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Bioassay method transfer: Regulator's perspective and case studies

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Outline

- Bioassay lifecycle
- Regulating changes
- USP <1224> *Transfer of Analytical Procedures*
- Submitted method transfer information
- Case studies
- Final thoughts

Bioassay lifecycle (1)

- Quantitative biological assays (bioassays) are used to measure the potency of therapeutic products.
- Potency is considered a critical quality attribute (CQA), therefore bioassays are implemented early, and incorporated into specification for the release and stability testing of the product.
- Because of this early integration into the control strategy, they tend to evolve in parallel with the product.
- Early in product development, bioassays must be **qualified**, *i.e.* confirmed as suitable for the intended use.
- By the time of filling of marketing authorization application, bioassays must be **validated**.
- This is both a GMP requirement (ICH Q7), and a requirement for all analytical methods included in the specification (ICH Q6B).

Bioassay lifecycle (2)

- Analytical method lifecycle is typically associated with changes that are necessitated by efforts to optimize the performance, to accommodate ongoing product development, and to respond to unforeseen circumstances.
- Each change has the potential to compromise the validated state of the analytical method.
- Changes that occur before the filing of marketing authorization application are addressed during preapproval review.
- Changes that are implemented post-approval are subject to regulatory reporting requirements.

Regulating changes (1)

- In Canada, the regulatory requirements for the reporting of changes to the manufacturing process and controls (quality) are outlined in a comprehensive guidance: *“Post-NOC Changes: Quality Document”*.
- Changes are categorized based on the expected resulting risk to the product quality, including Level 1 (substantial), Level 2 (moderate), Level 3 (minimal), and Level 4 (none expected).
- Accordingly, pre-approval is required for Level 1 (Supplement) and Level 2 changes (Notifiable Change), while Level 3 changes (Annual Notification) must be reported post-implementation.

Regulating changes (2)

- It is recognized that an effort to introduce an analytical method qualified or validated in one laboratory, to another (method transfer) has a clear potential to compromise its validated state and established performance.
- Each laboratory (testing facility), by virtue of its specific environment (equipment, critical reagents, personnel, procedures), provides a critical framework for the validated state of its analytical methods.

Regulating changes (3)

- Accordingly, the Canadian guidance specifically addresses the “transfer of QC activities”.
- The guidance recognizes that method transfers involving bioassays have higher potential for adverse effects on product quality, considering their relatively high complexity, and expertise associated with their execution.
- Therefore, while a distinction is made between the transfer of other types of pharmacopoeial (Level 3 or Level 4) and non-pharmacopoeial analytical methods (Level 2 or Level 3), the transfer of “a potency assay or bioassay”, whether pharmacopoeial or not, is designated an obligatory Level 2 change (Notifiable Change).
- An exception is made for transfers (relocations) to a different room within an approved building, which is designated a Level 3 change (Annual Notification).
- The requirement for supporting data for method transfer is two-fold: (1) Evidence that the new company/facility is GMP compliant; and (2) Information demonstrating technology transfer qualification.

Regulating changes (4)

Evidence that the new company/facility is GMP compliant

- The new testing facility should have current evidence of GMP compliance.
- The evidence must be based on inspection by Health Canada or a trusted regulatory partner (MRA, PIC/S, EDQM, WHO, or others who inspect against ICH Q7 guidelines).
- A drug tested at the new site cannot be released in Canada until the new testing site is listed on the sponsor's Drug Establishment License.
- The timeline for processing amendment requests is 250 calendar days, which should be considered when establishing timelines for the intended method trasfer.
- Contact Drug Establishment Licence Unit, Health Products Compliance Directorate, Regulatory Operations and Regions Branch (del_questions_leppp@hc-sc.gc.ca)

Regulating changes (5)

Information demonstrating technology transfer qualification

- The guidance provides no specifics as to the type or extent of supporting evidence deemed necessary or adequate.
- This is not surprising, given the possible spectrum of scenarios, from relocation of an approved laboratory from one building to another, to a simultaneous transfer of a new analytical method from the development to multiple QC laboratories at multiple physical sites.

