

## Letter to the Editor

# Improving laboratory efficiencies through significant time reduction in the preanalytical phase

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Total turnaround time (TAT) in laboratory testing has been traditionally characterized as the time from specimen collection to the reporting of results (1, 2). Despite improvements in analytical testing systems (i.e., automation), little to no measurable improvements have been demonstrated for the preanalytical phase of TAT. Efforts to address some aspects of the preanalytical phase, specifically specimen transport (i.e., pneumatic tubes), as well as efforts to streamline laboratory processes (i.e., Lean), have had little impact on TAT. Total laboratory TAT remains a pertinent issue in today's healthcare environment (3).

In addition, with the growth in the aging population, the volume of medical services, particularly in the clinical laboratory, has increased. Since the information utilized for patient diagnosis and treatment management is often based on laboratory results, this increase may also cause additional pressure to optimize the length of the total testing process in order to assure effective patient care and to reduce unnecessary delays and costs (4–6).

In a Q-probes survey from the College of American Pathologists on Emergency Department (ED) TAT, laboratory TAT was felt to cause delayed treatment and increased length of stay in the ED more than half of the time (7). Therefore, total TAT continues to be a factor in assessing laboratory

performance and reinforces the challenge to collectively search for innovative solutions to improve any or all phases of total TAT.

In reference to this, we initiated a study at Charles University and Faculty Hospital Motol in Prague, Czech Republic. Our goal was to ascertain whether the combination of a specimen collection device that provides serum in <5 min, followed by a shortened centrifugation time of 3 min, would impact the preanalytical phase of total TAT. This combination of BD Vacutainer<sup>®</sup> Rapid Serum Tube (RST) with a thrombin clot activator [(BD RST), Franklin Lakes, NJ, USA] and StatSpin<sup>®</sup> Express 3 centrifuge (Westwood, MA, USA) was compared with the combination of the BD Vacutainer<sup>®</sup> SST<sup>™</sup> II *Advance* with a silica clot activator [(BD SST<sup>™</sup> II *Advance*), Plymouth, UK] and Heraeus Sepatech Megafuge (Waltham, MA, USA) swing bucket centrifuge. The clinical performance for select chemistry analytes for the BD RST and BD SST<sup>™</sup> II *Advance* was evaluated using both the Roche COBAS Integra<sup>®</sup> 400 (Rotkreuz, Switzerland) and the cobas c 111 (Rotkreuz, Switzerland).

Following approval of the University Hospital Motol Institutional Review Board, and receipt of informed consent from each subject, blood was obtained from 100 healthy adult subjects with randomization of each subject's phlebotomy sequence. The IRB approved the collection of only two additional tubes per subject. From each subject, specimens were collected into one BD SST<sup>™</sup> II *Advance* (control) and one BD RST (evaluation); the total amount of blood collected was ~9.0 mL/patient. All tubes were mixed by five inversions immediately after collection and then transported by the lead operator from the collection room to the central laboratory located one floor above. The BD SST<sup>™</sup> II *Advance* were allowed to rest for a minimum of 30 min and the BD RST for a minimum of 5 min prior to centrifugation to allow for clotting. Visual observations of clot formation were made by the lead operator who checked for clot formation throughout the clotting time (maximum of 5 min for BD RST and 30 min for BD SST<sup>™</sup> II *Advance*) by tilting the tube and looking for a clot. The presence of thrombin as the clot activator considerably shortened the BD RST clotting time when compared to the BD SST<sup>™</sup> II *Advance*. Both tubes were processed in the respective centrifuges to separate serum from the cells. Serum samples from the BD SST<sup>™</sup> II *Advance* and BD RST were then tested for 11 selected chemistry analytes – albumin, aspartate aminotransferase, chloride, cholesterol, creatinine, creatine kinase, glucose, potassium, sodium, total bilirubin and triglycerides – using

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both the Roche COBAS Integra® 400 and Roche cobas c 111. The results were reviewed and compared with predefined acceptance criteria to assess the clinical performance of the evaluation tubes. In addition, preanalytical TAT was evaluated by recording the times of collection, clotting, centrifugation and loading onto the analyzer.

