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MeDD - Task 1.1. Comparison - supplement report

Introduction

In the context of MeDD (Metrology for Drug Delivery [2]) an intercomparison between primary standards has been performed (piloted by LNE-CETIAT). The aim of intercomparison task is to validate the uncertainty of 4 primary standards (LNE-CETIAT, DTI, IPQ, EJPD) for liquid flow rates ranging from 10 ml/min down to 10µl/min (ambient pressure and temperature). This report deals with the supplement of this intercomparison, in which VSL and Bronkhorst High-Tech participated, much of this report will therefore be similar to the main intercomparison report [1].

The comparison has been performed by calibration of 2 transfer standards (TS) by all participating laboratories (both Coriolis meters). The first flowmeter has been calibrated at 2; 6; 20; 60 and 200 g/h and the second at 200 and 600 g/h. Calibrations were performed using the individual procedures and flow generators of each laboratory.

Transfer standards

The transfer standards have been transported only by road (to avoid possible influence of low pressure around the meter during air transport) in 1 transportation box. This box contained:

- Instructions sheets.
- One Bronkhorst M12P flowmeter (ref: M12P-AGP-11-0-S; S/N: B12200826A).
- One Bronkhorst M13 flowmeter (ref: M13-AAD-33-0; S/N: B8200211A).
- Two Mass Blocks (used for flowmeter stability).
- One Bright converter to check communication if needed.
- A CD with the required software.
- Electrical wires and converters and the necessary connectors.

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In Figure 1 and Figure 2 respectively the contents and arrangement are shown.

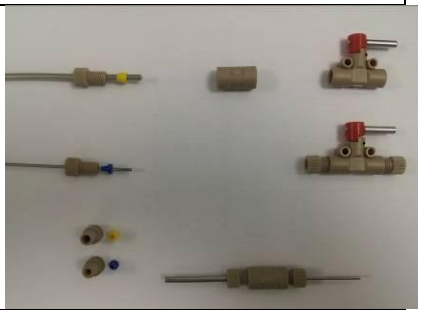
		
M12P + 2kg Mass block + valves	M13 + 2kg Mass block + Bright	CD
		
Electrical wire + signal cable	Electrical adaptators	Hydraulic connectors

Figure 1 Contents transfer standard package

For the comparison, the M12P and M13 flowmeters were sent around with 1/8" stainless steel tubing upstream and downstream from the flowmeter. Fast connecting valves (from Upchurch company) were used to connect the flow meter to the various calibration facilities, see also Figure 1. The connections have been realized as follows:

1) Install the connectors (Nut + Ferrule) on the tubes (blue ferrule for 1/16", yellow ferrule for 1/8") as shown in the figures.


2) Insert the tube in the valve until it touches the valve.
3) Screw the Nut firmly while ensuring that the end of the tube stay in contact with the inner part of the valve.
4) Test the water tightness.

