Improvement of Coagulation Laboratory Practice in Thailand

The First-Year Experience of the National External Quality Assessment Scheme for Blood Coagulation

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• ***Context.*—In Thailand until 2005 there had been no external quality assessment scheme at the national level for blood coagulation tests. Only a few laboratories had an external quality assessment for these tests. In the year 2005, the Thailand National External Quality Assessment Scheme for Blood Coagulation was founded.**

***Objectives.*—To describe the establishment of the Thailand National External Quality Assessment Scheme for Blood Coagulation (including problems encountered and solutions), its progression and expansion, and the improvement of coagulation laboratory practice in Thailand during 2 trial surveys and 4 formal surveys conducted in the first 1½ years.**

***Design.*—Between 2005 and 2006, the external quality assessment samples for prothrombin time/international normalized ratio and activated partial thromboplastin time were distributed to the participants as well as the instructions and suggestions for the improvement of laboratory practice. From the data collected, the all-method coefficient of variation of the international normalized ratio and activated partial thromboplastin time was calculated for each survey.**

***Results.*—The number of participants increased during the first 1½ years that the surveys were conducted, from 109 to 127. Survey data demonstrate an improvement in response rate and an increase in the number of laboratories that determine their own reference ranges and repeat this for every change of reagent lot, using the appropriate anticoagulant. The increased precision of tests is indicated by the decrease of the all-method coefficient of variation of the international normalized ratio and activated partial thromboplastin time. Examples of individual laboratory improvement through feedback are also described.**

***Conclusions.*—The improvement of coagulation laboratory practice both through the instructions provided and liaison with participants was observed during the course of this scheme.**

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Coagulation tests are essential laboratory assays to investigate bleeding disorders and thrombotic disorders, as well as to monitor the effectiveness of the anticoagulant. Like other medical laboratory tests, external quality assessment (EQA) is a necessary part of quality assurance. It is also a powerful tool for improving the quality of the laboratory service.[1] Previously in Thailand there was no EQA scheme for blood coagulation tests conducted at a national level. Only a few laboratories had an EQA for these tests, due to the fact that the international EQA schemes have limited accessibility or are costly.[2] In the year 2005, the Thailand National External Quality Assessment Scheme (NEQAS) for Blood Coagulation was founded with the encouragement of World Health Organization International External Quality Assessment Scheme for Blood Coagulation (WHO IEQAS), of which the Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, is a member. This scheme is under the responsibility of this department and the Thai Society of Clinical Pathology. The first preliminary trial survey was carried out in July 2005, followed by the second trial survey in December 2005. The first formal survey began in 2006 with quarterly sample distributions.

We describe here the establishment of the Thai NEQAS for blood coagulation, including problems encountered and solutions, its progression and spread, and the improvement of coagulation laboratory practice in Thailand during the first trial survey through the last survey of the year 2006.

MATERIALS AND METHODS

Members

To form the first group of members, 220 questionnaires were sent to provincial and regional public hospitals, to university hospitals, and to large private hospitals that were expected to be able to perform coagulation tests. These hospitals were asked to participate in the NEQAS for blood coagulation tests. Because there is no national policy that hospitals of a certain size should have the ability to provide coagulation tests, we did not have a more accurate mechanism to recruit the participants.

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The questionnaires contained questions concerning their laboratory practices to investigate those common practices that should be improved, the details of which were described elsewhere.[2]

Scope of Tests

Tests included in the EQA were prothrombin time (PT) and international normalized ratio (INR) as well as activated partial thromboplastin time (aPTT) and aPTT ratio.

Survey Materials

Commercial control plasmas, both normal and abnormal level (Citrol, Dade Behring, Marburg, Germany), donated by Sysmex Corporation, Kobe, Japan, were used in the surveys. The stability was tested by keeping the lyophilized plasmas in a non–air conditioned room for at least 20 days. In formal surveys, each participant received 3 samples, 1 normal and 2 abnormal.

Distribution

The survey samples were distributed by an express mail service, which guaranteed the time of delivery would be within 1 to 3 days.

