Report:

Deliverable D9: "Evidence of contributions to or influence on new or improved international guides, recommendations and standards with a specific focus on the following guides and committees: ISO/TC 48, ISO/TC 84, ISO/TC 210, ISO/TC 30, ICE/TC62D. Examples of early uptake of project outputs by end-users"

This report was written as part of WP5 from the EMPIR Metrology for Drug Delivery (MeDD II) project. The three-year European project commenced on 1st June 2019 and focused on providing evidence of contributions to or influence on new or improved international guides, recommendations and standards with a specific focus on the following guides and committees: ISO/TC 48, ISO/TC 84, ISO/TC 210, ISO/TC 30, IEC/TC62D and examples of early uptake of project outputs by end-users. For more details about this project, please visit www.drugmetrology.com

This report was written by:

Elsa Batista	IPQ	*ebatista@ipq.pt*
Hugo Bissig	METAS	*Hugo.Bissig@metas.ch*

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1 Contents

Introduction to the EMPIR Metrology for Drug Delivery project

The overall aim of this project is to improve dosing accuracy and to enable the traceable measurement of volume, flow and pressure in existing drug delivery devices and in-line sensors operating at very low flow rates. This will be achieved through the development of new calibration methods and by expanding the existing metrological infrastructure. This project will also investigate fast changing flow rates, which are step changes between two flow rates within a second, the physical properties of mixtures of liquids and occlusion phenomena in multi-infusion systems in order to prevent inaccurate measurement results and thus to improve patient safety.

The specific objectives of the project are:

1. To develop new traceable techniques for generating and measuring the response or delay time of drug delivery devices regarding changes in flow rate, from 5 nL/min to 100 nL/min, using Newtonian liquids (WP1). For steady flow rates an uncertainty of 1 % (k=2) or better is expected, whereas for fast changing flow rates an uncertainty of 2 % (k=2) or better is expected. The techniques developed will be used to characterise and validate the different response times of at least 3 different types of drug delivery devices (including infusion analysers) (WP3 and WP4) and one type of flow sensor, to accurately measure the administered flow and volume with the required uncertainties.

2. To upgrade the existing flow facilities and knowledge of the partner NMIs in order to enable the traceable in-line measurement of the dynamic viscosity of Newtonian liquids, as a function of the flow rate and pressure difference, with a target uncertainty value of 2 % (k=2). The measurement uncertainty will be validated using Newtonian liquids with traceable dynamic viscosity calibration. Additionally, tests with non-Newtonian liquids will be performed in order to prove the concept. To calibrate transfer standards for the in-line measurement of dynamic viscosity and other physical properties of liquids, in order to use these transfer standards for flow measurement and to determine the mixing behaviour of different liquids.

3. To develop and validate novel calibration procedures for existing medical flow devices (e.g. infusion pumps, pain controllers and infusion pump analysers) with traceability to a primary standard and with a target uncertainty value of 2 % (k=2) for a range of 5 nL/min up to 600 ml/min and also to develop a proof-of-concept on-chip microfluidic pump used as a transfer standard in drug discovery and organon-a-chip applications for flow rates lower than 100 nL/min.

4. To design and develop a multi-infusion system containing check valves, 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, to be able to analyse the effects of pressure-equalising devices and to detect occlusion phenomena and bad mixing configurations.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (i.e. accredited laboratories, instrumentation manufacturers, etc.), standards developing organisations (ISO/TC 30, ISO/TC 48, ISO/TC/SC 62D, ISO/TC 69, ISO/TC 76, ISO/TC 84, ISO/TC 150, ISO/TC 210) and end-users (i.e. hospitals and health centres).

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Overall Objective: To provide evidence of contributions to international guides, recommendations and standards with a specific focus on the following guides and committees: ISO/TC 48, ISO/TC 84, ISO/TC 210, ISO/TC 30, ICE/TC62D, and to provide examples of early uptake of project outputs by end-users.

Once agreed by the consortium, the coordinator will then submit the deliverable to EURAMET as **D9**
All the partners of this consortium have contributed to this deliverable.

