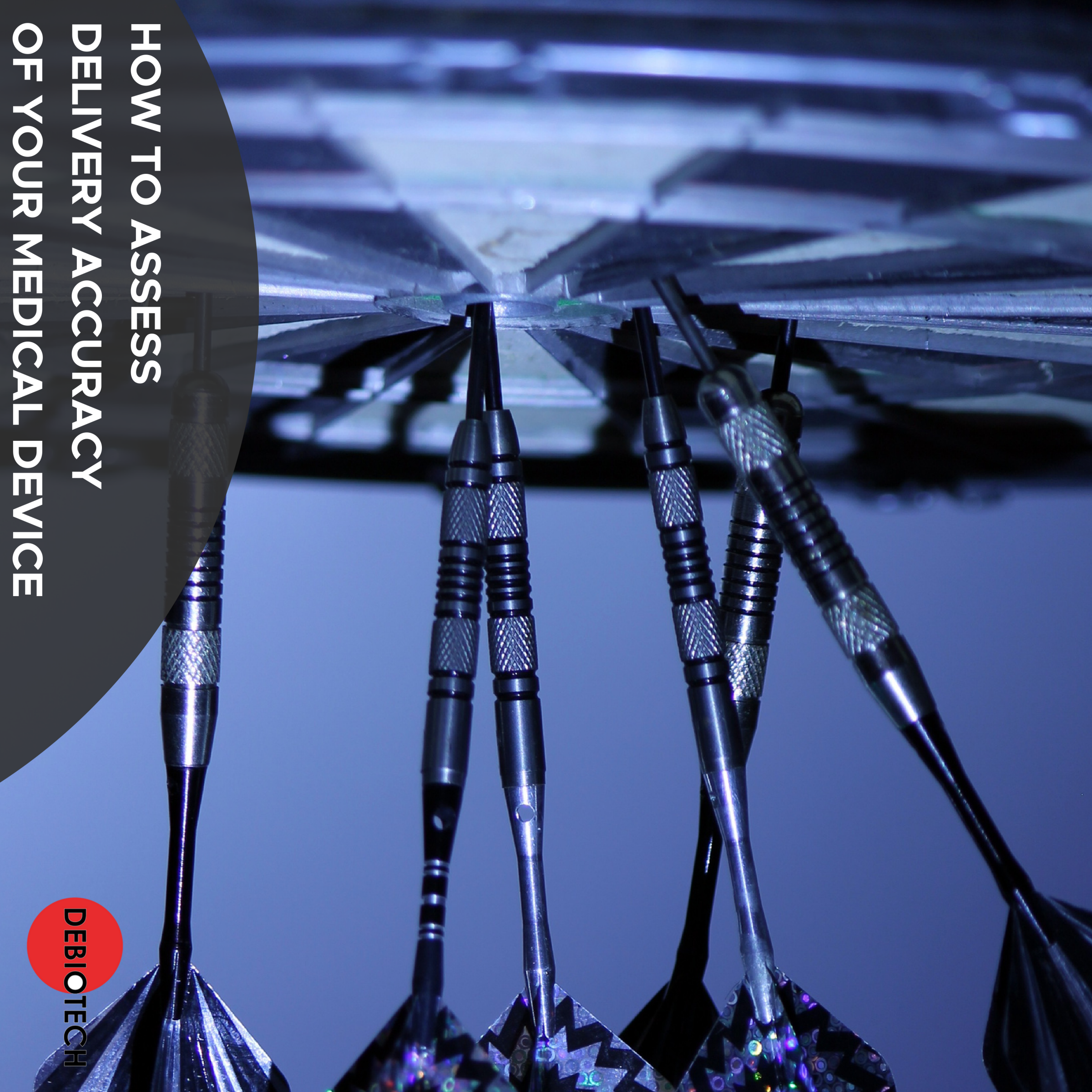
HOW TO ASSESS DELIVERY ACCURACY OF YOUR MEDICAL DEVICE



DEBIOTECH

FOCUS ON MICROFLOW MEASUREMENTS.

Some Drug Delivery Devices can infuse at a flow rate as low as a few microliters per hour or less. Using a micro flowmeter may be an effective solution for a steady flow, but pulsatile flows are trickier to measure.

We will present you some tips to assess the delivery accuracy of your device whatever the flow profile. Particular attention is paid to microflows typically observed in diabetes treatment when a low basal rate is programmed, or in pain management using implantable pumps.

