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Method transfer and cross validation under ICH M10: comparing calibration across sites.

When a validated method moves to a second laboratory, ICH M10 calls for partial validation, and for cross validation when both sites contribute data to one study. M10 asks for an assessment of bias, not a pass/fail limit. Comparing calibration level by level between the sites covers the LLOQ, which the cross validation QC set does not include.

METHOD TRANSFER
7 MIN READ
OCTOBER 2026
PUBLIC

DOCUMENT

WLTR Insights 17

VERSION

1.0

DATE

October 2026

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ORGANIZATION

WLTR, Inc. • Nevada C-Corp

CLASSIFICATION

Public

THE SHORT VERSION

- 01 ICH M10 treats a bioanalytical method transfer between laboratories as a partial validation, and requires cross validation when two laboratories or methods contribute data to one study or when data from different methods are combined or compared across studies to support special dosing regimens or regulatory decisions.
- 02 M10 asks for an assessment of bias between the sites or methods, using QCs and study samples, and sets no pass/fail acceptance criterion.
- 03 The validated weighting and range describe the sending site's instrument, so WLTR recommends comparing calibration performance level by level between sites, with the LLOQ in view.

01 • A METHOD TRANSFER IS A PARTIAL VALIDATION UNDER M10

A method transfer is a partial validation under M10.

ICH M10 names the case directly. For both chromatographic methods and ligand binding assays, its list of changes that call for partial validation includes “Analytical site change using same method (i.e., bioanalytical method transfers between laboratories)” (Sec. 6.1)¹. FDA issued M10 as final guidance in November 2022².

The items in a partial validation follow “the extent and nature of the changes made to the method” (Sec. 2.2.2)¹. The scope can run from one within-run accuracy and precision determination to a nearly full validation, and stability established at one facility does not necessarily need to be repeated at another (Sec. 6.1)¹.

The standard does not change: “The parameters of the partial validations should meet the full validation criteria” (Sec. 6.1)¹. For calibration, that means back-calculated standards within $\pm 15\%$ of nominal ($\pm 20\%$ at the LLOQ) for at least 75% of standards and at least six levels (Sec. 3.2.4)¹. The M10 Q&A adds no item on transfers or cross validation³.

02 • WHEN M10 REQUIRES CROSS VALIDATION, AND HOW TO DESIGN IT

When M10 requires cross validation, and how to design it.

M10 defines cross validation as an assessment of potential bias between two methods, or between laboratories running the same method (Sec. 9)¹. It is required in three situations (Sec. 6.2)¹:

- 01 **Two methods, one study.** Different fully validated methods produce data within a study.
- 02 **Two laboratories, one study.** Different laboratories produce data within a study with the same method.
- 03 **Two methods, pooled studies.** Different fully validated methods produce data across studies that will be combined or compared to support special dosing regimens or regulatory decisions on safety, efficacy and labeling.

For different methods whose data will not be combined across studies, cross validation is not generally required. Using more than one method for the same analyte in one comparative BA/BE study is strongly discouraged (Sec. 6.2)¹.

The design is brief. Run the same low, medium and high QCs at least in triplicate, plus study samples (if available) spanning the study range, $n \geq 30$, in both laboratories or with both methods, before study samples are analyzed where possible. “Bias can be assessed by Bland-Altman plots or Deming regression,” or by other agreement measures such as the concordance correlation coefficient (Sec. 6.2)¹.

03 · M10 ASKS FOR BIAS, NOT A PASS/FAIL VERDICT

M10 asks for bias, not a pass/fail verdict.

Section 6.2 sets no acceptance criterion; it names tools for assessing bias¹. Vazvaei-Smith and colleagues describe M10 as emphasizing bias over pass/fail, “removing the need for acceptance criteria in cross-validations”⁴. Fjording, Goodman and Briscoe call for statistical methods and close collaboration with clinical pharmacology and biostatistics⁵.

