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Intercomparison of micro-liquid flow standard system in APMP

S. H. Lee[1], Y. Zeng[2], K.-C. Tsai[3], K.-H. Cheong[4], T. Chinarak[5]

[1]KRISS, Daejeon, Korea
*[2]NMC A*STAR, Singapore*
[3]CMS, Hsinchu, Chinese Taipei
[4]NMIJ, Tsukuba, Japan
[5]NIMT, Pathumthani, Thailand

E-mail (corresponding author): seokhwan.lee@seokhwan.lee

Abstract

A pilot study was conducted to compare the microflow rate from 2 to 200 g/h in the APMP TCI project (TCFF_01_TCI2019). A syringe pump (Chemyx Nexus 3000) and Coriolis flowmeter (Bronkhorst M12) were used as the transfer standards. The comparisons were coordinated in the KRISS institute, which was also responsible for the pilot study. The volumetric flow rate was measured using a syringe pump and the measured flow rates were 33, 100, 333, 500, and 1000 µL/min and the institutes that participated in the international comparison of micro-liquid volumetric flow rates were KRISS, NMC A*STAR, and CMS, all of which used water as the working fluid. To measure the mass flow rate, a Coriolis flow meter was used; the flow rates were 2, 6, 20, 60, and 200 g/h and the institutes that participated in this international comparison of micro-liquid mass flow rates were KRISS, NMC A*STAR, CMS, NMIJ, and NIMT. All of the participating institutes used water as the working fluid, except for the NMIJ, which used light oil. The E_n values for the syringe pumps and mass flow meters were calculated based on reference values and were less than 1 for all the flow rates determined by the participating institutes. Therefore, the international equivalence of the micro-liquid flow standard system of the participating APMP institutions was confirmed.

1. Introduction

Drug delivery devices are widely used in clinical environments; therefore, several national metrology institutes (NMIs) have investigated traceable calibration facilities for microfluidic devices and have developed primary standards for micro-flow rates based on the gravimetric principle [1–2]. A comparison of micro-flow rates (0.12–200 g/h) was conducted in Europe, at the NMI level, through the EURAMET research project “MeDD I” [3], wherein several investigations were performed on the development of new traceable techniques for measuring flow rate from 5 to 100 nL/min. An uncertainty of 1% (k = 2) or better was expected for steady flow rates, whereas for fast changing flow rates an uncertainty of 2% (k = 2) or better was expected. The project investigated different flow rate regimes, liquid mixing behaviour and occlusion phenomena in multi-infusion systems with the purpose of improving dosing accuracy in each infusion line [4].

In addition, there were NMIs that established a micro-flow standard system in the APMP region. Therefore, a pilot study is required to compare the new system. The KRISS, NMC A*STAR, CMS, NMIJ, and NIMT institutes participated in international comparisons, and the KRISS institute was responsible for the pilot study. A syringe pump and a Coriolis mass flow meter were used for the comparison, with the syringe pump ranging from 33 to 1000 µL/min and the mass flow meter ranging from 2 to 200 g/h. The results of the participating NMIs were evaluated as E_n values and were ≤1 in all flow ranges.

2. Description of the transfer standard

2.1 Syringe pump

A syringe pump (Nexus 3000, Chemyx®) was used to measure the volumetric flow, as shown in Figure 1. The syringes were made of H-TLL with a PTFE seal (manufacturer ILS Innovative Labor System GmbH).

Figure 1: Chemyx Nexus 3000 syringe pump.

2.2 Coriolis flow meter

A Coriolis flow meter (Bronkhorst High-Tech) was used to measure the mass flow rate, as shown in Figure 2 (ref: M12P-AAD-22-0-S; S/N: M17212955A), with 1/8" stainless-steel tubing and fast-connecting valves (Upchurch).

Figure 2: Coriolis flow meter including mass block from Bronkhorst High-Tech.

3. Measurement procedure

3.1 Measured quantity

The intercomparison was based on comparing the relative error of the transfer standards as determined by the participating institutes. The relative error ε (%) is defined as

$$\varepsilon = \frac{q_{indicated} - q_{ref}}{q_{ref}},$$

where $q_{indicated}$ denotes the flow rate indicated by the flow meter or set point of the syringe pump and q_{ref} denotes the reference flow rate. For the syringe pump, the volumetric flow rate was measured, whereas the mass flow rate was used for the Coriolis flow meter.