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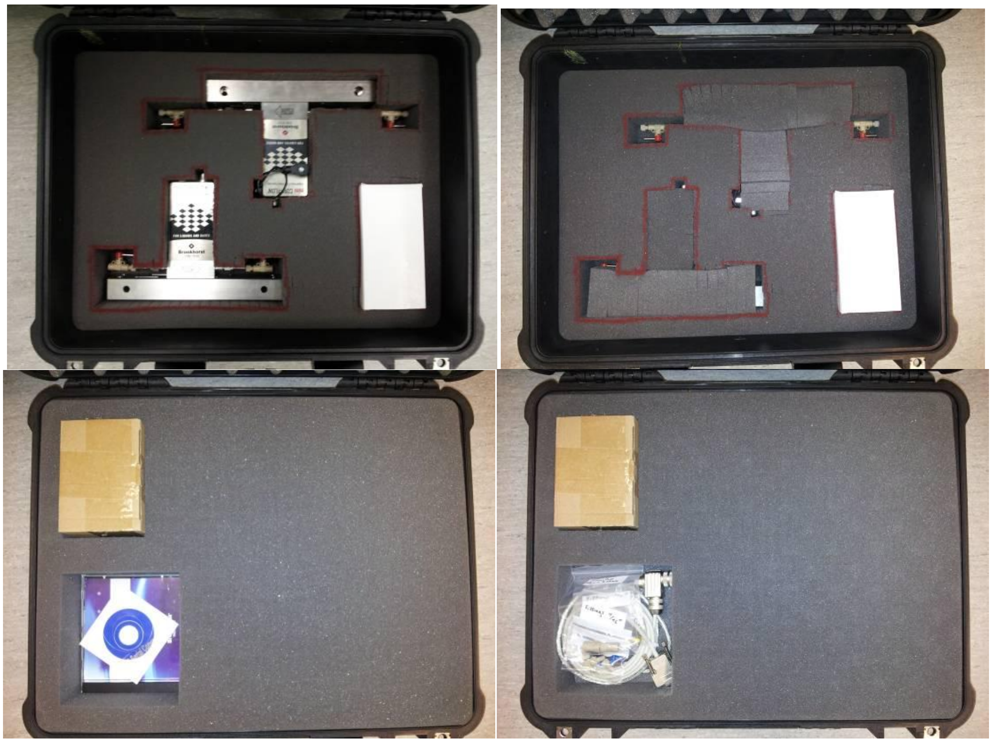

Figure 2 Arrangement transfer standard package. The CD, cables and connectors are stored on an additional layer of soft foam.

Participants and time schedule of the intercomparison

In Table 1 the participants of the intercomparison and this supplement are shown.

Table 1 Participants of the intercomparison (1-1 to 1-5) and the supplement (2-1 and 2-2)

Step n°	Laboratory (Country)	Contact Person	Date
1-1	LNE-CETIAT (France)	Christopher DAVID christopher.david@cetiat.fr +33 643 960 142	16th August 2012 to 3rd September 2012
1-2	DTI (Denmark)	Claus Melvad cmd@teknologisk.dk +45 7220 2098	7th September 2012 to 2th November 2012
1-3	EJPD (Switzerland)	Hugo Bissig hugo.bissig@metas.ch +41 31 32 34 915	19th November 2012 to 18th December 2012
1-4	IPQ (Portugal)	Elsa Batista ebatista@mail.ipq.pt	8th January to 29th January 2013

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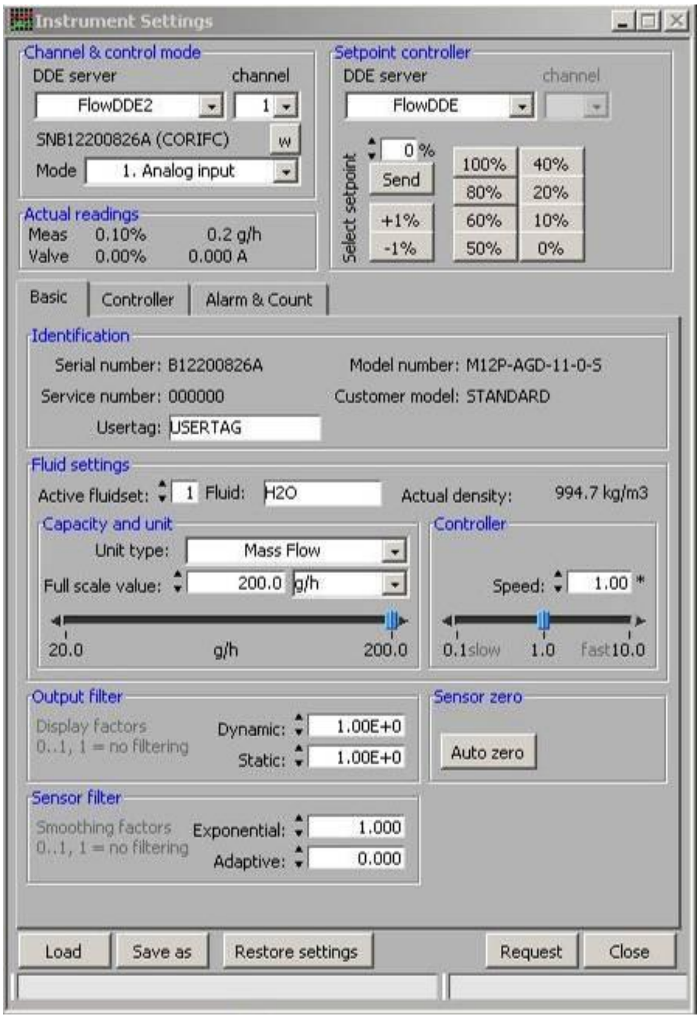
		+351 212 948 167	
1-5	LNE-CETIAT (France)	Christopher DAVID christopher.david@cetiat.fr +33 643 960 142	29th January 2013 to 3rd February 2013
2-1	Bronkhorst High-Tech (Netherlands)	Joost Lötters J.C.Lotters@bronkhorst.com	July 2013 to 26 Augustus 2013
2-2	VSL (Netherlands)	Harm Tido Petter htpetter@vsl.nl +31 15 269151677	1 September 2013 to 1 December 2013