INFUSION PUMP CLASSIFICATION AND STANDARDS

Most electromechanical pumps are ruled by IEC 60601. Part 2-24 of this standard describes the requirements for the basic safety and essential performance of infusion pumps and controllers [1]. Simpler infusion systems, such as insulin pens or Wearable Bolus Injectors, are governed by the ISO 10608 standard [2], while the particular requirements for active implantable medical devices are specified in ISO 14708 [3].

The standard IEC 60601-2-24 defines an infusion pump as Medical Electrical Equipment intended to regulate the flow of liquids into the patient under pressure generated by the pump.

The infusion pumps may provide one or more of the following types of flow:

- type 1: continuous infusion;
- type 2: non-continuous infusion;
- type 3: discrete delivery of a bolus;
- type 4: profile pump;

TEST SETUP

Gravimetry is the preferred method to characterize delivery accuracy.
A typical setup is described in Fig.1. The drug delivery device is connected to an administration set or tubing ended by a needle immersed into a partly filled beaker. The test medium shall exhibit fluidic properties similar to the drug itself.
Purified water (e.g. ISO class III), which shows the same viscosity as insulin (1 $mPa.s$), is considered a representative test medium for insulin pump characterization. The test setup may include an elevator to put the device and the water meniscus in the beaker at the same level. The scale is connected to a computed for data storage.
To design your fluid line (i.e. inner diameter and length), consider the maximum flow rate your device can be programmed. Then evaluate, using Hagen-Poiseuille's law, the maximum pressure drop you can generate without perturbing the test outcome. This is the preferred method as no calibration of the fluid line is required and no rationale is needed to justify further data manipulation during the test results analysis.

ISO 60601-2-24 suggests a rationale for the needle inner diameter selection and a minimum scale resolution for tests performed at the minimum infusion rate. However, these criteria should be adjusted when considering microflow rates.
Challenges associated with microflow measurements and the related improvements to the test setup are discussed at the end of this paper.

