Guidelines for the Calibration of Drug Delivery Devices and Infusion Device Analysers

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Flow

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This document gives guidance on measurement practices in the specified fields of measurements. By applying the recommendations presented in this document laboratories can produce calibration results that can be recognized and accepted throughout Europe. The approaches taken are not mandatory and are for the guidance of calibration laboratories. The document has been produced as a means of promoting a consistent approach to good measurement practice leading to and supporting laboratory accreditation.

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Version 1.0 (02/2024)

Guidelines for the Calibration of Drug Delivery Devices and Infusion Device Analysers

Purpose

This document provides guidance for the calibration of drug delivery devices (DDD) and Infusion Device Analysers (IDA), normally used by hospitals, and accredited laboratories to verify the accuracy of the DDD and IDA related to the quantities: flow rate, volume (bolus) and occlusion pressure. This document does not include information about conformity assessment based on verification tests results.

The guide aims to harmonise the general procedures used by organisations to calibrate these instruments in their laboratories or hospitals. Several calibration methods and uncertainty calculation examples are presented.

The current version reflects the actual practice applied in European National Metrology Institutes in terms of calibration procedures.

Content

1 INTRODUCTION

Infusion therapy is used globally to treat numerous diseases and is one of the most commonly used forms of therapy in health care.

Treatment of patients demand on the delivery of medication or fluids intravenously and for safety and accuracy infusion therapy is used with drug delivery devices. Drug delivery devices are one of the standard treatment modalities in and out of hospitals.

Depending on the use of drug delivery devices, the intended flow rate indicated by the device or application is more or less important. For general anaesthetics in adults, the accuracy (systematic error) of the flow rate may not be a critical factor as the variety in response to anaesthetics varies greatly among individuals. However, for infusion treatment of premature or new-born infants a correct and accurate administration of the drug may be vital [1, 2].

Accuracy in a medical context can also be referred to mean long term flow rate accuracy (MFRA), but for critical delivery of short half-life drugs at low rates, the ‘short term’ behaviours including start-up delay, cyclic fluctuation of mechanism and stick slip (‘stiction’) may play the most critical role since these drugs are ‘titrated to effect’.

Figure 1. Neonate incubator

Regardless of the type of treatment or patient group, knowledge about the accuracy of the infusion device is of great importance [3].

Patient vital signs such as heart rate, blood pressure, oxygen content in the blood may reveal dosing errors resulting from an adjustment of one flow rate of an infusion pump in multi-infusion setups. Calibration is a process that allows the determination of the flow rate and delivery dose errors and their associated uncertainties, in combination with the knowledge of the effects occurring in multi-infusion setups. The delivery of a mixture of drugs, changes by increasing or decreasing the flow rate of an infusion pump and greatly depends on the multi-infusion setup. The actual dosing conditions, beyond the mixing point

in the infusion line, might not be known and it could differ from the intended dose of the drug. In practice, the clinicians titrate the effect on clinical signs as patient's vital signs. Adjusting dose effect interaction demands, the understanding of possible effects in a multi-infusion setup for the delivery of the drug mixture due to flow rate changes depends on the accuracy of delivery of each infusion pump. Inaccuracy and misunderstanding of multi-infusion setup create a clinical safety risk. Therefore, a well-defined traceability chain is needed to validate that the precision and accuracy of the infusion pumps are within the manufacturer specifications, and/or meet the clinicians expectation. The results of a calibration of DDD and IDA must be traceable to SI units, as explained by Niemann A. et al [4].

Several partners of the EMPIR project 18HLT08 MeDDII - Metrology for drug delivery [5] tested and characterised different types of DDD (syringe pump and insulin pump) and an IDA with one channel to determine the best calibration procedure for each instrument tested.

2 TERMINOLOGY AND SYMBOLS

Symbols, whose signification are not self-evident, will be described at their first appearance in the text.

The terminology used in this document is mainly based on existing documents, GUM [6], VIM [7], IEC 60601-2-24 [8], AAMI TIR101 [9], but there are some specific definitions that are explained below.

2.1 Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
DDD	Drug Delivery Device
DUT	Device Under Test
EMPIR	European Metrology Programme for Innovation and Research
GUM	Guide to the expression of uncertainty in measurement
IDA	Infusion Device Analyser
IEC	International Electrotechnical Commission
ISO	International Organisation for Standardization
LVP	Large Volume Pumps
MeDD	Metrology for drug delivery
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl chloride
SI	International System of Units
TIR	Technical Information Report
VIM	International Vocabulary of Metrology

2.2 Administration set

Accessory used to connect the DDD to the patient such as tubes, filters and valves.

2.3 Bolus

Discrete quantity of liquid (single dose), which is intended to be delivered by the instrument under test.

2.4 Calibration

Calibration, in the context of this guide, is the operation that, under specified condition, establishes the difference between the indications of the DUT and the corresponding reference standard with an associated measurement uncertainty.

2.5 Infusion system

An Infusion system is the complete set of equipment to be used for a given drug delivery procedure – supply, tubing, filters, pump, disposables syringes, wirelessly connected servers, etc.

2.6 Mechanism cycle time

The time it takes to finalise a total cycle e.g. the revolution of a mandrel that drives the plunger in a syringe pump.

For LVP it is the sum of the time corresponding to the filling, holding and delivery phases of operation. These cycles have the potential for the greatest impact on serum drug level variation for short half-life medications. Flow measurement times for calibration should include an integer number of at least two mechanism cycles to avoid aliasing with variations within each cycle.

Insulin syringe drivers provide both timed and on-demand boluses of 1 microlitre or less and may also provide basal flow quasi-continuously at less than 1 μL/h. Depending on the pump design, the basal insulin flow may be provided in discrete aliquots (‘shots’ according to IEC 60601-2-24 [8]) occurring at periods of 15 minutes or less. The basal (baseline flow) rate can be presented as a flow rate on the insulin pump display and is usually expressed in U/h (units of insulin per hour). The repetition interval of the discrete shots (increments) [10] is considered in IEC 60601-2-24 in sampling flow to compute both short- and long-term (mean) flow accuracy. The cycle time of the discrete doses (increments) is an important time constant for calculating the average flow rate and the insulin delivered by the insulin pump. The average flow must be averaged over a time window that is an integer multiple of this cycle time.

2.7 Long-term variability

The capacity of a pump to infuse at the set flow rate when measured over typically one hour or more. It can also be mean flow rate accuracy.

2.8 Observation window

An averaging period for a certain amount of time. The observation window may be used for several types of analysis including mean flow rate but also measurements of reaching stability (steady state flow) and short-term variation of flow (PKCV in AAMI TIR 101 [9] and Trumpet variation max/min values in IEC60601-2-24 [8]).

2.9 Short-term variability

Variation of the pump flow over short intervals which can cause variability of the blood level concentration of the medication being delivered (see AAMI TIR 101 subsection 5.1.3 [9]). In the metrological terminology this can also be defined as the instant flow.

2.10 Time window

The time window is an observation period with a defined start and end time. When performing measurements during calibration of DDD, measurement deviations are determined by data obtained in this time frame. The correct selection of the time window is often crucial for the correct assessment of the performance of the instrument under test.

2.11 Trumpet curve

Graphical representation of the *short-term* variation in drug delivery device flow (see AAMI TIR 101 Annex C [9]).

2.12 Set flow rate

The flow rate programmed into the DDD.

2.13 Response time or stabilisation time

Duration of the time interval between the instant of the step change of an input variable and the instant when the output variable reaches for the first time a specified percentage (95% for example) of the difference between the final and the initial steady-state value [8].