Form

Participants were identified by code. In the form of data collection, information was requested on the following items:

- Date of receipt and specimen analysis
- Name of the responsible person
- The concentration of sodium citrate used for specimen collection
- Analyzer and reagents used
- International sensitivity index of the prothrombin reagent
- Reference ranges of PT and aPTT
- The source of reference ranges and denominators for the calculation of PT ratio (consequently INR) and aPTT ratio
- Number of healthy subjects used for establishing reference ranges
- Whether the determination of the ranges is repeated on every change of reagent lot
- The results of PT and aPTT
- Interpretation of the PT and aPTT results (normal, borderline, abnormal)
- INR and aPTT ratio

In the sixth survey, which was conducted in December 2006, aPTT ratio was not reported; the central data center calculated the test-normal ratio by dividing the result by midpoint of the individual laboratory reference range, according to WHO IEQAS' methods. International normalized ratio calculation was done by the participating laboratory.

The Length of Closing Period

The closing period was around 20 days for the first to fourth surveys. It was shortened to 15 days for the fifth and sixth surveys.

Evaluation

The target values were calculated from the results of the participants who performed the basic standard criteria: determination of their own reference ranges by using fresh plasma samples from at least 20 apparently healthy volunteers[3] and repeating this for every change of reagent lot.[4] The results of INR and aPTT ratio (or aPTT test-normal ratio in the sixth survey) submitted by all laboratories that met the criteria were used to calculate ''overall median'' (all-method median). If there were 10 or more of these laboratories using the same reagent, the ''reagent specific median'' was calculated, and the results of laboratories that belonged to each reagent group were compared with this median. Otherwise, performance was compared with the overall median. The result of a given parameter that was within a 15% deviation from the target median was classified as ''within consensus.'' Results outside this limit were defined as ''outwith consensus.''[5] This method of evaluation was derived from WHO IEQAS. In the sixth survey, we compared the results of performance assessment by using the INR submitted by the laboratories and the PT ratio (test-normal ratio) calculated by dividing the result by midpoint of the individual laboratory reference range. However, performances assessed by comparison of INR were reported to each participant.

Table 1. Stability of the Lyophilized Control Plasma, Both Normal and Abnormal Samples, Kept in a Refrigerator (2°C–8°C) and a Non–Air Conditioned Room for 20 and 30 Days*

Type of Samples	Test	Refrigerated	Room Air	% Difference
Normal (20 days)	PT, s	13.2	13.3	0.76
	INR	1.10	1.11	0.91
	aPTT, s	26.9	26.9	0.00
Abnormal 1 (20 days)	PT, s	47.9	48.2	0.63
	INR	4.16	4.19	0.72
	aPTT, s	46.4	48.7	4.96
Abnormal 2 (30 days)	PT, s	38.7	38.7	0.00
	INR	3.34	3.34	0.00
	aPTT, s	45.8	46.6	1.75
Abnormal 3 (30 days)	PT, s	39.8	40.2	1.01
	INR	3.43	3.47	1.17
	aPTT, s	45.5	46.9	3.08

* PT indicates prothrombin time; INR, international normalized ratio; and aPTT, activated partial thromboplastin time.

Education

Comments on possible errors were added to the EQA report. The instructions about how to establish the reference range and denominators for PT and aPTT ratio, the recommended concentration of sodium citrate, and appropriate international sensitivity index were appended to the instructions that accompanied the surveys. We also cooperated with the Global Alliance for Progress in Hemophilia (GAP program) of the World Federation of Hemophilia to organize workshops for the improvement of laboratory diagnosis of hemophilia and other bleeding disorders.

Membership Fee

The 2 trial surveys were free of charge. The membership fee for the NEQAS was 2000 baht (approximately US $60) per year.

RESULTS

The Stability of Lyophilized Plasmas

The stability of lyophilized control plasma, both normal and abnormal samples, was studied during the storage at 2°C to 8°C and at ambient temperature (day, 32°C; night, 27°C). Table 1 shows that the differences between the results of the PT and INR in both conditions were minimal. The aPTT results were slightly higher in the non–air conditioned room for 20 days in abnormal samples.

