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Metrology in health: challenges and solutions in infusion therapy and diagnostics

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Abstract: The significance of Metrology in infusion therapy and diagnostics, both critical in health care safety and quality, is discussed in this article. Although infusion therapy is the most used form of drug administration, infusion errors are often made with reported dramatic effects in different applications, especially in neonatology. Adverse incidents, morbidity, and mortality have often been traced back to poor or inaccurate dosing. For critical infusion applications to vulnerable patients, well-controlled medication administration might be accomplished by improved dosing accuracy, traceable measurement of volume, flow, and pressure in existing drug delivery devices and in-line sensors operating at very low flow rates. To this end, the contribution of recently upgraded metrological infrastructures in European Metrology Institutes to a safer infusion therapy in health care is described in detail. Diagnostics, on the other hand is a sector characterized by rapid developments further triggered recently by the necessity for the management and prevention of infectious diseases like COVID-19. In this context, the impact of metrology in future large-scale commercialization of next generation diagnostics (e.g., point-of-care) is highlighted. Moreover, the latest contributions of Metrology in the development of traceable testing methods and protocols to ensure the sensitivity and accuracy of these devices are described.

Keywords: diagnostics; dissemination; health; infusion; metrology; microfluidics; standards.

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Introduction

Health care quality is a true measure of social welfare while it relies not only on financial resources but on scientific excellence and technological progress as well. Undoubtedly, the validity of this concept has been proven during the past two years where the global scale dimensions of Covid-19 pandemic have demonstrated in the most dramatic terms the importance of the quality of health care services in saving human lives. In intensive care units (ICUs) in particular, the endurance of health care systems is put under heavy stress. Moreover, additional ICUs, or regular care units provisionally modified to serve as ICUs, are needed while the medical staff required for their operation remains in most cases practically unchanged while being exhausted by the unprecedented working conditions. Nevertheless, ICU staff must follow drug administration protocols and supervise the drug delivery to patients often under severe stress conditions prone to procedural errors. Moreover, under pandemic conditions hospitals have limited resources to disposables and often the care personnel are forced to deviate from strict drug administration protocols. Such practices, however, imposed by emergency conditions like COVID-19 pandemic, when combined with lack of awareness, may cause severe implications to patients often decisive for their lives.

Metrology and drug delivery

One of the most common forms of therapy in ICUs is infusion therapy, which implies that drug delivery is critical in this sector. The widespread application of infusion therapy in health care is recently argued to be linked to underestimated infusion errors often made even under ideal working conditions, with reported often serious effects in different applications in the health sector, especially in neonatology [1, 2].

Various existing infusion technologies, from the early gravity-driven drug delivery systems to the newer technologies involving syringe, electromechanical or peristaltic pumps they all can be thus subjected to human errors or operational faults with potentially dangerous effects on the patient's health. There have been numerous injuries, deaths and adverse health effects in the past associated with the use of infusion pumps which have highlighted significant safety

issues [2–4]. For example, approximately 80–90% of hospitalized patients in the UK receive intravenous (IV) therapy using infusion devices to deliver medication, fluids, and nutrients into patients [5, 6]. According to recent studies intravenous medication is associated with the greatest risk of medication errors, the negative effects of which are difficult to mitigate due to the immediate distribution into the patient's blood stream [7]. Among these errors occlusion alarms are considered to be high-priority alarms while they are intended to avoid the clinical consequences of extravasation (erroneously delivered drug outside the vessels which may cause tissue necrosis), non-delivery at low flow rates of critical medications and embolism. Infusion for neonates and children, on the other hand, is particularly challenging due to the limited number of venous access sites, the small bore of catheters, and small drug volumes [8]. Highly concentrated solutions of high-risk drugs are commonly delivered at low infusion rates, in order to avoid volume overload but through the same line, thus increasing the risk of drug incompatibilities [9]. According to studies 13.7% of simultaneous drug infusions in Pediatric ICUs and 74% in Neonatal ICUs are incompatible or have not been tested [10, 11]. Occlusions because of drug incompatibilities can have potentially harmful consequences such as pulmonary embolisms and/or granulomas or systemic inflammatory response syndrome [12–15]. There have been no studies evaluating if drug incompatibilities (e.g., due to different fluid properties as viscosity) might be involved in the occurrence of occlusion alarms. Therefore, it is extremely important that the delivery of medication and other fluids is precisely controlled over time and the delivered dose is accurately known, especially for critical drugs at high concentration [16, 17].