3 DEVICES UNDER TEST

These guidelines are intended for the calibration of several DDD types hereafter also called as DUT, such as infusion pumps, syringe pumps, insulin pumps and also IDA.

3.1 Infusion pump

Infusion pumps are electrical medical instruments widely used in adult, paediatric and neonatal patients, with the purpose of delivering fluids in an intermittently or continuous manner. These instruments can be used in clinical environments or at home. An infusion pump is normally constituted by a fluid reservoir and a generating flow device. It can also have flow control functions and a set of accessories (lines, administration sets, filters, etc.) that allow the fluid to be transported from the reservoir to the patient. Regardless of the type of infusion pump, the main components of these systems are the control circuit of the pump associated with the control panel, the alarms and the display, the motor, the infusion mechanism, the existing sensors and the accessories that enable the fluids to be delivered to the patient. According to the international standard IEC 60601-2-24 [8], infusion pumps can be volumetric (peristaltic) or with a syringe.

There are some purely mechanical “pumps” which employ spring energy and an escapement (clock-like) mechanism to control speed of a plunger or a spring to apply force to a plunger and a restrictive calibrated tube to regulate flow rate (for specific applications).

3.1.1 Peristaltic Infusion pump

In peristaltic infusion pumps (Figure 2), a mechanical trigger causes the liquid within the tube to move by peristaltic action, thus enabling the administration of medications and nutrients or food. This mechanism can be classified as rotary or linear [11].

- The rotary mechanism is made of a main rotor, completed with rollers that press a tube (Figure 2).

- The linear mechanism is the most common type, and it is composed of several independent fingers that press a silicon tube sinusoidally. These fingers carry out a peristaltic movement, forcing the passage of the flow by pressing the infusion line against the door of the equipment.

- Some large volume pumps employ a refillable chamber or piston contained in a rigid plastic cassette along with valves to allow filling and delivery. The lower compliance of these designs results in higher accuracy and less susceptibility of flow variation due to intake and outlet pressure.

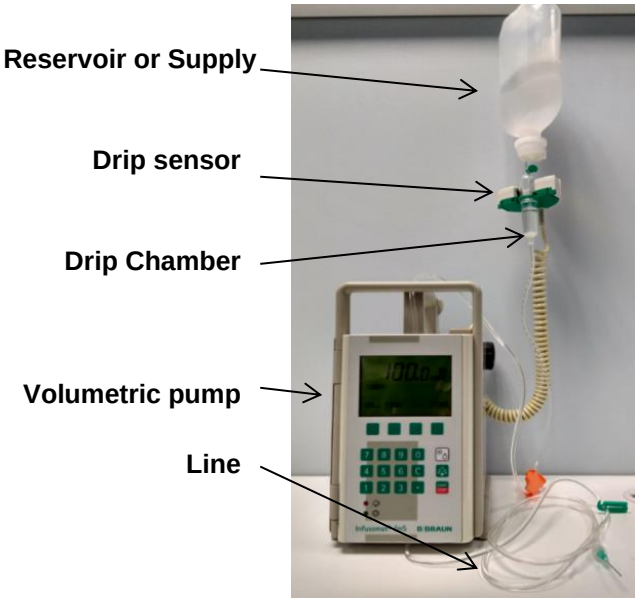

Figure 2. Peristaltic infusion pump[1]

The mechanism is activated by a stepper motor with a reducer and controlled by an electronic circuit, which indicates on the display the flow and the amount of fluid that is to be administered. The majority of rotary and linear volumetric infusion pumps have a drip sensor, occlusion pressure sensors and an air sensor in the line. Generally, flow rates range from 0,1 mL/h to over 1200 mL/h.

It is recommended that these instruments are calibrated using the gravimetric method.

3.1.2 Syringe pump (or “syringe driver” per ISO 7886 standard)

Syringe pumps (drivers) deliver medication from a disposable plastic or glass syringe with plunger and stopper elements. The pump is comprised of a drive head moving linearly to displace the syringe plunger/stopper. The flow rate given is defined by the product of the drive head speed and the syringe internal cross section area. Generally, flow rates range from 0,01 mL/h to over 1000 mL/h depending on the syringe capacity.

[1] Figure taken from IPQ good practice guide [11].

The pump system is composed by and external electronic infusion pump, an infusion line and a syringe that is compatible with the system and which is usually disposable [11, 12] (Figure 3).

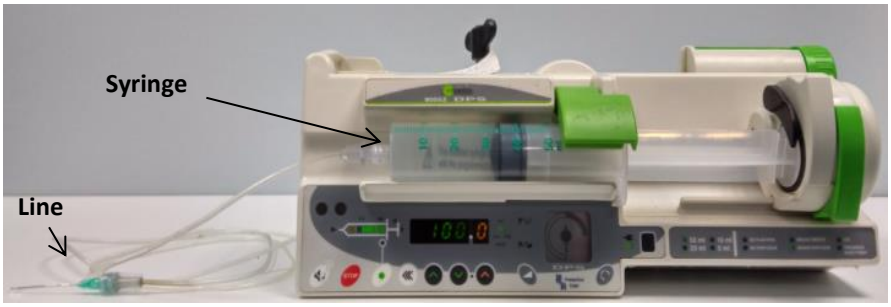

Figure 3. Syringe pump[2]

A compatible syringe, typically but not necessarily of the same brand as the pump, should be used and should follow the requirements and specifications established in the syringe manufacturer's manual.

The syringe is filled with the prescribed fluid, the extension set is connected, and the user manually primes the line ensuring no bubbles are present. Then the syringe is fitted to the pump using a barrel retainer/size gauger and a barrel flange retainer. The user confirms/selects both size and brand of the fitted syringe. Using this information, the pump control software computes the drive head movement per mL of fluid to be delivered. When a specific flow rate is programmed, the linear drive head speed is set to deliver that flow rate.

According to the specifications of ISO 7886-2 [12], the volume of the disposable syringe is limited by its dimensions and respective manufacturer's specifications.

It is recommended that these instruments are calibrated using the gravimetric method or optical methods for the lower flow rates. Commercial disposable syringes have tolerances of their average *overall* cross-sectional area ranging from ±1 % for large syringes to ±3 % for the smallest [12]. Larger deviations can occur over portions of the barrel. Commercial medical syringe drivers typically specify the plunger drive speed accuracy to ± (1-2) % [12]. Total system flow rate and volume accuracy is then the combination of drive head speed/position variation with specific syringe cross sectional area tolerance.

3.1.3 Insulin pump

Insulin pumps are battery-powered, portable, often body-carried, medical instruments that deliver precise continuous and on-demand doses of insulin (Figure 4). The pump mechanism consists of a stepper motor that moves a syringe plunger incrementally expelling the drug through a subcutaneous cannula. The syringe capacity is typically 3 mL of insulin formulated as 100 U/mL.

In adults, a post-meal (post-prandial) on-demand bolus is dependent on carbohydrate intake as well as blood sugar level and is typically a volume of (10 -100) μL. In children the

[2] Figure taken from IPQ good practice guide [11].

post-prandial dose may be 1 μL or less. For some patients a continuous “basal” flow is given to maintain a baseline glucose level. Adult basal flows are typically 10 μL/h or more and basal flows in children may be 1 μL/h or less [13]. Depending on the basal flow rate and the volume of the demand dose the basal flow cycle time may vary.

In most cases, insulin pumps deliver medication through a catheter coated with a material that does not react with insulin to avoid the absorption of the liquid (with loss of insulin) and clotting of the catheter. It is the catheter that allows insulin to be administered to the patient body.