This may also account for the conspicuous shortage of clear guidance on analytical method transfer, considering its obvious criticality and relative frequency.

USP <1224> *Transfer of Analytical Procedures*

- An outlier in this regard is USP chapter <1224> which provides very general points to consider during method transfer, classifying the different approaches as (1) comparative testing; (2) co-validation between two or more laboratories; (3) revalidation; and (4) transfer waiver.
- Transfer waivers, apply to a receiving laboratory, which is assumed qualified in the absence of inter-laboratory comparative data.
- Therefore, this strategy is not expected to be suitable for complex analytical methods such as bioassays.

Co-validation

- Co-validation is expected to occur typically during the initial full validation of an analytical method involving simultaneously a single qualified originating laboratory, and multiple receiving laboratories.
- The coordinated collaborative effort amongst multiple laboratories generates the data necessary for the assessment of reproducibility (inter-laboratory precision) as described ICH Q2(R1).
- Therefore co-validation is expected to be performed most frequently before the filing of marketing authorization application or in support of a new bioassay implemented post-approval.

Revalidation (1)

- Revalidation constitutes a full or partial assessment of the analytical method performance characteristics at the receiving laboratory as described ICH Q2(R1).
- Revalidation confirms that the analytical method remains in a validated state, *i.e.* the performance characteristics meet the acceptance criteria in place during the original validation.
- Only those performance characteristics expected to be affected by the method transfer may be reassessed.

Revalidation (2)

- All performance characteristics should be initially considered, including accuracy, precision, linearity, range, and specificity.
- The exclusion of performance characteristics from revalidation should be justified based on a formal risk assessment, or another systematic evidence-based approach.
- The risk assessment should consider such factors as the assay complexity, its established ruggedness and historical performance, differences in equipment or data analysis software, modifications to procedures, differences in critical reagents.
- Acceptance criteria for the assessed performance characteristics should be aligned with those defined in the original validation exercise.
- However, even if receiving and originating laboratories are validated/revalidated in isolation according to ICH Q2(R1) against identical acceptance criteria, the absence of bias between the results is not guaranteed.

Comparative testing (1)

- Comparative testing listed in USP <1224> provides that linkage by analyzing the same sample a predetermined number of times at both the originating and receiving laboratories.
- Testing should be conducted at the originating and receiving laboratories concurrently or within a predetermined suitable time frame.
- A single lot of representative material may be adequate as a test sample, *e.g.* commercial drug product or assay control.
- The number of samples analyzed should be justified and statistically powered to detect the predetermined difference between results generated by the two laboratories.
- The difference between test results from the originating and receiving laboratory should be analyzed by an appropriate statistical method for similarity or equivalence (not “non-difference”), *e.g.* a two one-sided t-test (TOST).

Comparative testing (2)

- The acceptance criteria (*e.g.* equivalence range) should be justified and based on an inter-laboratory difference/bias deemed practically meaningful.
- Acceptance criteria that are too wide may result in the acceptance of a “poor” laboratory resulting in an increased consumer risk (type I error).
- Conversely, acceptance criteria that are too narrow may result in the rejection of a “good” laboratory resulting in unnecessary delay and cost associated with the method transfer process (type II error).

Revalidation and comparative testing: The full picture

- Although USP <1224> classifies comparative testing and revalidation (full or partial) as separate approaches to method transfer, the assurance of the validated status of the analytical method, and of the consistency of results generated by multiple laboratories often cannot be achieved by one or the other alone.
- This notion seems to be supported by examples of actual method transfer protocols submitted to Health Canada.

Submitted method transfer information (1)

Reviewers like a good story, yet…

- Method transfer summaries submitted in Module 2, are often too general to provide the reviewer with sufficient detail to perform a conclusive assessment.

To fill in the information gaps…

- Source documents used for the summaries should be submitted in Module 3, *e.g.* the method transfer protocol, method transfer report, the original method validation report.
- Risk assessments, statistical analyses, and other supporting information, should be also provided, if not included in the main documents.