Members and Response Rate

From the dispatch of 220 questionnaires, 124 (56.4%) were returned. There were 12 hospitals that performed no coagulation tests. Among 112 responding hospitals that had coagulation tests, 108 of them indicated they would like to join the EQA for coagulation tests. The number of participants in each survey and the response rates are shown in Table 2. The number of participants increased by 16.5% during 1½ years. All laboratories that sent their report back before the day of analysis were considered as

Table 2. The Number of Participants, Number of the Participants That Submitted Results, and the Response Rate of Each Survey

Survey No.	Participants, No.	Responses, No.	Response Rate, %
1 (trial)	109	88	80.7
2 (trial)	118	97	82.2
3	120	110	91.7
4	120	116	96.7
5	123	114 (117*)	92.7 (95.1*)
6	127	120 (122†)	94.5 (96.1†)

* Results sent by mail from 3 laboratories.

† Two laboratory results arrived after closing and the analysis was completed.

Table 3. Reasons Why the Laboratories Did Not Send the Results in Time*

Survey No.	Labs, No.	Lost Specimen	Already Sent	Already Analyzed	Not Done	Failure to Contact
4	26	1†	11	5	5	4
6	26	0	14	4	1	7

* The external quality assessment (EQA) specimens were not received (lost specimen), the results had been sent by post or facsimile (already sent), the specimens had already been analyzed and the results had yet to be sent (already analyzed), the analysis was not done (not done), and failure to contact the persons who take responsibility of the EQA. Labs indicates laboratories.

† See the detail of this case in the text.

Table 4. The End-Point Detection Techniques Used by Participants in the Sixth Survey

End-Point Detection Technique, Manufacturer	Users, No.
Manual	3
Chromotimer, Behring (Marburg, Germany)	1
Fibrintimer, Behring	2
Option Series, bioMérieux (Marcy l'Etoile, France)	3
Cascade M, Helena (Beaumont, Tex)	1
Humaclot Junior, CHEM-LABS (Nairobi, Kenya)	4
ACL series, Instrumentation Laboratory (Milano, Italy)	12
Futura/Plus/Advance, Instrumentation Laboratory	1
MLA Electra series, Medical Laboratory Automation (Mt Vernon, NY)	1
Coag-a-Mate MTX, Organon Teknika (Boxtel, Netherlands)	2
CA50, Sysmex (Kobe, Japan)	18
CA500 series, Sysmex	64
CA1500, Sysmex	9
Thrombotimer, Behnk Elektronik (Norderstedt, Germany)	3
Not clearly stated	3
Total	**127**

responders, even though their results arrived later than the closing date.

The response rate in the third survey, the first formal survey, was higher than from the trial surveys because we eliminated 5 laboratories that did not return survey results for 2 consecutive trial surveys, and replaced them with others that were interested in being participants. We also telephoned some laboratories for their results after the closing date. In the fourth survey, we called all 26 laboratories that did not return the results in time (Table 3). One laboratory did not receive the specimens. After checking with the post office, it was discovered that the survey

Table 5. Prothrombin Time (PT) Reagents Used by Participants in the Sixth Survey

PT Reagent, Manufacturer	Users, No.
Thromborel S, Dade-Behring (Marburg, Germany)	97
DiaPlastin, DiaMed (Cressier sur Morat, Switzerland)	3
DG-PT, Grifols (Barcelona, Spain)	2
PT/FIB Recombinant, Instrumentation Laboratory (Milano, Italy)	14
Simplastin Excel S, Organon Teknika (Boxtel, Netherlands)	6
Neoplastin CI Plus, Diagnostic Stago (Asnières, France)	2
Not clearly stated	3
Total	**127**