1 Introduction

In this project, procedures and methods for the calibration of drug delivery devices that are already on the market were developed. The consortium supplied this information to the relevant ISO technical committees (TC) and ensure that these results were incorporated in any updates to standards (e.g. IEC 60601-2-24, ISO 7886-2 and ISO 8655-9) or guidelines. Also, the results obtained by the project were disseminated by end users and metrologist trough workshops, and this is considered an early uptake of the project.

2 Relevant standards to which comments by MeDDII consortium were sent and incorporated

In Table 1 it is described the standards and respective technical comities to whom technical inputs from the MeDD consortium were supplied, all the comments sent by the consortium are be provided in a separate file. Letters/emails were sent by several TC chairs (signed in the table with "*") about the importance of these contributions to the development of the relevant standards, the documents sent are in Annex 1.

Table 1 – Standards and relevant TC were MeDDII made contributions.

ISO TC/Other TC	Standard	Status
ISO TC 84 - Devices for administration of medicinal products and catheters	ISO 7886-2:2020 - Sterile hypodermic syringes for single use	IPQ participated in the meetings revision of DIS and FDIS. The standard was published during the life time of the project. This was a follow up of project MeDD where 70 % of the comments were accepted.
ISO TC 210 - Quality management and corresponding general aspects for medical devices	ISO/TR 24971:2020 - Medical devices	Active participation in the discussion and elaboration of the document by IPQ. The standard was published during the life time of the project.
*TC62/SC62D/MT23 - Medical	ISO/IEC 60601-2-24:2012 - Medical electrical equipment - Part 2-24: Particular	Under revision

equipment, software, and systems	requirements for the basic safety and essential performance of infusion pumps and controllers	But stopped due to TIR 101 work. Follow up of project MeDD IPQ participated in initial meetings.
*AAMI - Association for the Advancement of Medical Instrumentation	AAMI TIR 101:2021 - Fluid Delivery Performance Testing For Infusion Pumps	IPQ participated actively in the revision meetings. 70% of the comments sent by the consortium accepted The standard was published during the life time of the project.
*AAMI- Association for the Advancement of Medical Instrumentation	AAMI TIR 111 - Infusion system performance related to occlusions, and unintended boluses	Under development. IPQ participated in the revision meetings.
*ISO TC48/WG4 - Liquid Handling Devices – Manual and Semi-Automatic	ISO 8655-1:2022 - Piston-operated volumetric apparatus — Part 1: Terminology, general requirements and user recommendations	70 % of comments sent by the consortium accepted. IPQ, project leader. The standard was published during the life time of the project.
*ISO TC48/WG4 - Liquid Handling Devices – Manual and Semi-Automatic	ISO 8655-1:2022 - Piston-operated volumetric apparatus — Part 1: Terminology, general requirements and user recommendations	70 % of comments sent by the consortium accepted. IPQ, project leader. The standard was published during the life time of the project.

*ISO TC48/WG4 - Liquid Handling Devices – Manual and Semi-Automatic	ISO 8655-9:2022 - Piston-operated volumetric apparatus — Part 9: Manually operated precision laboratory syringes	80 % of comments sent by the consortium accepted. IPQ, project leader. The standard was published during the life time of the project.
*ISO TC48/WG4 - Liquid Handling Devices – Manual and Semi-Automatic	ISO_DTR 20461 - Determination of uncertainty for volume measurements made using the gravimetric method	Under development. 90 % of comments sent by the consortium accepted. IPQ, project leader.
*ISO TC48/WG5 - Liquid Handling Devices- Automatic	ISO 23783-1:2022 - Automated liquid handling systems — Part 1: Vocabulary and general requirements	90% of the comments sent by the consortium accepted IPQ and HS included in the elaboration of the document. The standard was published during the life time of the project.
*ISO TC48/WG5 - Liquid Handling Devices- Automatic	ISO 23783-2:2022 - Automated liquid handling systems — Part 2: Measurement procedures for the determination of volumetric performance	90% of the comments sent by the consortium accepted. IPQ and HS included in the elaboration of the document. The standard was published during the life time of the project.

