

BIOMEDICAL ENGINEERING BIOMEDIZINISCHE TECHNIK

*Joint journal of the German Society for Biomedical
Engineering in VDE and the Austrian and Swiss Societies
for Biomedical Engineering*

2015 · VOLUME 60 · NUMBER 4 · PAGES 269–388

EDITOR-IN-CHIEF

Olaf Dössel, Karlsruhe

ASSOCIATE EDITORS

Peter Augat, Murnau

Hartmut Gehring, Lübeck

Jens Haueisen, Ilmenau

Stefan Jockenhövel, Aachen

Thomas Lenarz, Hannover

Steffen Leonhardt, Aachen

Gernot Plank, Graz

Klaus Radermacher, Aachen

Georg Schmitz, Bochum

Erik Schkommodau, Muttentz

Thomas Stieglitz, Freiburg

Herbert Witte, Jena

EDITORIAL BOARD

Ulrich Boenick, Berlin, Germany

Branislav Jaramaz, Pittsburgh

Marc Kraft, Berlin, Germany

Harry van Lenthe, Leuven, Belgium

Benny Lo, London, UK

Luca Mainardi, Milano, Italy

Silvestro Micera, Lausanne, Switzerland

Thomas Penzel, Berlin, Germany

Andrea Robitzki, Leipzig, Germany

Klaus-Peter Schmitz, Rostock, Germany

Tobias Schaeffter, London, UK

Jess G. Snedeker, Zurich, Switzerland

Leif Sörnmo, Lund, Sweden

Nobuhiko Sugano, Osaka, Japan

Jürgen Werner, Bochum, Germany

Erich Wintermantel, Munich, Germany

Werner Wolf, Neubiberg, Germany

DE GRUYTER

Contents

Special Issue: Low Liquid Flows in Medical Technology

Guest Editors: Stephan Klein and Peter Lucas

Stephan Klein and Peter Lucas

Low liquid flows – an important aspect in medical technology — 269

Peter Lucas and Stephan Klein

Metrology for drug delivery — 271

Roland A. Snijder, Maurits K. Konings, Peter Lucas, Toine C. Egberts and Annemoon D. Timmerman

Flow variability and its physical causes in infusion technology: a systematic review of *in vitro* measurement and modeling studies — 277

Hugo Bissig, Harm Tido Petter, Peter Lucas, Elsa Batista, Eduarda Filipe, Nelson Almeida, Luis Filipe Ribeiro, João Gala, Rui Martins, Benoit Savanier, Florestan Ogheard, Anders Koustrup Niemann, Joost Lötters and Wouter Sparreboom

Primary standards for measuring flow rates from 100 nl/min to 1 ml/min – gravimetric principle — 301

Peter Lucas, Martin Ahrens, Jan Geršl, Wouter Sparreboom and Joost Lötters

Primary standard for liquid flow rates between 30 and 1500 nl/min based on volume expansion — 317

Martin Ahrens, Bodo Nestler, Stephan Klein, Peter Lucas, Harm Tido Petter and Christian Damiani

An experimental setup for traceable measurement and calibration of liquid flow rates down to 5 nl/min — 337

Elsa Batista, Nelson Almeida, Andreia Furtado, Eduarda Filipe, Luis Sousa, Rui Martins, Peter Lucas, Harm Tido Petter, Roland Snijder and Annemoon Timmerman
Assessment of drug delivery devices — 347

Holger Jannsen, Stephan Klein and Bodo Nestler
An adjustable flow restrictor for implantable infusion pumps based on porous ceramics — 359

Annemoon M. Timmerman, Roland A. Snijder, Peter Lucas, Martine C. Lagerweij, Joris H. Radermacher and Maurits K. Konings
How physical infusion system parameters cause clinically relevant dose deviations after setpoint changes — 365

Stéphanie Genay, Bertrand Décaudin, Sébastien Lédé, Frédéric Feutry, Christine Barthélémy, Gilles Lebuffe and Pascal Odou
***In vitro* comparison of two changeover methods for vasoactive drug infusion pumps: quick-change versus automated relay — 377**

Annemoon M. Timmerman, Suzanne M. Oliveira-Martens, Roland A. Snijder, Anders K. Nieman and Toine C. Egberts
How to use current practice, risk analysis and standards to define hospital-wide policies on the safe use of infusion technology — 381

Editorial

Stephan Klein* and Peter Lucas

Low liquid flows – an important aspect in medical technology

DOI 10.1515/bmt-2015-0141

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. For that reason all aspects of dosing, handling, and measuring of low liquid flows are current topics of many research activities. The results of this efforts are presented and discussed at conferences like, e.g. the International Conference on Microfluidic Handling Systems (the 2nd conference took place in 2014) [11], the European Conference on Microfluidics (the 4th took place in 2014) [5], or the International Flow Measurement Conference (the 16th took place in 2013) [4]. Many other examples can be found in this issue.

This special issue focuses on low liquid flows in medical technology, mainly with regard drug delivery and infusion systems. Most of the contributions are based on results from the joint EURAMET – Metrology for Drug Delivery (MeDD) research project [10]. The project was carried out by the national metrology institutes VSL (NL, coordinator), CETIAT (F), CMI (CZ), DTI (DK), METAS (CH), IPQ (PT), and UME (TK) as well as UMC (University Medical Centre, Utrecht) (NL) and Luebeck University of Applied Sciences (GE). Although the project funding ended in the summer of 2015 the work will partly be continued by some of the partners. 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 two contributions introduce the subject. They explain the background of metrology for drug delivery [8] and offer an overview of studies related to flow variability [16].

