Application Note

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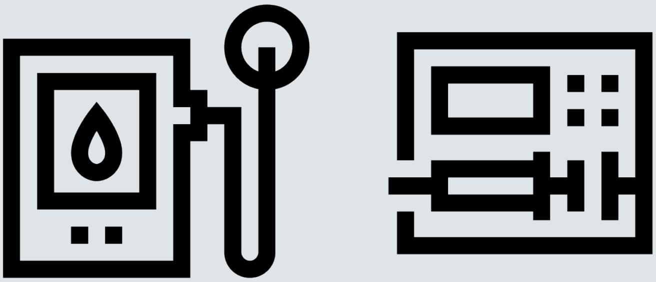
Challenges in testing of dosing accuracy according to IEC 60601-2-24 and AAMI TIR-101



Overview

In the world of medicine, accurate medication dosages are critical for patient well-being. Leveraging years of expertise and advanced technology, we have created lab balances that meet the stringent requirements for dosing accuracy verification. This application note examines the characteristics of the Sartorius Cubis® and Cubis® II Balances together with B.Braun. It will address the ideal configuration of these balances and analyze prevalent sources of error to comprehend their impact and prevention strategies.

Focus

- Requirements for the balances
- Frequent sources of error
- Setting of the balances
- Presentation of the relevant standards and norms
- Applications (insulin pumps, dosing pumps, micropumps)
- Challenges with flow rates from µL/h to L/h

Introduction

Advancements in medical device development and drug delivery technologies have led to increased demands on the precision of such devices. Infusion pumps exemplify this trend, with dosing accuracy capabilities improving significantly. Historically, flow rates of 1 milliliter per hour (mL/h) were standard, but modern infusion pumps now operate routinely at 0.01 mL/h, with some achieving dosing accuracy in the nanoliter range.

The precision of drug delivery is critical, particularly when administering highly concentrated medications for targeted disease treatment and personalized therapies, such as in neonatal care. Given the small volumes and high drug concentrations, slight deviations in flow rate can have substantial effects on patients. For instance, an insulin overdose could induce severe hypoglycemia.

To mitigate such risks, infusion pumps undergo rigorous type testing, including flow rate assessments using the gravimetric method as outlined in IEC 60601-2-24:2012 standard and AAMI TIR-101 technical information report.

The gravimetric test method presents challenges that balances must overcome. At very low flow rates, such as 0.01 mL/h, the infusion pump's motor movements are minimal and must be accurately detected by the balance. The balance must maintain stable measurements between pump activations. Conversely, at high flow rates, such as 1200 mL/h, the infusion pump dispenses nearly continuously. These maximum and minimum values require a balance capable of rapid response and precise time-stamped data acquisition. (Table 1).

Figure 1: *Cubis® II High capacity micro-balance (MCA66S). Recommended according to AAMI TIR-101 for tests with flow rates < 0.1 mL/h.*

Further challenges and potential sources of error related to balance performance in the context of infusion pump testing are elaborated in the "Sources of error" section.

Standards

There is currently one standard and one technical information report (based on that standard) that can be used to check the dosing accuracy,

IEC 60601-2-24:2012 "Particular requirements for the basic safety and essential performance of infusion pumps and controllers" is a standard issued by the International Electrotechnical Commission (IEC). It remains the principal guideline for infusion pump manufacturers globally. This standard outlines the fundamental safety and performance requirements that infusion pumps must meet, ensuring their reliability and effectiveness in medical settings.

AAMI TIR-101 "Fluid delivery performance testing for infusion pumps" is a technical information report published by the Association for the Advancement of Medical Instrumentation (AAMI). This report provides detailed guidance for manufacturers on testing infusion pumps across various clinical scenarios and conditions. It encompasses aspects such as flow rates, measurements, and labeling, and broadens the scope of testing to include a wider range of operational test cases beyond those specified by the IEC standard.

While IEC 60601-2-24 focuses mainly on testing under nominal laboratory conditions - with a few deviations in terms of flow rates and outlet pressures – AAMI TIR-101 extends the scope of testing to include additional test cases covering the operating range of the device.

In addition, ISO 7886-2 is of interest as it specifies requirements for disposable syringes with fixed or removable plungers and associated needles intended for medical use (such as use in syringe pumps). It specifies the dimensions, construction, performance and marking of these syringes.