Software

The software to read out the flow meters is available on the CD ("FlowDDE.msi" and "FlowPlot.exe"). Alternatively, the latest version can obtained on net.



The following settings need to be made (example is given on the left):

- No filters on the output and sensor signal (see the following figure)
- Acquisition sample time 100ms
- Full scale corresponding to the TS under test (200g/h for M12P and 2 000g/h for M13)

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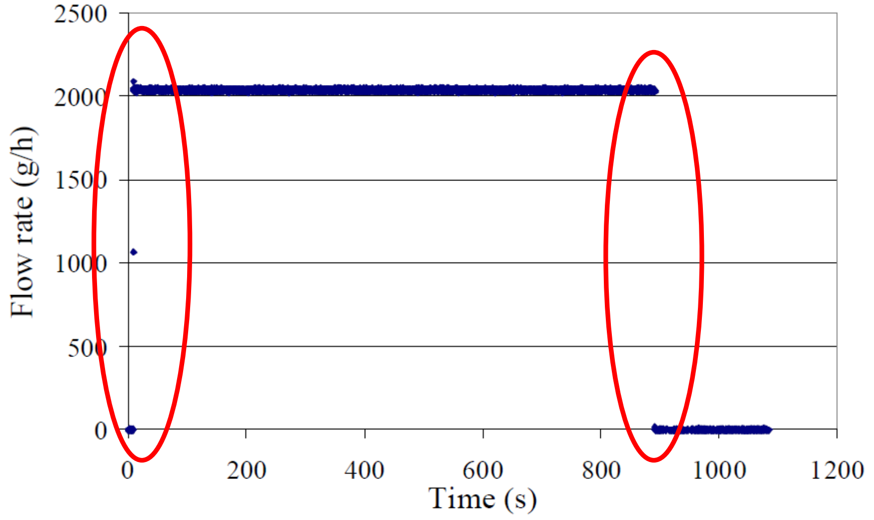
Calibration procedure

The calibration procedure has been the following (when possible):

- Upstream pressure: 0,5 to 2,5 bar
- Water temperature: 20°C +/- 1°C
- Water flows : 600 and 200 g/h for the M13 (with a minimum of 3 points)
- Water flows : 200; 60; 20; 6 and 2 g/h for the M12P (with a minimum of 3 points)

Before the first calibration is started it is recommend to prime for at least 30 minutes. Therefore, verify whether the system is fully degassed. This can be checked by quickly opening and closing a valve (less than 1s) just upstream and downstream of the meter. If the flow meter curve presents a sharp change in flow rate (less than 1s answer with no oscillation of the flow, see below example), one can expect that the system is properly degassed.



Finally, before the first calibration is performed the meter should be zeroed. Therefore close the upstream and downstream valves (with the pressure corresponding to the calibration to be performed) and perform the “zero” procedure. The “zero” procedure was repeated only one time for each flowmeter and then calibration points were realized according to partner procedures. At least 3 independents points were realized for each flow value (2 repetitions).

