Wrap Up Summary
CMC Strategy Forum

Bridging Analytical Methods
Jan 27, 2014
Common Messages – Industry and Regulatory

Method lifecycle includes several elements that occur over time as needed to assure accurate, reliable measurement of product quality and stability and maintenance of a control strategy appropriate for pre and post approval products:

– Pre-Clin (tox) – Selection, development, optimization

– Phase 1 - Validation of safety methods; Qualification, of other methods (Phase 0 = scientifically sound methods)

– Phase 2 - Begin to define validation parameters, set tentative val acceptance criteria for method performance

– Phase 3 – Qualification of characterization methods; strongly recommends validation prior to Ph 3 (especially for potency and stability methods)

– BLA – Validation of all GMP methods

– Post-licensure – trend analysis of method performance, method replacement as needed

– KEY PRINCIPLE: Analytical testing strategy evolves with process and product knowledge!
### Common Messages – Industry and Regulatory

- Making changes in the methods are driven by several factors:
  - Improved product characterization/comparability assessment
  - Better understanding and control of product quality
  - Better monitoring of product stability
  - More robust/rugged methods’; higher throughput; faster TAT; lower cost of testing
  - Harmonize methods between labs, across sites, around the world
  - Replace techniques no longer supported by vendors (reagents, instruments)
  - (A biosimilar version of your product found something with their new methods that you didn’t see with your old methods)

- Not always a clear distinction; must consider pros and cons for total impact on strategy:

<table>
<thead>
<tr>
<th>Benefits of CEX Method:</th>
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<tbody>
<tr>
<td>Used throughout process and product development lifecycle</td>
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<tr>
<td>CEX is more amenable to analysis of in-process samples at lower concentrations</td>
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<tr>
<td>Provides additional control for other attributes within a single method (e.g., acidic species)</td>
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<tr>
<td>Ease of implementation into QC and global laboratories</td>
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<th>Concern of CEX Method:</th>
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<tbody>
<tr>
<td>Control limits on Basic peak must consider the levels of other product variants (e.g., C-term lysine) based on characterization, process, and stability data; therefore, the correlation of MetOx with decreased FcRn binding is indirect</td>
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<table>
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<tr>
<th>Benefits of Focused Peptide Map Method:</th>
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<tbody>
<tr>
<td>Increased specificity, sensitivity, and precision for the MetOx variant as compared to CEX</td>
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<tr>
<td>Direct correlation of MetOx measurement to decreased FcRn binding can be leveraged to set control limits</td>
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<table>
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<tr>
<th>Concerns of Focused Peptide Map Method:</th>
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<tr>
<td>Limited historical data set</td>
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<tr>
<td>Complexity of method decreases ease of implementation into QC and global laboratories</td>
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It is very challenging to roll out global methods changes – can take years to complete all regions, so changes for global products require careful consideration and planning
Common Messages – Industry and Regulatory

• There are existing CFRs and guidance documents for making changes in methods. Although formally applicable to licensed products, the basic principles are useful to consider during product development
  – GFI Changes to an Approved Application: Biological Products
  – GFI: Changes to an Approved Application for Specified Biotechnology Products and Specified Synthetic Biological Products
  – GFI Demonstration of Comparability of Human Biological Products, Inc Therapeutic Biotech-Derived Products
  – GFI Comparability Protocols – Protein Drug Products and Biological Products, CMC Information
  – ICHQ2(R1) Validation of Analytical Procedures
  – ICHQ5E Comparability of Biotech/Biological Products Subject to Changes in their Manufacturing Process
  – 21CFR 601.12 Changes requiring FDA Notification
  – FDA GFI Post-Approval Changes – Analytical Testing Laboratory Site (PAC-ATLS)

• Reporting category of changes (Major, moderate, minor) depend on nature of change, amount of data needed, and impact on approved specifications

Risk assessment is strongly encouraged to evaluate the impact of the change in the context of the entire analytical control strategy to support product safety and efficacy
Common Messages – Industry and Regulatory