	Min.		Max.	
Dosage	0.01 mL/h		1200 mL/h	
Measuring interval	10 s	30 s	10 s	30 s
Theoretical mass change per measuring interval	0.028 mg	0.083 mg	3300 mg	10000 mg

Table 1: *Representation of the theoretical mass changes per measurement interval (AAMI TIR-101 or IEC 60601-2-24).*

Which balances to use and how to set them

Selecting the appropriate balance is crucial for verifying the performance of infusion pumps, syringe pumps, container pumps, and volumetric infusion pumps in compliance with the IEC 60601-2-24 standard and the AAMI TIR 101 technical guideline. Three key parameters must be carefully considered:

- The **readability** or **resolution** of a balance is the smallest measurable graduation on the scale of a balance. It stands for the accuracy of the balance and indicates the smallest weight difference that can be determined or displayed. Smaller graduation values mean greater precision and the ability to measure smaller weight differences. A balance is categorized by its readabilty in precision balances (1 mg), analytical balances (0.1 mg), semi-micro balances (0.01 mg) and micro balances (0.001 mg). IEC 60601-2-24 does not recommend which balance should be used for which flow rate. However, the TIR 101 contains a table which gives recommendations for the resolution value for flow rates of less than 0.1 mL/h to more than 1000 mL/h.
- The **capacity** of a balance describes the maximum weight that it can accurately record. It defines the upper limit of the weight range in which the balance can maintain its accuracy and precision. Exceeding this capacity could lead to inaccurate measurements and even damage the balance. A high capacity is particularly advisable when testing infusion and syringe pumps. A higher capacity allows longer test periods (according to IEC 60601-2-24 up to 96 hours in some cases) without the test vessel having to be emptied or emptied less frequently.
- The **linearity deviation** of a balance indicates how accurately the measured values lie on a straight line over a certain weight range. It measures the balance's ability to provide consistent and accurate readings across different weights. Smaller linearity deviations mean better performance and accuracy in maintaining proportionality between the displayed weight and the actual measured weight.

