Instituto Português da Qualidade

GOVERNO DE PORTUGAL | MINISTÉRIO DA ECONOMIA

EURAMET
European Association of National Metrology Institutes

EMRP
European Metrology Research Programme
Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

Development of a microflow primary standard – IPQ

MeDD – Metrology for Drug Delivery

2014 European Flow Measurement Workshop
Ultrasonic and Coriolis Metering – Lisbon, Portugal

Resume

- ✓Introduction
- ✓IPQ
- ✓IPQ gravimetric system
- ✓Future work
- ✓Applications
- ✓EMRP-MeDD
- ✓MeDD Outlook
- ✓EMPIR

Introduction

- With the development of science and nanotechnology, the measurement of fluid flow quantities is getting smaller, in the order of microliter per minute or even nanoliter per minute.

- In order to provide traceability to industry and laboratories, in such fields as health, biotechnology, engineering and physics, it was identified the need of developing primary standards for microflow measurement.

- In the scope of the EMRP project MeDD, a new standard for micro flow measurements was developed at the Portuguese Institute for Quality.

IPQ – Portuguese Institute for Quality

It's a government institute founded in 1986 and has the main mission to manage and coordinate the Portuguese Quality System. The main activities are:

- Standardization
- Metrology

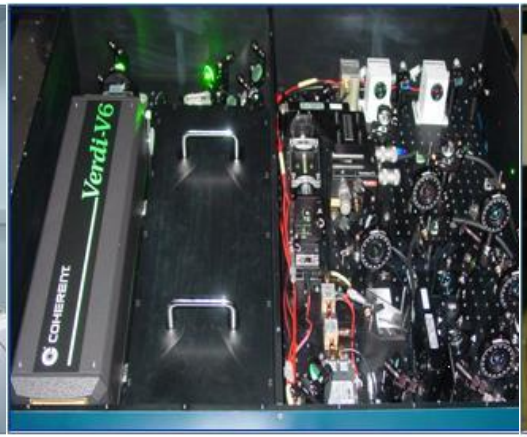
www.ipq.pt

Metrology Department of IPQ

- 56 Laboratories
- 32 Technicians
- 27 with university degree
- 2200 m^2 laboratory area
- 10000 m^2 construction area
- 150 international comparison participation
- 134 CMC e 21 matrix
- 3000 calibrations per year

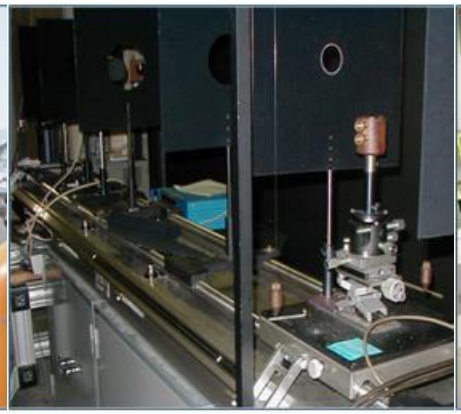
Data from 2012

Laboratories






Volume and flow laboratory of IPQ

- Small volume, from 1 μL up to 10 L
- Large volume, from 10 L up to 5000 L
- Liquid flow measurements from 100 nL/min up to 10 mL/min

Small Volume Laboratory

Large Volume Laboratory

IPQ gravimetric microflow system

There are three main elements in the gravimetric microflow system of IPQ:

- Flow generator
- Collecting device
- Data acquisition system, with a volumetric flow determination model

