Table 9: Platform Methods – How Much Optimization Should be Necessary?

Session 1
Facilitator: Elisabeth Krug, *Eli Lilly and Company*

Session 2
Facilitator: Kevin Strozyk, *Seattle Genetics, Inc.*
Scribe: Abbie Esterman, *Bristol-Myers Squibb Company*

Scope:
The pharmaceutical and biopharmaceutical industries strive to develop new products to improve the lives of patients. As such, there is a continuous effort to reduce the time and expense associated with development in order to introduce drugs to the market efficiently. Analytical method development is a balancing act, juggling demands to meet faster timelines while still producing high quality methods. Platform methods/ first-to-try conditions may be an answer to the challenge for most molecules within molecule platforms.

Utilizing platform methods to monitor product quality and process consistency is a common strategy to streamline early phase development efforts. The platform concept requires basic understanding of the product and assumes similar molecules will behave similarly under specified method conditions. As platform methods become more common in the industry, it is important to contemplate how much optimization is necessary to ensure the method is suitable and the results are fit for purpose.

Questions for Discussion:
1. What separates a Platform method versus a Product specific method?
2. Are platform methods evaluated for appropriateness for a new molecule or is it assumed to be okay?
3. How is the evaluation of appropriateness of platform methods done? What method attributes and tolerances are investigated?
4. What are the expectations for method performance, i.e., what is good enough for a platform method?
5. Are platform methods used to test GMP material or is a molecule specific method required? What are the criteria for making the decision?
6. If a platform method is used early, what criteria are used to judge that it is appropriate as a commercial method? When is that decision made? When to begin method optimization? How to approach optimization?
7. How much effort should be placed upfront to develop a platform method? If DoE is employed, how are the number of primary factors and potential interactions determined?
8. How many molecules should be evaluated before setting the “platform” conditions? Should a full DoE be performed on each product?
9. Should orthogonal techniques be used to evaluate platform method performance, and when should this comparison be performed?
Discussion Notes:

Session 1:
1. What is a platform?
   a. A method with conditions that runs regardless of the molecule being tested
      i. Does heating time and temperature fall into the platform?
         1. Mixed responses, majority tests these if not other conditions against the platform for new molecules
   b. Should be tested on everything, if it doesn’t work, what is needed to make it work, and then will be a non-platform method, derived from the platform method based on the molecule
   c. Want to prepare for a future pipeline
      i. Integration parameters, include time temp, denaturing agent
      ii. Should include sample preparation
      iii. Magic number for platform: works for 75% 80% of the molecules?
   d. Platform method with product specific forms---contain product specific information, typically just denaturing temperature

2. What do you look at when evaluating the platform, when does a platform not apply?
   a. Expect a typical profile (ce-sds NR/R)
      i. When extra species is found, is this method induced? Need to be evaluated further to see if it is the platform or molecule induced
      ii. Time temperature pH for each new molecule
   b. Use platform as the beginning for optimization for product specific
      i. Generally optimized for each molecule
   c. What is good enough for sticking to a platform?
   d. Repeatability, and short term stability, have a commercial molecule that they use for their platform reference standard
      i. Will produce a reference electropherogram to use going forward
   e. Adjustment of SDS for some molecules to ensure full denaturing
   f. Also adjustment of pH for molecules to make sure fragmentation isn’t being induced
      i. More for NR
   g. What parameters on PA800+ are adjusted:
      i. no adjustment to voltage capillary etc.
      ii. Just pH
   h. Manipulation of gel for CGE
      i. No manipulation of capillary besides forward or reverse side
         1. Precut has eliminated many issues
         2. Cutting issues are more pronounced with longer capillaries
      j. Electrokinetic vs pressure injection: most use electrokinetic
         i. In-process samples: buffer exchange usually required
            1. Use same sample for CE and CIEF
   3. DoE
      a. Optimization of sample conditions for the molecules
         i. Look at highest single impurity to look at heat induced fragmentation
   4. iCIEF needs more flexibility – no platform condition possible
a. carrier ampholytes
b. assume that it needs some specialization for molecules

