although the calibration principles highlighted in this guide refer to syringe pumps, they can be applied to other types of pump.

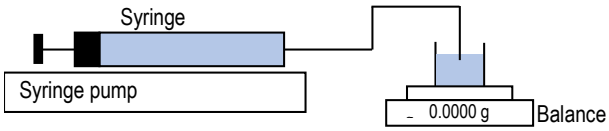
Syringe pump for medical use

How to Calibrate Infusion Pumps

A common calibration method to determine the flow rate error of an infusion pump involves the use of an infusion device pump analyser, which can give information on the flow rate, volume and pressure. The analyser functions as a master calibrator to quickly test infusion pumps performance, however, it is important that it is calibrated regularly. This method is used in hospital facilities.

The gravimetric method is used extensively in the laboratory by National Metrology Institutes (NMIs) and accredited laboratories, as a very accurate way to calibrate pumps and flow meters. This method uses a balance to weigh the mass of liquid (*i.e.* water, the specification of water is defined in ISO 3696 [4]) that is delivered by the pump into a weighting vessel on the balance. As the density of the water is known at the temperature of the test (usually 20 °C), this is used to calculate the volume of liquid delivered (volume = mass/density). The volumetric flow rate is determined from the quotient of the total liquid volume and time taken for the delivery of that liquid. Details on how to test infusion pumps are provided in IEC 60601-2-24:201 [5]. This standard provides criteria for testing the performance and safety of pumps including detailed calculations on how to assess the performance using a gravimetric calibration method. However, it should be noted that this standard is currently under review and, therefore, subject to change.

A simplified schematic of the gravimetric calibration setup is shown below.



From drug metrology research conducted by several NMIs, it is recommended that the equation provided in Appendix B of ISO 4787 [6], the international standard which gives detailed information on how to accurately calibrate volumetric equipment, is used in order to more accurately determine the volume of the liquid mass on the balance. The equation in ISO 4787 includes additional factors that take into account the effect of air buoyancy and the thermal expansion of the disposable syringe [6,7]. The volumetric flow rate is determined from the quotient of the total liquid volume and the time taken for the delivery of the liquid.

The volumetric flow rate (Q) can be expressed as:

$$Q = \frac{1}{t_f - t_i}\left[(I_f - I_i) \times \frac{1}{\rho_w - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times [1 - \gamma(T - 20)]\right]$$

Where t_f is the final time, t_i is the initial time, I_f is the final balance reading, I_i is the initial balance reading, ρ_w is the density of water used for the calibration, ρ_A is the density of air, ρ_B is the density of the mass standards used to calibrate the balance, Υ is the coefficient of thermal expansion of the disposable syringe and T is the temperature of the water used. More information on the expansion coefficients is provided in ISO 4787.

It is recommended that additional correction factors should be used including a correction for the evaporation of water during the calibration and a correction for the buoyancy effect of the needle immersed in the water in the beaker. To reduce the evaporation of the water during the calibration, the use of special evaporation traps, similar to those used for piston pipette calibrations, can be used. Alternatively, a layer of oil, such as paraffin, on top of the water, as described in ISO 7886-2, can be used to reduce evaporation [8]. During the calibration, environmental effects on the balance performance, such as draughts and temperature fluctuations, should be considered.

The relative flow rate error of a pump is given by:

$$error = \frac{Q_{pump\ set\ point} - Q_{reference}}{Q_{reference}} * 100\%$$

Where $Q_{\text{pump set point}}$ is the target flow rate set on the pump and $Q_{\text{reference}}$ is the actual flow rate determined in the calibration. A negative error means the pump is delivering over its target flow rate and a positive error means that it is delivering less fluid than desired. This definition of error complies with metrological standards [9, 10].

However, it should be noted that a different definition is used in medical standards, such as in IEC 60601-2-24:201 [5], where the error is given by:

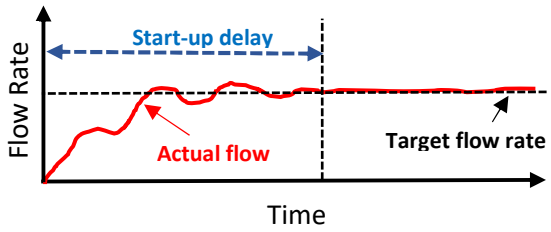
$$error = \frac{Q_{reference} - Q_{pump\ set\ point}}{Q_{pump\ set\ point}} * 100\%$$

It is important to identify how the error is calculated as otherwise false corrections may be applied. More detailed information on these conflicting definitions is provided in [**11**].

