

WHITE PAPER · CALIBRATION IN PRACTICE

STANDARD STABILITY · INSIGHTS 30

Calibration standard stability: why curves drift up, drift down, or fail a new lot.

A standard that has changed in the bottle still produces a clean curve. The ICAL and the CCV agree with each other, because they are made from the same aging solution.

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NOVEMBER 2026

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SUMMARY

Calibration standards change after they are made. Solvent evaporates and concentrates them, analytes degrade and dilute them, and a new lot may not match the old one. This paper sets out the replacement and stability rules in EPA Method 8260D, ICH M10 and SANTE 11312/2021, then works two illustrative cases. In both, the calibration and the CCV keep agreeing while sample results move, because only an independent standard can see the change.

THE SHORT VERSION

01 Evaporation concentrates a standard and makes samples read low; degradation dilutes it and makes them read high.

02 A CCV made from the same solution agrees with the ICAL no matter how far the solution has moved.

03 Set replacement intervals, compare new solutions with old ones, and trend a truly independent check.

The standard that changed in the bottle.

The stock comes out of the refrigerator twice a week. It warms, it is opened, a few hundred microlitres are drawn, and it goes back. Six months later the curve still passes and the CCVs still pass. The proficiency test result comes back low.

Nothing in the run was wrong with the instrument. The standard had changed, and every check in the run was made from that same standard.

What the methods say about replacing standards.

EPA Method 8260D sets replacement intervals [1]:

01 **Stock standards.**
Vendor solutions by the manufacturer's expiration date. Stocks prepared in house replaced after one year (Sec. 7.6.1).

02 **Working standards.**
Most compounds replaced after four weeks, and gases after one week (Sec. 7.7).

03 **Storage.**
Minimal headspace, protected from light, at 6 degrees Celsius or below (Sec. 7.13).

ICH M10 asks labs to determine the stability of stock and working solutions of the analyte and IS. Where stability varies with concentration, test the lowest and highest. M10 also states that making new stock and working solutions from reference standards solely to extend the expiry date is not acceptable [2].

SANTE 11312/2021 v2, the EU pesticide residue guidance, notes that most pesticide stocks are stable for several years when stored well. Compare an old solution with a new one using at least five replicates each. The means should not normally differ by more than ±10% [3].

Drifting up: solvent loss concentrates the stock.

Every time a volatile solvent is opened warm, some of it leaves. The analyte stays. Assume an illustrative 0.4% solvent loss per opening, twice a week.

WEEK	STOCK VS LABEL	CCV FROM SAME STOCK	FRESH SECOND-SOURCE ICV	SAMPLE BIAS
0	+0.0%	100% PASS	100% PASS	+0.0%
4	+3.2%	100% PASS	97% PASS	−3.1%
8	+6.6%	100% PASS	94% PASS	−6.2%
12	+10.1%	100% PASS	91% PASS	−9.1%
18	+15.5%	100% PASS	87% PASS	−13.4%
26	+23.1%	100% PASS	81% PASS	−18.7%

Illustrative calculation, not measured data. The CCV is prepared from the same stock as the ICAL. The second-source ICV is prepared fresh from an independent stock and read on the curve from the concentrated stock.

By week 12 the stock is more than 10% above its label. Standards made from it are too strong, so the curve credits each unit of response with too little analyte. Samples read −18.7% by week 26.

The CCV reads 100% the whole time. It came from the same bottle, so it moved with the curve. Only the independent ICV moves, and even at week 26 it reads 81%, inside a 70% to 130% window.

A check made from the same bottle as the curve can only tell you the bottle agrees with itself.

Drifting down: the analyte leaves the solution.

A labile analyte does the opposite. Assume a working standard loses an illustrative 2% of one analyte per week. After four weeks it holds 92% of its label. Samples calibrated against it read +8.4%.

This is why 8260D sets four weeks for most working standards and one week for gases. The interval is a ceiling, not a guarantee. A lab with a known labile analyte should set a shorter interval from its own stability data.

New lot, different answer.

A new lot of a certified standard can disagree with the old one. Both may be within the supplier's stated uncertainty and still differ from each other by several percent. The day the lot changes, every CCV shifts, and the instrument gets the blame.

SANTE's old-against-new comparison is a good model even outside pesticide work. Run both solutions in replicate, compare the means, and record the difference before the new lot goes into service.

Catching a change the calibration cannot see.

A change in the standard is invisible to every statistic computed from that standard. RSD, r^2, refit error and CCV recovery all compare the solution with itself.

So the defence has to come from outside. Keep a truly independent second source and trend its recovery across calibrations. Treat a slow walk in one direction as a stability problem until shown otherwise. Log every opening of a volatile stock, and aliquot stocks into single-use vials where you can.

A standard stability checklist.

01 **Set replacement intervals.**
From the method, tightened by your own stability data.

02 **Aliquot volatile stocks.**
Single-use vials beat repeated warm openings.

03 **Compare old and new solutions.**
In replicate, before the new one is used.

04 **Use an independent second source.**
A CCV from the same bottle cannot see drift.

05 **Trend the independent check.**
A slow walk in one direction is a stability signal.

06 **Never remake to extend expiry.**
ICH M10 says that practice is not acceptable.

Where WLTR fits.

A standard that has changed still produces a calibration that looks healthy. Seeing every standard's back-calculated error under every model, run after run, is what shows a trend that the passing statistics are built to hide.

WLTR is calibration data integrity infrastructure for regulated analytical laboratories. For each analyte, it derives nine calibration regression models: average response factor, plus linear and quadratic fits across four weightings each. It scores every model against fifteen ICAL parameters, including RSE. All of it is computed orthogonally to the CDS, under U.S. Patent 12,038,448 B2 [P].

CALIBRATION VERIFICATION

See every calibration standard back-calculated under every regression model and weighting, computed orthogonally to your CDS.

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SOURCES

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3. European Commission, Analytical Quality Control and Method Validation Procedures for Pesticide Residues Analysis in Food and Feed, SANTE 11312/2021 v2, implemented 1 January 2024, paras. F1, F4 and F9. food.ec.europa.eu/document/download/d4786faf-c574-4222-a5c6-45086b3920b8_en
4. U.S. Patent 12,038,448 B2, inventor Walter “Chip” Hinchman Sr. patents.google.com/patent/US12038448B2

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