Guest Editorial

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Medical flow and dosing measurement metrology in drug delivery

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"The flow of liquids inside or outside the human body plays a key role in medical technology. Safety and reliability of many medical devices or their components, e.g. dialysis machines, infusion devices, or liquid-handling systems for in-vitro-diagnostics, require safe and reliable dosing of liquids" [1]. This citation from the editorial of the first special issue of this journal related to low liquid flows, published in 2015, is still valid.

Drug delivery is a critical aspect in health safety because infusion therapy is the most commonly used form of therapy in hospital and clinical environment [1, 2]. Accurate flow and dosing measurements are essential to ensure that the "real" dose is delivered to the patient in hospitals or at home care by self-operated drug delivery devices preventing incorrect drug deliveries and improving significantly patient safety. This is particularly important for the cases where critical drugs are delivered at very small flow rates administering very low doses for neonates.

For this reason, this special issue focuses on medical flow and dosing measurement metrology in drug delivery. Most of the contributions are based on results from the joint EMPIR – Metrology for Drug Delivery (MeDD II) research project [3], involving 16 partners, including nine National and Designated Metrology Institutes (IPQ – Portugal, coordinator; CETIAT – France; CMI – Czech Republic; DTI – Denmark; METAS – Switzerland; NEL – United Kingdom; NQIS – Greece; RISE – Sweden; and KRISS – Korea), four companies (DNV GL – The Netherlands; HSG-IMIT – Germany; INESC MN – Portugal; BHT – The Netherlands) and three universities (TH L – Germany; UMCU – The Netherlands; UoS-UK). This project will last until the end of 2022 and has the overall aim to improve dosing accuracy and enable traceable measurements of volume, flow and pressure of existing drug delivery devices and inline sensors operating at very low flow rates (lower than 100 nL/min). This has been achieved through the development of new calibration methods and improved metrological infrastructures. Another goal of this project is to investigate the influence of different flow rate regimes, physical properties of the infused fluids (e.g. viscoelasticity), and occlusion phenomena in multi-infusion systems.

This special issue has therefore the character of a status report of ongoing research and discusses the major findings. The contributions of this special issue are categorized as follows. The first contribution introduces the subject. It explains the challenges and solutions in metrology for health [4] and offers an overview of several bibliography studies related to the subject.

The second paper deals with the development of calibration methods for flow rates down to 5 nL/min and its validation [5]. This paper gives quite a good overview of the European activities at flow rates lower than 100 nL/min and presents the results of EURAMET comparison 1508 [6]. This comparison allowed the publication of new calibration measurement capabilities (CMC) at the BIPM JCRB – The International Bureau of Weights and Measures Key Comparison Database [7] of several metrology institutes that participated in this project. The third paper is related to the optical methods described in [8], and mainly deals with measurement of internal diameters of capillaries or syringes using gravimetric and optical methods for microflow applications. These capillaries or syringes are used in some facilities, where the methods are described in [5]. The fourth paper is related to in-line measurement of the physical and thermodynamic properties of single and multicomponent liquids [9]. The fifth paper is the application of the techniques developed in paper [5] for the assessment of drug delivery devices working at microflow rates [10]. Performance analysis of a syringe pump and an infusion device analyser (IDA)devices are described in detail.

The sixth paper [11] describes various measurement methods for the calibration of insulin pumps and improves the method described in IEC 60601-2-24 in order to shorten

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the measurement time and applying relevant time windows for the performance test.

The next paper is the description of the development and manufacture of a new microfluidic pump [12] that can generate very low flow rates with high accuracy. Another paper [13] describes the effect of anti-return valves on the time-of-arrival of new medication in a patient after syringe change in an infusion set-up. Paper [14] deals with Holographic particle image velocimetry for nanoscale flows, applications and range of work. The final paper is related to user application of drug delivery devices and deals with unexpected dosing errors due to air bubbles in infusion lines with and without air filters [15].

Three technical workshops were organized by the "Metrology for Drug Delivery II" group: one by CETIAT in November 2020, another by Technische Hochschule Lübeck in September 2021 and a final one in November 2022 by IPQ, where the final results of the project were presented. While the first one focused mainly on the presentation of MeDD II project-results, the second one was more directed to infusion technology applications. All presentations can be downloaded at the drug metrology project website [16]. Also, four workshops for end-users were developed by the partners in order to disseminate the information of this project and create awareness of the importance of traceability and metrology in drug delivery devices.

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References

1. Lucas P, Klein S. Metrology for drug delivery. Biomed Eng Biomed Tech 2015;60:271–5.
2. Sutherland A, Canobbio M, Clarke J, Randall M, Skelland T, Emma W. Incidence and prevalence of intravenous medication errors in the UK: a systematic review. Eur J Hosp Pharm 2020;27:3–8.
3. Batista E, Pereira J, Ferreira M, Bissig H, Graham E, Furtado A, et al. New EMPIR project - metrology for drug delivery. Flow Meas Instrum 2020; 72:101716.
4. Metaxiotou Z, Bissig H, Batista E, Ferreira M, Timmerman A. Metrology in health: challenges and solutions in infusion therapy and diagnostics. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0045.
5. Mills C, Bissig H, Batista E, Ogheard F, Boudaoud A, Büker O, et al. Calibration methods for flow rates down to 5 nL/min and validation methodology. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0049.
6. EURAMET project 1508 - pilot study intercomparison of ultra-low liquid flow rates in range below 100 nL/min, at http://www.euramet.com/ [Accessed 2 Nov 2022].
7. Batista E, Alvares M, Martins R, Ogheard F, Gersl J, Godinho I. Measurement of internal diameters of capillaries and glass syringes using gravimetric and optical methods for microflow applications. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0033.
8. http://www.bipm.org/ [Accessed 2 Nov 2022].
9. Bissig H, Büker O, Stolt K, Graham E, Wales L, Furtado A, et al. In-line measurements of the physical and thermodynamic properties of single and multicomponent liquids. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0039.
10. Niemann A, Batista E, Gersl J, Bissig H, Büker O, Lee SH, et al. Assessment of drug delivery devices working at microflow rates. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0053.
11. Bissig H, Büker O, Stolt K, Batista E, Afonso J, Zagnoni M, et al. Calibration of insulin pumps based on discrete doses at given cycle times. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0040.
12. Silvério V, Canane P, Martins T, Afonso R, Cardoso S, Batista E. Development of a microfluidic electroosmosis pump on a chip for steady and continuous fluid delivery. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0051.
13. Konings M, Gevers R, Mejri S, Timmerman A. Effect of non-return valves on the time-of-arrival of new medication in a patient after syringe exchange in an infusion set-up. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0054.
14. Miotto G, Thiemann K, Rombach M, Zengerle R, Kartmann S. Holographic PIV/PTV for nanoflow rates – a study in the 70 to 200 nL/min range. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0055.
15. Konings M, Haaijer K, Gevers R, Timmerman A. Unexpected dosing errors due to air bubbles in infusion lines with and without air filters. Biomed Eng Biomed Tech 2022. https://doi.org/10.1515/bmt-2022-0056.
16. http://www.drugmetrology.com/ [Accessed 2 Nov 2022].