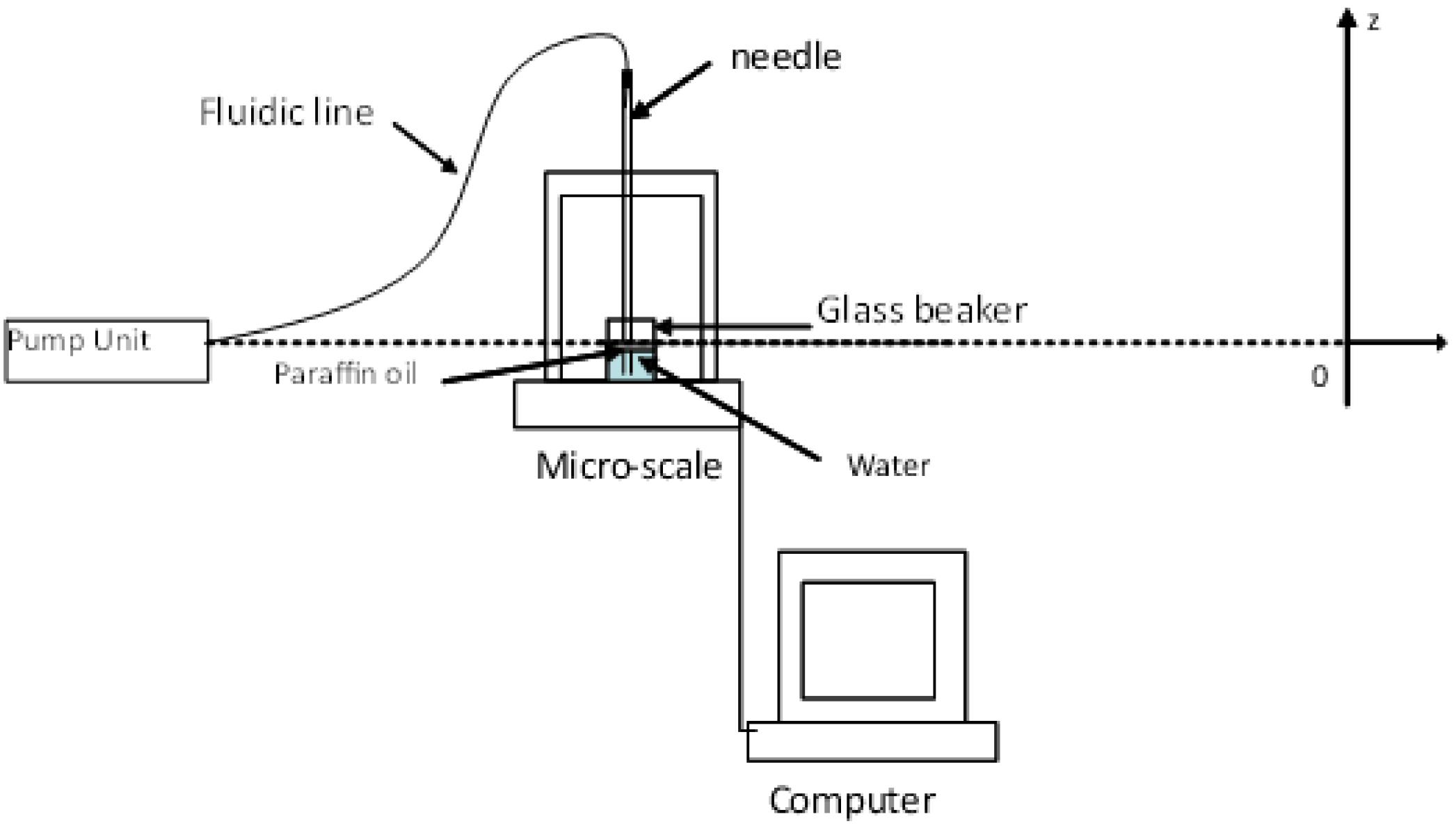


Figure 1: Test setup for different types of infusion pumps including profile patch pumps.

CALIBRATION STRATEGY

For Engineering Testing, you can consider a yearly calibration plan for the measurement equipment and an even longer time frame for the calibrated weights themselves. Please make sure that these weights correctly cover the expected measurement range. Also, include in your calibration protocol criterion related to off-centering and linearity, this later parameter being crucial during flow rate assessment.
For critical tests (e.g. verification tests), we recommend calibration before and after each test campaign. This advice avoids the risk of invalidating all tests carried out on the test equipment in the year preceding an out-of-specification calibration.

TEST SET-UP VALIDATION

For verification testing, the test setup including the data transfer and processing shall be validated (see e.g. clause 6.101 of [3]).

START-UP GRAPHS AND TRUMPET CURVES

Once you have determined the exact classification of your device and built and validated your test setup, you shall implement the test methods described in the standard to determine, among other characteristics, the delivery accuracy of your device through:

- Start-up graphs
- Trumpet curves

START-UP GRAPHS

An example of a start-up graph is shown in Fig. 2. Measuring the flow rate over time from the start of the infusion allows us to determine the typical time necessary to reach the set rate.

