Proficiency testing performance: a case study with modeling

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Abstract

Objectives: Previous literature has approached proficiency testing (PT) performance by defining the minimum levels, and combinations of imprecision and bias, necessary to meet PT requirements. In this case report, current PT performance was assessed and modeling performed to prioritize our quality improvement efforts.

Methods: A total of 1006 chemistry challenge results from Ontario’s Laboratory Proficiency Testing Program (LPTP, now QMPLS) performed on 69 tests during 1999 and 2000 were used for this retrospective analysis. Peer group means, all method means and results from reference labs were used for comparison. QMPLS flagging and recommended performance criteria were compiled, and modeling performed to predict different levels of performance.

Results: Our internal imprecision is <5% for 72% of our 69 tests; however, only 20% of our tests had a CV/PT <25%. Of the 1006 challenges performed, 136 (13.5%) results were outside PT limits, 55 (5.5%) results were flagged, and 12 requests were received from QMPLS seeking clarification on 24 (2.4%) results. Follow-up identified 9 (38%) nonanalytical errors, 8 (33%) method bias errors, 4 (17%) random errors, 2 poor methods, and one with no error identified. Modeling predicted flagging rates of 2.4% using QMPLS recommended precision performance, 1.6% using our current internal imprecision, 2.2% or 7.0% if we included an overall 20% or 50% relative bias rate with our current imprecision levels, or 15.0% when an estimate of our actual bias for each analyte was considered along with our current imprecision levels.

Conclusions: If imprecision were the only cause of PT errors, our flagging rate for this study period would be 1.6%, and we would need to formally investigate 8 results a year. In practice, strict application of the QMPLS PT criteria would result in 68 investigations annually; however, judicial review of the results before request for clarification significantly reduced this number to 12 investigations (of which 38% were nonanalytical errors). At the present time bias is a significant cause of poor PT performance in a variety of assays. Individual laboratories need to address the problem of bias, and ultimately so do manufacturers. It would be helpful if PT programs also acknowledged this necessary evolution in both their criteria and processes. © 2002 The Canadian Society of Clinical Chemists. All rights reserved.

Keywords: Proficiency testing; Bias; Imprecision; Flagging criteria; Quality improvement

1. Introduction

Proficiency testing (PT) is an important factor in maintaining the quality of laboratory results as well as in promoting consistency of results between laboratories. PT programs, by definition, are mandatory for maintenance of laboratory certification, accreditation, and licensing. Occasionally, PT may be viewed as both a bane and a boon to laboratories. Participation in external quality control (ExQC) programs is often able to complement (increased frequency, variation in testing concentrations, etc.) and substantiate the information obtained from PT results. Given the ultimate goal of both PT and ExQC programs to optimize laboratory performance and patient care, it is important to make the most of the time and money invested in these programs.

Both bias and imprecision influence PT performance. As a laboratory’s bias and/or imprecision increases, a higher percentage of results fall outside the PT ‘acceptable range’ or “limits” [1]. Studies have suggested that maintaining a CV (SD *100/mean) of less than 33% of the PT limit will virtually guarantee passing PT events under CLIA 1988
Some studies have questioned whether current PT flagging limits are appropriate. Although flagging limits based on a given number of standard deviations from a target value are statistically grounded they have several inherent problems. Steele et al. [4] noted that applying this approach with a precision limit of \(3 \text{ SD}\) would allow laboratories using imprecise methods to perform ‘acceptably’ because they are compared to similarly imprecise methods. Tightening the limits to \(2 \text{ SD}\) is probably inappropriate for a regulatory program because 1 in 20 will fail due to chance alone [5]. This would result in a large number of unnecessary investigations into otherwise acceptable laboratories. The use of PT criteria based on the state-of-the-art laboratory performance has been questioned [4]. Westgard et al. noted that the basis for PT criteria for CLIA was not “well-documented”, and suggested the use of medically relevant PT criteria [6]. More recently, biologic variation has been advocated by Fraser for the determination of PT limits [7].

The use of statistically determined limits would be expected to distribute unacceptable results among all participating laboratories. In contrast, the use of fixed limits (percentage of the target value) has been shown to identify the same frequency of unacceptable results but with greater specificity for laboratories using imprecise methods [8]. The use of fixed limits also effectively obviates the creation of strict performance limits due to the influence of methods with small intra-laboratory variation [9]. Thus, fixed limits are beneficial by avoiding a ‘majority rule’ situation.