Data from the samples were obtained for select chemistry analytes and assessed using various statistical calculations. The mean and standard deviation (SD) (which includes a between-subject component) were calculated for each tube type. The units and study range of test results for each analyte on both analyzers, which was the range of test results obtained for each tube for all subjects, were measured (Table 1). Also, we documented the mean and SD for each tube type, the sample size (n) and number of reported values. The results indicate that the means for the BD RST are in close agreement with the control tube for all analytes.

Analysis of variance (ANOVA) procedures, followed by a predetermined set of multiple comparisons, were used to determine whether there was a significant tube effect and to obtain the mean standard error for the confidence limits. Mean tube biases and 95% confidence limits (corresponding to 95% equivalence tests) for system comparison were calculated.

To determine clinical equivalence between each system, the mean bias and the 95% confidence limit were compared with the clinical acceptance limit (CAL) for each analyte. The CAL represents an estimate of the maximum allowable difference in analyte test results between each system. These values may reflect the opinion of investigators from the clinical trial and, therefore, may not be constant from one study to another. The laboratory should evaluate the data presented and make its own determination concerning the acceptability of results. There were no clinically significant biases (i.e., both the 95% confidence limits and the mean biases were contained within the  $\pm$ CAL) for all analytes and for both system comparisons. In addition, the BD RST tube has been shown in other studies to yield results on the selected analytes that are comparable to the BD SST™ tube on additional instrument platforms including the Roche COBAS Integra® 800 (Rotkreuz, Switzerland) and Olympus AU5200 (Hamburg, Germany) (data not shown). To further determine equivalence between BD RST and BD SST™ II *Advance* tubes, the following 19 general chemistry analytes were tested and shown to be clinically equivalent (data not shown): alanine aminotransferase, aspartate aminotransferase, albumin, direct bilirubin, total bilirubin, blood urea nitrogen, calcium, carbon dioxide, chloride, cholesterol, creatine kinase, creatinine,  $\gamma$ -glutamyltransferase, glucose, high-density lipoproteins, iron, lactate dehydrogenase, lipase, low-density lipoproteins, magnesium, phosphorus, potassium, sodium, unbound iron binding capacity, total protein, transferrin, triglycerides, uric acid, total iron binding capacity and amylase using the Roche COBAS Integra® 800 and Olympus AU5200. In addition, the BD RST tube was validated for testing of the following special chemistry analytes: follicle stimulating hormone, folate, free thyroxine, free triiodothyronine, luteinizing hormone, testosterone, thyroxine, triodo-

thyronine, vitamin B12, cortisol, ferritin, thyroid stimulating hormone, creatine kinase-muscle band, myoglobin, troponin I, pro-brain natriuretic peptide, troponin T,  $\beta$ -human chorionic gonadotropin, estradiol and progesterone on the Siemens Advia Centaur (Tarrytown, NY, USA), Siemens Immulite (Flanders, NJ, USA), Beckman Coulter Access II (Chaska, MN, USA), Abbott AxSym (Abbott Park, IL, USA), Roche Elecsys (Rotkreuz, Switzerland) and Ortho Clinical Vitros eCI (Raritan, NJ, USA) (data not shown). BD RST and StatSpin Express 3 centrifuge results for follicle stimulating hormone, folate, total thyroxine, total triiodothyronine, testosterone, vitamin B12, cortisol, ferritin, thyroid stimulating hormone, troponin I,  $\beta$ -human chorionic gonadotropin and estradiol were shown to be equivalent to the control on the Beckman Coulter Access (data not shown).

To calculate the preanalytical TAT, average time differences (in minutes) with 95% confidence intervals (CI) were determined as follows (Figure 1):

- collection time to actual specimen clot time
- actual specimen clot time to centrifugation time
- centrifugation time to load time
- preanalytical phase turnaround time (pre-TAT) = collection time to load time

Negative time differences indicate that the average times with the BD RST were shorter (i.e., faster) than with the BD SST™ II *Advance*. Overall, it was determined that the use of BD RST along with shortened centrifugation (StatSpin® Express 3 centrifuge) led to significantly faster preanalytical TAT by an average of 38.5 min with a 95% CI of  $-42.4$  to  $-34.6$  min. The largest gain in time was between the clot and centrifuge times; a more rapid clot to centrifuge time was observed with the BD RST by an average of 30.5 min with a 95% CI of  $-36.5$  to  $-24.4$  min. Additional time savings were noted between the collection and specimen centrifugation (mean =  $-4.9$  min, 95% CI =  $-10.9$  to  $-1.1$  min) and centrifugation to instrument load (mean =  $-3.2$  min, 95% CI =  $-9.2$ – $2.9$  min).