Although patient monitoring gives an indication of possible dosing errors, the patients' vital signs are influenced by multiple parameters and therefore give only indirect information on the quality and quantity of drug delivery [18]. Similarly, infusion monitoring as indicated by the infusion device alarm frequency and duration is highly dependent on the type of fluids administered but, unfortunately, also on care area, time of day, day of week, shift, personnel awareness, maintenance, and calibration status, etc., [19]. In multi-infusion applications the actual dosing conditions, beyond the mixing point in the infusion line, are not known. They are affected by several parameters with undefined inter coupling (dead volume, occlusion, air in line, etc.) and might deviate from the intended drug dose. Hence, the accuracy of flow rate set point adjustments, based on the patient's vital signs and/or registered alarms, which constitutes the established practice in ICUs, is insufficient to ensure the safe and accurate delivery of drugs to patients. This situation is further worsened when it is combined with conditions of high working stress as in the current global COVID-19 pandemic.

The risks in infusion therapy may be attributed to four major reasons:

- Lack of reliable quantitative actual data on drug dosage available for all delivered drugs simultaneously.
- Lack of awareness of the health care personnel and/or manufacturers of infusion systems.
- Incomplete understanding of the operation of the complete drug delivery system.
- Lack of a proper metrological infrastructure especially for low drug delivery flow rates.

These deficiencies of infusion therapy can be effectively remediated using state-of-the-art knowledge acquired during recent developments in Metrology. Innovative progress and upgraded metrological infrastructure can provide drug delivery device manufacturers with reliable information on the actual "in use" performance of these devices. Consequently, manufacturers will be able to determine the expected drug dose at the point of entry in the patient preventing incorrect drug administration and thus significantly improving patient safety.

The role of metrology in the development of microfluidic diagnostic devices

The worldwide spread of COVID-19 infection during the past years that results in the death of millions of persons, has dramatically affected health, economy, and welfare on a global scale. At the same time, the current pandemic status, characterized by fast and unpredictable changes due to the appearance of new and more infectious virus variants, has demonstrated in the most emphatic way the importance of developing reliable diagnostic tools for the timely prevention and monitoring of the spread of the SARS-CoV-2 virus infection. To this end, the fast development of microfluidics in conjunction with the progress in micro electro-mechanical systems (MEMS) technology and nanotechnology offer the technological basis for the production of a series of portable, miniaturized, low-cost devices for the so-called point-of-care (POC) diagnostics (also known as on-site, near-patient, bedside testing) of various infectious diseases. Recent progress in the development of such POC devices, including lab-on-a-chip, organ-on-a-chip, lab-on-a-disc and microfluidic analytical devices offers several advantages compared to the labor- and time-consuming traditional diagnostic methods. Among them, faster diagnostic speed, better sensitivity and specificity, lower cost, higher efficiency, independence of

expensive lab equipment and consumables, ability of on-site detection, minimal consumption of reagents are some worth noticing [20–23].

During the last decade, microfluidics has shown a phenomenal growth. So far, quality production of microfluidic devices has been established mainly based on the manufacturer's expertise, without reliance on well-established calibration procedures or standards that could have streamlined and accelerated production. Despite the expected impact of microfluidics (societal, health, well-being, environment), success stories are rare in comparison with the number of laboratory developments. The main reason is the gap between laboratory microfluidic devices (home-made chips and connections, customised test protocols, materials not compatible with high volume production, etc.) and a reliable and reproducible product.