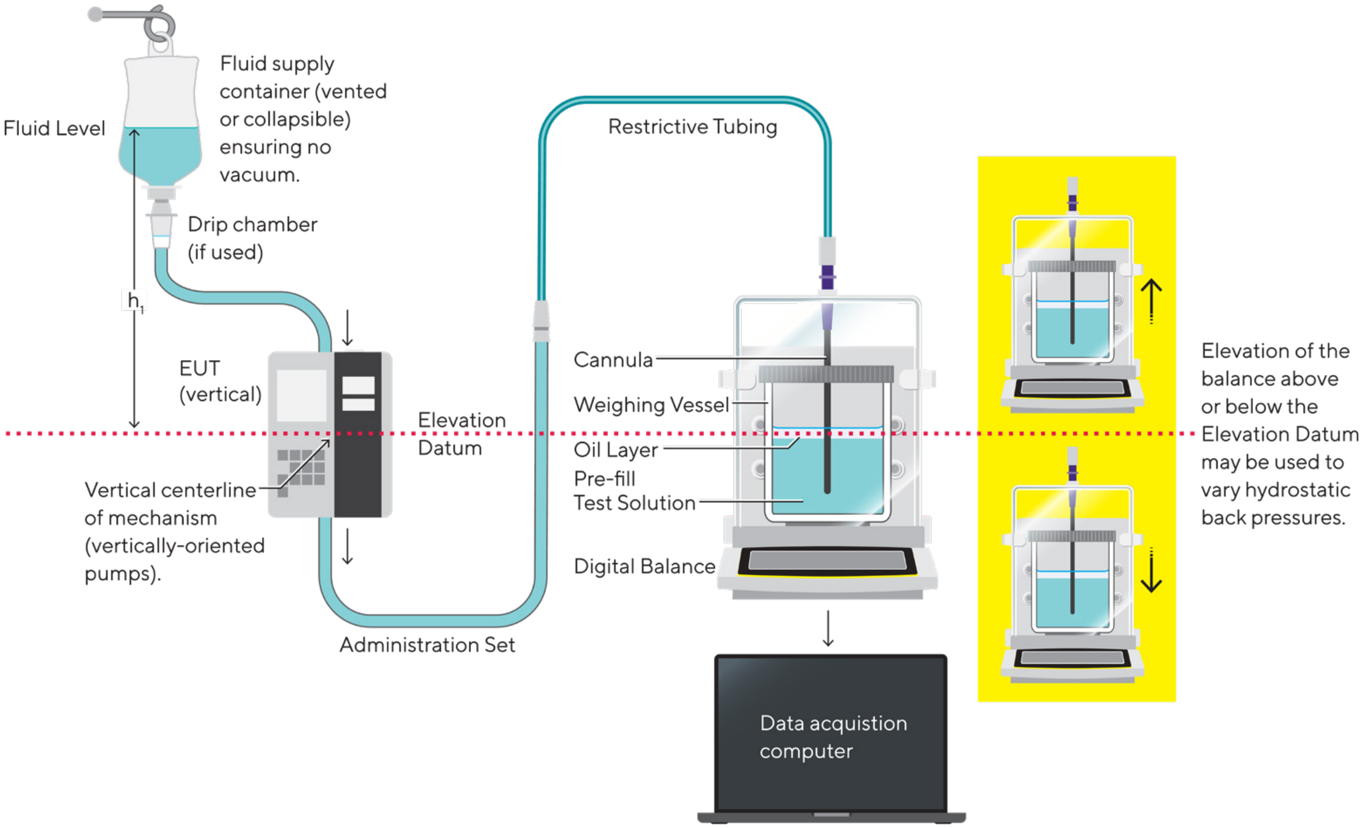


Figure 2: *Setup structure according to IEC 60601-2-24.*

Measurement Parameter and Range	Balance interval / g	Recommended Cubis® II Balance
Balance (Nominal capacity > 1000 mL/h)	0.001	Precision Balance **MCA5203S or MCA14202S (0.01 g)**
Balance (Nominal capacity 10 mL/h to 1000 mL/h)	0.0001	Analytical Balance **MCA524S**
Balance (Nominal capacity 0.1 mL/h to 10 mL/h)	0.00001	Ultra-High Resolution Semi-Micro Balance **MCA225S**
Balance (nominal capacity < 0.1 mL/h)	0.000001	Ultra-High Resolution Micro Balance **MCA66S**

Table 2: *Recommended balance intervals according to AAMI TIR-101.*

The Cubis® II platform offers a broad portfolio of different balances (from precision to High Capacity micro balances) that provide intelligent and precise solutions to overcome the challenges of checking dosing accuracy. The Cubis® II balances can deliver high resolution, due to a low readability and high capacity, with minimal linearity deviation in real lab conditions, which is of crucial importance for reliable measurements.

Each Cubis® II balance incorporates a monolithic weighing system that minimizes weighing drift caused by environmental changes such as temperature or humidity fluctuations. This feature is critical for ensuring the consistency and reliability of the weighing process.

In addition, all Cubis® II balances are 21CFR part 11 and EU Annex 11 compliant and offer a tamper-proof, time-stamped electronic log file with their test protocol. This enables the reconstruction of events related to the creation, modification and/or deletion of data records. The data can be easily displayed, filtered and exported. This will help for audit reports and simplify your investigations for experiments.

The balances recommended by Sartorius can be found in Table 2.

For the analytical, semi-micro, and micro Cubis® II balances, an optional built-in ionizer is available to neutralize electrostatic charges from the weighing vessel or the plastic components of the Equipment Under Test (EUT). This feature ensures that electrostatic effects do not compromise the measurement accuracy.

The draft shield of the balances offers additional protection. Beyond shielding the balance from air currents, the draft shield's electrically conductive coating transforms it into a Faraday cage. This design prevents external electrostatic effects from affecting the measurements inside the balance, thereby enhancing the accuracy of the weighing results.

Many sources of error – when measuring the flow rates of infusion pumps – can be eliminated from the outset with the help of Cubis® II balances. The effects or sources of error that still have an influence are discussed in the next chapter.

Sources of Error

In this section - with the help of the data provided by B.Braun - we will take a look at possible sources of error on the measurement side. The following possible sources of error are examined:

- Balance drift
- Temperature change
- Relative humidity change
- Dynamic weighing
- Displacement of the cannula in the sample solution
- Electrostatic

The various sources of error are interpreted in order to clarify how each effect can be minimized or interpreted in order to obtain a reliable result in the flow rate check.

Balance drift

Temperature and humidity changes can cause balance drift, an unwanted change in weight value without additional dosing. This phenomenon is influenced by environmental factors, with temperature fluctuations playing a significant role. Humidity and vibrations may also contribute to balance drift.