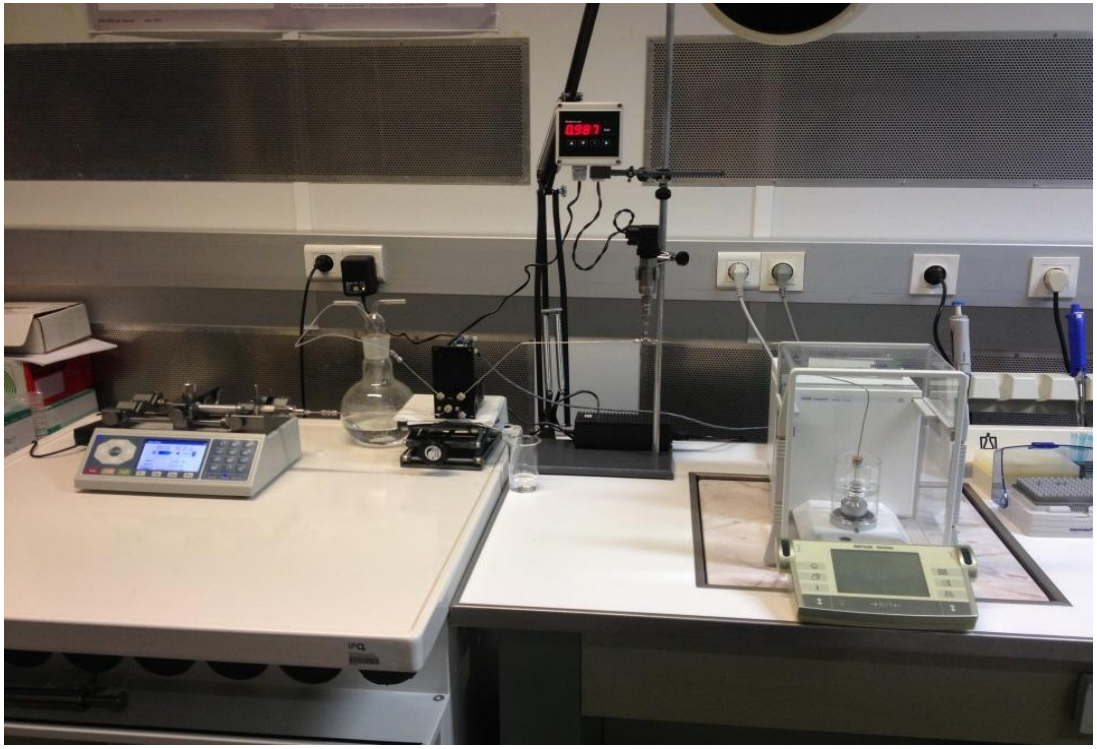
$$Q = \frac{1}{t_f - t_i}\left[\left((I_L - I_E) - (\delta m_{buoy})\right) \times \frac{1}{\rho_w - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times [1 - \gamma(20 - T_0)]\right] + \delta_{evap}$$