Nijem and colleagues assay 100 incurred samples from four concentration quartiles once by each method and call the methods equivalent when both bounds of the 90% confidence interval of the percent difference fall within $\pm 30\%$, with quartile analyses and a Bland-Altman plot for concentration-dependent bias⁶. Yan and colleagues pair Bland-Altman plots with equivalence testing of the mean log10 difference against validation-based boundaries, in place of strict limits on Deming parameters⁷. Gu and colleagues combine ISR criteria, Bland-Altman analysis and Deming regression⁸.

The statistics predate the guideline. On agreement, Bland and Altman wrote, “The use of correlation is misleading,” and plotted the difference between methods against their mean, with limits of agreement⁹. Cornbleet and Gochman showed that imprecision in the x-axis method can make the least-squares slope incorrect and found Deming's method the most useful¹⁰. Passing and Bablok's regression makes no special assumptions about the distribution of samples or errors¹¹.

04 · THE VALIDATED CURVE DESCRIBES THE SENDING SITE'S INSTRUMENT

The validated curve describes the sending site's instrument.

M10 fixes the model at validation: “The regression model, weighting scheme and transformation should be determined during the method validation” (Sec. 3.2.4)¹. The right weighting follows from how the standard deviation of the response changes with concentration¹². That choice came from the sending site's instrument. The receiving instrument can differ in noise, linear range and response at the top of the curve.

A partial validation shows that the receiving site meets the criteria. It does not show that the validated weighting still fits the receiving instrument's variance, or that its response is as straight at the top. Nor does the cross validation QC set reach the bottom: the low QC sits within three times the LLOQ (Sec. 3.2.5), and the LLOQ is not among the QCs in Section 6.2¹.

WLTR's recommendation, not an M10 requirement: compare calibration performance between the sites, level by level, and keep it in the transfer package as supporting evidence.

01 Accuracy profile by level. Back-calculated %RE at every standard, both sites, all runs.

02 Slope and shape. Absolute slopes differ between instruments; the shape of the response factor (area ratio over nominal concentration) should not.

03 Low-end behavior. LLOQ %RE and the intercept in concentration units.

05 · ONE CURVE AT TWO SITES: AN ILLUSTRATIVE COMPARISON

One curve at two sites: an illustrative comparison.

Illustrative data. One LC-MS/MS method in human plasma, eight non-zero levels from 1 to 1,000 ng/mL, validated at the sending site as linear, $1/x$. That weighting is this example's premise; Insights 14 covers how to justify one. Each site runs three analytical runs with 2% random error per standard. The sending site's response is proportional to concentration; the receiving site's bends slightly, with a response factor 10% lower at 1,000 ng/mL than at the low end.

NOMINAL (NG/ML)	SENDING, $1/X$ (%RE)	RECEIVING, $1/X$ (%RE)	RECEIVING, $1/X^2$ (%RE)
1 (LLOQ)	-0.8	-16.0	-0.4
2	-0.4	-6.4	-0.9
5	-1.1	+1.8	+1.2
10	+0.5	+8.2	+5.4
50	-1.0	+6.8	+2.5
100	+2.9	+5.9	+1.4
500	+0.2	+1.2	-3.2
1,000 (ULOQ)	-0.3	-1.6	-5.9
Intercept (ng/mL)	0.03	0.27	0.07
Runs meeting M10 Sec. 3.2.4	3 of 3	3 of 3	3 of 3

Illustrative data. Linear fits; mean %RE of three runs per site; intercept divided by slope.

Every run at both sites meets the M10 calibration criteria. The sending site is within $\pm 4.2\%$ at every level in every run, with $1/x$ or $1/x^2$. At the receiving site, the validated $1/x$ model reads the LLOQ at -13.2%, -15.5% and -19.4%. The line tilts to follow the top of the curve, and the intercept carries the error down: 0.27 ng/mL, about a quarter of the LLOQ, against 0.03 ng/mL at the sending site.