Measurement results

In Table 2 to Table 10 the measurement results obtained by Bronhorst, VSL and the intercomparison are shown. For the M12p, VSL performed only measurements for the larger two flow points because of difficulties with the set up (damaged mass flow controller).

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For the average results from the intercomparison a distinction is made between all results and the results where the outliers have been discarded. For the measurements on the M12p, all results from lab 1 have been discarded because of an apparent systematic error. Furthermore, for the measurements on the M12p, the results from lab 4 for the lowest flow point have been discarded because these results are far off from the results obtained by lab 2, lab 3 and Bronkhorst. In Figure 3 and Figure 4 the average results are shown. Note that most deviations are negative which implies that leakages are not important (a leakage typically leads to a positive error because the meter 'sees more fluid than the balance').

During the intercomparison the reproducibility has been checked for the M12P, however not after the supplement. Therefore, it is assumed that the meter has not significantly drifted. The good confirmation between the results confirm a no drift (later discussed).

Table 2 Average results intercomparison.

		All results		no outliers	
target flow rate	Transfer standard	weigthed error	weighted uncertainty	weighted error	weighted uncertainty
(g/h)	(-)	(%)	(%)	(%)	(%)
2.00	M12p	-0.29	0.18	-0.51	0.27
6.00	M12p	-0.19	0.11	-0.17	0.11
20.00	M12p	-0.27	0.10	-0.16	0.11
60.00	M12p	-0.23	0.07	-0.17	0.07
200.00	M12p	-0.20	0.07	-0.16	0.07
200.00	M13	-0.08	0.05	-0.08	0.05
600.00	M13	-0.03	0.06	-0.03	0.06

Table 3 All measurement results for the M12p obtained by VSL

point	target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(-)	(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
1	60	NA	1.33	59.76	59.66	0.12	-0.17	0.20
2	200	NA	1.74	198.58	198.35	0.18	-0.12	0.09
3	200	NA	1.85	196.52	196.23	0.18	-0.14	0.09
4	200	NA	1.78	193.40	193.13	0.16	-0.14	0.08

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Table 4 Average results for the M12p obtained by VSL

target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
60	NA	1.33	59.76	59.66	0.12	-0.17	0.20
200	NA	1.79	196.16	195.91	0.17	-0.13	0.09

Table 5 All measurement results for the M13 obtained by VSL

point	target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	reference uncertainty
(-)	(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
4	200	NA	11.1	203.6	203.7	0.2	0.07	0.11
5	200	NA	11.7	207.8	208.0	0.2	0.06	0.11
6	200	NA	3.5	207.7	207.9	0.2	0.11	0.12
7	200	NA	3.5	206.6	206.8	0.2	0.06	0.08
1	600	NA	5.8	605.3	604.6	0.7	-0.11	0.12
2	600	NA	5.8	590.9	591.1	0.7	0.04	0.11
3	600	NA	5.8	596.3	595.9	0.7	-0.07	0.11

Table 6 Average results for the M13 obtained by VSL

target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	reference uncertainty
(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
200	NA	7.4	206.4	206.6	0.2	0.08	0.11
600	NA	5.8	597.5	597.2	0.7	-0.05	0.11

Table 7 Average results for the M12p obtained by Bronkhorst

target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
2	NA	5.97	2.01	2.00	0.01	-0.55	0.31
6	NA	5.88	6.01	6.00	0.01	-0.23	0.11
20	NA	5.57	20.03	20.00	0.01	-0.15	0.06
60	NA	5.20	60.09	59.99	0.03	-0.16	0.05
200	NA	4.55	200.34	199.98	0.09	-0.18	0.05