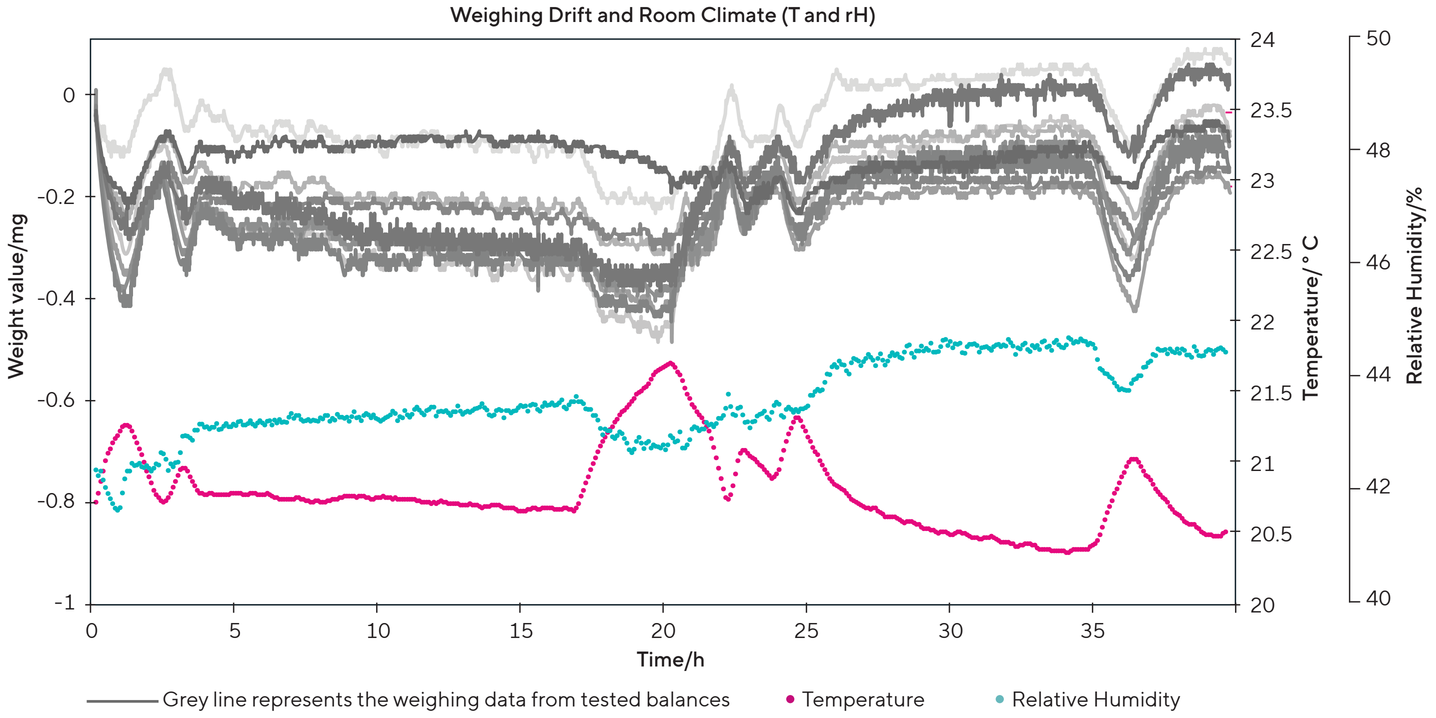


Diagram 1: *Plot of weighing drift [mg] and relative humidity [% rH] against time [h] for the Cubis® Semi-micro balances.*

It has been observed that the balance drift generally only has a significant influence on the flow rate measurement results at dosing rates of less than 10 mL/h.

B.Braun has intensively studied the balance drift of semi-micro balances (with 5-digit display) and generously shared the results.

Ten semi-micro balances were used for the study, which recorded a measured value every 30 seconds over a period of 40 hours. A weight of 135 g was used as a preload.

The results were plotted by showing the change in weight in milligrams (mg) on the Y-axis against time on the X-axis. It was noticeable that the curves on the different balances were remarkably similar, indicating that external influences were responsible for the observed changes and were not generated by individual balances.

Interestingly, the individual balances responded differently to the same perturbation, with the maximum observed change being around 0.4 mg (equivalent to 40 digits).

In order to quantify the relationship between the weighing drift and the flow rate to be determined, the measured values, which contained measurement errors resulting from the weighing drift, were converted to a flow rate of 1 mL/h.