AX26 System

AX26 System

Mettler Toledo AX26 of 22 g maximum capacity and 0,001 mg resolution

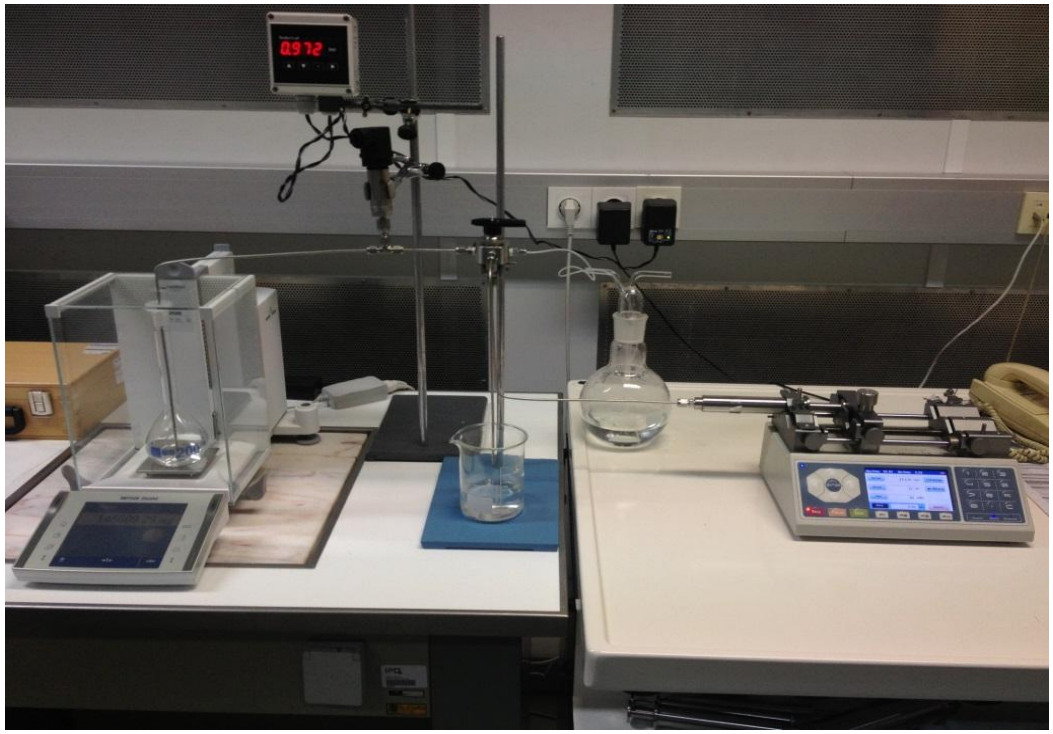
From 100 nl/min up to 0,33 ml/min



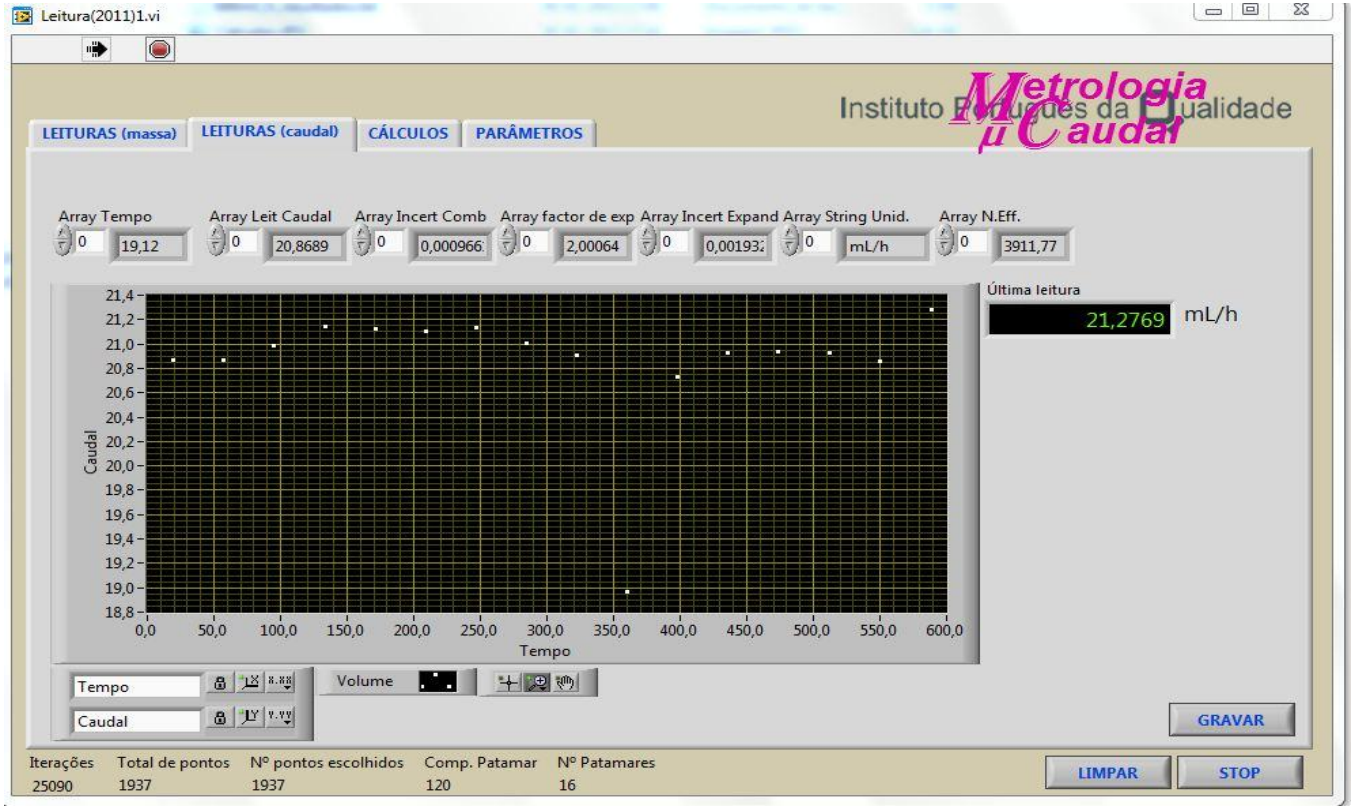
Larger flow system

XP205 System

Mettler Toledo XP205 of 300 g maximum capacity and 0,1 mg resolution will be used for larger flows, from 0,33 ml/min up to 10 ml/min



