



Internal quality control in routine analysis

Internal quality control (IQC) ensures that factors determining the magnitude of uncertainty do not change during the routine use of an analytical method over long periods of time. Together with validation, IQC forms the mainstay of quality practice in chemical analysis. Broadly speaking, validation comprises the estimation of the uncertainty of results resulting from the use of a method under given conditions. Analysts can then judge whether the method is fit for purpose by comparing that uncertainty with the end-users' requirements. Internal quality control (IQC) is a process for checking that the uncertainty at validation does not deteriorate after validation, that is, when the method is in routine use.

IQC is conducted by inserting one or more control materials into every run of analysis. The control materials are treated by an analytical procedure identical to that performed on the test materials. The results are plotted on control charts, which are interpreted in the usual fashion—simple!

Well, not entirely simple. There are factors that need careful consideration if the IQC system is to represent the routine analytical operation adequately. But first the good news. IQC is already traceable via the validation process. Its only purpose is to check that the analytical system has not changed since validation. Like all statistical control, IQC operates on the basis of the mean result and standard deviation of the analytical process.

“Measures to address the quality of quality control itself comprise a significant gap in the management of data quality”

Within-run precision

At this point we have to consider the exact meaning of the word ‘run’. A run is a set of test materials that is analysed under repeatability conditions, that is, within a ‘short time’. Within a run, there should be no changes in the magnitude of errors. However, repeatability in that sense is an ideal that is never realised. There are always systematic changes within a run, however short the time span from the first to the last analysis. So in practice we have to settle for ‘negligible change’ rather than ‘no change’. We can do that by treating ‘repeatability conditions’ and ‘run’ as mutually defining. For example, a run could comprise a sufficient number of test materials to provide three hours continuous analysis. We then treat the variations within the run as random and attribute them to repeatability.

Between-run (‘intermediate’) precision

Internal quality control, however, is based on *between-run* precision, closeness of agreement between results obtained in separate runs of analysis. This necessarily has a greater dispersion than within-run precision, owing to an additional source of error affecting individual runs differently. This additional source is introduced by uncontrolled changes such as those brought about by a change of analyst, new reagents, recalibration and changes in the laboratory environment.

To estimate between-run standard deviation in an unbiased manner, the control materials have to be placed at random positions in the analytical sequence of the run. If for example the control materials were always first in the sequence, they would be analysed just after the instrument had been calibrated, with little time for systematic changes to manifest. The replicated results would consequently tend to underestimate the between-run standard deviation.

Setting control limits

Most textbooks tell us that control limits are determined by the parameters (μ, σ) of the controlled process. However, we never know the parameters: we know only the corresponding statistical estimates (\bar{x}, s) calculated from replicated results. This distinction has important implications that are often overlooked, and it makes setting up the control chart a little trickier than might be expected.

Firstly, to obtain a realistic estimate of between-run standard deviation, the measurements must be replicated in successive runs. The whole analytical system has to be set up from scratch each time, for example by switching on equipment from cold, renewing reagents, recalibrating etc, as appropriate. The control materials should be handled as ordinary test materials would be in routine analytical operations, that is, interspersed among a number of test materials. That would be impracticable as part of validation *per se* (it could take several weeks) and is necessarily conducted when routine operations are already underway.

The practical strategy is therefore to start routine operations with a provisional control chart. Such a chart could be based on the repeatability statistics (\bar{x}, s_r) readily established during validation, but with control lines wider than usual, at (say) $3s_r$ and $4.5s_r$ from the mean. (This would reflect the observation that between run standard deviation is often about $1.5s_r$.) Control lines at $2s_r$ and $3s_r$ would be too narrow, resulting in an excessive number of out-of-control

* It is often prudent to run a check solution at the beginning of a run to ensure that the calibration was carried out correctly, but that type of checking must be distinguished from IQC.

events.) Alternatively, temporary control lines based on fitness-for-purpose considerations could be used.

After sufficient runs and replicated results have been collected from the analysis of the control materials, estimates of the between-run statistics can be used to set up the control chart. However, this is not completely straightforward. Firstly we have to recognise that a newly adopted method is prone to produce results that are more erratic than those from a familiar one. Early results may be atypically error-prone and might need to be discarded before we estimate the standard deviation. In any event, a robustified procedure is recommended to avoid undue influence from outlying results. The second problem is that we need a surprisingly large number of results to obtain a stable estimate of standard deviation, and the control lines that depend on it. For example, if we were to collect the usual 10 results there would be a 10% probability that the estimated standard deviation would deviate from its true value by more than 40% (under the assumption of independence and normality). The control limits, therefore, have to be reviewed after a greater number of results have accumulated.