If the information is not submitted…

- Information requests (clarifaxes) result in delays
- Post-approval commitments
- Lot Release Group reassignment
- Negative decision

Submitted method transfer information (2)

Method transfer protocol should define the key elements of a method transfer process, including but not limited to

- The responsibilities of participating laboratories and overview of quality agreements
- The prerequisite training activities
- The analytical method procedure with assay and sample acceptance criteria; differences between laboratories
- The type of samples (representative of materials to be tested), and method of preparation for simulated samples (*e.g.* forced degradation for stability)
- The equipment /instrumentation and settings
- The data analysis software and settings; confirm outputs identical between laboratories
- The selected method performance characteristics and associated acceptance criteria, both with justification
- Number of replicates for each method performance characteristic with justification.
- The study design (*e.g.* number of distinct analysts, assays, days) and reportable value calculations.
- The retest strategy

Submitted method transfer information (3)

Method transfer report should document the outcome of the method transfer process, including but not limited to

- The raw data acquired during the method transfer study
- The reportable results for all selected method performance characteristics
- The results of statistical analyses
- Deviations from the method transfer protocol with justification, and a summary of follow-up actions if applicable
- Assay and sample acceptance criteria failures with justification; comparison of frequency at originating and receiving laboratory

The method transfer report should support the conclusion that the method transfer was successful.

Case study 1

- Enzyme activity assay
- Initial DP testing was transferred from Site A to Site B. After the implementation of higher strength DP, its testing was validated at Site A, and the proposed testing at Site B was said to be supported by the original method transfer.
- The requested comparative testing data indicated that test results were consistently lower at Site B by approx. 2.5%.
- Negative decision was recommended due to unresolved systematic differences, and concerns over the integrity of the stability program (stability testing performed only at Site A).

Case study 2

- Cell-based assay
- Testing was relocated from Site A to Site B.
- Three simulated mix samples were prepared using 3 DP lots, tested in three assays at both sites, and the results assessed against release acceptance criteria.
- Direct comparison of results obtained from the two test sites was deemed unnecessary due to the high variability of the bioassay.
- Approval was recommended considering the relatively low risk associated with test site relocation, and the robust system suitability testing. In addition, increased vigilance is required during the review of bioassay results submitted in the annual product report.

Case study 3

- Cell-based assay
- Testing was relocated from Site A to Site B.
- Assay control samples were tested a predetermined number of times at both sites, and equivalence assessed by TOST.
- The equivalence range derived as ±2SD of historical assay control data was deemed too wide to be informative. However, approval was recommended considering the relatively low risk associated with test site relocation, and the observed narrow confidence interval associated with the difference, well within the equivalence range.

Case study 4

- Cell-based assay
- Testing was co-validated at Site A and B, and subsequently transferred from Site B to Site C.
- Co-validation involved simulated potency samples analyzed a predetermined number of times at both laboratories, and then analyzed as a single data set to establish accuracy, repeatability, intermediate precision/reproducibility, linearity, and range.
- The method transfer involved partial revalidation for intermediate precision at the receiving laboratory, comparative testing with equivalency assessment by TOST (both using assay control), and confirmatory testing of a single DP lot.
- The provided data for the implementation of the bioassay at Site A, B, and C were found acceptable, and approval was recommended.

Final thoughts

- Bioassay lifecycle starts early in product development, and therefore changes are inevitable.
- The impact of changes on bioassays, including the method transfer, is determined in part by their complexity and robustness. At worst, it may not be feasible to pursue the implementation of some bioassays in multiple laboratories.
- Bioassay transfer studies must confirm that the method performance is consistent with the original validation, and the assay outputs are consistent amongst the multiple laboratories.
- The approach to bioassay transfer study design should be systematic to ensure that the required data are collected, yet flexible to achieve the study goals efficiently, considering the relevant circumstances.
- The documentation submitted to regulators should include sufficient background to provide context for the transfer study design (*e.g.* specific challenges during the bioassay development), and the rationale for its various elements.
- Data generated by the multiple testing facilities should be monitored to ensure that bias does not develop over time.

Thank you for your attention!