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Table 8 All results for the M12p obtained by Bronkhorst

point	target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(-)	(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
5	2	NA	5.92	2.01	2.00	0.01	-0.56	0.31
10	2	NA	5.93	2.01	2.00	0.01	-0.62	0.31
15	2	NA	6.01	2.01	2.00	0.01	-0.50	0.31
20	2	NA	6.01	2.01	2.00	0.01	-0.51	0.31
4	6	NA	5.88	6.01	5.99	0.01	-0.24	0.11
9	6	NA	5.91	6.01	5.99	0.01	-0.23	0.11
14	6	NA	5.88	6.01	6.00	0.01	-0.23	0.11
19	6	NA	5.84	6.01	6.00	0.01	-0.22	0.11
3	20	NA	5.57	20.03	20.00	0.01	-0.15	0.06
8	20	NA	5.55	20.03	20.00	0.01	-0.15	0.06
13	20	NA	5.62	20.03	20.00	0.01	-0.15	0.06
18	20	NA	5.55	20.02	20.00	0.01	-0.14	0.06
2	60	NA	5.25	60.09	59.99	0.03	-0.16	0.05
7	60	NA	5.17	60.09	59.99	0.03	-0.16	0.05
12	60	NA	5.25	60.10	60.00	0.03	-0.16	0.05
17	60	NA	5.15	60.09	60.00	0.03	-0.15	0.05
1	200	NA	4.59	200.32	199.96	0.09	-0.18	0.05
6	200	NA	4.40	200.37	200.01	0.09	-0.18	0.05
11	200	NA	4.72	200.34	199.99	0.09	-0.18	0.05
16	200	NA	4.51	200.32	199.98	0.09	-0.17	0.05

Table 9 All results for the M13 obtained by Bronkhorst

point	target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(-)	(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
1	200	NA	3.65	200.28	199.98	0.09	-0.15	0.05
2	200	NA	3.65	200.24	199.97	0.09	-0.14	0.05
3	200	NA	3.81	200.25	199.95	0.09	-0.15	0.05
4	200	NA	3.71	200.25	199.98	0.09	-0.13	0.05
5	200	NA	3.65	200.25	199.95	0.09	-0.15	0.05

Table 10 Average results for the M13 obtained by Bronkhorst

target flow rate	water temperature	upstream pressure	reference flowrate	indicated flowrate	uncertainty	error	uncertainty
(g/h)	(°C)	(barg)	(g/h)	(g/h)	(g/h)	(%)	(%)
200	NA	3.69	200.25	199.97	0.09	-0.14	0.05

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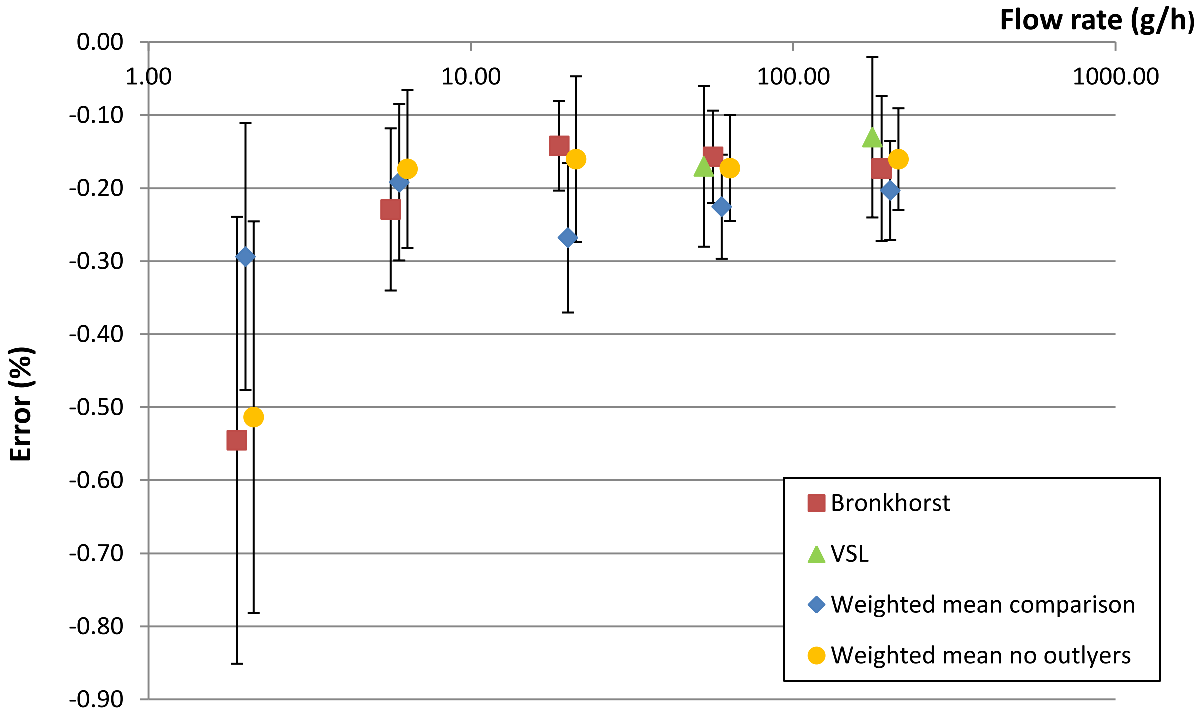

