A BALANCING ACT: STREAMLINING METHOD TRANSFERS WITHOUT COMPROMISING COMPLIANCE OR SCIENCE
• Introduction
• The Improved Comparative Study
• Real World Examples and Their Challenges
• Waivers: When Less is More?
• Pitfalls, Panic, and Pain-points
INTRODUCTION: TRANSFER, TRANSFER, TRANSFER!

- New business drivers mean an unprecedented level of method transfer activity
- Method transfers need to be simultaneously efficient while minimizing risk to:
  - Longer term issues: high invalid rates, unexpected results, unacceptable bias, or adverse trends
  - Be nimble to support manufacturing tech transfer globally
  - Reduce regulatory questions and expedite approvals
- The focus today is on later stage product specific method transfers (pivotal through MAA and post-launch)
## THE BIG PICTURE: RIGHT WORK AT THE RIGHT TIME

<table>
<thead>
<tr>
<th>Early Stage</th>
<th>Pivotal</th>
<th>Late Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Optimization</td>
<td>FIH</td>
<td>PPQ Initiation*</td>
</tr>
<tr>
<td>pre-clinical</td>
<td>CPD</td>
<td>Filing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Launch Post Launch</td>
</tr>
</tbody>
</table>

- Careful consideration should be given to method transfers at pivotal stage
  - Investment of resources earlier in the method lifecycle
  - Analytical consistency during clinical trials
  - The manufacturing tech transfer strategy between clinical and launch
- Late stage method transfers must be rigorously performed

This approach ensures continuity of data between labs at critical points in the commercialization program.
THE IMPROVED COMPARATIVE STUDY

• Regulatory and industry guidance requires a comparative study between the transferring and receiving labs
  – Real time side-by-side execution of a study has been the status quo across the industry

• Use of historical data from the transferring lab(s) creates a novel advantage on many fronts
  – A more accurate picture of method performance and sources of variability over time, thus ensures consistent product trending
  – Often a larger data set for more robust statistical analysis and meaningful acceptance criteria
  – Allows transferring staff to focus on assessment of performance in the receiving lab
OVERVIEW OF TRANSFER STRATEGIES FOR PRODUCT SPECIFIC METHODS (PURITY, BIOASSAY, ID)

• Quantitative methods: set equivalency and precision criteria using historical data and perform study at receiving lab
  – A statistical test of equivalence is used to ensure the bias between the two labs is small enough that measurements from the receiving lab can be used for the intended purpose.
  – Assess equivalency using TOST (using a two-sided 90% confidence interval)
  – Consider the method validation precision criteria and outcome

• Qualitative methods: set criteria based on specification (non-statistical) and perform study at receiving lab
  – Consider raw data comparison to transferring lab
  – Use of blind positive and negative samples
A SIMPLE STUDY DESIGN IN RECEIVING LAB: A KEY TO SHOWING EQUIVALENCY AND GAINING EFFICIENCY

• Equivalency and Intermediate Precision
  – Product Reference Standard or Assay Control
  – A standard 8 assay format
  – 24 determinations that account for method-specific sources of variability (i.e., analyst, day, column and/or instrument)

• Verify all applicable sample types under actual conditions of use
  – Various formulations
  – In-process samples
  – Stability or forced degraded samples
THOUGHTFUL SETTING OF ACCEPTANCE CRITERIA CANNOT BE OVER-EMPHASIZED!

• Equivalency
  • Two One-Sided T-Test: The bounds of the two-sided 90% confidence interval for the difference in the receiving lab mean from the historical data set mean must fall entirely within the method intermediate precision (standard deviation) estimated from the historical data set

• Intermediate Precision
  • Based on validated level of variation for the method, or
  • Upper bound for tolerance interval for the variation in the historical data set

• Sample Type Verification
  • Method Sample Result Acceptance Criteria
  • Release/Stability Specification
  • Tolerance Interval from Historical Data, or
  • Transferring Lab result for the specific sample
STANDARD VISUAL OUTPUTS ENABLES INTUITIVE ASSESSMENT AND SUPPORTS CONCLUSIONS

Figure A.1: Equivalence and Scatter Plots

PASS

The bounds of the 90% CI for the difference in the means met the predefined acceptance criteria, indicating that the receiving laboratory’s performance of the method is equivalent to the transferring laboratory’s performance.

-2.181  2.181

-0.265  1.127

-2  -1.7  -1.4  -1.2  -0.7  0.2  0.3  0.8  1.3  1.8

Provided January 6, 2017, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.
CHALLENGES OF THE HISTORICAL DATA SET

• Minimal variability
  – Criteria may be set too narrow compared to validation, specification, or intended use

• Use of multiple sites
  – Shifts the paradigm of a single transferring lab
  – Uses a global holistic perspective of method lifecycle
  – Can potentially widen the criteria, appropriate or not!

• What data to use? How do I get it?
  – Requires companies to have strong data handling systems/processes
SIZABLE HISTORICAL DATA SETS CAN BE A BLESSING OR A CURSE

- Historical data set of the product Reference Standard over one hundred points from long term commercial test site with minimal variability
- Specification is ≥ 88%
- Investigation must consider
  - Is the criteria overly tight?
  - Is there a meaningful technical difference between the labs that could impact product trending?
USING MULTI-SITE HISTORICAL DATA SET ENSURES MEANINGFUL CRITERIA

• Example 1: primary test lab and two contract labs
  – A clear picture of method performance AND variability

• Example 2: two existing test sites show bias
  – Statistically different but not practically important
EXAMPLE 1: THE RIGHT HISTORICAL DATA AND CRITERIA MAKE ALL THE DIFFERENCE

• Initial transfer: data from early method development and wide criteria (±2.2) allowed for a bias that resulted in unconfirmed OOS results
• Subsequent transfers of the same method used pooled commercial multi-site data and equivalence criteria based on 2SD (±1.8)
EXAMPLE 2: A SUCCESSFUL TRANSFER OUTCOME!

An unnecessary investigation avoided while clear demonstration of consistent results

Provided January 6, 2017, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.
WAIVERS: WHEN LESS IS MORE?

• Performing a transfer study may not be necessary in all situations
  – Similar method for similar product or sample types
  – No new specialized techniques required
  – Low risk assessed for receiving lab, product safety, company, filings
  – Clear documentation of justification

• Supported by some industry guidance documents (USP <1224>, PDA TR no. 57)

• Real world application seems limited to compendial methods

• Risk increases through the product and method lifecycle
PITFALLS, PANIC, & PAIN POINTS: THE MOST COMMON TRANSFER ISSUES

- Mis-alignment of prioritization at involved sites
- Incomplete assessment of equipment or material equivalency
- Inadequate training
- Inadequate detail in method documents
- Inappropriate criteria
- Delay of data review and investigation
- Samples: unavailability, handling/storage, failure to include all types
- Data handling: integration, calculations
- Excessive invalids
BEST TEAMS USE BEST PRACTICES

- COMMUNICATION!
- Ownership and decision maker(s): Receiving lab accountability to defend transfer outcome
- Technical support identified up front
- Global forum: real time case studies, lessons learned, regulatory feedback
- Transfer plan: setting up for success
- Present transfer data to stakeholders
- Monitor post-transfer method trending in Quality systems