Common Issues with the Calibration of Infusion Pumps

- *Air bubbles* – a sufficient volume of water should be passed through the piping to purge any air bubbles.
- *Flow stability and pump response time* – there is a need to wait until the target infusion flow rate has been reached, as large errors will occur before this. The time taken before the required target flow rate is achieved is often referred to as the start-up delay or delayed onset and depends on the flow rate, type of pump and disposables used. More information on this can be found In IEC 60601-2-

24:201. These factors are illustrated in the diagram below:



- *Incorrect syringe diameter* - this can lead to large dosing errors, e.g. 5 % error in the syringe diameter can lead to a 10 % error in the delivered drug flow rate. Different syringe models and brands can have different diameters, so it is always important to check this.
- *Water evaporation* – if not controlled properly this can cause an underestimation of flow rate measurements.
- *Fluid connection leaks* - this refers to the incorrect connection between the tubes, the disposables and the pump and will result in a reduced measurement of flow rate.
- *Equipment compliance* – this refers to expansion effects in the components from the elasticity of the materials, e.g. the expansion of a plastic syringe when the pressure increases during the start-up of the pump. Expansion of components can also occur when the flow rate is increased; this increase in the pressure can cause the infusion line, syringe, and other equipment to expand. The expansion results in the internal volume increasing hence can cause a delayed response for flow rate changes. ISO 7886-2 [8] provides information on measuring the compliance of a syringe; however, it does not take into account additional contributions such as the infusion lines, which can also expand.

Performance Characterisation of Infusion Pumps

The assessment of the performance of a pump being calibrated cannot be entirely based on the determination of the error even if it is found to be within ±2 %, which is normally stated by the manufacturer as the maximum permissible error. The uncertainty of the calibration must also be considered in metrological conformity. The uncertainty of the measured value (*e.g.* 10 mL/h), could be ±1 % at the 95 % confidence level. This means the true reference flow rate can be anywhere within 10.1 and 9.9 mL/h. Hence, the maximum permissible error is a combination of the measured error and the uncertainty. ISO 7886-2 specifies a long-term accuracy of 2 % for the percentage flow rate error when measured over a one-hour time period, a short-term accuracy of 5 % for the maximum flow rate variation when measured over a two-minute time period, and an accuracy of 2 % when measured over a five-minute time period [8].

This highlights the need for a low measurement uncertainty on calibration techniques to assess the metrological performance of pumps. Uncertainty contributions in the calibration of pumps are attributed to:

- Environmental conditions changing, *e.g.* room temperature, drafts, humidity *etc*.
- Repeatability of measurements (spread in repeated measurement data)
- Flow rate instability
- Resolution of calibration equipment used
- Calibration of the measurement equipment (*e.g.* balance, temperature sensors)
- Equations used to determine density and expansibility
- Buoyancy corrections for the needle submerged in the collected liquid
- Air buoyancy corrections
- Leakage through the tubing or connectors
- Drift of equipment
- Timing errors
- Evaporation corrections
- Calibration technician experience
- Auxiliary equipment used and the compliance (elastic expansion) effect (*e.g.* infusion lines)

- Dead volume – this is the volume of liquid contained between the pump under test and the reference measurement device. If the temperature of the connecting tubing and fluid are different at the start of a calibration from the corresponding temperature at the end of the calibration, the quantity of fluid held within this volume will have changed, hence leading to underestimation or overestimation of the quantity of fluid passed between the pump and the reference.

For the calibration of a single pump in the laboratory, there will be very low back pressure as the liquid flows into a beaker at atmospheric pressure. However, in infusion setups, the back pressure will be higher as the drugs are flowing into veins or arteries.

Multi-Infusion Setups

Calibration techniques are used to test single pumps, but things get much more complicated when using multiple pump infusions where the fluids from each pump are combined before a single injection point into the patient. Multi-infusion setups are very common in hospitals where several different drugs need to be administered at different dosing rates using separate infusion pumps for each drug.

Dosing accuracy can be affected by the interaction between the pumps and the dead volume [12]. The dead volume effect results from the drug injected from one pump needing to travel through the infusion line between the mixing point and the inlet to the patient; this volume is known as the dead volume. The interaction between the pumps and the dead volume can cause dosing issues and preferably this volume should be a small as possible. Positioning the pumps closer to the patient would be a solution but often it is necessary to provide some flexibility for patient movement by using longer drug delivery lines.

The effect of multi-infusion setups has been modelled and the flow rate and concentration of drugs assessed for different setups [12]. Advanced modelling and validation are currently being investigated by NMIs as part of a collaborative European research project on drug delivery metrology.

Patient with monitor and infusion pumps in an intensive care unit

New Calibration Methods for Ultra-Low Flow Rates

The gravimetric calibration method is limited when trying to measure ultra-low flow rates, as the measurement uncertainty of this method increases substantially and evaporation becomes a critical error factor. Special setups for gravimetric calibrations have been performed by NMIs down to 6 µL/h (100 nL/min) [13]. However, new developments in pumping technology, e.g. insulin pumps, can deliver extremely low flow rates typically 10 µL/h and much lower. To test these new devices, novel calibration techniques are being developed by NMIs that are capable of measuring flow rates down to 5 nL/min. Some of these new calibration techniques are based on optical measurements, for example, tracking the displacement of a meniscus along a capillary.

Insulin pump

Summary

This guidance note highlights the importance of the regular calibration of medical infusion pumps to reduce safety risks by identifying any performance issues and ensuring the correct dose to patients. The gravimetric calibration method is recommended as an accurate method that can be used for assessing the performance of an infusion pump analyser and other pumps. Recommendations on how to perform a gravimetric calibration, referencing to appropriate standards, have been outlined.

Further Reading

EMPIR Metrology for Drug Delivery website – http://www.drugmetrology.com/

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