For Type I diabetes (insulin dependent), these syringe pumps deliver a basal flux[3] or flow that is sufficient to ensure that the patient receives the necessary volume of glucose during the night and between meals. The basal flux is defined in units of insulin per hour (U/h). On the other hand, in patients with Type II diabetes (non-insulin-dependent) or with gestational diabetes, the dosage of insulin is administered as an ‘on-demand’ bolus determined by the patient’s carbohydrate intake.

Some pumps have the capacity to store data and switch off automatically to stop the administration of insulin after a pre-programmed period, thus avoiding states of hypoglycaemia.

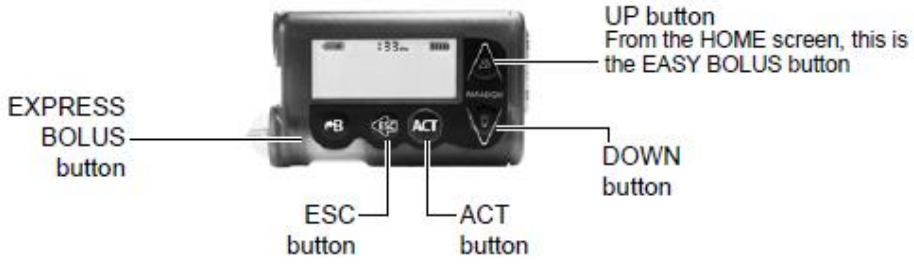

Figure 4. Insulin pump[4]

It is recommended that these instruments are calibrated using the gravimetric method or optical methods for the lower flow rates. The cycle time of the discrete doses is an important value for calculating the average flow rate of step function flow. The average flow rate must be computed over a time window which is an integer multiple of this volume shots to avoid aliasing errors.

3.2 Infusion Device Analyser

Infusion devices analysers (IDA) (Figure 5) are laboratory instruments used to measure the accuracy of a variety of infusion pumps. They measure both the mean flow of the pump

[3] The basal flux corresponds to the dose of insulin which is continuously administered in order to maintain a stable level of glucose in the blood.

[4] Figure taken from Paradigm® Veo™ User Guide
https://www.medtronic-diabetes.com.au/sites/default/files/veo-instruction-guide-english.pdf

and the instant flow and check the downstream occlusion detection system by measuring the occlusion pressure and detection time. IDAs are often used by hospital maintenance officers/biomedical engineers to check the performance of drug delivery devices in use. IDAs do not detect supply side occlusions.

Figure 5. Infusion Device Analyser

The measuring principles varies between manufacturers but is typically a miniature burette with infrared sensors along its length and sophisticated electronics basically tracking the meniscus of the collected fluid or a bubble introduced into a precision glass pipette. The instantaneous flow is displayed by the device as well as the flow averaged value. These devices typically do not allow for setting the averaging interval and thus can report erroneous flow mean results particularly at low flow rates due to aliasing error.

It is recommended that these instruments are calibrated in accordance with manufacturer recommendations using displacement methods, e.g. using a calibrated high precision syringe pump or a piston prover.

4 CALIBRATION TECHNIQUES

4.1 Volume calibration (bolus determination)

Volume calibration or bolus determination of a DUT can be performed according to the specifications and procedures described in ISO 4787:2021 [14] or ISO 8655:2022 [15]. The uncertainty determination can be done according to EURAMET cg 19 [16].

4.2 Pressure calibration (occlusion pressure determination)

The calibration laboratory should calibrate the DDD and IDA to verify that the occlusion pressure errors are within the accuracy declared by the manufacturer, by the user of the device or regulated in national legislation. All the DUT shall be operated as specified in the manufacturer's instructions.

For the occlusion pressure error determination, a pressure standard is connected to the DUT, using the appropriate connectors. Pressure is then generated and a direct comparison between the DUT and pressure standard results is performed.
If the pressure standard does not allow pressure generation, a system to generate pressure must be used. For example, a bottle of pressurised nitrogen that must be included in the circuit and allowing adjustment of the allowed value.

Note: Calibration is performed in relative pressure mode, i.e. gauge mode.

4.3 Flow calibration

The calibration laboratory should calibrate the DDD and IDA to verify that the mean flow rate errors are within the accuracy declared by the manufacturer, by the user of the device or regulated in national legislation. All the DUT shall be operated as specified in the manufacturer's instructions.

For flow determination the DUT shall be started and pre-run for a minimum of 1 h or 2 mechanical cycles whichever is the longest to ensure flowing is in 'steady state'. The data is similarly taken for a minimum of 2 h or 2 mechanical cycles whichever is the longest. Several calibration methods can be used to determine the flow of a DUT. These methods are explained below.

4.3.1 Gravimetric method

The most common method for calibration of DDD is the gravimetric method as described by Bissig et al., [17]. This method can, for example, be used for the calibration of peristaltic and syringe pumps and for flow meters. IDA can also be calibrated using this method.

Gravimetric facilities for micro flow calibrations usually consist of a flow generator (e.g. a piston prover used as a flow generator, a syringe pump, a pump and flow controller system, etc.) and a flow rate reference system realised by a weighing scale and a "stopwatch", enabling the measurement of liquid mass delivered in a certain time. The use of linear least squares fit mitigates this noise source. An example of a gravimetric setup can be found in Figure 6.

Gravimetric micro flow calibration facilities require special precautions for the transport of liquid in the tubes that are delivering the liquid of the DDD in a beaker. The beaker is placed on a balance to collect and weigh the mass of the liquid (usually water) and the needle/tube is immersed into the liquid in the beaker.

In order to minimise the evaporation, various gravimetric facilities use various methods, such as evaporation traps, oil layer to cover the liquid surface in the beaker, etc.

The general principle of a gravimetric procedure is: the mass flow rate Q_m is determined as the liquid mass collected in the beaker divided by the time (Δt) needed to collect the mass (Δm), see Equation (1). The time Δt is determined by an oscillator system (or other clock system) to allow traceability to the SI units. IEC 60601-2-24 and AAMI TIR 101 describe dynamic acquisitions and logs of sequential mass samples each of 10 seconds. Demineralised (or ultrapure) and degassed water should be used as the calibration liquid to avoid bubble formation in the small tubing (such as outer diameter (OD) 1/32" or 1/16" tubes). The mass flow rate can be converted into a volume flow rate by dividing the mass flow with the density of the water. The density of liquid is dependent on the water temperature and therefore the water temperature must be measured. Thus, for example,

the density can be determined using the formula of Tanaka et al., [18], which is commonly accepted. Many parameters must be taken into account, corrected or included in the measurement uncertainty budget. These parameters include, but are not limited to:

- evaporation (a subtle source of evaporative loss is water vapor porosity of the delivery tubing; in the case of LVPs, some elements of the pump set. At very low flow rates such as 0,01 mL/h, PVC tubing can account for (10-20) % of the fluid to be delivered. Use of polyethylene, polytetrafluoroethylene, PTFE or equivalent low water vapour porosity tubing's can avoid this error – though in practice may need to be accounted for clinically if PVC tubing's are employed);
- water degassing;
- flow stability;
- time measurement;
- temperature stability;
- buoyancy correction of the liquid delivered;
- buoyancy correction for the immersed tube (needle) in the liquid;
- jet force of the immersion tube, stick/slip of liquid on the tube (needle);
- drift and linearity of the balance.