*ISO TC48/WG5 - Liquid Handling Devices- Automatic	ISO 23783-3:2022 - Automated liquid handling systems — Part 3: Determination, specification and reporting of volumetric performance	90% of the comments sent by the consortium accepted IPQ and HS included in the elaboration of the document. The standard was published during the life time of the project.
*ISO TC48/WG5 - Liquid Handling Devices- Automatic	ISO/AWI TR 6037 - Automated liquid handling systems – Uncertainty of the measurement procedures	Under development IPQ and HS included in the elaboration of the document.
ISO/TC 150/SC 6 - Implants for surgery	ISO 14708-4:2022 - ISO 14708-4:2022 - Implants for surgery — Active implantable medical devices — Part 4: Implantable infusion pump systems	Only 20 % comments accepted No partners participated in the meetings. The standard was published during the life time of the project.
ISO/TC 212 - Clinical laboratory testing and in vitro diagnostic test systems	FDIS ISO 15189:2012 - Medical laboratories — Requirements for quality and competence	Under development Comments sent by the MeDDII consortium.

The majority of the comments sent by MeDDII consortium were of technical and metrological nature, e.g. criteria for test conditions, information on the best procedure to be applied, accurate calculation formulas and information on uncertainty determination. Also, in all the standards that MeDDII make comments it was also suggested to include EURAMET cg guides, the VIM and the GUM in the bibliography. The comments were sent by consortium P members or thought EURAMET as liaison organization. Several of the standards had project leaders that are also partners of the consortium.

For TC 30, no relevant standards were revised during the project life time.

3 Examples of early uptake of project outputs by end-users.

3.1 Calibration facilities update

Several end users/manufactures have asked for calibration of drug delivery devices to several partners of MeDDII, like IPQ (table 2), METAS (table 3), CETIAT (table 4) and RISE (table 5), that have updated and published their new CMC in the KCDB during 2022 following the work developed in this project. For example: Metas had more than 20 requested of calibration of Instrument devices analyser (IDA), IPQ had more than 6 calibration requests of these IDA and two for syringe pumps, CETIAT had more than 20 syringe pumps calibrations requests and an insulin pump calibration was also performed.

Table 2 – IPQ facilities

	Microflow Facilities characteristics before the project		Microflow Facilities characteristics after the project		Microflow Range and uncertainty validated by comparisons		CMC: Yes/No
Method	Range	Uncertainty (%)	Range	Uncertainty	Range	Uncertainty (%)	
Gravimetric	120 µL/h – 2000 mL/h	2.5 to 0.11	10 µL/h to 2000 mL/h	2.6 to 0.11	120 µL/h – 2000 mL/h	2.5 to 0.11	Yes
Interferometric			0.1 µL/h to 5000 µL/h	1.9 – 0.9	0.0003 ml/h- 0.12 mL/h	2.7 to 1.3	Yes
Front track			0.1 µL/h to 5000 µL/h	7-1.5			
Dop method			100 µL/h to 1000 µL/h	10-3			
Displacement			0.5 mL/h to 1200 mL/h	4-1			

A PhD by Elsa Batista was performed and concluded during this project intitled ”Innovative contributions on calibration methodologies towards reliable microflow measurements” by the University FCT /UNL in Lisbon. http://hdl.handle.net/10362/134197

Table 3 – METAS facilities

	Microflow Facilities characteristics before the project		Microflow Facilities characteristics after the project		Microflow Range and uncertainty validated by comparisons		CMC: Yes/No
Method	Range (μL/h)	Uncertainty (μL/h)	Range (μL/h)	Uncertainty (μL/h)	Range (μL/h)	Uncertainty (μL/h)	
Piston Prover	6 – 2*10^7	0.042 - 60	1.2 - 2*10^7	0.012 - 2*10^4	1.2 - 60000	0.012 - 2*10^4	Yes
Gravimetric method	6 - 2*10^7	0.042 - 60	1.2 - 2*10^7	0.012 - 2*10^4	1.2 - 60000	0.012 - 2*10^4	Yes

Table 4 – CETIAT facilities

	Microflow Facilities characteristics before the project		Microflow Facilities characteristics after the project		Microflow Range and uncertainty validated by comparisons		CMC: Yes/No
Method	Range (mL/h)	Uncertainty (mL/h)	Range (mL/h)	Uncertainty (mL/h)	Range (mL/h)	Uncertainty (mL/h)	
Gravimetric	1.10^3-1.10^7	6-100			1.10^3-1.10^7	6-100	Yes
Front Tracking			0.06-1000		0.6-90	0.072-0.138	Yes