Table 6. Activated Partial Thromboplastin Time (aPTT) Reagents Used by Participants in the Sixth Survey

aPTT Reagent, Manufacturer	Users, No.
Actin FS, Dade-Behring (Marburg, Germany)	92
Pathromtin SL, Dade-Behring	5
Cephascreen, Diagnostic Stago (Asnières, France)	2
DiaCelin L, DiaMed (Cressier sur Morat, Switzerland)	3
APTT-L, Grifols (Barcelona, Spain)	2
Hemostat APTT-EL, HUMAN (Wiesbaden, Germany)	2
APTT-SP (Liquid), Instrumentation Laboratory (Milano, Italy)	6
Platelin LS, Organon Teknika (Boxtel, Netherlands)	5
CK Prest, Diagnostic Stago	1
Synthail, Instrumentation Laboratory	8
Not clearly stated	1
Total	**127**

was received by the hospital administration; however, it was not delivered to the laboratory. Most participants informed us that the results had already been sent by post. Some of them had assayed the survey samples but did not yet deliver the results to us. In these cases, we asked them to send the results by facsimile. Some participants had not performed the assay; however, after our call, they completed the assay and sent the results as soon as possible. The others could not be contacted. In the sixth survey, only 1 laboratory had not yet assayed the specimens (Table 3).

The response rates were slightly decreased in the fifth and sixth surveys (Table 2) because of the shorter closing period, which was chosen to improve turnaround time to be within 1 month. Some results sent through the normal postal system did not arrive in time.

The end-point detection techniques and reagents used by the participants are displayed in Tables 4 through 6, using the data from the sixth survey.

Number of Laboratories That Performed Basic Standard Criteria

The number of laboratories that met the basic standard criteria increased from 16% (14/88) in the first trial survey to 58% (70/120) in the sixth survey (Figure 1). In the first survey, the reagent specific median could be calculated only in a group of laboratories using the PT reagent Thromborel S. From the second until the sixth survey, reagent specific median was additionally calculated in a group of laboratories using the aPTT reagent Actin FS.