Equation (1) can be used as a model for the gravimetric method. However, other approaches can also be used, see reference [19].

$$Q_{20} = \frac{1}{t_f - t_i}\left[\left((I_f - I_i) - \left(\delta m_{buoy}\right)\right) \times \frac{1}{\rho_w - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times [1 - \gamma(T - 20)]\right] + \delta_{evap} \quad (1)$$

Where:

Q_{20} : the volume flow rate at 20 °C,

t_i : the initial time,

t_f : the final time,

I_i : the initial mass,

I_f : the final mass,

δm_{buoy}: the buoyancy correction,

ρ_w : the density of the liquid,

ρ_A : the density of the air,

ρ_B : the density of the standard weights,

T : the liquid temperature,

γ : the expansion coefficient of the material used e.g. in a syringe [11],

δ_{evap} : the evaporation correction.

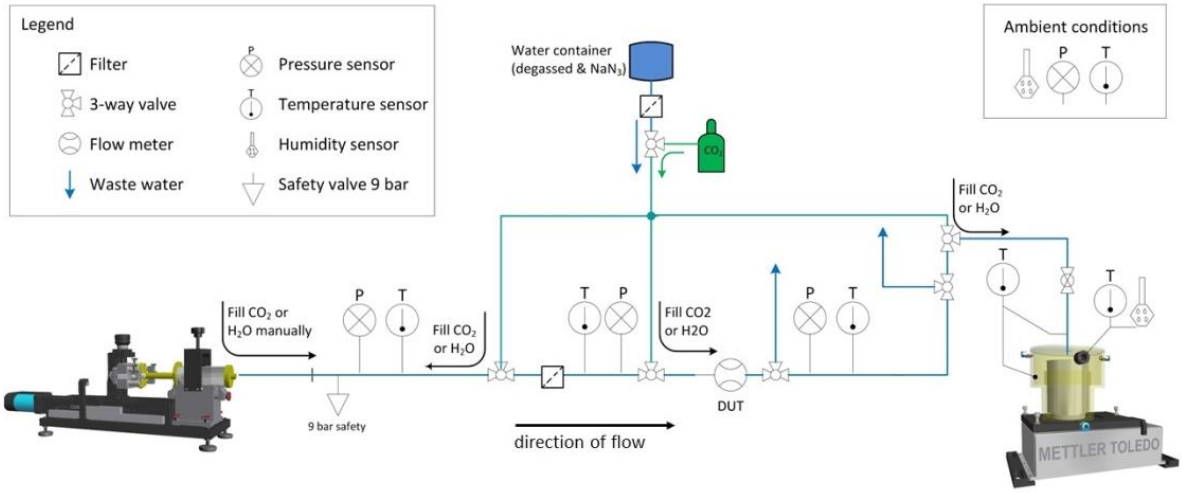

Figure 6. Schematic of the gravimetric method setup at METAS [17]

4.3.2 Front tracking method

Meniscus (or front) tracking consists of measuring the displacement as a function of time of a liquid/air or liquid/liquid interface moving inside a glass capillary tube that is connected to a flow generating device. Equation (2) presents the typical measurement model used in front tracking method.

$$Q = \left(\frac{\Delta x}{\Delta t}\right)\pi R^2 \qquad (2)$$

Where Q is the flow rate, Δx is the liquid front displacement between two images, Δt is the time difference between two images, and R is the radius of the capillary.

Images of the moving meniscus can be acquired by a high-speed camera, Digital Image Correlation, and then to deduce the flow rate from the calculated velocity and the previously measured inner diameter of the capillary [20].

Traceability of the front tracking method to the SI units is ensured by the calibration of the camera pixel's size using a calibrated target (also called an "object micrometre"), the calibration of the framerate or the signal generator triggering the camera, and the measurement of the capillary's inner diameter, usually using the same camera.
An example of a front tracking setup is shown in Figure 7.

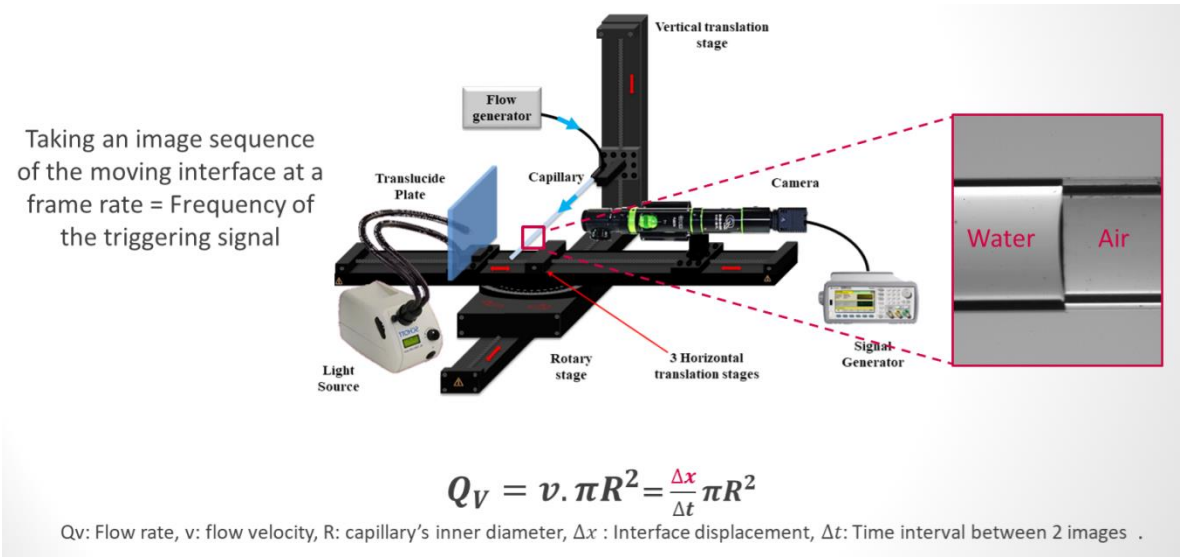

Figure 7. Schematic of CETIAT's front tracking measurement system [20]

The front tracking method allows the measurement of flow rates down to 1 nL/min. However, some precautions should be taken in order to reduce the measurement uncertainty, such as:

- Measuring the capillary's diameter at the meniscus location or ensuring the diameter's homogeneity all along the capillary.
- Avoiding stick-and-slip effect by cleaning the inner surface of the capillary, and, if needed, coating it with a hydrophobic chemical.
- Avoiding any trapped bubble in the system, by using degassed liquids and avoiding dead volumes along the flow path.
- Choosing a capillary's diameter adapted to the measurement duration needed, given the flow (and thus the velocity) to be measured.
- Ensuring the perpendicularity of the camera's axis with the one of the capillary.
- Using a telecentric objective to reduce distortion within the image. Alternatively, calibrating the camera at different positions of the calibrated target allows for quantifying the distortion effect on the pixel size.

4.3.3 Displacement method

High precision syringe pumps or piston provers are generating pulse-free and accurate flow rates by displacement of a piston plunger. The high precision syringe pumps can be operated with commercially available syringes made of glass or stainless steel, whereas the piston provers are mainly made of stainless steel. The position and the speed of the plunger as well as the inner diameter of the piston can be calibrated dimensionally to obtain traceability to the meter. The length metrology is using the interferometric method to calibrate the position of the plunger of the high precision syringe pump or piston prover. A mirror has to be mounted on the pusher block that moves the plunger. Thus, the measurement of the travelled distance of the mirror will reflect the travelled distance of the pusher block. Adding a traceable time stamp to the measurement of the positions results in traceable speed measurements. The volume flow rate is then determined by multiplying

the speed with the traceable cross section of the syringe or piston according to the following equation:

$$Q = v \times A = \frac{x_2 - x_1}{\Delta t} \times \pi r^2 = \frac{d\pi r^2}{t} \quad (3)$$

where Q is flow rate, v is velocity, A is area, x_1 and x_2 are the start and end position, Δt is the measured time, r is the syringe radius, and d is the distance.