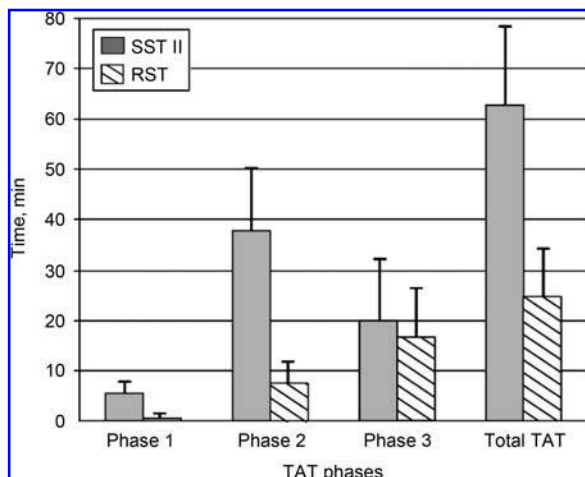
This shortening of the preanalytical phase can contribute to overall time savings for total TAT. Of course, the time saved for total TAT will be dependent on the specific tests ordered and the analysis system used to perform the tests. Each instrument/test system has different times for analysis for the different methods. Even if a laboratory uses instrumentation with a slower throughput, the savings in preanalytical time can improve the overall total TAT.

In summary, the combination of the BD RST using a 3-min centrifugation time on the StatSpin® Express 3 centrifuge led to significantly faster preanalytical TAT by an average of 38.5 min. In addition, clinical equivalence was demonstrated for the BD RST as compared to the BD SST™ II *Advance* with both the COBAS Integra® 400 and Cobas c 111 for all assays evaluated.

Thus, integration of a combined system (BD RST and StatSpin® Express 3) could vastly improve total TAT and contribute to more rapid diagnostic capabilities for various laboratory settings [Core or STAT Labs, Physician Office Labs (POLs)] and enhance patient treatment and management.