Our laboratory tries to subscribe to at least one ExQC program (e.g., College of American Pathologists-CAP or the Murex/BioRad program) in addition to our PT program (QMPLS, formerly known as LPTP) for every possible analyte. To maximize the information from these reports and to minimize unnecessary time directed toward investigation of questionable results, we have developed an Excel spreadsheet to collate and graph our data (Table 1 and Fig. 1). Our system has evolved over the last 10 years, so that our secretary can now enter the data before we review the reports. This has facilitated the ease and speed with which we can determine and/or direct further troubleshooting if it is warranted.

Despite our efforts in optimizing the analysis and follow-up of our ExQC and PT results, we were still disappointed with the number of PT response letters we were writing. This led us to wonder how many flags we should expect to receive based on the number of PT challenges we perform. We knew this would be based not only on the PT flagging limits, but also on our internal imprecision. Given the trend of continually improved PT performance criteria, we were concerned that we would soon be writing even more letters as these criteria approached the ultimate capability of our methods. As we recognized that bias is a factor over which we have little control at the present time, we optimistically hoped to identify a couple of assays that would benefit from tighter precision control. With a mandate to provide effective laboratory services for quality patient care in cost efficient way, we hoped to set evidence-based objectives for our PT performance that were complementary and supportive of this mission.

### Table 1

Typical example of spreadsheet used for monitoring PT and ExQC results

<table>
<thead>
<tr>
<th>Test: Lactate Dehydrogenase</th>
<th>Codes:</th>
<th>Expected (IU/L)</th>
<th>Observed (IU/L)</th>
<th>% Difference</th>
<th>Cum % Difference</th>
<th>+10%</th>
<th>−10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey date</td>
<td>Month</td>
<td>Code</td>
<td>Program</td>
<td>C = CAP (ExQC program)</td>
<td>L = LPTP/QMPLS (PT program)</td>
<td>M = Murex/BioRad (ExQC program)</td>
<td></td>
</tr>
<tr>
<td>99.08.27</td>
<td>8</td>
<td>C</td>
<td>CAP</td>
<td>535.3</td>
<td>539</td>
<td>0.691</td>
<td>0.691</td>
</tr>
<tr>
<td>99.08.27</td>
<td>8</td>
<td>C</td>
<td>CAP</td>
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<td>159</td>
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<tr>
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<td>C</td>
<td>CAP</td>
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<td>8</td>
<td>C</td>
<td>CAP</td>
<td>539.9</td>
<td>541</td>
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<td>99.08.27</td>
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<td>M</td>
<td>MUREX</td>
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<td>83</td>
<td>1.840</td>
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<tr>
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<td>8</td>
<td>C</td>
<td>CAP</td>
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<td>529</td>
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<td>MUREX</td>
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<td>149</td>
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<td>2.126</td>
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<tr>
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<td>MUREX</td>
<td>83.5</td>
<td>83</td>
<td>−0.599</td>
<td>1.528</td>
</tr>
<tr>
<td>99.11.29</td>
<td>11</td>
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<td>MUREX</td>
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<td>328</td>
<td>0.000</td>
<td>1.528</td>
</tr>
<tr>
<td>99.12.14</td>
<td>12</td>
<td>M</td>
<td>MUREX</td>
<td>151</td>
<td>150</td>
<td>−0.662</td>
<td>0.865</td>
</tr>
<tr>
<td>00.01.17</td>
<td>1</td>
<td>M</td>
<td>MUREX</td>
<td>330</td>
<td>327</td>
<td>−0.909</td>
<td>−0.044</td>
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<tr>
<td>00.01.18</td>
<td>1</td>
<td>M</td>
<td>MUREX</td>
<td>82.1</td>
<td>84</td>
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<td>LPTP</td>
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<td>447</td>
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<td>LPTP</td>
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<tr>
<td>00.01.26</td>
<td>1</td>
<td>L</td>
<td>LPTP</td>
<td>385</td>
<td>373</td>
<td>−3.117</td>
<td>−20.526</td>
</tr>
</tbody>
</table>