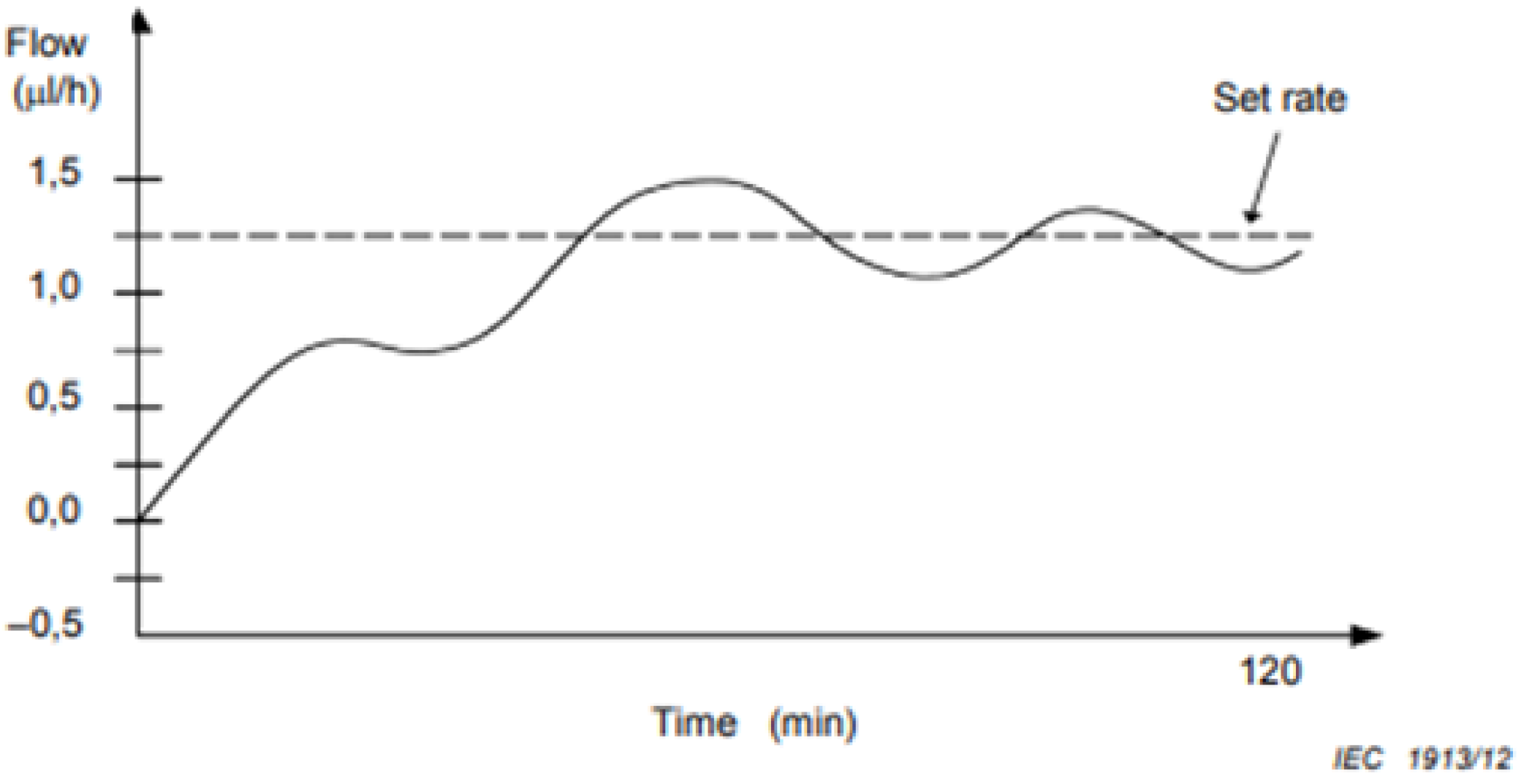


Figure 2: Start-up graph. From [1].

TRUMPET CURVES

The so-called trumpet curves represent the maximum percentage deviation from the expected dose for a given time interval, known as the 'observation window', at any time during the infusion of the drug or solution. The upper and lower curves correspond respectively to maximum and minimum measured errors in observation window of specified duration $E_{P(\max)}$ and $E_{P(\min)}$ as defined in IEC60601-2-24 [1].
As the accuracy also depends on the set flow rate, two or three sets of curves are usually included in the user manual of the infusion pump. Ideally, these curves should be drawn under the most unfavorable conditions as defined in your risk analysis.
Using these graphs, the physician can correlate the onset time of the administered drug with the corresponding observation window interval in the graph and decide if the pump meets the expected delivery performance.
The longer the time interval, the more accurate the dose. This is notably true for syringe pumps wherein the stick-slip effects of the piston against the syringe negatively impact the short-term accuracy (random error), inducing a widening of the left part of the trumpet curve. Systematic errors are evidenced by an offset of the overall percentage error.