3 of 3

Receiving runs meeting M10 calibration criteria

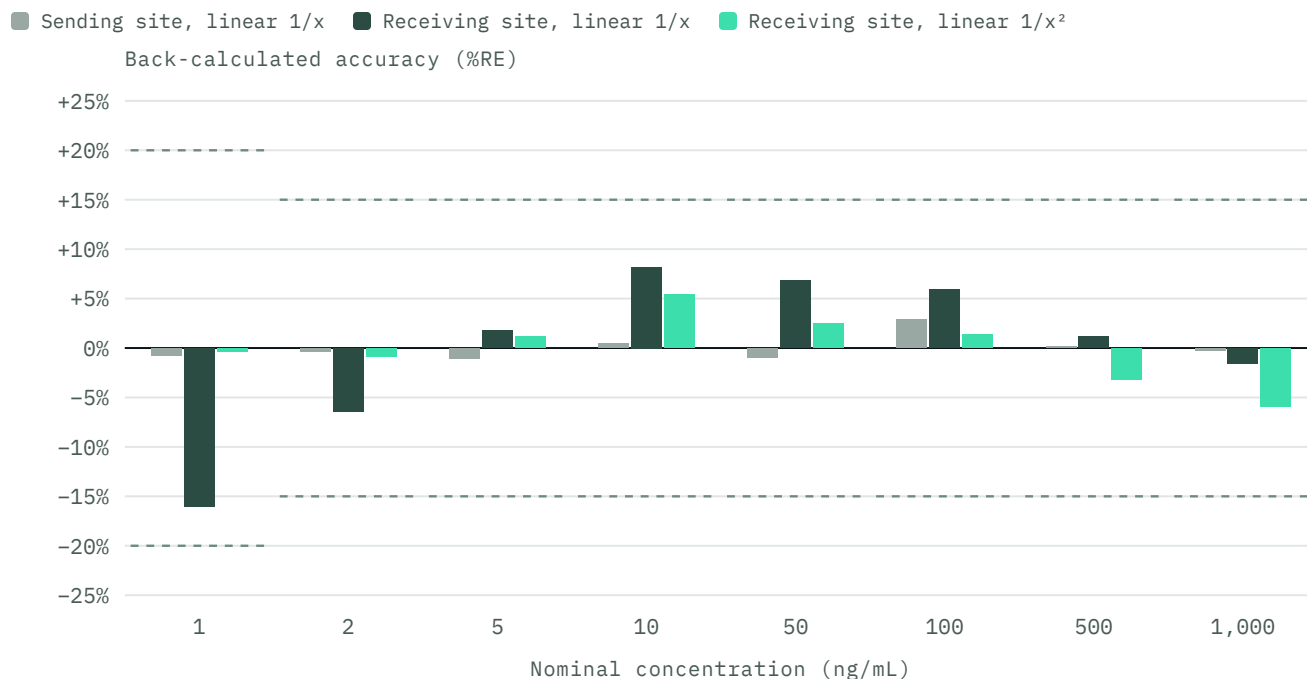
-16.0%

Receiving LLOQ, validated 1/x, three-run mean

3.6%

Largest between-site QC difference

FIGURE 1 Back-calculated accuracy by level at two sites



Illustrative data. Mean %RE of three runs per site; the band marks the M10 limits of $\pm 15\%$, or $\pm 20\%$ at the LLOQ.

Under $1/x^2$, the receiving site's LLOQ reads -0.4% and its ULOQ -5.9% . Without any regression, its response factor at $1,000 \text{ ng/mL}$ is 0.91 of its low-end value, against 0.99 at the sending site. The cause sits at the top of the range: dropping the $1,000 \text{ ng/mL}$ level brings the $1/x$ LLOQ to -9.6% .

The weighting decides where a bend in the response shows up. It does not remove the bend.

The M10 QC set shows little of this. Low, medium and high QCs (3 , 400 and 800 ng/mL) in triplicate differ between the sites by $+0.3\%$, $+3.5\%$ and -3.6% ; a 1 ng/mL sample differs by -10.8% . Whether study samples reveal the trend depends on how many sit near the LLOQ, which is why a by-concentration view matters⁶.