An example of an implementation of displacement method can be found in Figure 8.

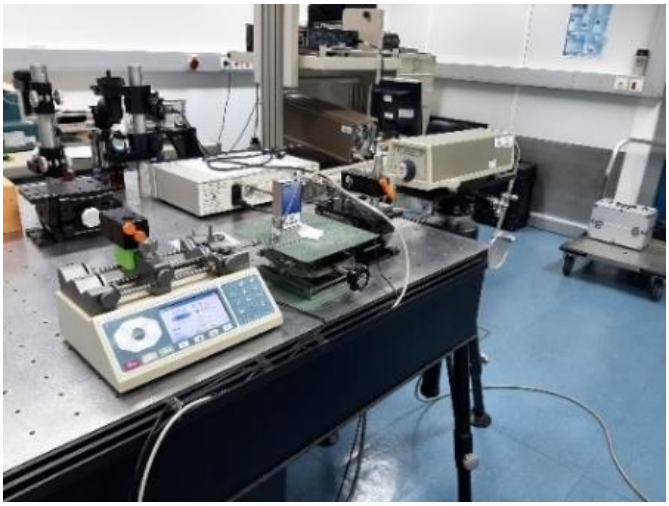

Figure 8. Assembly of interferometric method setup at IPQ [20, 21]

While the displacement method can precisely determine the “unloaded movement” of the syringe driver head, the actual performance with real sterile plastic/rubber syringes may differ due to compression of both the drive system and the syringe stopper.
Additionally, variation of the stopper cross section from syringe to syringe and from place to place in a given syringe contribute further to the overall uncertainty. More information on this method and the uncertainty components associated can be found in the work of E. Batista et al. [21].

4.3.4 Micro PIV/Micro PTV method

Alternative methods for micro/nano flows are, for example, the two well-known velocimetry techniques: Particle Tracking Velocimetry (PTV) and Particle Image Velocimetry (PIV), in which the flow velocity in a microchannel is determined on the basis of the velocity and position of the tracer particles entrained in the flow. While PIV calculates velocities from image regions, by dividing the video frames into small patches and estimating the velocity by cross-correlating corresponding patches in successive frames. PTV calculations refer to individual particles by tracking their position across a sequence of frames.

An example of a measurement setup consists of a transparent, custom-made straight microfluidic channel with a rectangular profile, a CMOS sensor and a light source (Figure 9). The fluid flowing through the channel is seeded with neutrally buoyant particles to make the flow visible to the sensor. Once an image sequence of the flow is recorded, each

holographic image is reconstructed and the flow velocity in the channel is estimated using a velocity measurement algorithm (see Figure 10).

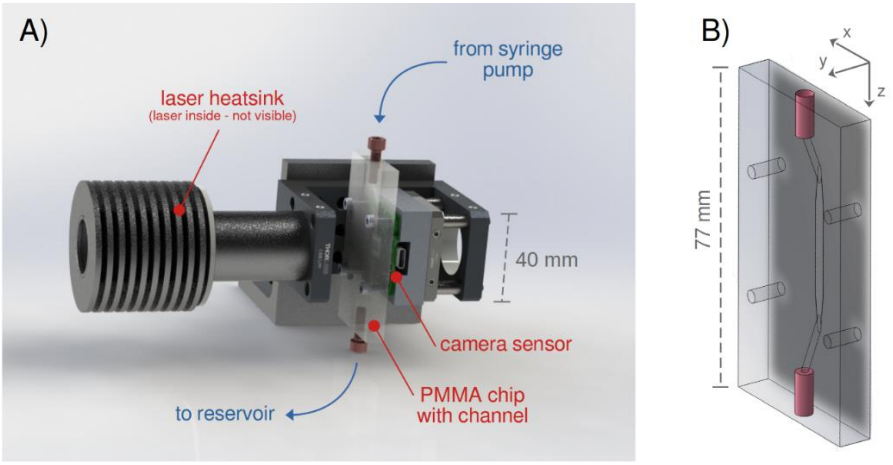

Figure 9. A) Experimental set-up. Channel is mounted vertically in flow direction from top to bottom. B) Microfluidic chip made of PMMA. Channel is milled, then sealed with adhesive tape. The sealed channel bottom is close contact to the image sensor, *y* aligns with the channel's height, *x* aligns with the channel's width, *s* aligns with the channel's length, with the flow direction, and with the gravitational acceleration.

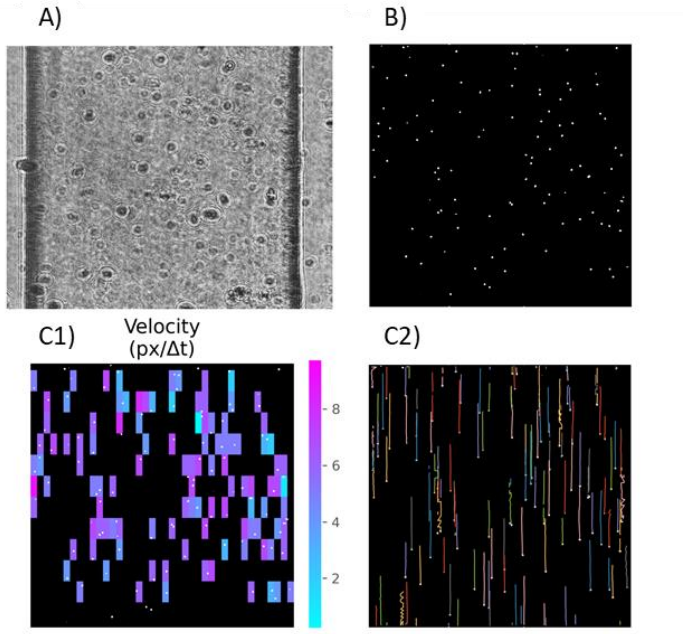

Figure 10. Example of processed video frames. For visualisation purposes, just a piece (800 × 800) pixel of a frame is shown here. The real frame is larger (800 × 2184) pixel. The modules are: A) Conversion to grey-scale, B) Particles segmentation, C1) PIV, C2) PTV.

For PIV; the *argmax* of the cross-correlation gives an estimate of the particle movement of that specific frame patch. By averaging each of the patch displacements, across all the

frames, it is possible to determine the average particle velocity in an image sequence. In a video with *n* frames, where each frame *F* is divided into *k* rows and *i* columns, the average particle velocity *v* can be estimated as:

$$v = \frac{pixel\_size}{(n-1) \times k \times i \times \Delta t} x \sum_{t=2}^{n} \sum_{z=1}^{k} \sum_{x=1}^{i} S(t,x,z) \quad (4)$$

Where *Δt* is the time interval in seconds (1 / frame rate), and *pixel_size* is the sensor's pixel size in µm. *S (t, x, z)* is the displacement estimated at frame *t* for the patch located at row *z* and column *x*:

$$S(t,x.z) = argmax\left(F_{t-1,x,z} \times F_{t,x,z}\right) \quad (5)$$

The output of the cross-correlation will generally be a 2D function. However, in the example of PIV implementation, the width of both patches is constrained to be the same; therefore, the output of the cross-correlation is simply a 1D function. In this way, the PIV method only measures displacements along the *z*-direction (the flow direction) and therefore reduces computational costs and the occurrence of spurious displacement estimates due to particles being wrongly correlated to their lateral neighbours.