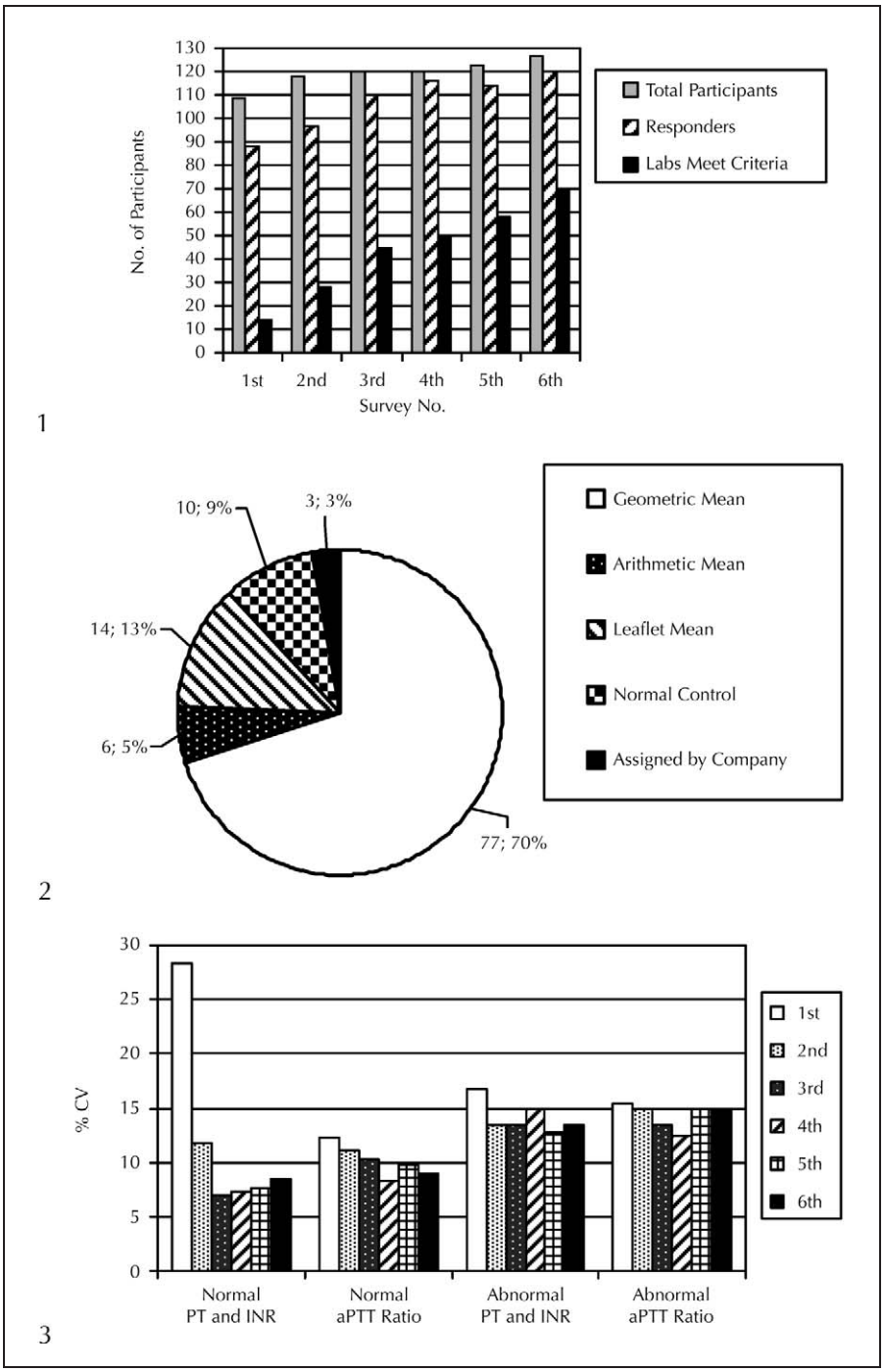

Figure 1. *Number of all participants and the laboratories returning the results (responders) and laboratories that established their own reference ranges by using fresh plasma samples from at least 20 apparently healthy volunteers and do so for every change of reagent lot (labs meet criteria).*

Figure 2. *The sources of denominators used for the calculation of prothrombin time ratio and consequent international normalized ratio in the sixth survey. Laboratories used mean of reference range from normal subjects (geometric or arithmetic mean), mean of reference range in manufacturer's instructions (leaflet mean), normal control value, or value assigned by a specialist from the company (assigned by company). The percentage of laboratories is shown after the semicolon (n = 121).*

Figure 3. *The coefficient of variation (CV) of each survey in both normal samples and abnormal samples (median international normalized ratio [INR] around 3, activated partial thromboplastin time [aPTT] ratio around 1.7). PT indicates prothrombin time.*

Difference Between the Performance Assessments Using INR or PT Ratio (Test-Normal Ratio)

Participant performances of PT assessed by using INR were within consensus much more often than when using the PT ratio (Table 7). The sources of the denominator for INR calculation were different as shown in Figure 2.

Improvement of the Preanalytical Phase

Information about the concentration of sodium citrate used for blood coagulation tests in the laboratories was asked in the form. After finding that some laboratories still used 3.8% sodium citrate, the recommendation that 3.2% should be the concentration of choice[6,7] was added to the instructions. Six laboratories changed the type of sodium citrate while 6 laboratories still used the concentration of 3.8%; there were 6 other laboratories that had not replied to this question. The percentage of the laboratories that used 3.2% sodium citrate in the last survey was 95% (115/121, if the no data participants were excluded) or 91% (115/127, for all participants).

Improvement of Analytical Variation

The performance standard indicated by the coefficient of variation (CV) of each survey is shown in Figure 3. For the fourth to sixth survey, all-method CVs of PT and aPTT are not more than 10% (range, 7.3%–9.8%) and 15%

Table 7. Comparison of Participant Performances Assessed by Using International Normalized Ratio (INR) and Prothrombin Time (PT) Ratio (n = 121)*

	Sample October 2006		Sample November 2006		Sample December 2006	
Consensus	INR	PT Ratio	INR	PT Ratio	INR	PT Ratio
Outwith, No. (%)	9 (7.4)	36 (29.8)	23 (19.0)	43 (35.5)	19 (15.7)	43 (35.5)
Within, No. (%)	112 (92.6)	85 (70.2)	98 (81.0)	78 (64.5)	102 (84.3)	78 (64.5)

* Test-normal ratio calculated by dividing each result by the midpoint of the individual laboratory reference range.