Stakeholders from industry, academia and government have recognised the need for globally accepted metrology standards for microfluidic devices and as a result a working group of the International Standardization Organization (ISO/TC48/WG3) was established to address this underpinning requirement [24].

Measurement accuracy and traceability of microfluidic devices is critical to improve healthcare, including medical diagnostics and drug development sectors. Assuring the reliability of various types of microfluidic and POC diagnostics in global health crisis like the one caused by SARS-CoV-2 virus, is of vital importance for the supervision and management of the pandemic. This, in turn, can only be guaranteed by appropriate state-of-the-art metrological infrastructures which are capable to provide traceable testing methods, appropriate measurement protocols and guidelines to facilitate the uptake of microfluidic devices and the large-scale manufacturing of new generation diagnostics.

Within the European Metrology Program for Innovation & Research (EMPIR) a consortium of several national NMIs, universities and manufacturers has proposed the development of novel metrological infrastructures suitable to provide solutions and support to this critical problem of our health care systems. The recent metrological developments and the impact of these initiatives as they have been realized in the framework of the EMPIR research projects are described in the following paragraphs.

EURAMET EMPIR research projects

Infusion therapy research

In 2004, a metrological effort to thoroughly understand and improve infusion defined the crucial performance aspects of an infusion system and established the importance of a patient receiving the right dose of the required substances in a given time [25]. This latter aspect of drug infusion is considered critical and has been identified as the most common administration error occurring in hospitals [7]. The situation is further complicated in multi-infusion setups (simultaneous administration of drugs by multiple infusion pumps) where the understanding and investigation of the delivered doses are not easy tasks, while these setups might represent the most critical medical treatments in ICUs. The first steps towards better knowledge of the real flow rates and concentrations of the drugs that are delivered to the patients' blood stream were made in EMRP JRP HLT07 MeDD project. The aim here was to prevent drug administration errors by upgrading calibration services and improving knowledge transfer to the end-user. The infrastructure, consisting of traceable calibration services for drug delivery systems for flow rates down to 100 nL/min was developed in five European National Metrology Institutes (NMIs) [26–29]. Syringe pumps and peristaltic pumps with accessories were tested [30]. The effects of variations in several physical parameters in infusion systems were incorporated in a predictive model describing a method for calculating the deviations from the intended drug dosages at the outlet of the infusion line, i.e., just before entering patient's bloodstream [31].

In order to realize the uptake of the key outputs of EMRP JRP HLT07 MeDD, thereby aiming to reduce the number of adverse patient incidents caused by multi-infusions, a new project 15SIP03 was funded by EURAMET in 2016. This project developed, in close cooperation with the European Society of Intensive Care Medicine (ESICM), an "Infusion Pumps" e-learning course on the risks and best practices of infusion technology that is freely available to the public [32]. It was launched in 2017 during the ESICM annual conference and is now part of the ESICM Academy, making it directly available for the relevant community. The e-learning will remain freely available to the public ensuring its further impact after completion of the project. Another outcome of the project was the contributions to the revision of ISO 7886-2 "Sterile hypodermic syringes for single use – Part 2: Syringes for use with power-driven syringe pumps" [33] in terms of technical instrumentation requirements and test methods descriptions and IEC 60601-2-24 "Medical electrical equipment – Part 2–24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers" [34]. Results from the EMRP JRP HLT-07 MeDD research project were presented to the ISO TC84/WG11 working group and IEC 62D/MT23 subcommittee. Both projects are already concluded.

In 2019 another EMPIR project, entitled "Metrology for Drug Delivery: MeDD II" [35], was launched with the aim to go beyond the research conducted in EMRP JRP HLT07 MeDD by investigating the influence of the fast-changing flow rates that result from a change in the pre-set flow rate in infusion pumps.