**Survey date** = Date when survey was conducted. **Month** = Month of survey. **Code** = Code of the program. **Program** = Program used for the survey. **Expected (IU/L)** = Expected value of the analyte. **Observed (IU/L)** = Observed value of the analyte. **% Difference** = Percentage difference between expected and observed values. **Cum % Difference** = Cumulative percentage difference. **+10%** = Percentage difference above 10%. **−10%** = Percentage difference below −10%.
2. Methods

All PT results from QMPLS surveys sent during 1999 and 2000 for all analytes tested in our core laboratory were used for this study (Ontario’s Laboratory Proficiency Testing Program is now known as the Quality Management Program-Laboratory Services). The core laboratory runs assays for chemistry, which includes general chemistry, blood gases, urine chemistry, enzymes, lipids, and cardiac markers, as well as assays for therapeutic drug monitoring (TDM) and endocrinology.

For the purpose of this study, these survey results were compiled in a new Excel spreadsheet identifying the survey date, the test type (e.g., endocrinology), and the analyte. The target value to which our results were compared depended on the analyte, and was stipulated by QMPLS as being one of: the ‘all methods mean’ (AMM), the peer group mean or median (PGM), or a value determined by a reference lab. For each result listed, the specific target value (AMM, PGM or reference lab value) was entered, along with the corresponding group size. The spreadsheet was formatted according to analyte to apply the QMPLS required decimal places for both our results and the target values.

The QMPLS flagging criteria were also entered (Appendix 1, and, for those analytes that have a flagging limit based on a defining concentration, the challenge concentration was taken into consideration. For those flagging limits expressed as the target value plus/minus an absolute concentration, these limits were converted to a percent by dividing the absolute concentration by the target value multiplied by 100. This conversion was performed to have all the PT limits with consistent units. Also entered was our internal imprecision in the form of CV determined from the monthly statistics for the year 2000 and the QMPLS recommended level of precision (QMPLS recommended CV) according to analyte and concentration level. The Excel spreadsheet was imported into SAS (statistical analysis software) for analysis.

The probability of failing a single challenge is a direct function of the magnitude of the CV and bias as a proportion of the PT limit [10]. Assuming that the percentage difference between a lab’s reported result and the target value follows a normal distribution, then the exact probability of failing a challenge can be calculated for any given combination of a) CV as a percentage of the PT limit (CV/PT), and b) bias as a percentage of the PT limit (relative bias). Furthermore, if it is assumed that the measurement error is independent between challenges, then the probability of failing each individual challenge can simply be summed across all challenges to get the total expected number of unacceptable results. For example, an analyte with CV/PT of 25% and no relative bias would be expected to fail approximately one in 16,000 challenges. On the other hand, if CV/PT and relative bias were both 50%, then almost one in every six challenges would fail.

The number of unacceptable results that were outside of the QMPLS defined acceptable range was determined by comparing our result to the upper and lower limits of the ranges calculated from the flagging limits. The number of unacceptable results was compared to the number of predicted challenge failures using our internal CV for each analyte and setting the relative bias to fixed levels of 0, 20% and 50%. The number of expected failed challenges using QMPLS recommended CV levels with relative bias levels of 0 and 50% was also calculated.

Since there were a number of challenges for each analyte, we were able to develop an estimate of our bias present in the QMPLS surveys for the data set by averaging the percent difference between each result and its target value. This was converted to ‘relative’ bias by expressing the bias as a percentage of the PT limit. The standard deviation of the bias estimate for each analyte was also determined. The number of unacceptable results was predicted using the standard deviation of the bias that reflected our actual performance, and a prediction of our actual performance was determined using the square root of the uncorrected sum of squares to reflect an assumption that we have zero bias [11].

It should be noted that CV/PT cannot be determined for analytes that have PT limits based on absolute concentrations (e.g., at low concentrations of many endocrine assays),
however, during this study period no flags were received for these assays.

3. Results

Table 2 compares our internal imprecision to CV/PT for each analyte. In this table the tests that would be expected to have the poorest PT performance due to their high imprecision and their high CV/PT are located in the bottom right-hand corner. The tests are plotted based on the largest internal imprecision achieved for the two different internal quality control concentrations performed in our laboratory.

