Table 2: Strategies for Instrument Replacement Implementation

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Scope:

With vendors making changes to an instrument to enhance its performance or aid in automation and high throughput capacities, what steps do different companies need to take for this transition? The adoption process often faces many challenges. This roundtable will discuss some of these challenges and how companies work with or around them. It can get perspectives from both users and vendors on the replacement of instruments in your workplace quicker and smoother.

The overall outcomes were focused on the following areas based on the participations from both users and vendors:

- Equivalency
- User friendliness/User experience
- Cost/Time/Resources
- Regulatory impact
- IS impact
- Reginal and global multisite impact
- Vendor support system
- Collaborations between vendor and users
- Extensiveness of the changes

Discussion Notes:

1. **What or who is the biggest challenge you need to face, to implement new/replacement instrumentation?**

   Equivalency to the existing instrumentation

- The users were questioning the equivalency data against the vendor claims from the previous experience when evaluating new against the existing models or new instruments. There were gaps between the users' bridging study results and the vendor's claims in the past that made users delay or hesitate in adopting new instrumentations.
- Lack of vendor support during the initial bridging study and understanding of the impact of the changes (hardware and software) on the output data similarity and data quality.

Regulatory Impact

- The need to update filing regional or globally, and some small global regions
- The lengthy approval time and complexity of global filing
- Require risk assessment on the data equivalency or consistency with historical data
- Possible specification changes and justifications for acceptance of the changes require change controls and involvement of many functional areas within a company at multisite globally.
- If the current model is no longer available, it may disrupt the current product timeline and data continuity for both data trending and regulatory data packages.

Vendor support

- Provide robust readiness with solid comparability data package
- Understanding of the impact of the changes and newly added features on the results include algorithm, naming, and functionality.
- Support training on software and hands-on operations

Cost/Time

- Impact on a product development timeline
- Human resource demand
- Financial costs (e.g., Sciex BioPhase 8800 with 8 multichannel fits more in the development space but not QC since 1 capillary fails, the entire cartridge with 7 good ones is tossed as waste, and results in a limited implementation in the development space only.
- The time needed for IS validation and implementation of new software
- Method validation across all sites includes global sites and CMOs
- Long regulatory approval time
- Readiness implementation of the new instrument in development versus QC/commercial spaces
- Impact multifunctional areas: IS, research, QC, QA, Regulatory, etc.
- Because of the long implementation time for a new instrument, it usually starts in the development spaces to gather enough data to support new programs before it can be justified for QC space implementation due the cost and time required. Users need to provide strong justifications and data packages for the capital budget before replacing the current models.

Past observed issues

- Automation/High throughput: heating blocks mixing mechanism, not same results: e.g., Bioassay uses liquid handler vs manual: variable results
- Variant analysis: MS: deamidation reproducibility (CE-MS (Zip Chip) MAM
- Lab to Lab variations

2. What kind of testing do you need to do to provide analytical acceptance to new instrumentation?

Bridging/Equivalency studies needed in both development and QC commercial spaces

- Perform impacted method equivalency/bridging studies needed by multiple labs at all sites and potentially globally impacted.
- Managing equivalency studies need to understand what changes are described in full detail in the vendor's data package.
- A risk analysis is also required from the users before making any changes to any analytical methods. For any regulatory filed methods and specifications, initiating change controls are needed. The process is lengthy and costly since it involves multi-functional areas like QA, regulatory, and testing laboratories.
- Additional data alignment is needed if changes are made to the result unit, naming of variables, or algorithm. Some additional data will be needed (iCE3 and Maurice were mentioned as past examples during the discussion).
- Vendor's new and better performance versus users' the same or better but equivalent
- Full method validation across all laboratories and all sites impacted
- With changing models or new instruments, complete method validation is required to happen at all sites using the method. It is not an easy process for any company. It requires support from the vendor.
- Many companies require two methods (the existing and new equipment) validation packages side-by-side.
- To receive acceptance as a regulatory strategy for the changes. It becomes a huge challenge to claim the two methods are equivalent because they are often not.
- To approve the change based on performance and result from output before the method validation, a seamless equivalency data package, not claims, but practical data evidence generated by users is a must.

IS validation

- feasibility and compliance evaluation and validation.
- Some problems observed: data output incomparability, changes in nomenclatures, calibration model (algorism) changes, etc.
- An improvement in sensitivity does not necessarily mean equivalency to the old data. One small change may lead to procedure and limit changes. It becomes a troublesome change control challenge and impacts the validation and equivalency conclusion.
- Time: it might take a year to complete validation if used in the GMP area.
- Provide information on the firmware version compatible with the new software or if the old version is upgradable.
- At any point, it is not an easy decision for a company to change or upgrade software. For example, changes in sampling rate, nomenclature change, or calculation change

(adjusted or not adjusted corrected peak area gives different result outputs) will produce non-equivalent data. During version release, provide the equivalent terms in the version upgrade manual.