Within this project new traceable techniques for generating and measuring the response or delay time of drug delivery devices in relation to changes in flow rate, from 5 nL/min to 100 nL/min are being developed [36–39]. The mixing behavior of the administered drugs as a function of their fluid properties (density, viscosity) is also being investigated.

In particular, the upgrade of the existing flow facilities and know-how of the partner NMIs enables the traceable inline measurement of the dynamic viscosity of Newtonian liquids, representative for the flow behavior of a vast amount of used medication fluids, as a function of the flow rate and pressure drop, with a target uncertainty value of 2% (k=2) [40]. These investigations will help to prevent dose fluctuations and they will improve occlusion alarm reliability. The measurement uncertainty is validated by measurements with Newtonian reference liquids with traceable dynamic viscosity reference values. Additionally, tests with non-Newtonian liquids, representative for flow behavior of nutrients or blood substitutes, will be performed to prove the concept. Transfer standards for the in-line measurement of dynamic viscosity and other physical properties of liquids are calibrated to be used for flow measurement and determination of the mixing behavior of different fluids.

Novel calibration procedures for existing medical flow devices (e.g., infusion pumps, pain controllers and infusion pump analyzers) are under development and validated by traceable primary standards with a target uncertainty value of 2% (k=2) for a range of 5 nL/min up to 600 mL/min [41]. In addition, a proof of concept on-chip microfluidic pump for the use as transfer standard in drug delivery and organ on-a-chip applications has been developed for flow rates lower than 100 nL/min [42].

A multi-infusion pilot study system containing check valves will be designed and developed with several options for testing how liquids with different viscosities mix and flow and how this affects drug concentration. The flow rates and pressures will be traceably calibrated in all infusion lines, as well as at the outlet of the syringe pump, in order to analyze the effects of pressure-equalizing devices and to detect occlusion phenomena and bad mixing configurations.

The knowledge gained in this project will enable the prediction models developed in EMRP JRP HLT07 MeDD to be upgraded by adding the effects of check valves and some of the physical properties of the flowing fluids (e.g., viscosity). This new model will reflect a more realistic mixing behavior in the infusion lines, and it will be validated by experimental results.

Within the EMPIR MeDD II joint research project, great efforts have been put towards the direction of raising awareness within the medical world about the issues discussed in this article. Diverse material has been published in the official site of the program (www.drugmetrology.com) in the form of newsletters, e-learning training material, posters and flyers, videos, Congress and Workshops publications, Calibration guides, etc., contributing to the overall improvement of the quality of health care. The project also encourages collaboration, knowledge sharing, dissemination of best practices, and the standardization of measurement uncertainty determination. The knowledge gained can be supplied to relevant International Organization for Standardization (ISO) technical committees (TC). This further supports the development and improvement of drug delivery devices.

The knowledge acquired within this European joint research project and related technological infrastructure developments are expected to have a major impact to the operational and safety aspects related to the use of infusion in drug administration in ICUs ultimately improving the overall quality of health care.

The dissemination of the work performed within the three research projects described above, created awareness in health care sector and manufacturers about the importance of metrology. The e-learning course is in constant improvement, several standards used by manufacturers were revised based on the project's results, mainly ISO 7886-2 and TIR101 and many papers and reports are available in the webpage of the project (www.drugmetrology.com) with more than 200 visitors per month. Several online and onsite workshops have been organized so far, reaching more than 500 persons that are working in hospitals or in clinical environment. Finally, a simulator for the multi-infusion process will be available at the end of MeDDII project.

Microfluidics related research

Measurement accuracy and traceability of microfluidic devices used in medical diagnostics and drug development is critical to improve healthcare. Recently, the COVID-19 pandemic accelerated the development of novel testing kits using microfluidics with integrated sensing components. The rapid production of, low-cost high-volume point-of-care (POC) tests that can be distributed to patients for swift detection of viruses clearly demonstrates the role and importance of microfluidics in tackling future healthcare crisis.