- **Major Principle:** The new method must perform ‘as good or better’ than the prior method in terms of the methods’ performance capabilities critical to its intended use(s) – e.g., product-related substances, product-related impurities/degradants, process-related impurities, potency, etc…
- **OR**
- There should be a data-driven justification why – even with less sensitivity, specificity, etc. – in the context of orthogonal methods or other control strategy elements, it is still a suitable alternative to the current method.
- **If NEW species are detected by the new method:** REMAIN CALM AND GET DATA!
Practical Examples/Case Studies

FDA (CDER)
- SDS-PAGE to CE-SDS
- Different procedures for SDS-PAGE between two labs
- IEF to cIEF
- Replace cell based assay with ligand binding assay
- Adding assays for other MoA (CDC and ADCC/phagocytosis)
- Commercial vs process specific HCP assay

FDA (CBER)
- SEC HPLC for RP HPLC
- Potency assay transferred from Lab A to Lab B

Industry
- MetOx focused pepmap to CEX HPLC (Amgen)
- Size distribution vs molecular masss analysis (Pfizer)
- Potency assay lifecycle: automated, manual, manual, automated + ref std change (Genentech)
- Binding to cell based assay (Medimmune)
- HP SEC to gel electrophoresis (Medimmune)

Each presenter gave excellent examples of experiences with method changes (physical and functional assays), which had different challenges and different outcomes (see their slides)
What factors should drive the need to consider one analytical technology versus another?

- Sensitivity, specificity, cost, speed, cross-lab harmonization, regulatory expectations?
- Any/all of the above, plus others – see prior slide in Common Messages
- BUT: Just because we CAN, does that mean we SHOULD? Depends on where you are now:
  - Do you have an analytical tool kit for biotech product quality characteristics (per ICHQ6B and product-specific reg agency CMC guidances) that are part of a total control strategy with capabilities for common impurities and degradants, inc platform methodologies used with other, similar products? – Maybe it will not be justified to add more tools solely for monitoring CQAs and process consistency
  - Are specific new moieties being reported as concerns in similar products (yours or others)? Is there any risk to product safety or efficacy? Is your tool kit deficient for major characteristics and typical CQAs for your type of product? Are you missing degradation pathways? – Yes, you might have to update and expand your tool kit
  - If it is a major change made post-approval, it is recommended that a risk assessment be performed that considers all elements that would be affected by the change. Question from audience: Is it possible that drug shortage could factor into consideration for impact of method changes as part of an overall risk assessment for certain critical products? Yes, FDA considers this in their own reviews of such products as a part of cost/benefit risk to patients
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

Do these factors change if the method is used in early vs late phase product development? Pre vs post method validation?

- Risk of method selectivity-sensitivity deficiencies / method performance problems increases during development (risk of missing degradants/impurities that could impact safety as more patients are given product lots; risk of data accuracy as method is used more frequently in QC with different lots of reagents, other instruments, many analysts)

- Development/qualification of selected platform methods for some parameters of similar products provides useful starting method procedure with minimal customization could reduce the risk of operational problems if they have been widely used in QC for other products (ie SEC of SDS-PAGE of Mabs).

- If methods are not suitably sensitive/specific/robust, there is a significant increase in risk going into Ph 3 (and process validation where you generate a very expensive, high risk data set!) due to the nature and amount of critical clinical data, process consistency data, product stability data that will be used to set final specs for BLA

- Early in development, you might not want to push business elements over rapid selection and qualification of classical methods or platform methods. Business factors such as quick turnaround time, high throughput, lower assay costs, reduced skill level required of analysts, reduced rate of invalids and global harmonization are usually magnified in QC labs doing release and stability testing of commercially approved products
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

How can you track/trend the history of the product’s test results across the transition between the old and new technologies?

• Most attendees track / trend data from reference standard, QC check samples, and other performance parameters that are independent of the product lots being tested (so the focus is on method performance, not process variability)

• All advised that you should monitor the performance of the method after changes to assure it remains in a state of operational control.

• It was noted that tracking/trending method performance is critical even in development; helps inform validation acceptance criteria), methods that are not in control should be addressed for why they are not, and remediated (don’t let your lab compliance inspector be the first one to see a trend!)

• Most attendees do track QC method invalid rates to be sure methods are suitably robust. Methods that have a high rate of repeat tests due to assay failures (invalids) are a red flag that the method may not be in operational control.