Labview computer program



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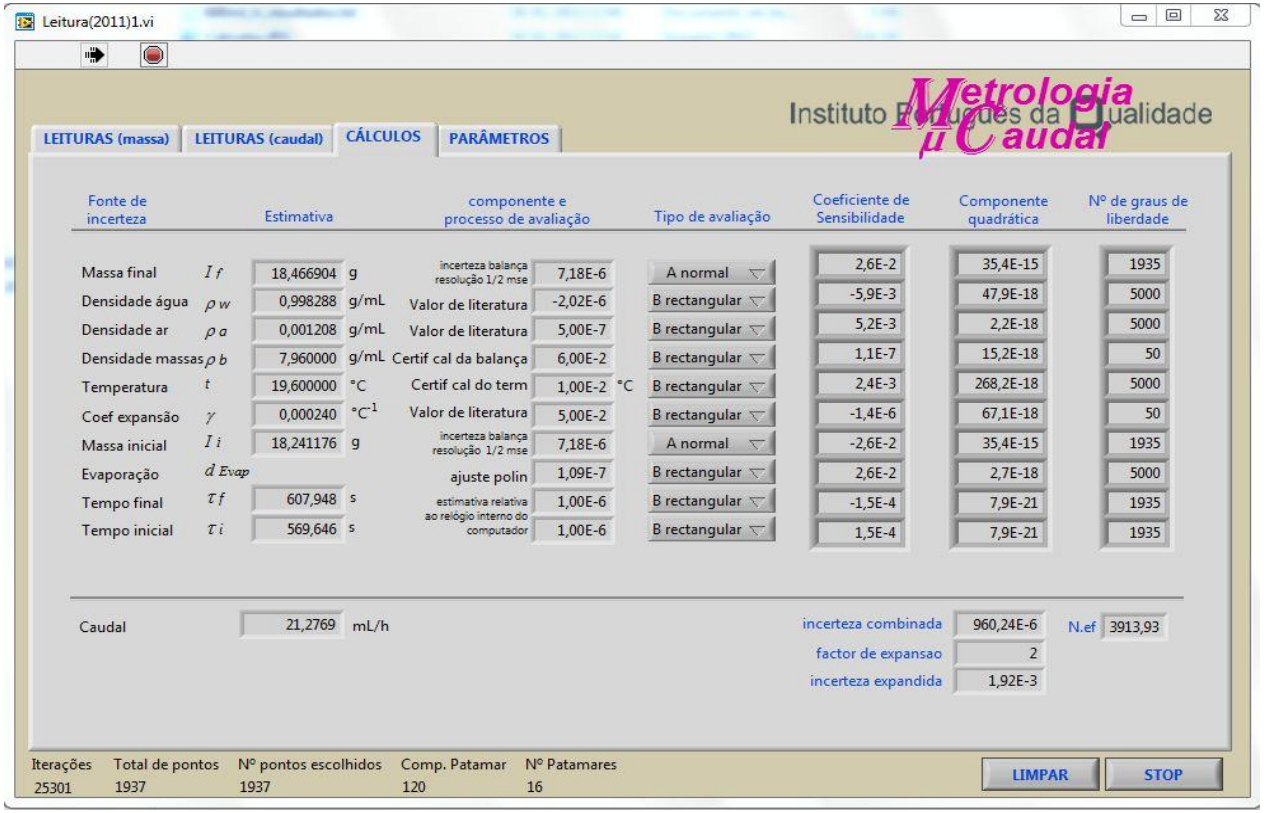


Uncertainty determination

1 μl/min using a 0,5 ml glass syringe and AX26 balance

Uncertainty components	Estimation	$u(x_i)$	c_i	$(c_i \times x_i)^2$
Final mass (g)	5.12	7.12×10^{-6}	5.25×10^{-4}	1.3982×10^{-17}
Density of water (g/mL)	0.9980639	9.00×10^{-7}	-2.72×10^{-5}	6.00614×10^{-22}
Density of air (g/mL)	0.001202	2.89×10^{-7}	2.38×10^{-5}	4.72819×10^{-23}
Density of weights (g/mL)	7.96	3.46×10^{-2}	5.15×10^{-10}	3.1831×10^{-22}
Temperature (ºC)	20.68	5.00×10^{-3}	-2.71×10^{-10}	1.84216×10^{-24}
Expansion coefficient (/ºC)	1×10^{-5}	2.89×10^{-7}	-1.85×10^{-5}	2.83938×10^{-23}
Initial mass (g)	5.06	7.12×10^{-6}	-5.25×10^{-4}	1.3982×10^{-17}
Evaporation (mL/s)	1.09×10^{-7}	1.12×10^{-8}	1	1.2544×10^{-16}
Initial Time (s)	0.249	5.77×10^{-5}	$1{,}42\times10^{-8}$	6.73403×10^{-25}
Final Time (s)	191	5.77×10^{-5}	-1.42×10^{-8}	6.73403×10^{-25}
Buoyancy (g)	0.0007	9.01×10^{-6}	5.25×10^{-4}	2.23655×10^{-17}
Flow (mL/s)	2.7254×10^{-5}			
u_{comb} (mL/s)	1.3×10^{-8}			
U_{exp} (mL/s)	0,1 %			