Figure 3 Graphical presentation measurement results

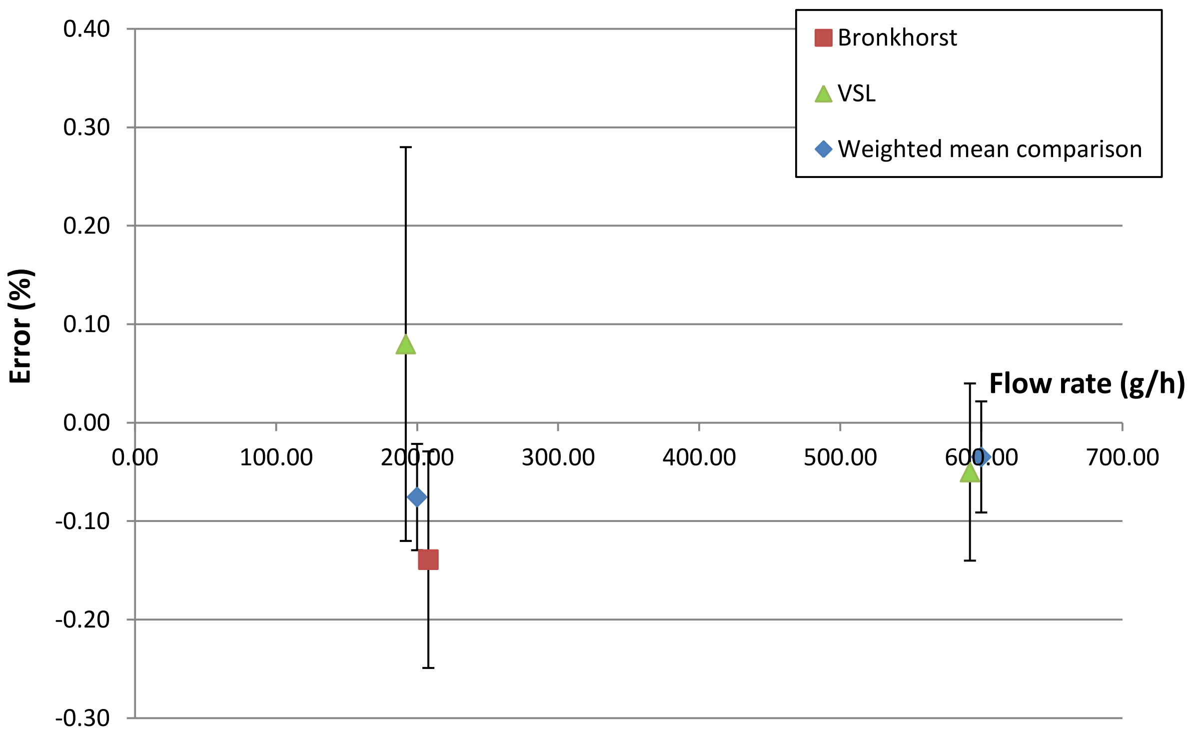

Figure 4 Graphical presentation measurement results

Discussion

The results are analyzed by the comparison of the average results of the participants. Here, the average results from lab 2 to lab 4 are treated as one participant. The well-known E_n value is determined by:

$$E_n = \frac{LAB - REF}{\sqrt{(U_{95}LAB)^2 + (U_{95}REF)^2}}$$

where

$$REF = \frac{\sum\left(LAB/(U_{95}LAB)^2\right)}{\sum\left(1/(U_{95}LAB)^2\right)}$$

and

$$U_{95}REF = \frac{1}{\sqrt{\sum\frac{1}{(U_{95}LAB)^2}}}$$

Table 11 and Table 12 display the average and E_n values for the various ‘participants’. This these tables show that all measurement results are in good agreement. Therefore, one can conclude that the primary standards and accompanying uncertainty budgets of VSL and Bronkhorst have been validated for the flow points measured. Finally, in Table 13 the average calibration values for the M12p and M13 are shown.

Table 11 Average results and E_n values for the M12p

	Bronkhorst			VSL			Intercomparison (no outlyers)		
flow rate (g/h)	error (%)	uncertainty (%)	E_n (-)	error (%)	uncertainty (%)	E_n (-)	error (%)	uncertainty (%)	E_n (-)
2.00	-0.55	0.31	0.05	NA	NA	NA	-0.51	0.27	0.04
6.00	-0.23	0.11	0.21	NA	NA	NA	-0.17	0.11	0.20
20.00	-0.14	0.06	0.05	NA	NA	NA	-0.16	0.11	0.11
60.00	-0.16	0.06	0.10	-0.17	0.11	0.05	-0.17	0.07	0.09
200.00	-0.17	0.10	0.14	-0.13	0.11	0.22	-0.16	0.07	0.04

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Table 12 Average results and E_n values for the M13

	Bronkhorst			VSL			Intercomparison (no outlyers)		
flow rate (g/h)	error (%)	uncertainty (%)	E_n (-)	error (%)	uncertainty (%)	E_n (-)	error (%)	uncertainty (%)	E_n (-)
200.00	-0.14	0.11	0.48	0.08	0.20	0.79	-0.08	0.05	0.03
600.00	NA	NA	NA	-0.05	0.09	0.13	-0.03	0.06	0.08

Table 13 Average calibration values for the M12p and M13

flow rate (g/h)	TS	weighted error (%)	weighted uncertainty (%)
2.00	M12p	-0.53	0.20
6.00	M12p	-0.20	0.08
20.00	M12p	-0.15	0.05
60.00	M12p	-0.16	0.04
200.00	M12p	-0.16	0.05
200.00	M13	-0.08	0.04
600.00	M13	-0.04	0.05

Conclusions

From the main intercomparison the following conclusions were drawn:

- Both flowmeters used for the comparison (M12P and M13) are repeatable enough to perform a comparison.
- Both flowmeters used for the comparison (M12P and M13) seem reproducible enough to perform a comparison.
- Except for the lowest flow point, the primary standards of lab 2 to lab 4 and the accompanying uncertainty budgets have been validated for the flow points carried out for the M12p. The uncertainties claimed by lab 1 are not in agreement with the results obtained. Later, it was found that lab 1 has a systematic error.
- The measurement results for the M13 are inconclusive.

From the supplement comparison, the following conclusions can be drawn:

- For the M12p, the results by lab-2, lab-3, lab-4, Bronkhorst and VSL are consistent for flow rates down to 6 g/h. For a flow rate of 2 g/h, lab-4 is somewhat off compared to the former mentioned. For all flow rates, lab-1 is off.
- For the M13, the results by lab-2, Bronkhorst and VSL are consistent, whereas lab-1 and lab-4 are off. However, one could argue that there are too few measurements to back this up.

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References

[1] David, C. *et al.*, *Project MeDD – Task 1.1 Comparison report*, technical report, available online at: http://www.drugmetrology.com/images/Publications/MeDD_-_final_comparison_report.pdf, 2013

[2] Lucas, P. *et al.*, *Metrology for drug delivery*, EU-funded research project, 2012 - 2015, partners VSL, Cetiat, CMI, DTI, EJPD, IPQ, Tubitak, web site at: http://www.drugmetrology.com

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