A total of 1006 PT challenges were received from QM-PLS in 1999 and 2000. Chemistry (general, urine, blood gases, enzymes, lipids and cardiac markers) accounted for 568 (56.5%), therapeutic drug monitoring (TDM) for 118 (11.7%), and endocrinology for 320 (31.8%) of the challenges. Of these 1006 results, QMPLS flagged 55 results and requested review of 24 of these analytes in 12 separate response letters. Letters were written for: (number of letters/number of flags): pO2 (2/7), phosphate (2/3), urine albumin (1/1), microalbumin (6/6), urine creatinine (1/1), HbA1c (5/5), salicylate (1/3), total protein (2/2), cardiac troponin I (2/2), and vancomycin (2/2). The remaining analytes that received flags were (number of flags): acetaminophen (1), bicarbonate (1), chloride (1), creatinine (1), digoxin (1), lithium (4), phenytoin (1), sodium (2), total bilirubin (1), triglycerides (3), urea (1), uric acid (3), urine protein (3) and valproic acid (1). Of the 24 results requiring response letters, nine were nonanalytical errors (38%), eight were attributed to method bias (33%), two were the result of a poor method (8%), and four were due to random error (17%). A final analyte was acceptable according to QMPLS flagging rules, but flagged anyway and also received a letter (4%). Six of the nine nonanalytical errors (66%) were due to a clerical ordering error for urine albumin instead of microalbumin. Now that this is a common test, this would not be expected to happen again. The other nonanalytical errors consisted of a transcription error and a mix-up of the PT testing bottles, both of which are significant PT errors but would not occur with routine patient testing.

In applying QMPLS flagging rules to our complete database (1006), we observed that 136 results were unacceptable when the criteria were applied in a strictly mathematical fashion. This is significantly higher than the 55 flags we eventually received following review of the data by the QMPLS committees. It was interesting to note that there was no association between the absolute value of our result minus the target value (the magnitude of deviation) and the occurrence of flags or the absolute level (e.g., 5%, 10%, 15%) of the QMPLS flagging limit (data not shown).

Table 3 compares the number of results determined to be unacceptable by QMPLS flagging rules (136) to various prediction models using: our internal imprecision (internal CV) calculated for each individual test and varying degrees of relative bias (0%, 20%, 50%); QMPLS’ recommended imprecision with 0% and 50% relative bias; our actual standard deviation and bias observed from the QMPLS challenges; and our actual standard deviation without a bias correction from the QMPLS challenges. The number of analytes included in these calculations varies because some tests (i.e., calculated LDL) do not have associated internal imprecision values in our laboratory, and approximately half of the tests did not have recommended internal precision limits issued by QMPLS.

4. Discussion

Improving laboratory performance to comfortably meet PT requirements is an ongoing challenge. A natural incli-
nation is to assume that most PT failures are due to imprecision. We reviewed our current imprecision for each of our 69 methods, summarizing performance as <2%, <5%, <10% or >10% CV. It was interesting to note that 72% of our assays perform below 5% CV. However, only 20% of our tests had an internal CV to PT limit ratio of less than one quarter (CV/PT < 25%). Thus, only 20% of our assays would be assessed as having a negligible chance of being flagged. Table 2 compares the internal imprecision to the CV/PT for each analyte. Note that while most of the requests for clarification were for tests with higher imprecision and CV/PT, even tests with good precision (<2%) and a desirable CV/PT were flagged.

One of the initial goals of this study was to determine if we were receiving too many QMPLS requests for clarification. It was thus surprising to discover that our flagging rate was significantly less than the actual rate based upon non-judicial direct application of the PT criteria (Table 3). We received 55 PT flags from QMPLS for a two-year period from 1999 to 2000. Following QMPLS committee review of the survey results, these 55 flags resulted in 12 requests for clarification on 24 challenges. In contrast to our initial expectations that imprecision would be a major focus for our PT performance improvement, the results of the different modeling options suggest that currently bias contributes more to an assay’s performance (Table 3). If total error was due to only imprecision alone, we would expect a flagging rate of 1.6% based on our current internal imprecision. This would be well within the rate expected of 2.4% if QMPLS’ recommended internal precision was achieved for all assays. The model that used our internal imprecision plus an allowance of 50% relative bias on all assays had a flagging rate of 7.0% and is more reflective of our 5.5% rate than the other models. In fact, approximately 16% of our assays had a relative bias between 50% and 100%, with a further 18% greater than 100%! This variability in bias rates was predicted by the model that included the actual SD and bias observed from the QMPLS challenges (15.0% flagging rate) and is consistent with our actual unacceptable rate of 13.5%.