5. Coolant being gone very fast?
   a. ensure it is clean, leak between gasket?
   b. Make sure all connections are sitting properly
   c. Don’t use the plunger to fill

6. What is platform sample concentration?
   a. 5 mg/ml before adding to sample buffer, this gets down to 1 mg/ml (for NR/R)
   b. 1mg/ml R 2 for NR
   c. UV methods 1mg/ml for both

7. Wash direction?
   a. Done in reverse but running forward (contributed to high baseline noise)
   b. Fluidics reversed but ran forwards
   c. All forward
   d. Shouldn’t ultimately matter

8. What’s the criteria for when to not use platform?
   a. Have a go to plan when accessing a new molecule on a platform
   b. Run the same DoE every time
   c. Optimization can be included, since you aren’t going from scratch

9. When do you have to re-validate a method,
   a. Anytime you change a parameter

10. Apply abbreviated validation for any new molecule when using an validated method

11. Transfer for a method, (validation holds, have them execute a transfer protocol, test the lab, not the method)
    a. As long as the method isn’t changing then it should be fine to still use
    b. Still need to demonstrate they are able to perform the method properly

12. Platform is in the instrumentation
    a. The optimized conditions are all within what is expected to be optimized, time temp sds

13. Reducing agent, most use BMe, only one participant used DTT

14. Buffer
    a. Most used kits, mostly pH9 Tris
    b. Only developing their own buffer, if needed or choose other pH for buffer

15. Alkylating agent
    a. IAM
    b. NEM for FQ LIF method (this is going to be their platform method, concentration is lower, drawback is use of KCN---validation of a UV method was very difficult, especially for integration, baseline is much better for the FQ method)
    c. Alkylate after reducing? Nope

16. IAM time of addition
    a. 5x sample buffer
    b. 1x sample buffer

17. Everyone is using Empower
    a. Follow the baseline when integrating
    b. Try to use autointegration
    c. LIF doesn’t have the wavy baseline
18. Sampling rate 4 Hz
   a. UV 2 Hz
19. Variability
   a. Method dependent
   b. Which peak are you accessing
   c. Purity <1% RSD
   d. Use as a criteria for using as a platform
20. System Suitability Criteria
   a. Resolution, relative migration time, TCA tracking (methods allow to adjust injected volume if low responses are received)
21. Criteria around migration time?
   a. As long as it doesn’t effect the results/ purity it shouldn’t matter so much
22. Multiple injections from same vial?
   a. Yes, have not seen (one method uses 6 injections for systems suit)

**Session 2:**
1. Goal of platform method is to standardize globally within an organization and meet fast to FIH needs
2. Can be applicable for early stage molecules
3. Need to have feasibility criteria to ensure molecule fits platform
   a. evaluation of e-grams
      i. peak shapes
      ii. resolution (can it be easily integrated)
   b. repeatability
   c. mini linearity (min 3 levels)
      i. accuracy and precision
   d. repeatability
   e. Force degraded material for stability indicating methods
4. Considerations for early platform methods (pre-tox and tox material)
5. Must be fit for purpose
6. For CE-SDS minimal upfront optimization is necessary
   a. an internal standard is necessary
      i. can be 10 kDa or other user defined peak
7. For icIEF platform needs to be flexible:
   a. molecules with low pI and high pI
   b. upper and lower pI markers
   c. Additives (ex. urea)
8. Reference material
   a. generic well characterized molecule used across all molecules
   b. molecule of interest can be used to provide information for selecting acceptance criteria
9. How is platform developed
10. select molecules from different IgG isotypes, bi-specific, fusion etc with different pIs, etc. (if available) NIST IgG can also be included in evaluation
11. previous knowledge, data from previous development can be used to select conditions and then tested
12. Robustness DOE should be included for multiple molecules
13. When are molecule specific methods needed
14. late stage before phase 3
   a. requires extensive robustness DOE
   b. requires final representative material
   c. Stability testing
15. Orthogonal methods
16. can be developed in parallel (ex. IEX and icIEF)
17. may be developed for characterization or formulation support activities