Filing changes and get regulatory approval

- IS will need to perform new software validation, which takes a lot of resources and time for software implementation, especially for the Need to notify the company regulatory team to file changes and receive approval. It requires a thorough risk assessment and bridging study.
- File changes to the established methods that are already filed with regulatory agencies locally or globally.
- FDA and EU require a risk assessment, but it is unknown for other small global regions.
- Impact release testing runs in other countries and potentially impacts supplies and program timelines.

3. How do your end user customers effect your decisions to adopt new instrumentation?

User friendly

- It is easy to use and a quick learning process for users. It does not create new problems and requires no or minimum customizations for creating methods and reports.
- Beta Tester: Users want to get involved
- Difficulties in dealing with extensive changes than small changes
- Users need to first understand the data output differences before being able to correlate historical data to prove equivalency in performance.

No misled possibility on equivalency

- Inequivalence during early evaluation caused by misleading beliefs from the information provided by the vendor or study reports could stop the implementation process entirely. It could arise from lacking knowledge from the user side or support from the vendors.
- Encounter difficulty in concluding equivalence depending on the extent or type of changes.
- Need to fit into current supporting systems (computer, Windows version, established software)
- The need to upgrade the system (software or hardware) means a high cost in financial, time, and human resources before implementation. It makes the approval more difficult internally and externally.

Impacted by a heavy front-end workload

- The question is how much work is involved in providing provide enough justifications before approval from both companies internally and regulatory agencies.
- Any added tasks (change controls, additional data generation, and filing tasks) will likely drive the implementation away from the users.
- Understand the reason or the need for a new instrument or a new model
- It is expensive when implementing the changes at multi or global sites.
- The approval needs to be supported by justification for a single point of failure by proving the old instrument no longer works or is not available, e.g., a discontinued instrument.

Some Suggestions

- Apply KASA: Knowledge Aided system assessment with a structured application for biologic products.
- Risk Assessment: Characterizations with high-quality prior knowledge and validation
- Development and characterization of a reference standard to support a change to compare data across all users.

4. How do regulatory agencies effect your decisions for new instrumentation?

Understand all the data packages needed for approval

- Number of bridging studies required for the change approval
- The degree of impact: small or big changes
- The time to get approval

Questions to answer if a new software is required

- What is the compliance status (21 CFR Part 11) if new software is required?
- Is any validation done or approved?
- Are there any data integrity issues if used in the QC environment?

Some impacts on product quality and historical data trending

- Data quality issue with assay variability
- Changes in similarity, sensitivity (LOD/LOQ), linearity, comparability, suitability, and specification (new specification, pre-approval, internal specification vs. specification, QC -multi-sites, etc.).
- Impact on analytical target profiles (ATPs)
- Revalidate at all sites
- Manage filing challenges and internal change control workloads
- Impact many methods and many products across all company sites
- Need to reevaluate design space and validation strategies

- Product timeline (slow approval)
- Impose a tighter control

5. **How much into the future do you plan for instrumentation changes?**

   How to move users to adopt the changes quicker?

   - Provide users opportunities to learn and evaluate new technologies and new equipment or new models
   - Learn or exchange evaluation experience with vendors or other users
   - Successful evaluation from a demo unit to get approved for budget
   - Significantly improve productivity and offer wide ranges of applications

   Costs

   - Big companies vs. small companies and companies with global footprints: some adopt changes almost annually depending on evaluation outcomes, functionality, automation, high throughput, user experience, and budget allocations, and others may take a few years.

   Time

   - The time is decided by if any newly added functionality meets the user's unmet needs and the cost of time and resources. It can be 1 year – 5 years.
   - Company operation footprints
   - Some small companies can adopt quicker (fewer sites are involved and fewer filed methods) or later (budget restraints and limited applications within the company).

6. **What are the asks from the instrument suppliers before implementation?**
   - The vendor provides a list of all the changes: performance and software.
   - The vendor or the vendor with the users can provide a cross-validation report to demonstrate equivalency or enhanced performance for the new compared to the current model, it will speed up the users' implementation plan.
   - Provide relevant and honest comparability study reports.
   - Vendor: It is challenging without relevant materials from users for the early evaluation and only relying on commercially available molecules. There is a legal burden for users to provide materials to vendors.
   - Suggestions: Increase collaborations between Vendors. Create opportunities to evaluate utilizing workshops or hands-on demos. Let users gain firsthand experience with the equipment and conclude equivalency outcomes together.

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