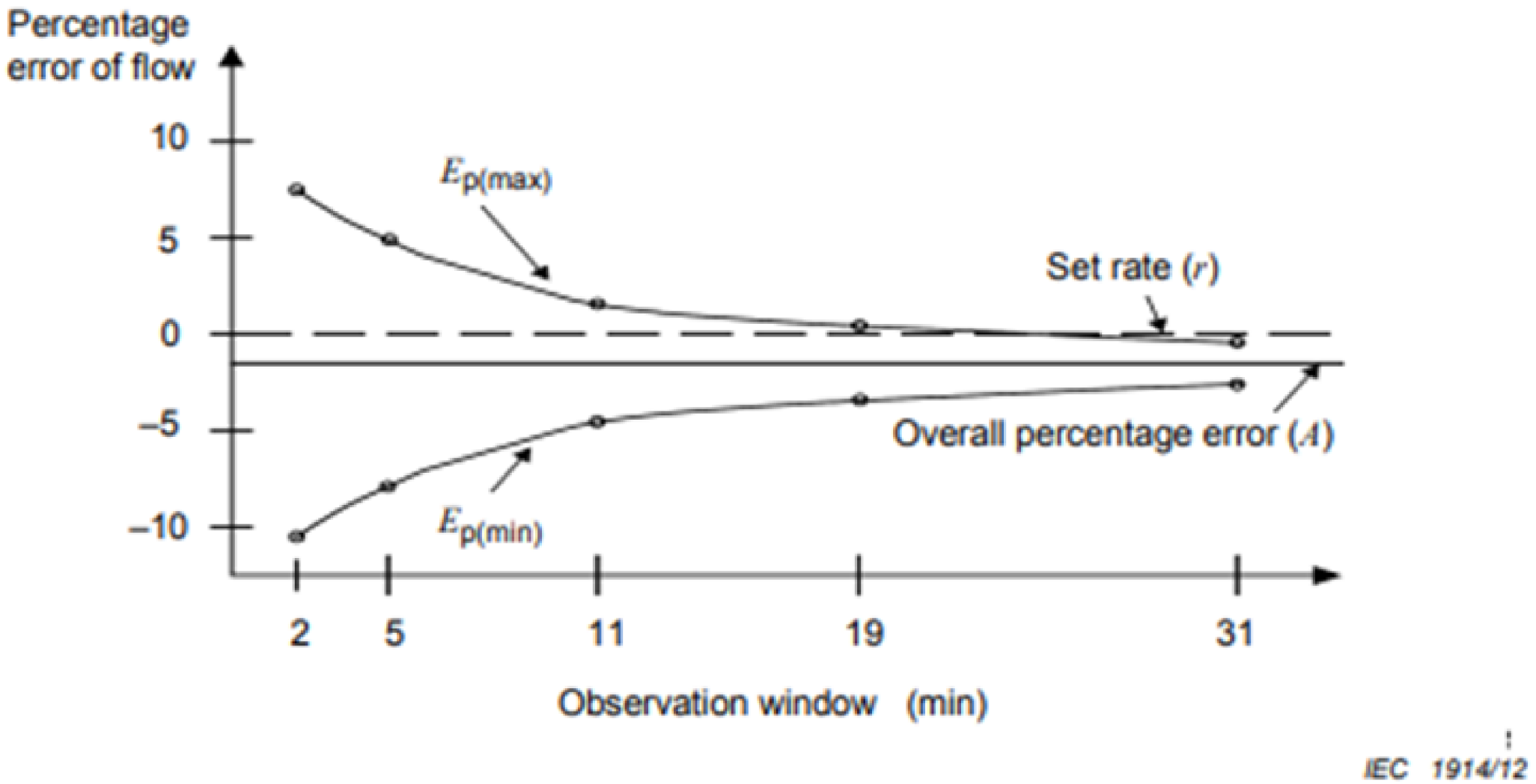


Figure 1: Trumpet curves. From [1]..

MEASUREMENT AND UNCERTAINTY

VOLUME VS FLOWRATE ACCURACY

Delivery accuracy can take two different forms depending on the therapeutic target. To illustrate this, we will consider basal and bolus infusions which are typical delivery modes in Diabetes care or pain management.
A Bolus is a given amount of drug delivered within a short period. In diabetes care, this bolus can be infused using a pen or a pump. The physical quantity that matters here is the total infused volume. The flow rate shall just remain within a broad range of values to prevent side effects like infusion pain.

The infused volume V is derived from the following formula: $$V(mL) = \frac{W(g)}{d(g/mL)}$$

Where W is the weight of the liquid infused during the bolus and d is the drug density. In basal mode, the drug is infused continuously at a low rate. This accuracy delivery at basal rate has a real impact on the efficacy of therapy. The overall flow rate is calculated using the following formula: $$Q = 60\frac{(W_j - W_k)}{100.S.d}$$

Where Q is the overall flow rate in ml/h, d is the infused liquid density, S is the time interval in minutes and $W_j - W_k$ is the mass difference between the end and the start of the analysis period (see the rationale for determining S in Annex AA of [1]).

SOURCES OF UNCERTAINTY

During the evaluation of the delivery accuracy, the following sources of uncertainty shall be considered and evaluated where appropriate:

- Scale resolution
- Scale linearity
- Repeatability
- Uncertainty on the time interval
- Density
- ...