Table 8. Laboratory A

Survey No.	Local Result	Reagent-Specific Median	% Deviation From Median
	International Normalized Ratio		
4	2.06	3.30	−37.6
	2.13	3.31	−44.6
5	3.43	3.26	5.2
	3.24	3.23	0.3
6	3.03	3.05	−0.7
	3.1	3.15	−1.3
	Activated Partial Thromboplastin Time Ratio (or Test-Normal Ratio in the Sixth Survey)		
4	0.98	1.69	−42.0
	0.98	1.77	−44.6
5	1.8	1.72	4.7
	1.86	1.79	3.9
6	1.72	1.69	2.0
	1.74	1.71	2.0

(range, 12.7%–15%) for normal and abnormal samples, respectively.

Examples of the Improvement of Individual Performance

In the first year, each survey contained 1 normal and 2 abnormal control samples, and the median results of the abnormal samples were very close. This was intended to differentiate whether the poor performance was caused by systemic or random error. Comments were added in some cases of outwith consensus. Some participants with poor performance contacted the scheme coordinator for suggestions. The scheme coordinator checked their performance to see if the problems had been solved.

Example 1.—Laboratory A had not established its own reference range. The results of normal control plasma done on the day of analysis were used as denominators for INR and aPTT ratio calculation. Its EQA performance in the fourth survey was outwith consensus in both abnormal samples. We suggested that the laboratory should investigate for possible errors and establish its own reference range and denominators. Thereafter, the laboratory changed its analyzer from semiautomation to full automation and established its reference range and denominators. Its performance moved to within consensus (Table 8).

Example 2.—Laboratory B had been outwith consensus in 2 consecutive surveys (third and fourth). The laboratory called for the technician from the manufacturer to calibrate the analyzer and found that the cooler of the reagent well of the machine was malfunctioning. So the laboratory made a change by keeping the reagent in a refrigerator and brought it out only when using it for analysis while waiting for the company to supply a new analyzer. The performance turned out to be acceptable in the fifth survey and also in the sixth survey, in which a new analyzer was used.

Table 9. Laboratory C Activated Partial Thromboplastin Time (aPTT) Ratio (or Test-Normal Ratio in the Sixth Survey)

Survey No.	aPTT of Laboratory C, s	Median aPTT, s	Local Result	Reagent-Specific Median	% Deviation From Median
5	44	47.4	1.41	1.72	−18.0
	45.7	48.9	1.46	1.79	−18.4
6	48.9	45.7	1.85	1.69	9.2
	46.8	46.4	1.77	1.71	3.3

Example 3.—aPTT ratio results of laboratory C deviated from the median of both abnormal samples to nearly the same extent (Table 9). This laboratory established its own reference range but did not do this for every change of reagent lots. We noticed that its aPTT results in seconds did not differ much from the average of the results using the same reagent and their reference range was rather high (25–38 seconds) compared with the other laboratories that used the same kind of reagent and instrument. Therefore, we suggested that the laboratory should verify the reference range of the new reagent lot. The laboratory followed the suggestion and found that the new reference value was shorter (21–32 seconds) and the performance now came to be within consensus when this new value was used.

COMMENT

External quality assessment is widely considered to be necessary for the maintenance or improvement of the quality of laboratory testing. The aim of setting up the EQA scheme for coagulation tests at the national level is to serve this need. Most of the laboratories in Thailand wish to participate in NEQAS, even though it is not mandatory, and thus the number of participants is continually increasing. The response rates rose when telephone contact was added to stimulate the participants. We considered phone contact very helpful in the early phase when the participants were not acquainted with the EQA. The most common cause of the delayed response was postal delay. We encouraged participants to send the results by e-mail but only 6 laboratories complied. Despite the fact that the response rate was rather high (94.5% for the sixth survey) compared with that of the EQA scheme for hemostasis in India, in which about two thirds of participants returned the results,[8] there were many results that did not reach the coordinator within the closing date. The timely return of the results should be improved. A Web-based program for submitting the results is currently being planned for future surveys.