3.2 Calibration protocol and measurement conditions

The participating NMIs used their own calibration procedures to calibrate the flow meter and syringe pump, described the calibration protocol, and provided the measurement conditions. It should be noted that a distinction was made between the syringe pump and the flow meter and the other measurement conditions were as follows.

3.2.1 Syringe pump

Table 1 summarizes the syringe volume, inner diameter, and measurement time according to the flow rate for measurement comparison of the syringe pump. The following measurement conditions were used:

- the working fluid was water,
- the water temperature was between 20 and 23 ℃,
- the measurement time followed the start/end position and plunger velocity,
- a minimum of three repetitions were conducted, and
- flow rates of 33, 100, 333, 500, and 1000 µl/min were used.

Table 1: Syringe and dispensed volumes and flow rates.

Flow rate (µl/min)	Syringe volume (ml)	Inner diameter (mm)	Dispensed volume (ml)	Measurement time (min)
33	5	10.30	1.5	45
100	25	23.03	3	30
333	25	23.03	3	9
500	25	23.03	3	6
1000	25	23.03	3	3

3.2.2 Flow meter

Table 2 summarizes the measurement time and full-scale values according to the flow rate for comparing the flow meter measurements. The following measurement conditions were used:

-the working fluid was water and light oil for NMIJ,
-the upstream pressure was between 0.5 and 2.5 bar depending on the required flow rate,
-the water temperature was between 20 and 23 ℃,
-the minimal measurement time depended on the setup; however, maintaining a stable flow rate for at least 1 min was sufficient,
-a minimum of three repetitions were conducted, and
-flow rates of 2, 6, 20, 60, and 200 g/h were used.

Table 2: Flow rates, measurement time, and maximum set flow rate of flowmeter.

Flow rate (g/h)	Measurement time (min)	Full scale value (g/h)
2	45	5
6	30	10
20	9	40
60	3	100
200	3	200

4. Measurement procedure

4.1 Stability of the transfer standards

4.1.1 Syringe pump

The stability of the syringe pump was checked by a pilot lab and the error at the beginning and end of the intercomparison was determined; the reproducibility of the syringe pump is shown in Table 3.

The uncertainty due to drift follows from the difference in the measured error, and assuming a uniform distribution, is expressed as

$$u_{drift} = \frac{\Delta\varepsilon}{2\sqrt{3}},$$

where u_{drift} (k = 2) is the uncertainty due to drift (reproducibility) and $\triangle\ \varepsilon$ is the difference in the measured error at the beginning and end of the intercomparison. The uncertainty due to the drift was added to the calibration uncertainty.

Table 3: Reproducibility for the syringe pump.

		Start of intercomparison		End of intercomparison		Reproducibility
Target flowrate (µl/min)	Syringe volume (ml)	Error (%)	Sample std (%)	Error (%)	Sample std (%)	△Error (%)
33	5	0.21	0.1	0.19	0.1	0.02
100	25	−0.15	0.2	−0.04	0.2	0.11
333	25	0.01	0.2	0.21	0.2	0.2
500	25	0.14	0.2	0.24	0.2	0.1
1000	25	0.00	0.3	0.20	0.3	0.2

4.1.2 Flow meter

The stability of the flowmeter was checked in a pilot lab, which determined the error at the beginning and end of the intercomparison. The reproducibility of the Coriolis flow meter is presented in Table 4 and the uncertainty due to the drift was added to the calibration uncertainty.

Table 4: Reproducibility for the Coriolis flow meter.

	Start of intercomparison		End of intercomparison		Reproducibility
Target flowrate (g/h)	Error (%)	Sample std (%)	Error (%)	Sample std (%)	△Error (%)
2	−1.42	0.7	−2.19	0.7	0.77
6	−0.20	0.5	0.11	0.5	0.31
20	0.02	0.2	−0.03	0.2	0.05
60	0.06	0.2	0.00	0.2	0.06
200	0.18	0.3	0.10	0.3	0.08

4.2 Laboratory results

4.2.1 Syringe pump

Table 5 shows the calibration results of the syringe pump determined by the participating institutes.