However, standardization of performance characteristics is needed for the different classes of microfluidic components, including test conditions, measurement protocols and operational guidelines.

To this end, a new EMPIR EURAMET research project entitled "Metrology Standards in Microfluidic Devices, MFMET" in the framework of HORIZON has been launched in June 2021 with main goal to meet the above urgent needs in the microfluidics industry and its novel applications, among others, in diagnostics.

The project will provide manufacturers with the necessary knowledge background to establish robust quality control procedures and provide product datasheets with standardised terminology for comparison with other products. Laboratories will have more confidence in using commercial products and to make comparisons on components as to the suitability for applications and connection to in-house fabricated devices, reducing thus costs and downtime. Complete integrated microfluidic systems will be tested with the standardised testing protocols as used by manufacturers and, thus, increasing the success rate of a technological transfer.

This project will directly benefit society because it will accelerate innovation, by allowing academia, end users, industry (health, pharmaceutical) and microfluidics devices manufacturers to develop and/or use standardized products with clear, traceable, and controlled specifications.

Improvements in the accuracy of instruments and devices will reduce manufacturing costs while improving quality and usability. This will be achieved through the wider uptake of traceable calibrations & test protocols and by improved knowledge of how to calibrate instruments involved in the whole manufacturing process of microfluidic devices, from the early stages of chip and prototype designs to end-user commercially available diagnostic tests [43].

Harmonization in terminology

The knowledge gap in supportive metrological infrastructure for infusion technology so far is accompanied by a rather outdated standardization system -if non existing in certain cases-which, besides being sometimes more than 10 years old, is not suitable to give guidance for recent infusion technology developments (microfluidics, implantable infusion pumps, etc.). Moreover, inconsistencies occasionally exist between standards used in the medical sector (e.g., infusion pumps) and established metrological terminology and practice as described e.g., in the International vocabulary of metrology – Basic and general concepts and associated terms (VIM), 3rd edition, JCGM 200:212 [44]. This fact may cause further confusion in applying good practices during use of medical devices within the health care system and contributes to limited awareness often prevailing among operators of medical devices including infusion pumps.

A typical example of lack of harmonization in applied practices and terminology related to medical equipment is the definition of the systematic error of a measuring instrument. In metrology (VIM) and medical standards (e.g., IEC 60601-2-24:2012, Medical electrical equipment – Part 2–24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers), respectively, two different definitions are applied [34, 44]. Comparing these two definitions, the systematic error of a measuring instrument not only carries opposite sign but also has different amplitude for specified calibration parameters. Consequently, corrections, usually applied to the indications of medical measuring instruments using the systematic error, might lead to different results depending on the interpretation of the calibration data as analyzed in detail in the following paragraph.

The calibration results of medical devices and their interpretation must therefore be understood by the end users as this is a prerequisite for establishing the recommended drug dosing administration to the patients in the drug delivery devices. If there is no common understanding of the error definition for a given device between manufacturers, metrologists and the end users, the appropriate corrections to be applied to the instruments in order to deliver the accurate drug dose might be wrong, compromising thus the administered drug dose and probably the condition of the patient.

Measurement error: two opposite definitions in metrology standards and medical standards

Fundamental definitions and concepts in metrology are established in the International vocabulary of metrology – Basic and general concepts and associated terms (VIM), 3rd edition, JCGM 200:212 [44] while the foundations of the estimation of measurement uncertainty are thoroughly described in GUM–Evaluation of measurement data–Guide to the expression of uncertainty in measurement (GUM), JCGM 100:2008 [45].

A metrology vocabulary, as VIM, is meant to be a common reference for scientists and engineers — including physicists, chemists, medical scientists — as well as for both teachers and practitioners involved in planning or

performing measurements, irrespectively of the level of measurement uncertainty and irrespectively of the field of application. It is also meant to be a reference for governmental and intergovernmental bodies, trade associations, accreditation bodies, regulators, and professional societies.