**Table 1** Summary statistics and acceptance criteria: chemistry analytes (n = 100).

Analytes, units Mean $\pm$ SD	BD SST™ II <i>Advance</i> ®/Roche Integra® 400 Mean $\pm$ SD	BD SST™ II <i>Advance</i> /Roche c111 Mean $\pm$ SD	BD RST Roche COBAS Integra 400 Mean $\pm$ SD	BD RST Roche cobas c111 Mean $\pm$ SD	Clinical acceptance criteria	BD RST vs. BD SST™ II <i>Advance</i> on Roche cobas c111	BD RST vs. BD SST™ II <i>Advance</i> on Roche COBAS Integra 400
Albumin, g/L	45.227 $\pm$ 2.470	44.982 $\pm$ 2.505	45.773 $\pm$ 2.359	45.411 $\pm$ 2.446	$\pm$ 5%	1.0%	1.2%
Aspartate aminotransferase, $\mu$ kat/L	0.354 $\pm$ 0.126	0.384 $\pm$ 0.125	0.349 $\pm$ 0.127	0.382 $\pm$ 0.130	$\pm$ 10%	0.6, 1.4 -0.8%	0.8, 1.6 -1.4%
Total bilirubin, $\mu$ mol/L	11.170 $\pm$ 6.319	11.302 $\pm$ 6.345	11.137 $\pm$ 6.457	11.362 $\pm$ 6.505	$\pm$ 1.71 $\mu$ mol/L	-2.1, 0.6 0.06 $\mu$ mol/L	-2.8, -0.1 -0.03 $\mu$ mol/L
Cholesterol, mmol/L	5.188 $\pm$ 0.931	5.269 $\pm$ 0.942	5.238 $\pm$ 0.920	5.306 $\pm$ 0.934	$\pm$ 5%	-0.09, 0.21 0.7%	-0.18, 0.11 1.0%
Creatine kinase, $\mu$ kat/L	2.040 $\pm$ 1.107	1.954 $\pm$ 1.089	2.050 $\pm$ 1.132	1.976 $\pm$ 1.115	$\pm$ 10%	0.2, 1.2 1.0%	0.5, 1.5 0.3%
Chloride, mmol/L	104.40 $\pm$ 2.18	104.23 $\pm$ 2.22	104.41 $\pm$ 2.26	104.16 $\pm$ 2.34	$\pm$ 3 mmol/L	0.3, 1.7 -0.1	-0.4, 1.0 0.0 mmol/L
Creatinine plus, $\mu$ mol/L	71.92 $\pm$ 15.21	72.81 $\pm$ 15.71	72.43 $\pm$ 15.67	73.60 $\pm$ 16.15	$\pm$ 10%	-0.2, 0.1 1.0%	-0.2, 0.2 0.6%
Glucose, mmol/L	5.578 $\pm$ 1.214	5.479 $\pm$ 1.185	5.819 $\pm$ 1.228	5.720 $\pm$ 1.190	$\pm$ 10%	0.1, 1.9 4.5%	-0.2, 1.5 4.4%
Potassium, mmol/L	4.377 $\pm$ 0.282	4.308 $\pm$ 0.274	4.378 $\pm$ 0.280	4.297 $\pm$ 0.261	$\pm$ 0.3 mmol/L	4.1, 5.0 -0.01 mmol/L	4.0, 4.9 0.0 mmol/L
Sodium, mmol/L	139.76 $\pm$ 1.78	136.69 $\pm$ 1.90	139.67 $\pm$ 1.79	137.00 $\pm$ 2.00	$\pm$ 3 mmol/L	-0.04, 0.02 0.3 mmol/L	-0.03, 0.03 -0.1 mmol/L
Triglycerides, mmol/L	1.441 $\pm$ 0.780	1.411 $\pm$ 0.761	1.458 $\pm$ 0.788	1.416 $\pm$ 0.765	$\pm$ 5%	0.1, 0.6 0.2%	-0.3, 0.2 1.2%
						-0.4, 0.8	0.6, 1.8



**Figure 1** Average cumulative preanalytical TAT (mean and standard deviation) over each interval per tube type in minutes. Phase 1, collection to clot time; phase 2, clot to centrifugation time; and phase 3, centrifugation to instrument load time.

However, it is important to note that whenever changing a manufacturer's blood collection tube type, size, handling, processing or storage condition for a particular laboratory assay, laboratory personnel should review data from the tube manufacturer, as well as their own data to establish or verify the reference range for a specific instrument/reagent system. Based on this information, the laboratory can then decide if a change is appropriate.

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### References

1. Lippi G, Salvagno GL, Montagnana M, Guidi GC. Preparation of a quality sample: effect of centrifugation time on stat clinical chemistry testing. *Lab Med* 2007;38:172–6.
2. Fernandes C, Worster A, Hill S, McCallum C, Eva K. Root cause analysis of laboratory turnaround times for patients in the emergency department. *Can J Emerg Med* 2004;6:116–22.
3. Hawkins RC. Laboratory turnaround time. *Clin Biochem* 2007; 28:179–93.
4. Sheppard C, Franks N, Nolte F, Fantz C. Improving quality of patient care in an emergency department – a laboratory perspective. *Am J Clin Pathol* 2008;130:573–7.
5. Howanitz J, Howanitz P. Laboratory results: timeliness as a quality attribute and strategy. *Am J Clin Pathol* 2001;116:311–5.
6. Holland L, Smith L, Blick K. Reducing laboratory turnaround time outliers can reduce emergency department patient length of stay. *Am J Clin Pathol* 2005;124:672–4.
7. Steindel S, Howanitz P. Physician satisfaction and emergency department laboratory test turnaround time. *Arch Pathol Lab Med* 2001;125:863–71.