The third to fifth articles deal with measurement technologies and assessment. Because the gravimetric method is a common method for a great deal of the relevant flow range, this method has been given specific attention in the project. Several calibration facilities have

been developed, validated and accredited during the project [3]. So this paper gives quite a good overview of the European activities. Another research project aiming at realizing calibration services for low liquid flow rates is, for example, carried out by NIST [12]. Also flow standards are needed to measure and calibrate fluidic devices. In this special issue how this method has been used to assess several drug delivery systems is discussed [2]. In addition to the common gravimetric method, new methods are also discussed that could be adopted for extremely low flows for which the gravimetric method is not suitable. This includes an optical front tracking method [1] and a flow source based on volume expansion [9].

This is followed by a transition to papers focusing more on application. The first describes the development of a new restrictor to adjust drug flows in gas-driven implantable infusion pumps [7].

Finally there are three papers dealing with the application of low flows in infusion technology in a clinical environment. The influence of components and their properties (e.g. compliance) on multi-infusion systems and their behavior (e.g. interference) is studied in [13]. The influence of two different methods to change syringes is investigated in [6]. Finally, how safety guidelines can be deduced from current best practices and the research conducted in the MeDD project is discussed in [15].

Two workshops were organized by the “Metrology for Drug Delivery” group, one in Luebeck, Germany at Luebeck University of Applied Sciences in September 2014 and one in Utrecht, The Netherlands at University Medical Center in the summer of 2015. While the first one focused mainly on the results of the MeDD project, the second one was more directed to safety aspects in infusion technology and tried to work out possible future work. All presentations can be downloaded at the corresponding websites [14, 17].

The Guest Editors would like to thank all those involved in this special issue, especially the authors for their contributions and the patience needed during the several stages of the review process. We also thank the reviewers for their valuable hints to improve the quality of this issue. We also thank the Editor in Chief and the publisher for their

willingness to publish this edition and for their support and for their help in coordinating this issue. We hope the readers will find hints and inspiration for their own work.

References

- [1] Ahrens M, Nestler B, Klein S, Lucas P, Petter HT, Damiani C. An experimental setup for traceable measurement and calibration of liquid flow rates down to 5 nl/min. *Biomed Eng-Biomed Tech* 2015; 60: 337–345.
- [2] Batista E, Almeida N, Furtado A, et al. Assessment of drug delivery devices. *Biomed Eng-Biomed Tech* 2015; 60: 347–357.
- [3] Bissig H, Petter H, Lucas P, et al. Primary Standards for measuring flow rates from 100 nL/min to 1 mL/min – Gravimetric Principle. *Biomed Eng-Biomed Tech* 2015; 61.
- [4] FLOMEKO 2013. 16th International Flow Measurement Conference. Available at: <http://www.flomeko2013.fr/>. Accessed July 14th, 2015.
- [5] μ Flu 14. 4th European Conference on Microfluidics. Available at: <http://microfluidics2014.eu/>. Accessed July 14th, 2015.
- [6] Genay S, Décaudin B, Lédé S, et al. *In vitro* comparison of two changeover methods for vasoactive drug infusion pumps: quick-change versus automated relay. *Biomed Eng-Biomed Tech* 2015; 60: 377–380.
- [7] Janssen H, Klein S, Nestler B. An Adjustable flow restrictor for implantable infusion pumps based on porous ceramics. *Biomed Eng-Biomed Tech* 2015; 60: 359–364.
- [8] Lucas P, Klein S. Metrology for drug delivery. *Biomed Eng-Biomed Tech* 2015; 60: 271–275.
- [9] Lucas P, Ahrens M, Geršl J, Sparreboom W, Lötters J. Primary standard for liquid flow rates between 30 and 1500 nl/min based on volume expansion. *Biomed Eng-Biomed Tech* 2015; 60: 317–335.
- [10] Metrology for drug delivery. Available at: www.drugmetrology.com. Accessed July 14th, 2015.
- [11] MFHS 2014. 2nd International Conference on Microfluidic Handling Systems. University of Freiburg. Available at: <https://www.mfhs2014.uni-freiburg.de/>. Accessed July 14th, 2015.
- [12] National Institute of Standards and Technology (NIST) <http://www.nist.gov/pml/div685/grp02/calibration-for-micro-flows.cfm>. Accessed July 14th, 2015.
- [13] Snijder RA, Konings MK, Lucas P, Egberts TC, Timmerman AD. Flow variability and its physical causes in infusion technology: a systematic review of *in vitro* measurement and modeling studies. *Biomed Eng-Biomed Tech* 2015; 60: 277–300.
- [14] Symposium on infusion technology. <http://www.drugmetrology.com/index.php/publications-logged-in-2>. Accessed July 14th, 2015.
- [15] Timmerman AM, Oliveira-Martens SM, Snijder RA, Nieman AK, Egberts TC. How to use current practice, risk analysis and standards to define hospital-wide policies on the safe use of infusion technology. *Biomed Eng-Biomed Tech* 2015; 60: 381–387.
- [16] Timmermann AM, Snijder RA, Lucas P, Lagerweij MC, Radermacher JH, Konings MK. How physical infusion system parameters cause clinically relevant dose deviations after set-point changes. *Biomed Eng-Biomed Tech* 2015; 60: 365–376.
- [17] 8th Workshop on Low Flows in Medical technology. <http://www.msgt.fh-luebeck.de/index.php?id=28>. Accessed July 14th, 2015.

***Corresponding author: Stephan Klein**, Medical Sensors and Devices Lab, Luebeck University of Applied Sciences, Moenkhofer Weg 239, 23562 Luebeck, Germany, E-mail: klein@fh-luebeck.de
Peter Lucas: VSL – Dutch Metrology Institute, Thijsseweg 11, 2629 JA Delft, The Netherlands