According to these two fundamental metrology standard documents [44,45], the measurement error is defined as:

a. *measurement error:* measured quantity value minus a reference quantity value (definition 2.16 [44])
b. *error (of measurement):* result of a measurement minus a true value of the measurand (definition B.2.19 [45])

Related to this, we can also define the relative measurement error as: error of measurement divided by a true value of the measurand (definition B.2.20 [45]).

Expressing the relative error in formula, 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:

$$A_{\text{Met}} = \frac{100\,(r - Q)}{Q}\,(\%) \tag{1}$$

where: Q is the reference flow rate determined by the reference measurement method (e.g. gravimetric method). r is the flow rate set at the instrument under calibration (e.g., 1 mL/h). A is the relative flow measurement error or systematic error.

One of the standards applied for medical electrical equipment is: IEC 60601-2-24:2012, Medical electrical equipment – Part 2–24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers [34].

The overall mean percentage flow error (relative measurement error) is defined in equation (5) in Section 201.12 in IEC 60601-2-24:2012 as:

$$A_{\text{Med}} = \frac{100\,(Q - r)}{r}\,(\%) \tag{2}$$

where: Q is the reference flow rate determined by the reference measurement method (e.g. gravimetric method). r is the flow rate set at the instrument (e.g., 1 mL/h). A is the relative flow measurement error or systematic error

According to the two definitions given in equations (1) and (2), the systematic error as defined in metrology and medical standards, respectively, not only carries opposite sign but also has different amplitude for the same values of r and Q. Consequently, corrections usually applied to the indications of measuring instruments using the systematic error might lead to different results depending on the interpretation of the data.

The calibration of a flow measuring instrument (e.g., syringe pump) gives the measurement error for a specific flow rate with respect to the reference flow rate as realized by the reference measurement method. In general, the measurement results of the instrument are then corrected with respect to their measurement errors. Using the following definitions [45]:

a. *corrected result:* result of a measurement after correction for systematic error (definition B.2.13)
b. *uncorrected result:* result of a measurement before correction for systematic error (definition B.2.12)
c. *correction:* value added algebraically to the uncorrected result of a measurement to compensate for systematic error (definition B.2.23)

Note 1: the correction is equal to the negative of the estimated systematic error (definition B.2.23)

Therefore, the correction applied according to [45] is:

$$\textit{Corrected result} = \text{uncorrected result} - \text{systematic error}$$

$$\textit{Corrected result} = \text{set flow rate r} - (\text{set flow rate r} - \text{Q})$$

where (set flow rate r–Q) is the systematic error

Depending on the definition of the systematic error, A, according to equation (1) or (2), the correction of the instrument indication is added algebraically with a different sign:

Equation (1) leads to:

$$\begin{aligned}\textit{Corrected result} &= \text{uncorrected result} \\ &\quad - \text{systematic error} \\ &= \text{set flow rate r} - (\text{r} - \text{Q})\end{aligned} \tag{3}$$

Equation (2) leads to

$$\begin{aligned}\textit{Corrected result} &= \text{uncorrected result} \\ &\quad + \text{systematic error} \\ &= \text{set flow rate r} + (\text{Q} - \text{r})\end{aligned} \tag{4}$$

If the measurement error or the relative measurement error is taken from a measurement report or a calibration report, the exact definition of the measurement error or the relative measurement error has to be known. The outcome of the correction applied to the uncorrected result will depend on that definition and obviously will affect the way the measuring instrument will be operated in use. If Equation (4) resulting from the error definition in the medical standard is used to correct for the systematic error and the systematic error is taken from a calibration certificate, where the systematic deviation has been

calculated according to Equation (1), then the correction will be wrong:

$$\begin{aligned}\text{Corrected result} &= \text{uncorrected result} + \text{systematic error}\\ &= \text{set flow rate r} + (\text{r} - \text{Q})\end{aligned}$$