Table 5: Error (%) of the syringe pump determined by the participating labs**.**

Flow rate (µl/min)	Syringe pump (ml)	KRISS	NMC A*STAR	CMS
33	5	0.21	0.41	-0.2
100	25	−0.01	0.15	0.00
333	25	0.00	0.14	0.10
500	25	0.14	0.33	0.10
1000	25	0.00	0.20	0.10

4.2.2 Flow meter

The calibration results of the flow meter determined by the participating institutes are shown in Table 6. As mentioned earlier, NMIJ used light oil as the working fluid and the rest of the participating institutes used water.

Table 6: Error (%) of the Coriolis flow meter as the function of the indicated flow rate determined by the participating labs.

Flow rate (g/h)	KRISS	NMC A*STAR	CMS	NMIJ	NIMT
2	−1.42	−1.54	−1.7		−1.486
6	−0.20	0.06	0.40		0.244
20	0.02	0.10	0.00	−0.057	−0.239
60	0.06	0.03	0.00	−0.014	0.046
200	0.18	0.29	−0.1	−0.004	0.154

4.3 Uncertainty

4.3.1 Calibration uncertainty for syringe pump flow points.

The calibration uncertainty (k = 2), including the difference in the syringe pump flow points, is given in Table 7.

Table 7: Calibration uncertainty, including the difference in the syringe pump flow points determined by the participating labs.

Flow rate (µl/min)	Syringe pump (ml)	KRISS	NMC A*STAR	CMS
33	5	0.30	0.28	2.50
100	25	0.31	0.12	0.90
333	25	0.23	0.15	0.41
500	25	0.21	0.12	0.31
1000	25	0.23	0.15	0.32

4.3.2 Calibration uncertainty for flow meter flow points

The calibration uncertainty (k = 2), including the drift of the flow meter, is given in Table 8.

Table 8: Calibration uncertainty, including the drift of the flow meter determined by the participating labs.

Flow rate (g/h)	KRISS	NMC A*STAR	CMS	NMIJ	NIMT
2	0.83	0.78	0.83		0.65
6	0.53	0.43	0.43		0.63
20	0.20	0.42	0.30	0.06	0.49
60	0.20	0.38	0.30	0.06	0.38
200	0.30	0.38	0.50	0.07	0.37

5. Evaluation

This section presents an evaluation of the results to determine whether the calibration results of the participating institutes were consistent. To determine consistency, the well-known E_n, was used. This value is defined as

$$E_{n_{lab-i}} = \frac{\varepsilon_{lab-i} - \varepsilon_{RV}}{\sqrt{U(\varepsilon_{lab-i})^2 - U(\varepsilon_{RV})^2}},$$

where $\varepsilon_{lab\text{-}i}$ denotes the error of lab-i for a certain flow point, ε_{RV} denotes the comparison reference value (RV) for the error, and $U(\varepsilon_{lab\text{-}i})$ and $U(\varepsilon_{RV})$ denote the expanded uncertainties (k = 2) of those values. The (expanded) uncertainty includes the uncertainty in the reference flow rate, repeatability, and reproducibility.

The value of E_n would imply the following:

-If $E_n \leq 1$, the results of the laboratory, for a certain flow point, are consistent (passed).

-If $E_n > 1.2$, the results of the laboratory, for a certain flow point, are inconsistent (failed).

For results between $1 < E_n \leq 1.2$, a "warning level" is defined and that particular laboratory is recommended to check its procedures and methodology.

The comparison reference value is the weighted average of the uncertainty error, which is determined as follows:

$$\varepsilon_{RV} = \frac{\sum_{i-1}^{n} \frac{\varepsilon_{lab-i}}{U(\varepsilon_{lab-i})^2}}{\sum_{i=1}^{n} \frac{1}{U(\varepsilon_{lab-i})^2}},$$

where, n denotes the number of participating institutes. The uncertainty of RV is defined as

$$u(\varepsilon_{RV}) = \frac{1}{\sqrt{\sum_{i=1}^{n} \frac{1}{U(\varepsilon_{lab-i})^2}}}.$$