• One attendee encouraged strong communications between the R&D and QC groups to stay on top of new methods to be sure they are running as expected; method changes are (should be!) triggered by chronic problems with the robustness of a QC method
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

How should the method bridging study be designed in terms of types of test samples to compare (e.g. intact, degraded, impure), number of product lots, number of method runs?

- Cannot simply compare method validation data; usually used only ref std, did not do head to head (H2H) comparison of split samples, val data was generated on diff instruments, diff times, diff analysts, so hard to compare

- Should design H2H comparison runs of old vs new method to get best direct comparison of inherent method capabilities

- There are very rare cases where it is truly impossible to run old method (ie CTO goes out of business, assay cell line is lost) – would require much greater consideration of which data to compare, and how

- Sample types should vary to span the range of types applicable to the methods’ intended use:
  - multiple lots, lots from the edges of the spec range
  - various degrees of purity/impurities/potency
  - Real-time and archived (frozen) ICH stability samples from target, accelerated, stress conditions
  - forced degradation samples (physical and chemical degradation pathways)

- Criteria for the acceptance of the method comparison runs should be established to define what constitutes ‘as good or better’ especially for methods that are not separating species (where you can see a new band or peak) like ELISA or potency assays
How should the method bridging study be designed in terms of types of test samples to compare (e.g. intact, degraded, impure), number of product lots, number of method runs? (cont’d)

- Plan should include re-testing of archived samples with new methods to assess newly-detected characteristics. But mindful of repository space for all varieties of samples!
- Dual/parallel testing can augment lack of adequate retains when data are needed to establish or adjust spec limits with new vs old method.
- Don’t have to do the comparative testing studies in QC labs, so long as the data are sound and come from the same method procedure as will be used in QC. But, beware that when R&D runs methods they may do tweaks and adjustments not in the SOP, and so not give realistic sense of QC operational robustness

- **How many lots should be tested?** It depends on the purpose of the bridging analysis
  - Multiple LOTS for the purposes of:
    - Checking to see if new species were in old lots
    - Establishing data for spec limits with new moiety
  - Multiple RUNS of few lots for the purposes of:
    - Verifying method performance capabilities separately of product variations
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

How should the method bridging study be designed in terms of types of test samples to compare (e.g. intact, degraded, impure), number of product lots, number of method runs? (cont’d)

- Number of runs/replicates should be based on precision of the method (see chart)
- Especially for non-separation methods, should do an equivalency correlation of results from both assays (assuming readout of measurements are able to be compared)
- But failure to show difference does not mean equivalence – it could mean more samples must be tested, or assay has large variability.

Example: mean difference (% bias)
Required # of runs to achieve 80% chance of success
assume true mean % bias = 0

<table>
<thead>
<tr>
<th>Acceptable Deviation</th>
<th>Intermediate Precision</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$\sigma = 10%$</td>
</tr>
<tr>
<td>$\Delta = 20%$</td>
<td>4</td>
</tr>
<tr>
<td>$\Delta = 10%$</td>
<td>8</td>
</tr>
<tr>
<td>$\Delta = 5%$</td>
<td>27</td>
</tr>
</tbody>
</table>

Bottom Line:

The width of CI gets smaller as variability, $s$, decreases or sample size, $n$, increases.
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

If bridging data indicate that the new technology is a suitable and necessary replacement for method currently in use, how should the new method be phased in to existing release testing? Should there be a period of parallel testing using both methods? Which test should be used to release material?

- In release testing, you are allowed (encouraged) to collect as much additional analytical data as desired in parallel to the CoA methods to determine suitability of new method vs old, to generate real-time data to assess new spec limits.
- Can always add new tests FIO to assess method and/or collect data for potential spec changes.
- But; Cannot DELETE any method in your regulatory filing without notification to agency (even for clinical materials). The CoA spec methods were approved by regulators as required to release each batch of product.
- FDA was asked if sponsors have to report whenever they want to add new tests FIO – answer was no, you do not necessarily have to report added FIO methods to FDA since they are added to, not in place of, the approved specification methods.
Bridging Analytical Methods for Release and Stability Testing: Technical, Quality and Regulatory Considerations

If the method is stability-indicating, are there critical timing considerations for transitioning it into ongoing vs upcoming stability protocols? Should they be used only in new protocols, or should they also be run in parallel in ongoing protocols?