Table 5 – RISE facilities

	Microflow Facilities characteristics before the project		Microflow Facilities characteristics after the project		Microflow Range and uncertainty validated by comparisons		CMC: Yes/No
Method	Range	Uncertainty (%)	Range	Uncertainty	Range	Uncertainty (%)	
Gravimetric	1 mL/h to 100 (200) mL/h	<0.5%	3*10^-4 mL/h to 100 mL/h	5% to 0.5%	3*10^-4 mL/h (5 nL/min) to 100 mL/h	5% to 0.5%	Yes

3.2 Workshops for metrologists and scientists

Three online workshops for metrologists and scientists organized by CETIAT, THL (figure 1) and IPQ were performed in 2020, 2021 and 2022 with more than 190 participants in total. The new methods developed during this project were presented to the audience and the feedback was very positive.

Figure 1 – 14th Workshop in Low liquid flow given by THL in cooperation with MeDDII consortium

3.3 End users training workshops

Several project partners performed 5 workshops for end users, namely:

- 4 workshop for end users, 3 of them online:
  - IPQ, 53 participants (figure 2)
  - CETIAT, 33 participants
  - NEL, 19 participants

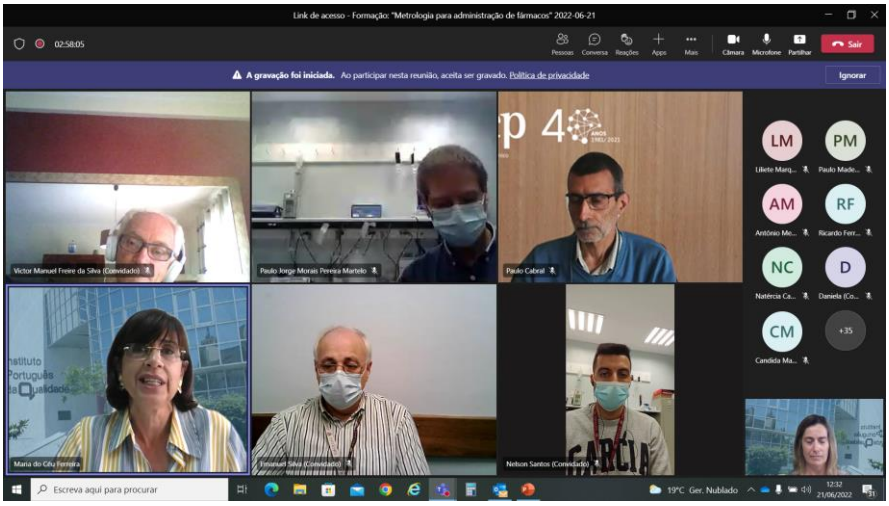

Figure 2 – online workshop given by IPQ

- one at European Society of Intensive Care Medicine (ESICM) live event 2022 on site with 25 participants (figure 3) where there was possible to use the new multi-infusion simulation software (figure 4) that was given by CETIAT and UMCU.