Finally, the chi-square test was applied to determine whether the errors and accompanying uncertainties could be expected based on a Gaussian distribution. The chi-squared test is defined for each flow point as

$${x_{obs}}^2 = \sum_{i=1}^{n} \left(\frac{\varepsilon_{lab-i} - \varepsilon_{RV}}{u(\varepsilon_{lab-i})} \right)^2,$$

where $u(\varepsilon_{lab\text{-}i})$ is the standard uncertainty (k = 1). The set of measurement results, for a certain flow point, is only accepted when

$$\Pr(x^2(n-1) > {x_{obs}}^2) < 0.05,$$

where Pr denotes the probability and $x(n)$ denotes the expected value of a Gaussian distribution. The CHIINV (probability, degrees of freedom−1) function from Excel can be rewritten as follows, for a consistent set (coverage factor 95 %):

$${x_{obs}}^2 < \mathrm{CHIINV}(0.05, \mathrm{n}-1).$$

Hence, if the observed chi-square value satisfies the above equation, the reference value is accepted. Otherwise, the result with the largest contribution to ${x_{obs}}^2$ was discarded, the test was repeated, and the degree of freedom was reduced by one.

5.1 Syringe pump

Figure 3 shows the syringe pump calibration results determined by the participating institutes. In Figure

4 and Table 9, the degree of equivalence (E_n) values are given. Table 10 presents the reference and uncertainty values of the syringe pump measurements and Table 11 lists the observed chi-squared value x_{obs}^2, population size n, and threshold $x^2(n-1)$ for the syringe pump intercomparison.

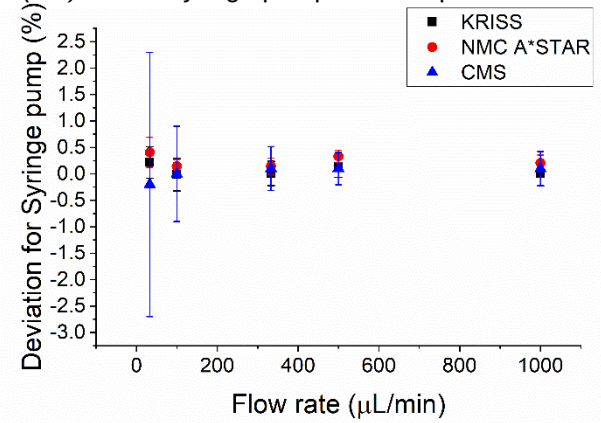

Figure 3: Intercomparison results of the syringe pump. The uncertainty includes the uncertainty in reference flow rate, repeatability, and drift.

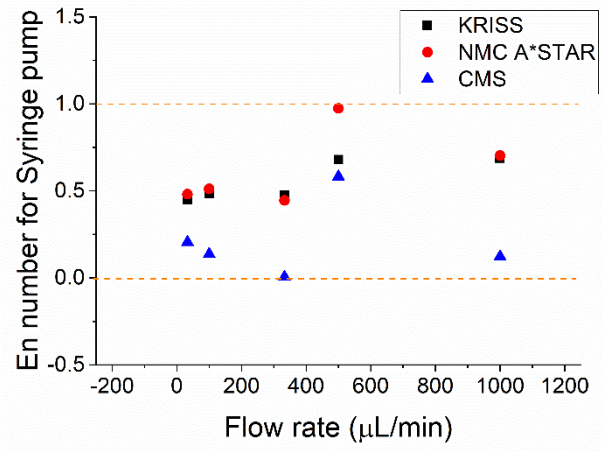

Figure 4: Degree of equivalence (E_n) for the syringe pump intercomparison.

Table 9: Degree of equivalence (En) for the syringe pump intercomparison.

Flow rate (μl/min)	KRISS	NMC A*STAR	CMS
33	0.45	0.48	0.21
100	0.48	0.51	0.14
333	0.48	0.45	0.00
500	0.68	0.97	0.58
1000	0.69	0.70	0.12

Table 10: Reference and uncertainty values of the syringe pump measurements.

Flow rate (μl/min)	Error	Uncertainty
33	0.31	0.21
100	0.12	0.11
333	0.10	0.12
500	0.27	0.10
1000	0.14	0.12

Table 11: Observed chi-squared value x_{obs}^2, population size n, and threshold $x^2(n-1)$ for the syringe pump intercomparison.