The practical issues involved in minimizing either imprecision or bias have altered significantly with the global move toward the routine use of manufactured kits. This issue is compounded by the significant changes that may occur between reagent lots or even calibrator lots for a single manufacturer. Even more significant are the between manufacturer biases that occur, especially for immunoassays with variations routinely up to 50% or even 100%. The ultimate issue is one of determining what can and should be altered within a particular laboratory, while remembering that the concerns observed in quality control specimens may not be mirrored in patient samples. To minimize imprecision, a laboratory could focus on sample quality (e.g., centrifugation or temperature) or instrument performance (e.g., maintenance frequency, supply source). In contrast, minimization of bias is more complex as the exact magnitude of the bias needs to be determined both across lots and in terms of a reference standard. Once this is determined, the decision to modify a calibration has inherent repercussions as a local change may result in a significant difference from peer results on PT testing, which in the past has been handled by some laboratories as back calculations for PT samples only. Further issues may arise when PT programs use all method means as the target value, especially when there is a preponderance of one particular method currently on the market. Use of objective target values verified by reference methods would address many of the above issues.

This study used the QMPLS flagging criteria that were in effect from 1999 to 2000 (Appendix 1). Over the last 2 years, some of these criteria have been reviewed and updated to even lower limits, emphasizing the importance for individual laboratories to address these issues. Many of these flagging limits are determined from state-of-the-art performance in anticipation that manufacturers with poorer performance will be pressured by individual laboratories to institute improvements.

So what are the options for improving our PT performance? For our imprecise methods, we will continue to hone our choice of kits and instruments to find the best method for the instrumentation that we currently have in the laboratory. When performance continues to be problematic,
our final option is to apply for new equipment via annual
capital budget requests. Testing in duplicate is an interim
option which may be implemented for certain assays. In
dealing with the multiple and extensive bias issues revealed
in this study, our options are few, especially for immuno-
assays where bias tends to be more prevalent. For instru-
mentation that allows use of different kit manufacturers,
different methods can be chosen. Consolidation of plat-
forms may eventually be self-limiting for this reason. The
option of in-house modification of calibrator values may
address the immediate PT problem, but is fraught with a
variety of potential pitfalls both for the individual laboratory
and for the PT program themselves. Perhaps, more clini-
cally important is the issue of revising population reference
ranges to account for method bias. For example, modification
of the reference decision limit for CEA from 4 to 6
ng/mL may be necessary when there is a proportional bias
of 25% between methods. While this might be feasible for
many assays, for assays like CEA in which the clinical
decision limits were defined early in the literature, such a
change would be confusing and probably inconsistently
applied. Perhaps a better avenue would be the introduction
of “reference value changes” instead of the use of popula-
tion ranges for the many tests with low intra- to inter-
individual biologic variation [7]. Then, not only could bio-
logic variation be the basis for the determination of
significant change in patient results, it could also be used
objectively to add clinical relevance to PT performance
criteria. For some tests the PT criteria would be stricter
(e.g., chloride, free thyroxine, lactate dehydrogenase, serum
and urine sodium, testosterone) while others would benefit
from wider limits (e.g., urine creatinine, lipids, magnesium,
phosphate, urea, total bilirubin). The goals could be graded
as “minimal” or “desirable” until technology advanced far
enough for “optimal” goals [7]. We noted with chagrin that
if 30% of the PT criteria had been updated based on biologic
variation consideration, this would have helped us with only
two of ten of our assays, while making two more actually
harder to achieve!