PTV, on the other hand, tries to find the particle in subsequent frames. Once this process is performed for all images, the trajectory of the individual particles can be calculated. From the length and time stamps of these trajectories the particle velocity can be determined. Finally, the average flow velocity *v* in *z*-direction can be estimated as the mean particle velocity.

For both velocimetry methods, the average flow velocity is calculated as a simple mean of all measured particle/patches velocities. The simple mean gives a valid estimate because the particles are fairly uniformly distributed in space. Finally, the flow rate in nL/min is calculated as:

$$q = 6 \times 10^{-5} \times (v - v_{sink}) \times ch_{area} \quad (6)$$

Where *v* is the average flow velocity in µm/s, v_{sink} is the average particle sedimentation velocity in µm/s (in *z*-direction, since the channel is mounted vertically), and *ch_area* is the channel area in µm². v_{sink} is estimated by evaluating the equation above for image sequences with no flow (syringe pump turned off). On average, in this example, particles sedimented at 15,6 µm/s.

4.4 Calibration liquid

The liquid used in DUT calibration must be distilled and degassed water of grade 3 according to ISO 3696 [22].

If liquids other than water are used for the calibration, care should be taken regarding evaporation, density and viscosity of the specific liquid.

4.5 Liquid temperature

The water temperature should be measured at least in the beginning of the test, e.g. before filling the syringe, and at the end of the test [9].

4.6 Ambient conditions

During the tests, the air temperature, the relative humidity and the atmospheric pressure need to be measured and recorded.

The test shall be carried out in a draught-free room with a stable environment. The test room shall have a relative humidity between 45 %rh and 80 %rh and a temperature of (20 ± 3) °C with a maximum variation of ± 0,5 °C during the test [9].

4.7 Thermal equilibrium

DUT, test equipment, calibration liquid and the test room should be stable for at least 6 hours [9] before starting the test (minimum equilibration time) and during the test itself, see clause 4.6.

4.8 Response or delay time measurement: general method and recommendations

To quantify the delay or response time of a given DUT, the following recommendations should be considered:

- Use a calibrated chronometer or software/instrument allowing the timestamping of the measured reference flow rate.
- Evaluate the uncertainties on both the reference flow rate and the response or delay time measured. For example, a known (and calibrated) sampling frequency of mass, volume, or flow data can be used to calculate a time interval.
- Use a defined and stated method to synchronise the starting of the delivery process and the timestamping of the mass, volume or flow data. For example, an operator can start the mass data recording of a weighing scale when they simultaneously push the "start" button on the drug delivery device. In any case, the uncertainty on synchronisation should clearly appear on the time uncertainties evaluation.
- Make sure the definition of the response or delay time is clearly stated in the test report.
- Clearly describe all test conditions likely to influence the response or delay time of the device under test:
  - accessories (syringe type/volume /material, administration set),
  - tube length and material for connecting the device to the reference system,
  - fitting types (in case of important dead volume),
  - liquid used (with or without degassing: bubbles significantly can increase the response time measured).

By satisfying the recommendations above and analysing the flow rate data recorded since the start of the drug delivery process from the device under test, then the operator is able to determine, by one of the definitions presented above, the response or delay time. See also clause 2.13.

4.9 Periodicity of calibration

The DUT needs to be calibrated regularly, depending on use, requirements or historical data that will be used to access the drift of the device over time. The time calibration periodicity is normally defined by the user/customer, but this information can also be described in regulation or by the manufacturer.

4.10 Adjustment

If DUT needs to be adjust based on user, manufacturer or standards requirements and this operation is allowed by the instrument, it shall be done based on the manufacturer instructions. In order to keep traceability on the instrument's drift, a calibration must be performed before and after every adjustment.

5 FLOW CALIBRATION PROCEDURES

5.1 General preparation

Leave the DUT, the test equipment, exchangeable parts, and test liquid to reach thermal equilibrium, for at least 6 hours.

Before any measurement starts, it is important to prime the DUT and all the tubing and ensure that no air is entrapped in the fluidic system.

Select the tested points according to user or manufacturer specifications, if no information is provided it is recommended to test at least 3 different flow points with 3 measurements at each point in order to estimate the device's repeatability.

All tests should be performed with appropriate disposables, if applicable, it is recommended to use the disposables of the user or manufacturer.

Record the liquid and air temperature, air humidity and air pressure, and other relevant conditions relevant for the DUT and calibration method.

5.2 Calibration using the gravimetric method

Choose the appropriate balance according to the flow rate to be tested. Select the flow rate in the DUT and connect the system to the balance ensuring that the end of the system is immersed inside the water in the beaker on the weighing scale according to [9]. Prime the system in order to remove any air bubbles. Initiate the test and wait stability time is reached. Collect the data for a sufficient period of time until you can perform a correct data analysis. The testing period can be defined according to [9].

The tests for syringe and infusion pumps using the gravimetric method are performed at different flow rates using the following conditions:

a) All the instruments and the water were in the same room for at least 6 hours.
b) Controlled room temperature is in the interval (20 ± 3) °C.
c) Room temperature shall not vary more than 0,5 °C during the measurements.
d) Humidity in the measuring room shall be above 45 %rh.
e) For syringe pumps, glass or plastic syringes with different volumes should be selected depending on the flow rate and the conditions of use.
f) Before starting the measurement, it is important to prime the DUT and all tubing and to ensure that no air is entrapped in the system.
g) The tube/catheter/needle is immersed into the water in the weighing beaker (vessel) on the balance to avoid droplet formation and to allow a continuous reading of the flow rate over time.
h) The mass data acquisition shall be carried out directly from the balance and can be chosen by the user depending on the applicability, DUT and flow rate and this has to be done simultaneously with the measurement of the elapsed time; the instantaneous flow rate can then be determined. The number of points to be

collected also depends on the DUT and flow rate. The average flow rate can then be determined.

i) The time is measured using a clock system (e.g. a computer) with traceable time stamps or sampling frequency.
j) Ultra-pure water with a conductivity of 0,05 μS/cm should be used as calibration liquid.

During the tests, the temperature of the water and the ambient air, the relative humidity and the atmospheric pressure shall be measured and recorded.

5.3 Calibration using the front tracking method

Chose the appropriate capillary according to the flow rate to be tested. Select the flow rate in the DUT. Prime the system in order to remove all air bubbles and connect the system to the capillary ensuring that there is no leakage. Initiate the test. Collect the data (images) for enough time and with the appropriate framerate to perform the correct data analysis. The testing period can be defined by AAMI TIR101 [9].

A DDD (in particular insulin pumps) can be calibrated with the front tracking method at very different flow rates and at the following conditions:

a) All the instruments and the water located in the same room for 6 hours.
b) Controlled room temperature is in the interval (20 ± 3) °C.
c) Humidity room above 45 %rh.
d) Before any measurement starts, it is important to prime the DUT and all the tubing and ensure that there is no entrapped air in the system.
e) The time interval defined by the user to take the pictures depends on the length of the capillary, flow rate, the applicable camera vision area and DUT cycle time.
f) Ultra-pure water can be used as calibration liquid, with a conductivity of 0,05 μS/cm.

During the tests, the temperature of the water and the air, the relative humidity and the atmospheric pressure need to be measured and recorded.