Choosing the control material(s)

The best materials for IQC are typical examples of the routine test materials, assuming that they are sufficiently stable for the purpose. The control materials do not have to be expensive certified reference materials (CRM). Indeed it is often better if they are not—it is seldom possible to procure a CRM exactly matching the matrix of the test materials. Well-matching control materials, however, can be prepared in large amounts in-house, so that the continuity of the control system can remain unbroken for a long period.

Control materials will not be *identical* with the test material, because in all likelihood they will have to be more finely divided to ensure a close approach to homogeneity before use, and may need further processing (*e.g.*, dehydration) to ensure stability. This may mean that the control material behaves slightly differently. For instance, a control material might be more (or possibly less) completely decomposed than a typical test material during the analytical treatment. The difference is unlikely to be important because, as we have seen above, IQC tests for consistency after validation rather than absolute accuracy.

Number and proportion of control materials

In many instances the range of concentrations of the analyte encountered in test materials will be relatively small, and in such cases a single control material is appropriate, with the analyte in mid-range. If the analysis is for testing the material against a legal or contractual limit for some constituent, the analyte concentration should be near that limit. Where the limit is close to the detection limit (or is zero), we must avoid censoring data that is to be used for quality control purposes. If the analyte concentration varies widely between the test materials, we should consider using two different control materials, with concentrations towards the quartiles of the usual range.

The proportion of control materials to be inserted into a run should be the minimum that will provide adequate control. This is difficult to specify in any detail, but some broad principles are obviously applicable. Runs comprising a large number of test materials will need perhaps as many as one control material per ten test materials. Systems that are

found to be typically stable might require fewer. Short runs will need at least one control material. Multiple insertions of a material in a run may benefit from the use of mean and range control charts.

External comparisons and traceability in IQC

Control materials do not have to be CRMs. Although some contractual arrangements for analysis require the use of one or more CRMs as control materials, in many ways it is better to keep the concepts of quality control and traceability distinct. The parameters of IQC describe the whole analytical system, but traceability is about the properties of the CRM alone. Moreover, the use of a CRM (where possible) on a scale appropriate for IQC is unduly expensive, but on a lesser scale ineffectual.

CRMs where available should certainly be occasionally analysed alongside test materials, but it is better to regard the outcome as a kind of one-participant proficiency test. “Z-scores”, $z = (x - x_c) / (u_c^2 + \sigma_p^2)^{1/2}$, could be calculated as from the result x , the certified value x_c , the uncertainty on the certified value u_c , and an uncertainty σ_p representing fitness for purpose. (Such a test would be pointless, however, unless $u_c < \sigma_p / 3$.) Such use of a CRM is on a footing comparable with participation in a proficiency test to provide an ongoing external reference. Where CRMs do not exist, proficiency tests are almost indispensable.

Further reading

- *Harmonised guidelines for IQC in analytical chemistry laboratories*. M Thompson, R Wood. *Pure Appl Chem*, 1995, **67**, 649-666.
- *Harmonised guidelines for single laboratory validation of methods of analysis*. M Thompson, S L R Ellison, R Wood. *Pure Appl Chem*, 2002, **74**, 835-855.
- *Quality control charting for the analytical laboratory. Part 1. Univariate methods. A review*. R J Howarth *Analyst*, 1995, **120**, 1851 - 1873.
- The quotation overleaf is from *Quality control techniques for chemical analysis: some current shortcomings and possible future developments*. M J Gardner, *Accred Qual Assur*, 2007, **12**, 653-657.

This Technical Brief was prepared for the Analytical Methods Committee by the Statistical Subcommittee and the Method Validation Subcommittee.

You can help the AMC in the production of Technical Briefs by posting queries, comments and suggestions on the AMC Discussions Web-board.
See www.rsc.org/amc.

CPD Certification I certify that I have studied this document as a contribution to Continuing Professional Development.

Name.....
Signature.....Date.....

Name of supervisor.....
Signature.....Date.....