06 • WHAT M10 REQUIRES, SCENARIO BY SCENARIO

What M10 requires, scenario by scenario.

The middle column is M10¹; the right is WLTR's recommendation.

TRANSFER SCENARIO	WHAT M10 REQUIRES	CALIBRATION EVIDENCE WORTH KEEPING
Receiving laboratory analyzes a study alone	Partial validation meeting full validation criteria (Sec. 2.2.2, 6.1).	Both sites' curves side by side: %RE by level, intercept, response factor.
Both laboratories analyze samples in one study	Partial validation (Sec. 6.1), then cross validation: low, medium and high QCs at least in triplicate plus study samples, if available, n≥30 (Sec. 6.2).	The same comparison during the study, with LLOQ %RE and intercept trended by site.
Different fully validated methods in one study	Cross validation (Sec. 6.2).	Each method's range, model and weighting, and their low-end overlap.
Different fully validated methods, data combined or compared across studies	Cross validation where data support special dosing regimens or safety, efficacy and labeling decisions (Sec. 6.2).	Each method's calibration history at its LLOQ.
Different fully validated methods, data not combined	Not generally required (Sec. 6.2).	Each method's own calibration record.

One case is not on M10's list: the same method at two sites in separate studies, pooled later. The list names two laboratories only within a study; the opening sentence of Section 6.2 is broader¹. If pooling is planned, decide with the sponsor whether to cross validate and record why.

07 • A CHECKLIST FOR THE TRANSFER PACKAGE

A checklist for the transfer package.

Items marked M10 trace to the guideline. The rest are WLTR's recommendation.

- 01 The validated method and report (M10).** Including the regression model, weighting scheme and range set at validation (Sec. 3.2.4)¹.
- 02 The partial validation plan and report (M10).** Scope tied to the change, full validation criteria met, and the basis for any stability not repeated (Sec. 2.2.2, 6.1)¹.
- 03 An instrument record for both sites.** Model, software version and acquisition settings at each site.
- 04 Every acceptable receiving-site curve.** With %RE at every level, as M10 asks for all acceptable validation curves (Sec. 3.2.4)¹.
- 05 A side-by-side calibration comparison.** Per-level %RE, intercept in concentration units and response factor at both sites, before study samples.

- 06 **Low-end checks on the receiving instrument.** LLOQ accuracy and precision, plus carry-over and selectivity if in scope, each limited to 20% of the LLOQ analyte response (Sec. 3.2.1, 3.2.6)¹.
- 07 **A cross validation plan before samples (M10, where required).** The QC set, study samples ($n \geq 30$, if available) and bias statistics (Sec. 6.2)¹, and how bias will be handled, agreed with clinical pharmacology and biostatistics⁵.
- 08 **A by-concentration cross validation report.** Bland-Altman or Deming output with bias by concentration range, not only the overall mean⁶.
- 09 **Reported values as measured.** Any correction factor is applied by whoever pools the data⁴.
- 10 **The summary table (M10).** All validation reports per analyte, including partial and cross validation reports (Sec. 8.1)¹.

08 · WHERE WLTR FITS

Where WLTR fits.

WLTR is a verification layer for the calibration data your CDS already produces. It reads the raw instrument export directly, records a SHA-256 hash of the original file and evaluates every candidate calibration model against the same 15 acceptance criteria per analyte, each set by your lab to its SOPs¹³. Back-calculated accuracy is checked at every level, so a low-end bias like the one above surfaces before it reaches a study report.

For a transfer, WLTR can trend calibration performance across batches, instruments and sites, with candidate regression and weighting choices side by side. It does not run M10 cross validation statistics or replace your CDS, LIMS or validation. Method configurations are frozen once results exist, and each exclusion is recorded with the user and the reason. Your validated method and SOPs decide which model is reported. WLTR verifies. Your lab validates.

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