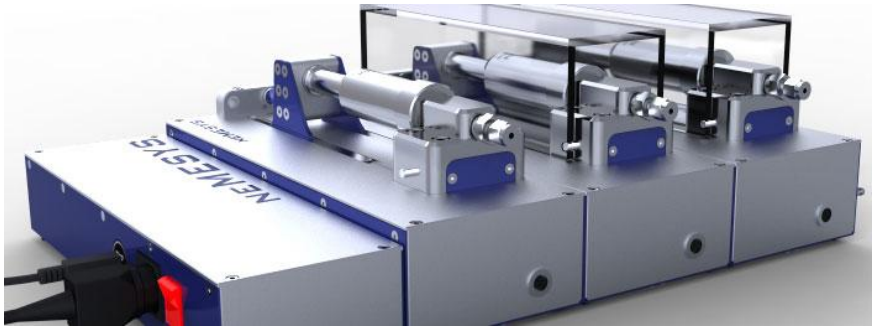
Future work

- Traceability in time (the necessary hardware is available now)
- Automatic collecting data of ambient conditions and water temperature
- Correct for capillarity and balance drift for flow under 1 ml/h

Aplications

Flow meters

Flow generators



Infusion devices

EMRP

The European Association of National Metrology Institutes, EURAMET, started, in 2007, the European Metrology Research Programme – EMRP.

This programme allows cooperation between National Metrology Laboratories, Universities and industry in Joint Research Programs – JRPs, in strategic themes. One of this themes is health.

EMRP

European Metrology Research Programme

Programme of EURAMET

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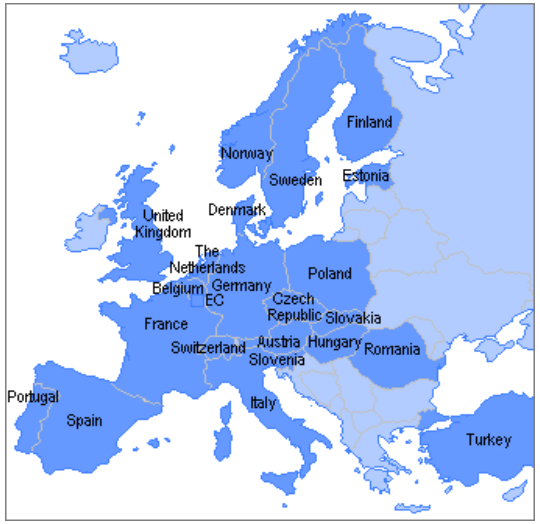


MeDD - Metrology for Drug Delivery, started in 2011

This project has the purposes:

- Developing a primary standard for flow measurements between 150 microliter per minute and 1 nanoliter per minute.
- Characterization of flow meters and flow generators already in the market.
- Assuring the traceability of the syringe pumps measurements used in drug delivery.