Flow rate (g/h)	n	x_{obs}^2	$x^2(n-1)$
33	3	1.75	5.99
100	3	1.84	5.99
333	3	0.94	5.99
500	3	3.85	5.99
1000	3	1.46	5.99

5.2 Flow meter

Figure 5 shows the calibration results of the flow meter. The uncertainty in Figure 5 includes the uncertainty in the reference flow rate, repeatability, and drift. In Figure 6 and Table 12, the degree of equivalence (E_n) values are given. Table 13 presents the reference and uncertainty values of the flow meter measurements and Table 14 lists, the observed chi-squared value x_{obs}^2, population size n, and threshold $x^2(n-1)$ for the flow meter intercomparison.

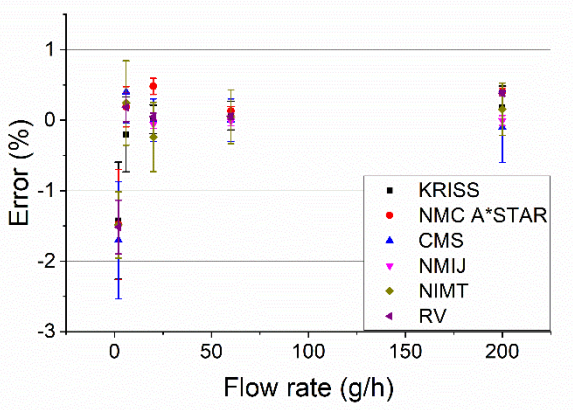

Figure 5: Intercomparison results of the flow meter. The uncertainty includes the uncertainty in reference flow rate, repeatability, and drift.

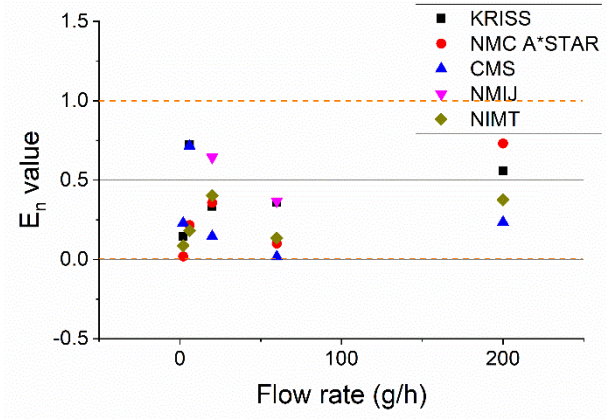

Figure 6: Degree of equivalence (E_n) for the flow meter intercomparison.

Table 12: Degree of equivalence (E_n) for the flow meter intercomparison.

Flow rate (g/h)	KRISS	NMC A*STAR	CMS	NMIJ	NIMT
2	0.15	0.02	0.23		0.09
6	0.72	0.22	0.71		0.18
20	0.37	0.36	0.16	0.37	0.39
60	0.36	0.10	0.02	0.37	0.13
200	0.56	0.73	0.23	0.84	0.37

Table 13: Reference and uncertainty values of the flow meter measurements.

Flow rate (g/h)	Error	Uncertainty
2	−1.53	0.38
6	0.14	0.24
20	−0.05	0.06
60	0.00	0.06
200	0.02	0.07

Table 14: Observed chi-squared value x_{obs}^2, population size n, and threshold $x^2(n-1)$ for the flow meter intercomparison.

Flow rate (g/h)	n	x_{obs}^2	$x^2(n-1)$
2	4	0.25	7.81
6	4	3.28	7.81
20	5	1.78	9.49
60	5	0.67	9.49
200	5	4.35	9.49

7. Conclusion

A pilot study was conducted to measure and compare the microflow rate from 2 to 200 mL/h in the APMP TCI project (TCFF_01_TCI2019). The volumetric flow rate was measured using a syringe pump and the measured flow rates were 33, 100, 333, 500, and 1000 µL/min and the institutes that participated in this international comparison of micro-liquid volumetric flow rates were the KRISS, NMC A*STAR, and CMS institutes, all of which used water as the working fluid. A Coriolis flow meter was used to measure the mass flow rates; the flow rates were 2, 6, 20, 60, and 200 g/h, and the KRISS, NMC A*STAR, CMS, NMIJ, and NIMT institutes participated in this international comparison of micro-liquid mass flow rates.

The E_n values of the syringe pump and flow meter were less than 1 for all flow rates measured by the participating laboratories. Therefore, the international equivalence of the micro-liquid flow standard system of the participating APMP institutions was confirmed.

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