5.4 Calibration using the displacement method

Connect the DUT to a high precision syringe pump or piston prover and prime the DDD at a reasonable high flow rate within the specifications. Set the reference flow rate and start the piston prover/syringe pump. Collect the data of the DDD and adapt the measurement time required for a correct data analysis.
If the DUT is an IDA, the manufacturer requires the measurement of a minimum delivered volume of 10 mL or 20 mL depending on the flow rate. Investigations of the indicated average flow rate as a function of the delivered volume showed that above a delivered volume of 3 mL the average flow rate remains unchanged. Thus, the measurement times at very low flow rates can be dramatically reduced by limiting the delivered volume to 3 mL [23].

The following procedure can be applied for the calibration of an IDA:

a) Switch on the IDA and leave it for at least 6 hours in the laboratory to stabilise the internal temperature which is affected by the heating effect of the electronics in the IDA.
b) Fill the piston prover/syringe pump with ultrapure water and purge the connection lines to remove remaining air bubbles.

c) Connect the IDA with a Luer Lock female connector to the connection line of the piston prover/syringe pump. Connect to the outlet connector of the IDA a silicon tube, which brings the water to a waste container.
d) Set the reference flow rate at the piston prover/syringe pump and start delivering the water.
e) If the required stability of the reference flow rate is reached and the priming of the IDA has ended (indication on display), start the data acquisition of the IDA. The measurement time is set to measure a delivered volume of at least 3 mL.
f) Use the software to collect data of the delivered volume and the average flow rate or read this data from the display.

Water and ambient temperature, relative humidity and atmospheric pressure have to be recorded during the calibration.

5.5 Calibration using the MicroPIV/MicroPTV method

Connect a piece of PTFE tubing to the inlet of the channel of a microfluidic device and fill the tube and microchannel with water containing microbeads (1 μm in diameter) and 0,1% Tween (to prevent beads from sticking to the walls). The following procedure can be applied for the calibration of an insulin pump as an example:

a) Connect the tube from the device inlet to the tube exiting the insulin pump syringe, making sure that no air is introduced.
b) The connection causes some pressure in the system, so monitor the beads in the channel under the microscope until the beads stop moving and the system has stabilised.
c) Set the desired flowrate in the insulin pump device and press start. Wait for at least one cycle of the step motor (depending on the set flowrate) before starting the measurements.
d) For each datapoint, collect 10-15 images and calculate the average flowrate.
e) Data points can be collected at certain intervals depending on the flowrate. This can be automated using software driving the camera.
f) Data for the calibration can be collected for many hours as necessary.

6 FLOW RATE ERROR DETERMINATION

According to the International Vocabulary of Metrology (VIM) [7], the measurement error is the measured quantity value minus a reference quantity value, equation (7).

According to IEC 60601-2-24 [8] the measurement error of the measured quantity is defined as reference value minus the quantity value, equation (8).

Expressing the relative error in formulas, according to the above-mentioned definitions and referring it to the case of a drug delivery device calibration, where the measurand is the flow rate of the delivered drug, we get the following formulas:

$$\text{Metrological error: } A_{Metro} = \frac{(Q_{set} - Q_{ref})}{Q_{ref}} 100(\%) \quad (7)$$

$$\text{Medical error: } A_{med} = \frac{(Q_{ref} - Q_{set})}{Qset} 100(\%) \quad (8)$$

where:

- A_{Metro} is the relative flow measurement error or systematic error as defined by VIM [7],
- A_{med} is the relative flow measurement error or systematic error as defined in the IEC 60601-2-24 [8],
- Q_{ref} is the reference flow rate determined by the reference measurement method (e.g., gravimetric method),
- Q_{set} is the flow rate set or the indicated flow rate at the instrument under calibration (e.g., 1 mL/h).

7 DATA ANALYSIS

The flow error and measurement uncertainty according to VIM can be determined for each DDD at each calibration point along with the associated uncertainty, according to GUM.

In the health care sector and device type approval other approaches for data analyses are applied according to IEC 60601-2-24 [8] that defines a procedure for evaluating the long-term variability in flow rate generated by a DUT (determination of the mean measurement error). This procedure leads to the so-called trumpet curves [8]. However, a recently published technical information report AAMI TIR101:2021 [9] proposes a different procedure that should provide a result that is easier for clinicians to interpret based on PK-CV curves.

8 PROCEDURE FOR ESTIMATING MEASUREMENT UNCERTAINTY

8.1 General procedure for the uncertainty calculation

The evaluation of measurement uncertainty described in this document follows the methods described in JCGM 100:2008 [5]. The method consists of the following steps:

a) Expressing, in mathematical terms, the relationship between the measurand and its input quantities.
b) Determining the expectation value of each input quantity.
c) Determining the standard uncertainty of each input quantity.
d) Determining the degree of freedom for each input quantity.
e) Determining all covariances between the input quantities.
f) Calculating the expectation value for the measurand.
g) Calculating the sensitivity coefficient of each input quantity.
h) Calculating the combined standard uncertainty of the measurand.
i) Calculating the effective degrees of freedom of the combined standard uncertainty.
j) Choosing an appropriate coverage factor k, to achieve the required confidence level.
k) Calculating the expanded uncertainty.

It should be noted that for steps a) to k) suitable computer programs exist which can replace manual calculation. Step a) is the most important part in the whole GUM procedure.

It is relevant to point out that special conditions can arise where the GUM uncertainty framework might not be the best approach to evaluate measurement uncertainty. This is particularly relevant when there is a dominant source of uncertainty with a non-Gaussian distribution. In such cases the alternative methods may provide a better approach, e.g. GUM supplement 1 [24] or a Bayesian method [25].

8.2 Parameters that affect the uncertainty in gravimetric flow determination

The main contributions to the combined standard uncertainty are:

- mass measurements (m),
- density of the mass pieces (ρ_B),
- density of the water (ρ_W),
- density of the air (ρ_A),
- evaporation rate (δQ_{evap}),
- water temperature (T),
- time (t),
- expansion coefficient (γ),
- standard deviation of the measurements (δQ_{rep}),
- and buoyancy on the immersed dispensing needle (δQ_{mbuoy}).

More information about the uncertainty components for the gravimetric determination can be found in MeDDII D1 - Report A1.2.5 [20].

A numerical example for the calibration of a syringe pump using the gravimetric method is described in Annex 1.

8.3 Parameters that affect the uncertainty in front tracking flow determination

The main contributions to the combined standard uncertainty are:

- capillary's inner diameter determination,
- calibration of the camera's pixel size,
- volume and volume flow determination by front tracking method, which includes the inaccuracy of the interface displacement determination and velocity calculation,
- water temperature (T),
- time (t),
- expansion coefficient (γ)
- standard deviation of the measurements (δQ_{rep}).

More information about the uncertainty sources and their estimation for the front tracking determination can be found in [20].

A numerical example for the calibration of an insulin pump using a front tracking method is presented in Annex 2.

8.4 Parameters that affect the uncertainty of the displacement method generating flow

The main contributions to the combined standard uncertainty of the displacement method are listed below:

- the time stamps and the position reading,
- the speed of the plunger of the piston (syringe),

- the piston cross section,
- the standard deviation of the measurements (δQ_{rep}),
- the effect of the temperature stability of the gradient along the tubing.

A numerical example for the calibration of an IDA using a displacement method is presented in Annex 3.

8.5 Parameters that affect the uncertainty of the MicroPIV method

The main contributions to the combined standard uncertainty of the microPIV method are:

- the dimensions of the microchannel,
- the influence of out-of-focus beads above and below the focal plane,
- the simplification of the actual 3-dimensional profile by only considering a 2-dimensional parabolic velocity profile,
- the standard deviation of the measurements (δQ_{rep}),
- the frame rate of the camera used to image the flow of beads with respect to the beads velocity.