The results are shown in Diagram 2 and illustrate that the influence of the balance drift in this particular case resulted in an error of 0.8 ± 0.4 %, which indicates that the balance drift plays a subordinate role in the measurement of flow rates.

In order to investigate the correlation between the indoor climate and the weighing data, the information from the indoor climate recording was linked to the weighing data in diagrams. First, we look at the room humidity.

A direct correlation can be seen here: the measured weight value increases with increasing humidity.

The temperature is shown as well in diagram 1 (magenta).

Interestingly, there is an opposite effect compared to humidity: as the temperature increases, the weight value decreases, and vice versa. The effect of the temperature change plays a much greater role than the humidity.

In summary, the greatest influence on balance drift can be minimized by maintaining a constant room climate (including humidity and temperature). In addition, it is advisable to use the balance close to its optimum working range and to avoid exposure to vibrations in the vicinity of the balances.

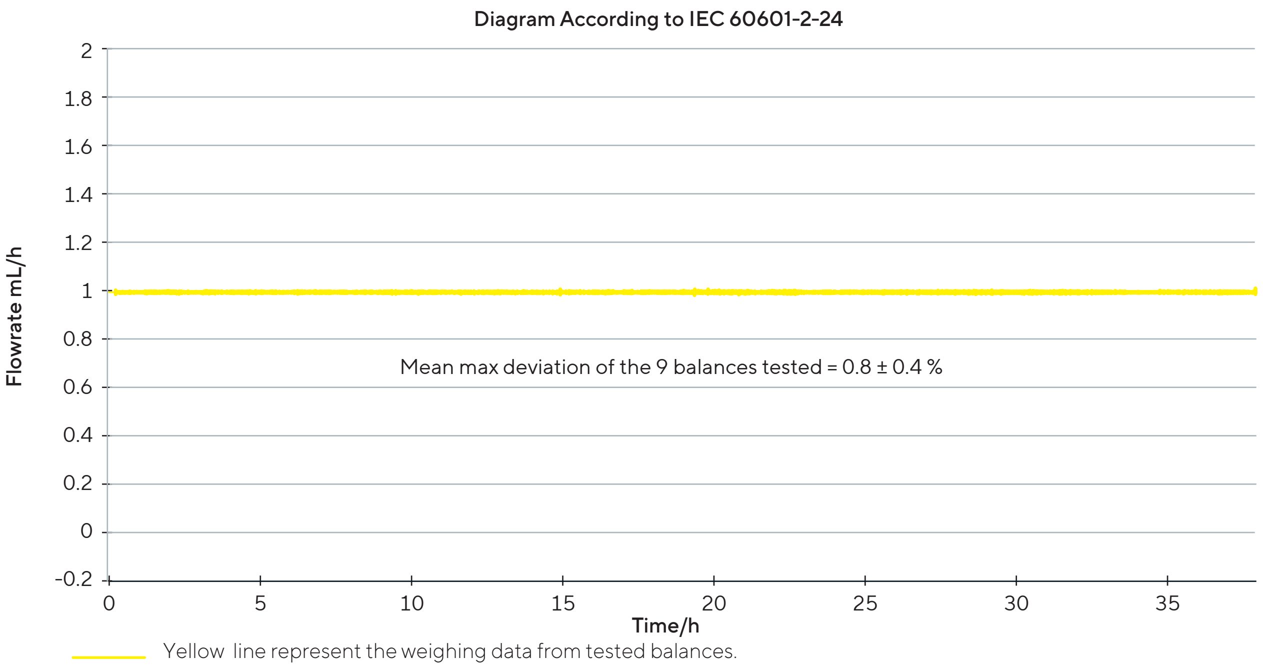


Diagram 2: *Influence of the weighing drift on a flow rate of 1 mL/h.*

Beyond that, the effect of balance drift (0.8 ± 0.4 %) could be illustrated. Under stable temperature and humidity conditions, the influence of balance drift is very small. However, it increases as soon as a change in temperature or humidity occurs.

It is important to emphasize that the Cubis® and Cubis® II balances have a monolithic weighing system, which reduces the balance drift to a minimum compared to conventional weighing systems with hundreds of individual parts (see diagram 3).

Quality of the Cubis® Balances in the dynamic weighing range

In order to gain a better understanding of the quality of the measurement results of the Sartorius Cubis® Semi-Micro balance in the dynamic weighing range, B.Braun carried out a test run with a high-precision pulsation-free pump (Cetoni Nemesys pump), a precision syringe (Hamilton glass syringe) and the Sartorius Semi-Micro balance, referred to as Setup 1.