Figure 3 – Training course on ESICM live event 2022

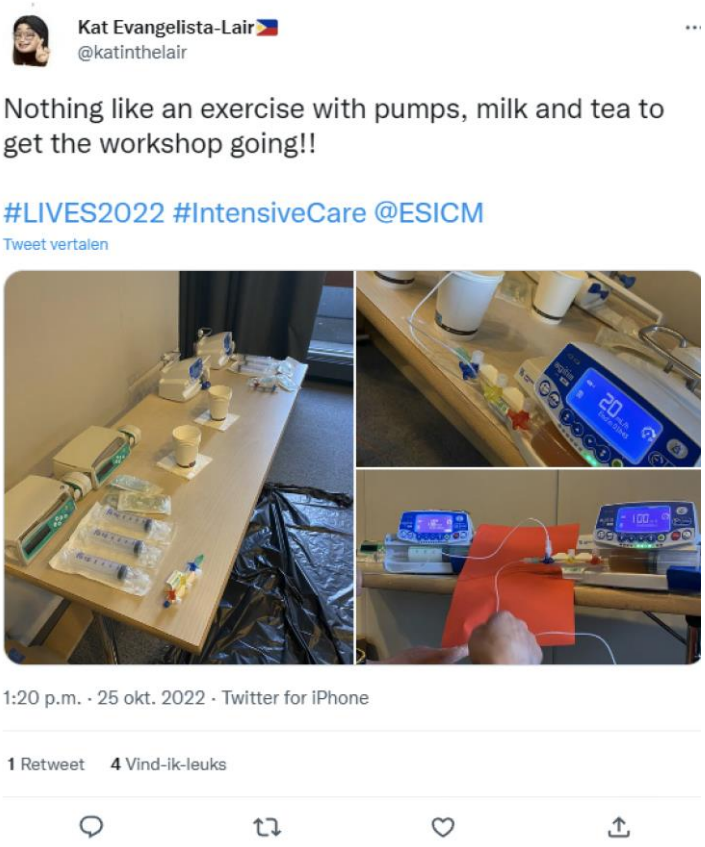

Figure 4 – Training course on ESICM live event 2022 and comments

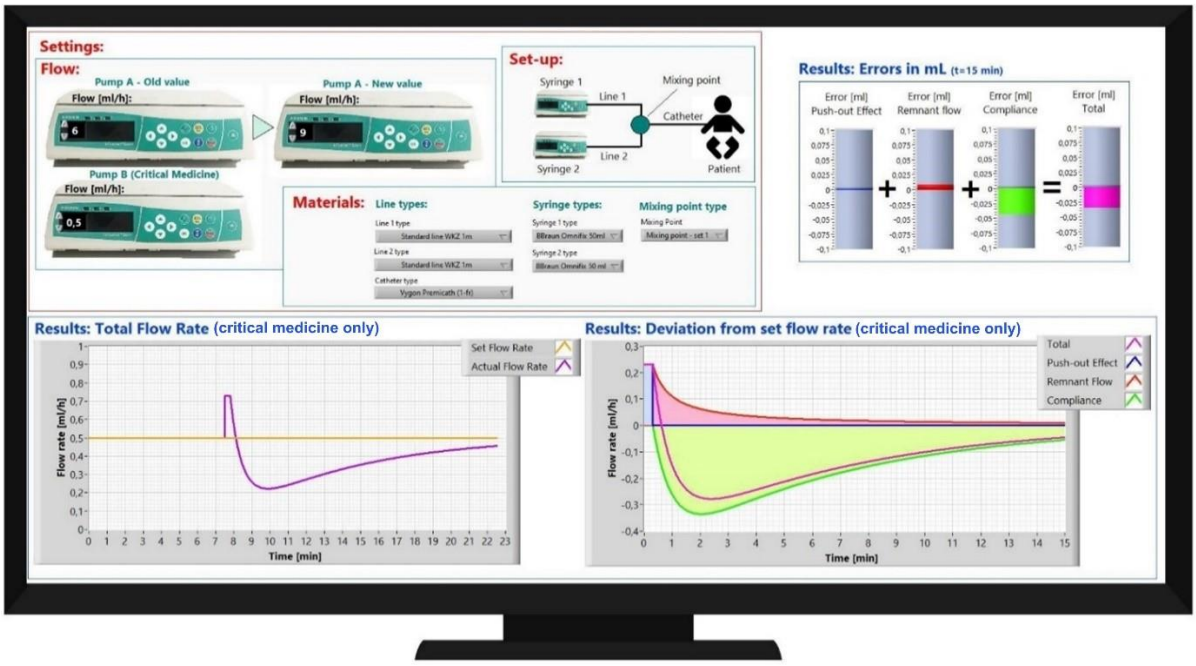

Figure 5 – Multi-infusion simulation tool used in the training course on ESICM live event 2022

- ❑ UMCU also gave a workshop to the Wilhemina Children's staff Hospital, on site, with 40 participants.

In total the training workshops for users had more than 170 participants, from nurses, doctors, maintenance officers of hospitals and regular hospital staff. The feedback from these workshops based on the questionnaires provided in each workshop, allowed us to conclude that this workshops had very good impact.