As example, we take the reference flow rate Q being measured at 20 mL/h, when the instrument flow rate is set to 19 mL/h. The correct correction should lead to the flow rate of 20 mL/h, when the instrument is set to 19 mL/h. In the example above using equation (1) and equation (4) instead of equation (1) and equation (3), we will correct the set flow rate of 19 mL/h to 18 mL/h. The correction was done algebraically with the wrong sign and the corrected flow rate is far away from the true flow rate.

These two opposite definitions of the systematic error might cause confusion in the interpretation of various kinds of calibration reports or even lead to application of different or erroneous corrections in the indications of various instruments affecting eventually their proper operation in use. In critical operations like the administration of drugs in patients using infusion devices, a misinterpretation of the systematic error and subsequent corrections might lead to erroneous drug administration protocols with possible adverse effects on the patient's health.

Standardization in drug delivery

The basis of effective standardization is consensus secured by the diligent accumulation of data, navigating the interdependencies of linked standards, and satisfying multiple direct and indirect interests. Ahead of a scheduled revision and despite clear potential for harm to patients from inaccurate dosing from infusion pumps, standards makers had not completely embraced the benefits of best practice flow metrology in device calibration procedures. The regulation (EU) 2017/745 specifies essential safety and performance requirements without mandating specific technical solutions [46]. Nevertheless, manufacturers are advised to adapt on a voluntary basis the International Electrotechnical Commission (IEC) standard IEC 60601-2-24:2012 "Particular requirements for the basic safety and essential performance of infusion pumps and controllers" [34]. This standard is now under revision as the technology and data analysis have been improved but is not yet reflected in the standard. There are other relevant standards that give information regarding testing of drug delivery devices. Indicatively, ISO 7886-2 – "Sterile hypodermic syringes for single use–Part 2: Syringes for use with power-driven syringe pumps" and AAMI TIR 101 – "Fluid delivery performance testing for infusion pumps" are worth mentioning [33]. They were published recently and already include the new developments and information obtained by the projects MeDD and MeDDII. Both projects support the development of the above-mentioned standards by providing robust calibration procedures, equipment, and conditions, capable of ensuring accurate drug delivery results and reduced risks of adverse patient incidents. This is fundamental for users, calibration laboratories and manufacturers.

General legislation for medical devices is in place but there are not specific legislative documents for each instrument, especially the ones with a measuring function that needs to comply with requirements for maximum permissible errors. Therefore, several interventions to EU authorities have been made explaining the importance of traceability in medical instruments and the need for harmonization of maximum permissible error definition for drug delivery devices.

Maintenance and calibration of medical devices

Regular calibration and maintenance of infusion pumps enables the identification of any issues with equipment and ensures the appropriate operational status of the instruments for correct dosage to patients, minimizing thus potential safety risks. Appropriate maintenance protocols, typically provided by infusion pump manufacturers should be strictly followed by the authorized technical personnel at the recommended service intervals. It is important for the personnel to be acquainted with the performance specifications and the metrological characteristics of this equipment to guarantee the reliable function of the infusion system [32, 47].

Regular maintenance schemes of this type of medical equipment cannot substitute the need for regular calibrations. A common calibration method to determine the flow rate error of an infusion pump involves the use of an infusion device pump analyzer, which can give information on the flow rate, volume, and pressure. The analyzer serves as a master calibrator to quickly test infusion pumps performance; however, it is important that it is calibrated regularly. These infusion device analyzers are used in the maintenance departments of the hospitals.