The results of this test should show that a Sartorius Cubis® semi-micro balance can fulfill the required accuracy according to ISO 7886-2 and IEC 60601-2-24.

Setup 1	Setup 2
Cetoni® Nemesys syringe pump	
Hamilton® glass syringe	One plastic syringe
Sartorius Cubis® Semi-Micro Balance	

Table 3: *Explanation of the different setups.*

In addition, the Hamilton syringe was replaced with a disposable plastic syringe in a second experiment (Setup 2) in order to check the extent to which the accessories of the measurement setup can contribute to a measurement error.

Diagram 3 shows the flow rate curves for setup 1 in blue and for setup 2 in magenta.

The flow rate curve for Setup 1 is notably consistent around 1 mL/h. The average value over 100 minutes is 0.99 mL/h ± 0.02 mL/h (Table 4), indicating that the Sartorius Cubis® Semi-Micro balance meets the accuracy requirements of ISO 7886-2 and IEC 60601-2-24. The results confirm the balance's precision, even with dynamic weight changes. Conversely, the flow rate curve for Setup 2 exhibits greater deviations from the target flow rate of 1 mL/h. The mean value over 100 minutes for this setup is 0.96 mL/h ± 0.32 mL/h, reflecting the influence of different syringe materials on the flow rate accuracy.

Evaluation	Setup 1	Setup 2
Mean value	0.99 mL/h	0.96 mL/h
Standard deviation	± 0.02 mL/h	± 0.32 mL/h

Table 4: *Mean value and standard deviation of the flow rate of Setup 1 and Setup 2.*

The experiment demonstrates that the Sartorius Cubis® balances are capable of accurately reproducing measured values in scenarios involving dynamic weight change, as well as in flow rate checks as required by IEC 60601-2-24. It also highlights that deviations from the ideal flow rate are frequently affected by the ancillary equipment utilized in the measurement setup.

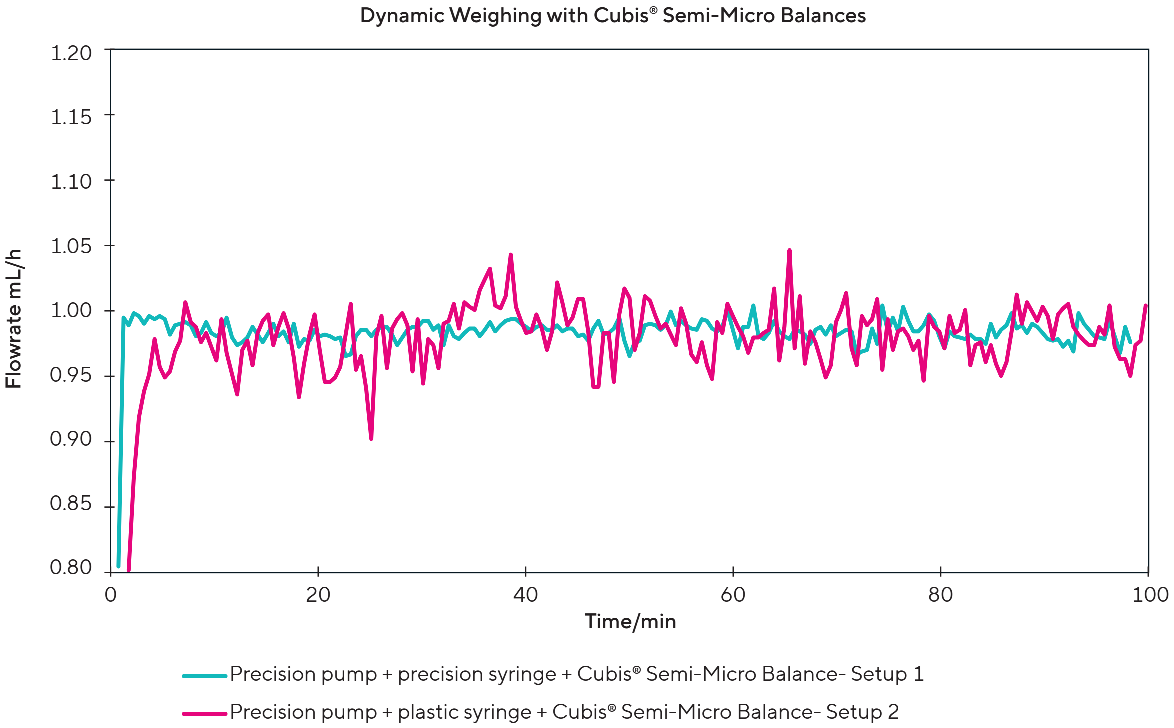


Diagram 3: *Checking the stability of a Sartorius Cubis® semi-micro balance using Setup 1 and Setup 2.*