Collaborators of the project: CMI, CETIAT, DTI, METAS, IPQ, VSL, UME

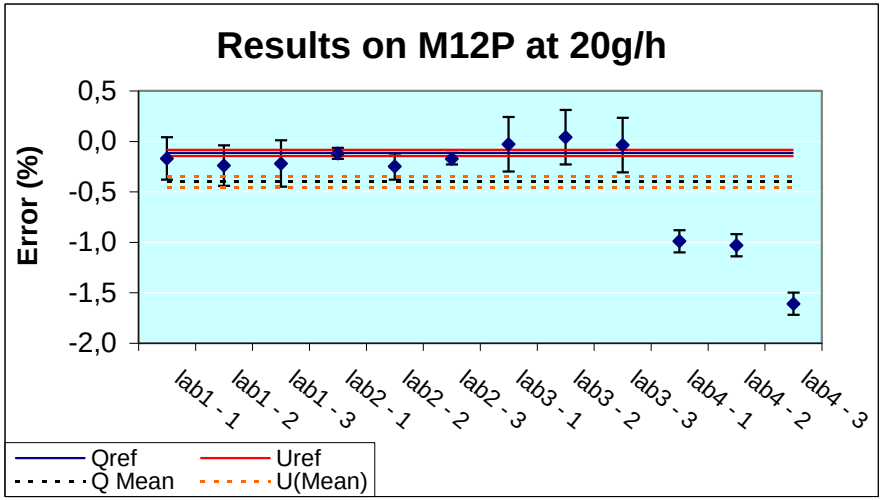
MeDD Project Status

- Primary standards completed:
  - ✓ CETIAT (not part of MeDD)
  - ✓ DTI (gravimetric – oil based cover to avoid evaporation)
  - ✓ METAS (gravimetric – water absorbing foam to avoid evaporation)
  - ✓ IPQ (gravimetric – evaporation trap/ 100% humidity to minimize evaporation)
  - ✓ VSL (gravimetric – evaporation trap/ 100% humidity to minimize evaporation(not a part of MeDD), volumetric-expansion)
  - ✓ FH Lübeck (front tracking of moving meniscus in capillary)

MeDD Comparison

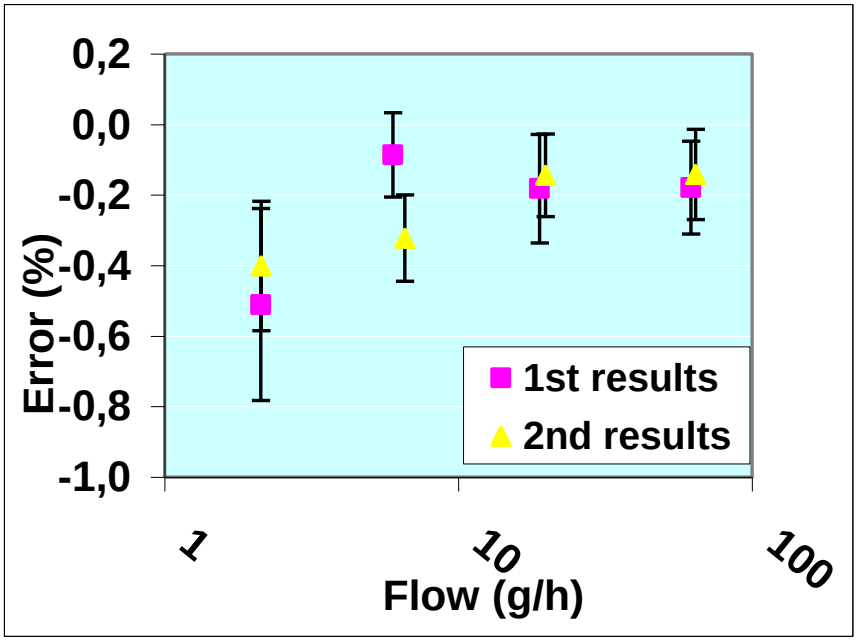
First comparison completed with Coriolis meters at 2 g/h; 6 g/h; 20 g/h; 60 g/h and 200 g/h and 600 g/h,

- ✓ There was some discrepancy, however in general the agreement was fair to good



MeDD Comparison

- ✓ Existing flow meters reproduce very well and are suitable for an intercomparison



MeDD Outlook

- Second inter comparison step has started February this year:
  - ✓ Flow meter (3 mg/h, 6 mg/h, 20 mg/h, 200 mg/h, 2000 mg/h): CETIAT, DTI, IPQ, METAS, VSL
  - ✓ Syringe pump (0.12 g/h, 0.60 g/h, 2 g/h, 6 g/h, 20 g/h): CETIAT, DTI, FH Lübeck, IPQ, MIKES, METAS, VSL
- Metrological assessment of flow meters and drug delivery devices
- Best practice guide in cooperation with health care community

www.drugmetrology.com

EMPIR

European Metrology Programme for Innovation and Research – EMPIR

EMPIR is currently a proposal of the European Commission being considered by the European Parliament and Council.

Main goals:

- Metrology research into societal challenges focusing on contributions for energy, environment and health;
- Research into novel measurement instrumentation aiming at industrial take-up of metrological technologies to stimulate innovation in industry;

EMPIR

- Pre-normative and co-normative metrology research and development for priority documentary standards;
- Metrology capacity-building activities on different technological levels aiming to achieve a balanced and integrated metrology system in Europe.

The main activities shall be carried out by NMI and DI.

EMPIR shall encourage and support the participation of other entities. This approach is expected to lead to around 15% of the budget of EMPIR going to those entities.

EURAMET and Stakeholders

- Need for cooperation between EURAMET and stakeholders in research activities.
- At the EURAMET Technical Committee for flow (TC-F) an inquiry on future flow measurements challenges is under preparation and will be sent to manufactures and industry.
- Responses are needed in order to developed a future research agenda.

Thank you

ebatista@ipq.pt