- Don’t do it unless you have to! Better to allow existing protocols to complete the testing with the current methods and bring new methods into new protocols

- But when you have to, plan it thoroughly... or you could lose the link between t=0 and early timepoint data and data from later timepoints to T = end of shelf life

- You can always add new methods into stability protocols to collect FIO data in parallel to the current method. But be sure to verify that there are adequate amounts of stability samples on allocation to run both methods through the end of the protocol (don’t want to cannibalize later timepoints)

- However, you CANNOT delete a method on an stability protocol unless/until permission is granted from regulatory authorities who approved it in your filing

- Pfizer noted that they do not like to do dual testing on formal stability protocols, so they do considerable method comparison work up front to generate adequate data that would allow methods to be introduced in new protocols
Open Forum Questions

Is there a threshold of types of changes you can make to a method that would not trigger a reporting requirement, and/or not require substantial data collection?

It is based on the nature of the change relative to the validated procedure. Does it change the wet chemistry, or just the format of the procedure? If just the format, how does the change affect accuracy, precision, linearity, etc...?

You should design the data set to support the nature of the change to return the method to a state of validation and control. Simply tracking sys suit might be ok but it depends on the type of procedural ‘adjustment’ that was made. System suitability might not be sensitive enough to detect the impact of some points of change in the procedure.

<table>
<thead>
<tr>
<th>Method 3</th>
<th>Method 4</th>
</tr>
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<tbody>
<tr>
<td>Mechanism of action</td>
<td>Same as BLA Method 1</td>
</tr>
<tr>
<td>Critical reagents</td>
<td>Same as BLA Method 1</td>
</tr>
<tr>
<td>Specifications</td>
<td>Same as Method 3</td>
</tr>
<tr>
<td>Dilution/loading</td>
<td>Manual</td>
</tr>
<tr>
<td>Format</td>
<td>Micro-titer Plate</td>
</tr>
<tr>
<td>Calculation Method</td>
<td>Interpolation</td>
</tr>
<tr>
<td>System Suitability</td>
<td>Correlation coefficient for Standard</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Control range: wider</td>
</tr>
<tr>
<td></td>
<td>CV wider</td>
</tr>
<tr>
<td></td>
<td>6 samples/ week</td>
</tr>
<tr>
<td></td>
<td>CV (tighter criterion due to improved assay precision)</td>
</tr>
<tr>
<td></td>
<td>CV narrower</td>
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<tr>
<td></td>
<td>Control range: narrower</td>
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<tr>
<td></td>
<td>Slope ratio</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>CV</td>
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<tr>
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<td>18 samples/ week</td>
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If you line up the old vs new method and work line by line through the method steps, you will see where elements are changing vs not changing, and then can assess what data would be needed to support bridging (and re-validating) the impact of the changes on method capability and method operational robustness.
Open Forum Questions

Does the degree of written detail of method procedures in product filings affect the notification to reg agencies for changes in the method procedure? IE if method summary is vague, sponsor has great latitude in making changes.

No – there needs to be enough detail for adequate communication to reviewers about the major elements of the method, but putting in minimal detail does not release you from GMP requirements to have written procedures that are subjected to change control with supporting data, plus the CFRs/guidances on making changes to methods and reporting to regulatory agencies.

Is there any possibility of establishing a pre-approved comparability protocol for METHOD changes in the same manner of PROCESS changes?

Hmm.. Good thought. Let’s discuss further. Seems this is a great interest for future discussions between industry and regulators.

Is there any possibility of garnering coordinated regulatory review for global methods changes?

FDA is aware of the problem welcomes suggestions on how to improve the situation. Joint reviews have been done between FDA and other reg agencies; not too often but it has occurred; one issue is impact to mutual deadlines.

FDA also noted the valuable role of CMC Forum in global dialog among reg agencies that can spur new ideas for streamlining review processes together.

Maybe there is more we can do to foster inter-agency communications in global Forums that can yield progress?