Table 3: Determining Lifecycle Appropriate Implementation of HOS Technologies

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SCOPE:
Development and eventual implementation of novel analytical technologies requires rigorous evaluation of performance metrics to demonstrate suitability for an intended purpose. Analytical technologies may be implemented at various stages throughout a product lifecycle including process development, characterization, quality control, comparability, and biosimilarity. This roundtable will include a discussion on recent innovation and technology that is or has the potential to improve the industry ability to select and accelerate the well-characterized products with appropriate lifecycle implementation. We will also discuss mechanisms (publication, interlaboratory studies, pre-competitive reference materials, and consortia) for establishing a technique and translation to appropriate implementation.

QUESTIONS FOR DISCUSSION:
1. What is the greatest challenge you face in gaining acceptance for a given analytical technology within your organization?
2. Are there higher barriers to implementation at different stages of product development?
3. Are there specific roadblocks with respect to regulatory acceptance for a given analytical technology?
4. Does publication accelerate uptake? Have pre-competitive materials aided in this endeavor?
5. How can the "power in numbers" approach, either through consortia or interlaboratory studies, be further utilized to benefit implementation of an analytical method?

DISCUSSION NOTES:
<u>Challenges in the implementation of new HOS technologies</u>

- There is sometimes a false dichotomy between technologies in the R&D and QC environments that can be overcome.
- GXP software compliance
    - The lack of GXP software compliance can inhibit transfer to the QC lab
    - However, pharma often pushes vendors so that the GXP compliance is appropriately developed
- The bigger challenge is often based on the technology itself
    - Is the technology specific to a highly trained user? Is it robust?
        - example: AUC, mass spectrometry

<u>The first question to ask when incorporating a technology into a products lifecycle is "What is the reason for running the assay?"</u>

- Any analytical assay incorporated into the lifecycle needs to evaluate an important quality attribute (QA).
- Ideally, the QA needs to be tied to clinical experience or historical experience with related product classes.
- HOS is largely considered to be a critical QA

- Bioassays are regarded as intrinsically taking into account HOS, however, the relatively large error bars require biophysical tools for support.
- Higher resolution techniques can be used to provide increased biochemical rationale for changes observed in bioassays.

The second question to ask is, "What designates an acceptable measurement result"?

- System Suitability Metrics are A Requirement for Method Acceptance
- Reference Materials (e.g., NISTmAb) are intended to ensure a technology is functioning as intended. They have proven useful to in companies attempting to create platform methods agnostic of the mAb product and/or technology development. An in-house molecule-specific standard, however, is still required for regulatory submissions.
- Every method may not be applicable to every class of molecule.
    - For some molecular classes, the 2D-NMR methods works well (e.g., IgG1). Other classes may not have the appropriate conformational dynamics for a rigorous spectral signature. An example is the IgG2 molecular class due to the number of serotypes
- An in-house standard is an absolute must for novel modalities

- 2D-NMR: what is an acceptable 2D-NMR fingerprint?
    - Luke Arbogast's paper on glycan remodeling shows sensitivity of method, when the total point-by-point spectral matrix is entered into the chemometric algorithms (Arbogast et al. *Anal. Chem.*, 2017, 89, 11839).

Does Publication accelerate uptake of a HOS technology?

- It depends on a number of factors:
    - Source of publication is a consideration
    - Publications are less helpful than full raw data → need to estimate S/N
- Publication is one of the many pieces of information to judge what is going on in industry
- Is it really valuable to keep analytics proprietary? Publication of analytics is often encouraged.
- Industry often writes papers knowing that regulatory agencies will read them. Publications therefore become part of the industry-wide conversation regarding product characterization.

Impact of Interlaboratory Studies and Consortia

- For the Industry and Regulators alike, these studies help to evaluate general picture of the current state of industry as well as identify what may be "missing" from a package.
- These studies help to understand where the industry stands as a whole: may help dictate which direction industry goes.
- It is important to note that these studies are often run by top experts in the respective field and therefore may represent those companies with deeper pockets.
- It is important to discuss "failure" in these studies.

- The method in such studies may be different from what is used to define a product. They may not impact decision on a specific product's development because every method needs further optimization for a given molecule.
- Importantly, these studies promote interaction of a company with participants (including regulators). It is also an expectation of (and for) the FDA to stay abreast of the latest technologies. Participation in these blinded studies provides this opportunity.