In summary, our study is a case report that provides
practical contrast to the theoretical considerations on PT
performance that have been previously reported in the lit-
erature. Over 70% of our assays now have a precision of
less than 5%, but 30% are subject to significant bias. For the
study period of 1999 to 2000, we wrote 12 PT response
letters a year (2.4% of annual challenges), of which 38%
were due to nonanalytical errors. If a laboratory main-
tained their imprecision below the QMPLS recommended internal
precision levels and had no significant bias, they could still
expect to have 2.4% of their QMPLS results flagged annu-
ally. Although bias is not specifically addressed in QMPLS
flagging criteria, it is accounted for during the process of
judicial review of results. Bias could be officially addressed by:

- Establishing target values by reference methodology
  whenever possible.
- Accounting for assay bias in PT criteria (e.g., via the
  use of peer group means), and
- Determining PT limits based on biologic variation
  and currently achievable performance for each assay.

Laboratories, manufacturers and proficiency testing pro-
grams all have the same ultimate goal of quality patient care
and each has a specific role in ensuring quality. This study
emphasizes the challenges in determining and monitoring
quality as assessed by PT performance.

References

and imprecision on laboratories’ ability to meet medical usefulness
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## Appendix 1

QMPLS flagging limits (1999–2000)

<table>
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<tr>
<th>Flagging Limit</th>
<th>Analyte</th>
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<tr>
<td>&lt;3%</td>
<td>Sodium, Sodium (WB)</td>
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<td>&lt;5%</td>
<td>Calcium, Chloride, Cholesterol, Ionized Calcium, Magnesium, Potassium*, Total Protein</td>
</tr>
<tr>
<td>&lt;7%</td>
<td>Glucose*</td>
</tr>
<tr>
<td>&lt;7.5% or 5 mmHg (whichever is greater)</td>
<td>pCO₂, pO₂</td>
</tr>
<tr>
<td>&lt;8%</td>
<td>Albumin, Creatinine*</td>
</tr>
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<td>&lt;10%</td>
<td>Acetaminophen, Bicarbonate, Digoxin, Ethanol, Gentamicin, HbA1c, LDL, Lithium, Phenobarbital, Phenytoin, Phosphate, Salicylate, Theophylline, Tobramycin, Total Bilirubin*, Urea, Uric Acid, Vancomycin</td>
</tr>
<tr>
<td>&lt;14%</td>
<td>AFP*, TT4*</td>
</tr>
<tr>
<td>&lt;15%</td>
<td>ALP, Amylase, AST, Carbamazepine, CK, CKMB, Cyclosporin, GGT, LDH</td>
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<td>&lt;16%</td>
<td>Myoglobin, Troponin, Valproic Acid</td>
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<tr>
<td>&lt;20%</td>
<td>FSH*, HCG*, LH*, Prolactin*, Vitamin B12*</td>
</tr>
<tr>
<td>0.03 units</td>
<td>pH</td>
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</table>

### Flagging Limit for (Lower End) Defining Concentration (i.e. below) Analyte

| 10 µg/L          | 70 µg/L | AFP |
| 4 IU/L           | 20 IU/L | Cortisol |
| 10%              | 130 µmol/L | Creatinine |
| 1.0 µmol/L       | 5 µmol/L | DHEAS |
| 60 pmol/L        | 300 pmol/L | Estradiol |
| 4.0 µg/L         | 20 µg/L | Ferritin |
| 1.0 mmol/L       | 5 mmol/L | Folate |
| 4 IU/L           | 25 IU/L | FSH |
| 2 pmol/L         | 10 pmol/L | FT4 |
| 10%              | 4 mmol/L | Glucose, Glucose (WB) |
| 4 IU/L           | 20 IU/L | HCG |
| 0.1 mmol/L       | 1.26 mmol/L | HDL |
| 4 IU/L           | 25 IU/L | LH |
| 10%              | 3 mmol/L | Potassium, Potassium (WB) |
| 2 mmol/L         | 10 mmol/L | Progesterone |
| 4 µg/L           | 25 µg/L | Prolactin |
| 0.4 µg/L         | 2 µg/L | PSA |
| 0.6 mmol/L       | 3 mmol/L | Testosterone |
| 20%              | 3 nmol/L | Total Bilirubin |
| 0.1 mU/L         | 50 mU/L | TSH |
| 10 mmol/L        | 75 mmol/L | TSH |
| 24 pmol/L        | 150 pmol/L | Vitamin B12 |

* Indicates the flagging limit for the higher concentrations of analytes that have flagging limits based on a defining concentration; the complimentary lower end flagging limit and defining concentration are listed in the second part of the table. (WB = whole blood)