The improvement of laboratory practice by the participants could be indicated by the increase in the number of laboratories that determine their own reference ranges and do it for every change of reagent lot. The changes of their

laboratory practices might be the result of the education provided through the survey, comments to individual laboratories, and workshops. We did not use the test-normal ratio as WHO IEQAS in the first year because many laboratories did not establish their own reference ranges and denominators. WHO IEQAS assessed the performance of PT by using INR merely in the samples derived from the plasmas of the patients receiving oral anticoagulant. In our survey, however, the numbers of the laboratories that were within consensus when INRs were used in comparison were higher than by using the PT ratio. This may be partly due to the different sensitivities of thromboplastins that could be harmonized by INR calculation. However, the inappropriate reference range used to calculate test-normal ratio of PT could be another reason due to the fact that 27 (25%) of the participants (Figure 2) use denominators for INR calculations derived from several sources apart from the mean of normal subjects, such as value of normal control plasma.[9] The performance evaluated using PT ratio calculated by the scheme center might not represent the laboratories' daily practices.

Lyophilized, artificially depleted control materials are used in our scheme like the other EQA schemes for blood coagulation in India,[8] in Indonesia,[10] and also in the Asian Quality Assurance Survey Program.[11] The effect of different types of lyophilized plasma in EQA, which include artificially depleted plasma and pooled plasmas of patients receiving coumarin, was reported. A large variation also existed between the artificially depleted plasma from different companies.[12] In the second year of our scheme, control plasmas from other companies were used and the effect of different plasmas should be studied. The stability of lyophilized plasma was acceptable. Although the aPTT of abnormal samples seemed to be a little bit higher when kept in nonrefrigerated room air for many days (Table 1), sample delivery took much less time than this. The date a specimen was received was recorded to recognize a delay in transport. More samples should be tested for stability.

Education and mutual consultation are very important aspects of EQA. Communication between the scheme organizer and the members can promote good laboratory practice, help to improve individual performance, and give rise to mutual experience. In addition, the overall analytical variations became smaller. According to the classification of precision in a study that reviewed the published experience of the College of American Pathologists proficiency testing program in hemostasis,[13] the precision of PT and aPTT of the formal surveys was high for normal samples and intermediate for abnormal samples, indicated by all-method CV (high precision, CV <11%; intermediate precision, CV 11%–20%). Compared with the performance of the College of American Pathologists proficiency testing program during 1969 and 1973 in that report, the all-method CVs of PT ranged from 5.7% to 18.6% and 5.8% to 14.7% for the 12 normal and abnormal plasmas, respectively. The CVs of aPTT ranged from 13.3% to 49.9%, although the data from the EQA scheme in India during 2004 and 2005 demonstrated that the CVs of the PT ratio varied from 11.4% to 28.0%, and those of the aPTT ratio were 20.9% to 39.9%.[8] For the preanalytical phase, the number of laboratories that used the appropriate anticoagulant (3.2% sodium citrate) increased to approach the level reported in the College of American Pathologists survey report in 2003, which showed that 92% of laboratories used this concentration.[14] For the postanalytical phase, we did not systematically evaluate if the laboratories calculated the INR correctly as demonstrated in this College of American Pathologists survey because there are many laboratories that did not fill in the value of denominators or international sensitivity index in the results form. We did find some laboratories for which results were outwith consensus due to miscalculation of the INR and have given them feedback.

External quality assessment samples were derived by donation for the trials and surveys conducted in 2005 and 2006. In 2007, some samples were bought. The cost of commercial control plasma is rather high (about US $10 per vial) compared with the membership fee. As this program has to be self-sustainable, local production of samples should be developed. Although this has not yet been successful, we have started a cooperation with the Christian Medical College (Vellore, India), which has produced its own EQA plasma since 2004[8] and will kindly provide our scheme with the samples at reduced cost in 2008.

In conclusion, with help from WHO IEQAS, the Thailand NEQAS for Blood Coagulation has been established. The improvement of coagulation laboratory practice can be observed through this scheme. Further development of the scheme is needed to solve the problems encountered and to provide even better service.

We wish to acknowledge WHO IEQAS for the support to establish the Thailand NEQAS for Blood Coagulation. We sincerely appreciate the laboratories that participated in our NEQAS, and Sysmex Corporation, Kobe, Japan, for the donation of the control plasma. We would like to thank Kosit Sripben, MD, Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, for his kind suggestions.

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