Roundtable Session 1 – Table 1 – Method Comparability Considerations

Facilitator: Scott Umlauf, *AstraZeneca, Gaithersburg*

Scribe: Marshall Davis, *Pfizer, Bothell*

Abstract:

Moving through the CMC lifecycle of a product, we often update our methods. Maintaining continuity of the product control narrative, we need to show that the new methods are "comparable" to what we've filed before.

Discussion Questions:

Does your company have a standard approach?

Do you run Method Comparability under a formal Protocol?

What parameters do you test?

What criteria do you use?

How do you set the criteria?

What material do you use for the testing?

How do you file method comparability in regulatory documents, i.e. how much detail do you provide?

Notes:

- People seem to generally agree there is not a hard and fast protocol in place
- "Talk to the guy who did the last one"
- Reg CMC – it's "ideal" to have a guideline. Asking what the last person did makes you very prone to NOT understanding the rationale behind what was done. Makes it more likely that you are going to miss a critical component and have to go back and cover.
- Reproducing part of the original phase appropriate validation (qual) – same linear range, similar accuracy
- When replacing a binding assay with a cell based assay, how problematic is the cell based assay being more variable?
- More MOA reflective, is a requirement of the FDA, cell based assay is often more sensitive to stability indicating changes. All make it likely you can accept slight increase in variability.

- Forced degradation studies are critical, and you can even prepare enriched samples
- Review phase 1 GMP lots – up to 5 to 10
- Some further discussion of this, doesn't necessarily have to be all, but want it to be representative of the entire manufacturing process changes
- T-test pairwise comparison between lots – use intrinsic assay variation to set how tight the results need to be
- Also evaluate the mean difference between all of them
- On stability indicating samples, want them in the same direction but does not necessarily have a quantitative cutoff
- For those forced deg samples, often there will be a phys chem method that is better at detecting those CQAs, so that is part of the justification for not necessarily having formal precision on those samples
- Regulatory filing: there is not guidance
- Perhaps a summary, name the statistical comparisons, and give the output, but probably not the raw data
- Most people agree to keep the comparability process separate from the validation
- Some groups do go back and run the old method on new samples
- What is happening in the clinic is generally going to be dictating when you file the change
- The group seems to feel no lots should be released until a regulatory update of the method has been filed – some groups have begun to release the material with the new method before filing, but were advised by regulatory to make sure they kept retains of the batches ready to re-test with the old method rapidly if asked by regulatory agencies
- Reg CMC perspective that rather than comparability this typically would be referred to as bridging – comparability is a process specific term so be careful
- Some in the group want to be able to use validation itself as a part of the bridging, even though the sample sets and test dates will be more separate
- This would be particularly compelling when the past method is no longer available
- "all the conclusions you have made in the past, you would also make with the new method you are proposing"
- If reference standard has changed you may need to do some paper exercises to justify
- Be careful how you word your regulatory updates, "we will use this assay for all development activities going forward" means you can never use the other assay again even if it is better suited for some dev activities