EVALUATION OF UNCERTAINTY

Let's consider a measurand Y that is determined from N other quantities $X_1, X_2, \dots, X_N$ using the relation:

$$Y = f(X_1, X_2, \dots, X_N)$$

According to the GUM edited by the Bureau International des Poids et Mesures [4], the combined standard uncertainty for indirect measures of the flow rate (Type B evaluation of standard uncertainty) is defined by:

$$u_c(y) = \left(\sum_{i=1}^{N} \left(\frac{\partial f}{\partial x_i} \right)^2 u^2(x_i) \right)^{\frac{1}{2}}$$

Where $u_c(y)$ is the standard uncertainty, i.e. an estimated standard deviation and characterizes the dispersion of the values that could reasonably be attributed to the measurand Y, x_i represents an estimate of the input quantity X_i and $u(x_i)$ its corresponding estimated standard uncertainty. Note that the nonlinearity of the function f is not considered here.

The application of the formula to the flowrate and the volume measurements gives respectively:

$$u_c(Q) = \sqrt{2u^2(W)\left(\frac{\partial Q}{\partial W}\right)^2 + u^2(d)\left(\frac{\partial Q}{\partial d}\right)^2 + u^2(S)\left(\frac{\partial Q}{\partial S}\right)^2}$$

And

$$u_c(V) = \sqrt{u^2(W)\left(\frac{\partial V}{\partial W}\right)^2 + u^2(d)\left(\frac{\partial V}{\partial d}\right)^2}$$

Note that the estimated standard deviation of an input x s sometimes simply noted Δx
The two former formulae may therefore take the following forms, in agreement with the error propagation law:

$$\left(\frac{\Delta Q}{Q}\right)^2 = 2\left(\frac{\Delta W}{W_i - W_k}\right)^2 + \left(\frac{\Delta S}{S}\right)^2 + \left(\frac{\Delta d}{d}\right)^2$$

And

$$\left(\frac{\Delta V}{V}\right)^2 = \left(\frac{\Delta W}{W}\right)^2 + \left(\frac{\Delta d}{d}\right)^2$$

The uncertainty of the measurement shall be ideally 1% or less whatever the set flow rate.

TIPS FOR MICROFLOW MEASUREMENTS

Microflow measurements require a precision scale with microgram resolution and other specific precautions, which are briefly discussed here. Indeed, several sources of noise become problematic at low flow rates.

EVAPORATION

The evaluation of the evaporation rate to correct the measurement data usually leads to a residual drift. A better approach consists of adding oil (e.g. silicone or paraffin oil) in the beaker to prevent evaporation. Bubbles at the interface between the test liquid and the oil at the surface shall be removed.

CAPILLARY EFFECTS AND STICK-SLIP WETTING HYSTERESIS

The presence of meniscus at the different interfaces will generate Laplace forces which in turn can generate noise sources. The contact angle between the liquid and the needle and the beaker will change during the infusion test due to a stick-slip wetting process [5]. To prevent this effect, and for a given beaker volume, it is recommended to consider a beaker with a larger diameter and a small height (small aspect ratio).

ARCHIMEDES FORCE ON THE NEEDLE

The Archimedes force that lifts the needle in the beaker will also change and affect the measurement accuracy over time. A small needle together with a large beaker diameter can be sufficient to make the correction of this effect unnecessary.

AIR BUOYANCY

The beaker is also submitted to the Archimedes force due to the surrounding air. Usually, buoyancy can be directly corrected using the scale setup parameters.

OTHER SOURCES OF NOISE: VIBRATION, THERMAL GRADIENT, AND CONVECTION/STABILITY TESTS

Special care shall be taken when setting up the scale, using for instance warmup time of several hours to 1 day. The scale shall be placed onto a marble plate isolated from building vibrations. Protection shields around the beaker are recommended to prevent the convective effect or influence of air-cooling systems.
Thermal protection around the infusing tubing may also be considered.

Finally, you shall consider, for your fluidic lines, a material that exhibits a very low diffusion rate to prevent air permeation.

References:

[1] IEC 60601 Medical electrical equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers (2012).
[2] ISO 11608 Needle-based injection systems for medical use - Requirements and test methods -
Part 6: On-body delivery systems (2022).
[3] ISO 14708 Implants for surgery - Active implantable medical devices - Part 4: Implantable infusion pump systems (2022).
[4] JCGM 100:2008 Evaluation of measurement data - Guide to the expression of uncertainty in measurement.
[5] De Gennes, P. G., Brochard-Wyart, F., & Quéré, D. Gouttes, bulles, perles et ondes. Paris: Belin (2005).

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