A numerical example for the calibration of an insulin pump using the microPIV method is presented in Annex 4.

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Annex 1. Numerical example of the uncertainty determination in syringe pump calibration using a gravimetric method

Standard uncertainty component $u(x_i)$	**Source of uncertainty**	**Value of standard uncertainty $u(x_i)$**	**Distribution**	**Evaluation**	$c_i \equiv \frac{\partial f}{\partial x_i}$	$u_i(V_0) \equiv \lvert c_i \rvert u(x_i)$ (L)	ν_{eff}
$u(m_{ind,f})$	Final mass (g)	2,86E-05	Normal	B	1,06E-03	3,03E-08	50000
$u(\rho_{w,b})$	Density of the water (g/mL)	6,21E-04	Rectangular	B	-2,60E-04	1,61E-07	50000
$u(\rho_a)$	Density of the air (g/mL)	2,89E-06	Rectangular	B	2,28E-04	6,57E-10	50000
$u(\rho_c)$	Density of the mass pieces (g/mL)	2,50E-03	Normal	B	4,79E-09	1,12E-11	50
$u(T)$	Temperature (ºC)	7,02E-01	Normal	B	-2,59E-09	1,82E-09	50
$u(\gamma_s)$	Expansion coefficient (/ºC)	2,89E-07	Rectangular	B	-5,94E-04	1,72E-10	50000
$u(m_{ind,i})$	Initial mass (g)	2,86E-05	Normal	B	-1,06E-03	3,03E-08	50000
$u(Q_{Evap})$	Evaporation (g/mL)	1,47E-08	Rectangular	B	1,00E+00	1,47E-08	50000
$u(t_f)$	Final time (s)	7,00E-04	Normal	B	2,74E-07	1,92E-10	50
$u(t_i)$	Initial time (s)	7,00E-04	Normal	B	-2,74E-07	1,92E-10	50
$u(\delta Q_{m_{buoy}})$ $\delta Q_{m_{buoy}} = Q_w(d_t/d_b)^2$	Buoyancy (mL/s)	2,38E-05	Normal	B	1,06E-03	2,53E-08	50000
$u(\delta Q_{rep})$	Repeatability (mL/s)	1,23E-06	Normal	A	1,00E+00	1,23E-06	24

Q (mL/s)	0,000259
ν_{eff}	24,919
K	2,11
Expanded uncertainty (mL/s)	2,61E-06
Expanded uncertainty (%)	1,01

Annex 2. Numerical example of the uncertainty determination in insulin pump calibration using a front tracking method

Standard uncertainty component	Source of uncertainty		Value of standard uncertainty $u(x_i)$	Distribution	Evaluation	$c_i \equiv \frac{\partial f}{\partial x_i}$	$u_i(V_0) \equiv \lvert c_i \rvert u(x_i)$ (L)	ν_{eff}
Inner dimensions of the glass capillary tube	Camera resolution		2,89E-08	Uniform	Type B	1	2,89E-08	2
	Camera calibration	Objective Micrometer	7,50E-08	Normal	Type B		7,50E-08	
		Position in the focal plane	3,30E-11	Uniform	Type B		3,30E-11	
		Position in the depth of field	3,30E-11	Uniform	Type B		3,30E-11	
	Intensity profile		2,89E-08	Uniform	Type B		2,89E-08	
	/		**8,54E-08**	/	/	**3,33E-09**	**2,85E-16**	
Interface displacement	Camera resolution		2,89E-08	Uniform	Type B	1	2,89E-08	300
	Camera calibration	Objective Micrometer	7,50E-08	Normal	Type B		7,50E-08	
		Position in the focal plane	3,30E-11	Uniform	Type B		3,30E-11	
		Position in the depth of field	3,30E-11	Uniform	Type B		3,30E-11	
	Motion plane angle		4,73E-10	Uniform	Type B		4,73E-10	
	Motion blur		4,08E-08	Uniform	Type B		4,08E-08	
	Correlation function		5,77E-08	Uniform	Type B		5,77E-08	
	/		**1,07E-08**	/	/	**7,85E-09**	**8,41E-16**	
Time Stamp	Calibration		1,67E-09	Normal	Type B	1	1,67E-09	300
	Resolution		9,62E-04	Uniform	Type B		9,62E-04	
	Exposure time		1,92E-03	Uniform	Type B		1,92E-03	
	/		**2,15E-03**	/	/	**-1,67E-14**	**-3,59E-16**	
Flow Velocity	Thermal expansion		1,92E-17	Uniform	Type B	1	1,92E-17	150
	Evaporation		2,10E-16	Uniform	Type B		2,10E-16	
	/		**2,11E-16**	/	/	**1**	**2,11E-16**	

System Configuration	Q (µL/min)	v (µm/s)	x (µm)	t (s)	d (µm)
Values	0,01	21,22	21,22	1	100
Configuration in S.I. units	Q (m^3/s)	v (m/s)	x (m)	t (s)	d (m)
Values in S.I.	1,67E-13	2,12E-05	2,1E-05	1	0,0001
C_i			C_x	C_t	C_d
Sensitivity coef., formulae		1	π/4*d²/t	π/4*d²/t²*x	π/2*d*x/t

Combined Uncertainty (nL/min)	5,88E-02
ν_{eff}	500000
k	2
Expanded uncertainty (%)	1,2

Annex 3. Numerical example of the uncertainty determination in IDA calibration using a displacement method

Standard uncertainty	**Source of uncertainty**	**Value of the Standard uncertainty (mL/h)**	**Distribution**	**Evaluation**	$c_i \equiv \frac{\partial f}{\partial x_i}$	$u_i(V_0) \equiv \lvert c_i \rvert u(x_i)$ (mL/h)	ν_{eff}
$u(FG)_{cal}$	Reference flow generator / FG	0,006	Normal	Type A	1	0,006	50
$u(IDA)_{res}$	IDA flow	0,01	Rectangular	Type B	1	0,01	5000
$u(\delta Qrep)$	Repeatability	0,01	Normal	Type A	1	0,01	500

Q (mL/h)	0,5
ν_{eff}	50000
k	2,0
Expanded uncertainty (mL/h)	0,02
Expanded uncertainty (%)	3,86

Annex 4. A numerical example for the calibration of an insulin pump using the microPIV method

Target (setpoint) flowrate	Target (setpoint) flowrate	Measured Flowrate	Measured Flowrate	STDEV Flowrate	Sampling frequency	Initial stabilisation time	Initial stabilisation time	Total acquisition time
(nL/min)	(µL/h)	(nL/min)	(µL/h)	(µL/h)	(Hs)	(min)	(s)	(min)
16,67	1,00	20,06	1,20	3,94	0,1	NA	NA	133
50,00	3,00	47,87	2,87	0,61	0,2	52,54	3152,40	66,4
83,3	5,00	104,82	6,29	12,32	0,2	20,58	1235,00	137,83
100,00	6,00	111,35	6,68	28,32	0,2	32,33	1940,00	184,83

Total acquisition time	Error	Medical error	Uncertainty	Average step interval time	
(HH:MM:SS)	(%)	(%)	(%)	(min)	STDEV
02:13:00	-16,90	20,33	2,07	14,96	0,08
01:06:24	4,45	-4,26	2,07	4,96	0,06
02:17:50	-20,50	25,78	2,07	2,98	0,03
03:04:50	-10,19	11,35	2,07	2,41	0,03

Note: The uncertainty of the method was calculated based only on the variation in the dimensions of the microchannel, this was because other uncertainties were negligible in comparison.

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