4 Conclusion

We believe that we accomplished the objectives of this deliverable and did extra work for AAMI TIR 101. EURAMET has published a case study on the project MeDDII concerning our collaboration with standardization in the revision of the relevant standards for syringe pump testing.

In general, the project supported the development of standards incorporating robust calibration procedures, equipment, and conditions, capable of supporting accurate drug delivery results and reduced risks of adverse patient incidents. It also contributed to the inclusion of uncertainty calculation procedures and reference to EURAMET calibration guides in several standards.

Several partners published new CMC following the facilities update allowed by the participation in this project and have already performed several calibrations of drug delivery devices for customers.

Also, several workshops for end users, scientists and metrologist were performed with very good feedback from the attendees.

Annex 1 – Information sent by Chairs of relevant TC regarding the project MeDDII contributions.

IEC 62, SC62D, MT23

Email send on 22-11-2022

To whom it concerns,

The author of these lines worked with Elsa Batista from the Instituto Portuges da Qualidade, IPQ both as a convenor of IEC Technical Committee 62, Sub-Committee 62D, MT23 Infusion Pumps as well as the then active co-chair for the AAMI Infusion Devices group. Elsa Batista deeply engaged in the work of both groups. She provided many contributions both as a reviewer of the documents under development: AAMI TIR 101 Fluid delivery performance testing for infusion pumps released in 2021, draft AAMI TIR 111 Infusion system performance related to occlusions, unintended boluses, and air-in-line detection, and draft IEC 60601-2-24 Particular Requirements For The Basic Safety And Essential Performance Of Infusion Pumps And Controllers3rd edition.

Elsa - as an expert in the field of metrology - educated both groups. She introduced both the international state-of-art in this field as well as her own work and learnings in the field of microflow from the MeDDII project. She helped ensure correctness of the information in the new standards. She helped the group including regulatory authorities develop a better understanding of the requirements of standards based type testing over validation of the infusion devices for safe use in their intended use environments. Her offer to host the international group on her premises could unfortunately not be realized at the time due to international travel restrictions.

Best regards,
Peter Rech, PhD

Partner SoftwareCPR
Crisis Prevention & Recovery, LLC
Convenor IEC TC62/SC62D/MT23 Infusion Pumps
peter@softwarecpr.com

ISO TC 48/WG4

Letter send on 29-11-2022

Valentin Lütke-Börding – Convenor of ISO TC 48 / WG04 2022-11-29

Impact of MeDDII project for Working programme of ISO TC 48 WG04

The project MeDDII, with Elsa Batista as representative, contributed to the development of ISO 8655-1 through ISO 8655-9 as well as ISO/TR 20461 and ISO/TR 16153.

Elsa's experience, expertise and feedback were essential in the development of the documents.

Hünxe, 2022-11-29

ISO TC 48/WG5

Email send on 17-11-2022

Hello Elsa,

I wanted to take a moment to express my appreciation to you and the project MeDDII consortium for your contributions to the work of ISO TC48 WG5. These contributions supported publication of ISO 23783 parts 1 thru 3 in August of 2022, while bringing a valuable metrology expertise and perspective. Similarly, the current draft of ISO/DTR 6037 focused on measurement uncertainty benefited greatly by contributions from the MeDDII project.

The project MeDDII consortium, with Elsa Batista as representative, was particularly effective in development ISO 23783 and TR 6037. Your experience, expertise, dedicated hard work, persistence and patience were some of the reasons for your effectiveness in representing the MeDDII consortium.

Thank you very much for your service.

Warm regards,
George Rodrigues, PhD
Convenor of ISO/TC48/WG5

AAMI

Email send on 29-04-2022

The project MeDDII consortium, with Elsa Batista as representative, provided important contributions to the development of TIR 101. Elsa's experience, expertise and feedback were very helpful in creating the TIR.

Please let me know if you need anything else, and once again, thank you so much for all of your help.

Best,

Ben

Ben Powers

Vice President of Infusion Systems

C: 617.251.6054

Ivenix, Inc.

50 High St., Suite 50, North Andover, MA 01845

www.ivenix.com