The gravimetric method (Figure 1) is used extensively in the laboratory by National Metrology Institutes (NMIs), accredited laboratories and by manufacturers as a very accurate way to calibrate pumps and flow meters. This method practically uses a balance to weigh the mass of the liquid that

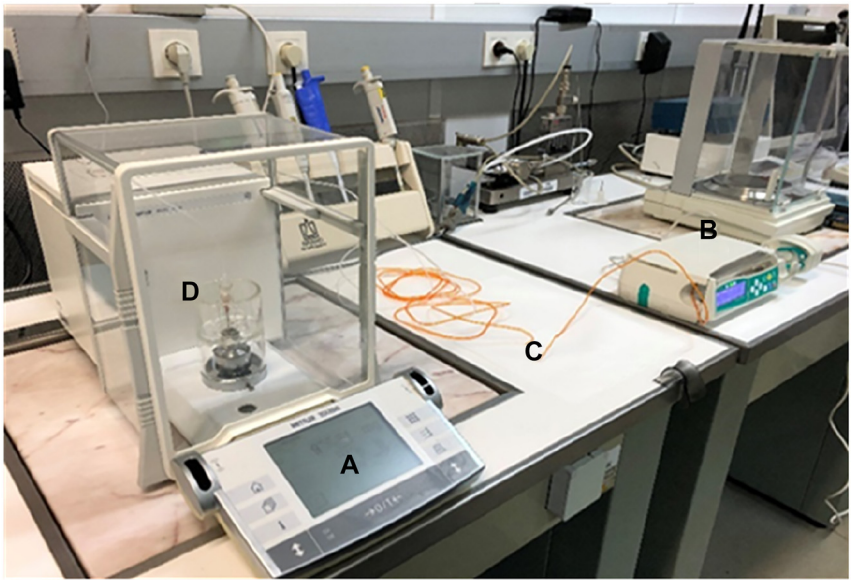

Figure 1: Set up for the gravimetric calibration of a syringe pump, where A is the balance, B is the syringe pump, C is the infusion line and D is the evaporation trap were the weighing beaker is included.

is delivered by the pump into a weighting vessel on the balance. As the density of the water is known at the temperature of the test (usually around 20 °C), it is used to calculate the volume of liquid delivered (volume = mass/density). The volumetric flow rate is determined from the quotient of the total liquid volume and the time taken for the delivery of that liquid [28]. This gravimetric method is also described in the standard IEC 60601-2-24:2012 [34], although a lot of details about the measurement procedure and uncertainty are not mentioned there but can be found elsewhere [48].

This technique has been successfully used for flow rates above 1 µL/min to cover medical equipment such as syringe and peristaltic pumps used in hospitals. However, there are limitations and complexities in extending the technique down to ultra-low flow rate applications. Therefore, several techniques have been developed in the scope of project MeDDII, mainly optical and displacement methods [28, 38].

Summary and outlook

Best practices in infusion technology are being established by recent state-of-the-art metrological research aiming to improve the reliability of drug administration to patients, minimize the incidence of infusion errors in critical treatments in ICUs and raise awareness within health care community about the potential infusion risks. Reliable knowledge on the actual dose delivered to patients is now supported by recently upgraded metrological infrastructure, simulation models and know-how.

At the same time, the metrological infrastructures developed within the European Union's Horizon 2020 EMPIR research and innovation program may guarantee traceable testing methods, appropriate measurement protocols and guidelines for the uptake of microfluidic devices and their application in large scale manufacturing of new generation diagnostics. The development of such novel, accurate, low-cost high-volume point-of-care (POC) diagnostic kits, based on microfluidics, has been imposed and accelerated by the COVID-19 pandemic and constitutes a powerful tool for the timely prevention and monitoring of the spread of the SARS-CoV-2 virus infection or any other future sanitary crisis.

Finally, critical spin-off effects of the recent metrological research target to the development of up-to-date standards for microfluidics and updated guidance documents for maintenance and calibration of medical equipment. The developments described in this article and their impact in infusion technology and microfluidic based diagnostics demonstrate the importance of Metrology on the quality and safety of health care and its future potential in critical sectors.

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