Electrostatics

Electrostatic charges also pose a challenge when determining dosing rates. To minimize this source of error, the Cubis® II High-Capacity micro balances and Semi-micro balances are equipped with 4 ionization nozzles (marked yellow in Figure 3).

The positioning of the nozzles is chosen to ensure the most efficient way to discharge any type of vessels or samples within the draft shield, whether they are small objects such as filters or large objects such as volumetric flasks. These nozzles generate ions by applying a high voltage to a thin wire. The high voltage causes electrons to be released from the air molecules, creating positive and negative ions. These ions are then released into the air, where they come into contact with the charged sample. The ions transfer their charge to the sample, neutralizing electrostatic charge.
If you are interested in how electrostatics affect the weighing system, how they occur and what Sartorius does to avoid them, scan the QR-Code to get access to an Application Note dealing with all of the above mentioned.

Figure 3: *Cubis® II high-capacity microbalance MCA66S. The 4 ionization nozzles are marked in yellow.*

Displacement Through Cannula

One factor that should not be underestimated is the change in weight caused by the change in liquid level. As the liquid rises, the cannula is also immersed deeper and therefore has an influence on the weight value.

Figure 4 shows an example of how strongly the effect of immersion influences the weight value. A change of more than 0.264 g was generated by immersing the cannula.

Even if the measured value is taken every 30 or 10 seconds, and therefore the change in the liquid level in this interval is small, the change in weight has an influence on the delivery error A, which results from the values of the 60th and 120th minute.

There are various ways to calculate the effect of cannula constriction. Two are discussed here.

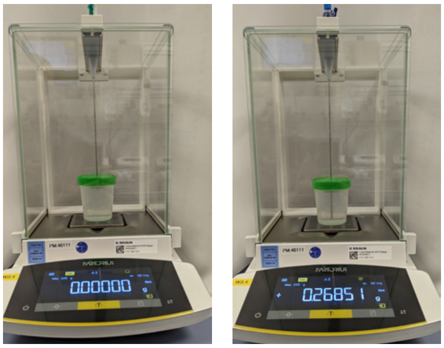


Figure 4: *Influence of the immersion of the cannula in the liquid on a Sartorius Cubis® II Semi-micro balance. Left: Cannula minimally immersed. Right: Cannula immersed deeper.*

The first approach is to completely fill the cannula and infusion set with liquid, attach it to a stand and immerse it only a few mm to the surface of the liquid in the vessel (Figure 4, left side). The weight value is then noted. The cannula is then lowered and immersed further into the liquid (Figure 4, right side). This second value is also recorded. The difference between the two readings is the error that needs to be corrected.

The second approach is mathematical. Here, the buoyancy correction (δm_{buoy}) is calculated using the final mass (l_L), the initial mass (l_E), the diameter of the immersed cannula and the diameter of the vessel used.

$$\delta m_{buoy} = \left((l_{\mathrm{L}} - l_{\mathrm{E}}) \cdot \left(\frac{D_{\mathrm{tube}}}{D_{\mathrm{tank}}} \right)^2 \right)$$

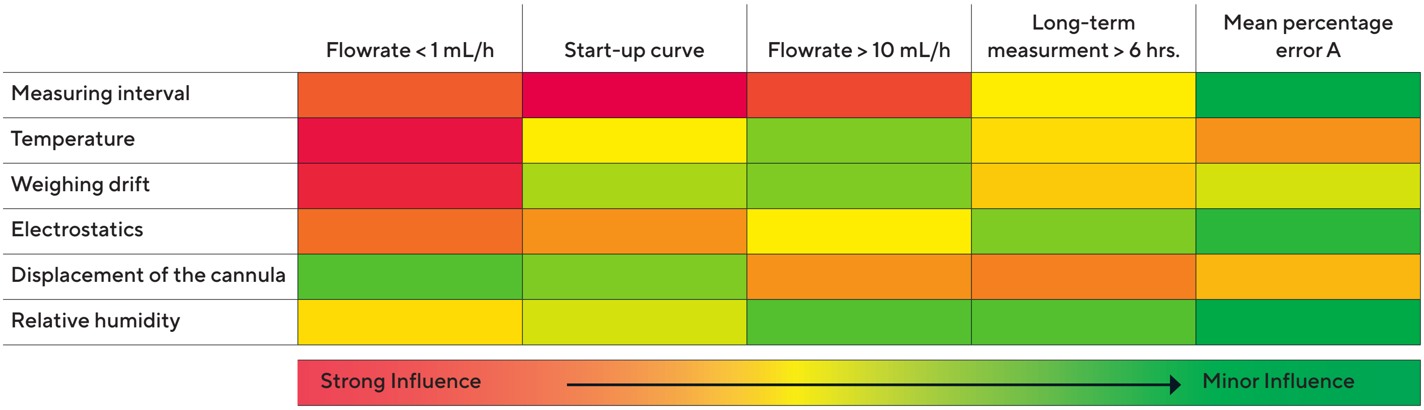
Figure 4 clearly shows that it makes sense not to neglect the displacement of the cannula in order to generate reproducible and valid measured values.

Summary

In the previous sections, various parameters were considered in detail, including temperature, weighing drift, electrostatics, cannula displacement, humidity and measurement interval (with an interval between readings of 30 seconds according to IEC 60601-2-24 and 10 seconds according to AAMI TIR-101).

In Table 5, the influence of all the parameters mentioned on the various test criteria of infusion pumps was examined and categorized. B.Braun's decades of experience were incorporated into the analysis.

The influence of a parameter is illustrated in Table 5 by the color of the corresponding field - green corresponds to a low influence and red to a strong influence. For example, it can be seen that the parameter "weighing drift" has a considerable influence on flow rates below 1 mL/h (red field). When selecting a balance, it is therefore advisable to ensure that it has a low balance drift for the investigation of low flow rates, for example by selecting a balance with a monolithic weighing system. Table 5 thus provides an overview of the influence of various parameters on the different test characteristics.



	Flowrate < 1 mL/h	Start-up curve	Flowrate > 10 mL/h	Long-term measurment > 6 hrs.	Mean percentage error A
Measuring interval	🟧	🟥	🟥	🟨	🟩
Temperature	🟥	🟨	🟩	🟨	🟧
Weighing drift	🟥	🟩	🟩	🟨	🟨
Electrostatics	🟧	🟧	🟨	🟩	🟩
Displacement of the cannula	🟩	🟩	🟧	🟧	🟧
Relative humidity	🟨	🟨	🟩	🟩	🟩

Strong Influence → Minor Influence

Table 5: *Influence of critical parameters on various test criteria.*

Conclusion

The combination of the particularly high resolution (up to one microgram) together with the high maximum capacity and the monolithic weighing system make the Cubis® II balances, in addition to a number of other important advantages such as the built-in ionizer and the electrically conductive draft shield, the ideal test equipment for determining the dosing rates in accordance with IEC 60601-2-24 and TIR 101.

With the help of B. Braun's measurement results, it was possible to show that influencing factors such as temperature and/or relative humidity have a marginal effect on the result of the dosing rate. In addition, a high-precision test set-up could be used to determine that the Cubis® II semi-micro balances meet the quality requirements of IEC 60601-2-24 and ISO 7886-2.

The collection of data has helped us to optimize the Cubis® II balances for this application in order to generate fast and reliable measured values with this dynamic weighing value change. Thanks to the experience gained in this application, Sartorius is able to respond quickly and competently to the challenges of infusion and insulin pump manufacturers. This helps to make the testing of dosing pumps more reliable and safer (simplifying progress).

Note

The application note was created by Dieter Peissig (B. Braun, expert for active medical devices) and Lucas Foerster (Product Manager Lab Weighing Applications). The data shown and analyzed in this application note was kindly provided by B.Braun (Dieter Peissig).

Cubis® II balances: High resolution, high capacity, monolithic weighing system.

Optimal for dosing rate determination according to IEC 60601-2-24 and TIR 101.

Influencing factors such as temperature and humidity have little effect on dosing rates.

Cubis® Semi-micro balances meet the quality requirements of IEC 60601-2-24 and ISO 7886-2.

Cooperation with B.Braun enabled optimization for reliable measured values with dynamic weight changes, especially for infusion and insulin pump manufacturers.

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