Apples to Apples Equivalency? A Bioassay Reference Material Bridging Approach for Method Lifecycle Management

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BioTherapeutics Pharmaceutical Sciences
Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

Presentation

1. What is a Reference Standard/ Reference Material?
2. Reference Material “Categories”
3. Requirements for Bridging Reference Material
4. Case Study Design
5. Case Study Results
6. Summary
7. Discussion

Reference Standard/ Reference Material

1. What is a reference standard/reference material?
   - A "highly purified compound that is well characterized“

     The US Food and Drug Administration

   - "highly characterized specimens of drug substances, excipients, reportable impurities, degradation products, compendial reagents, and performance calibrators”

     The US Pharmacopeia (USP)

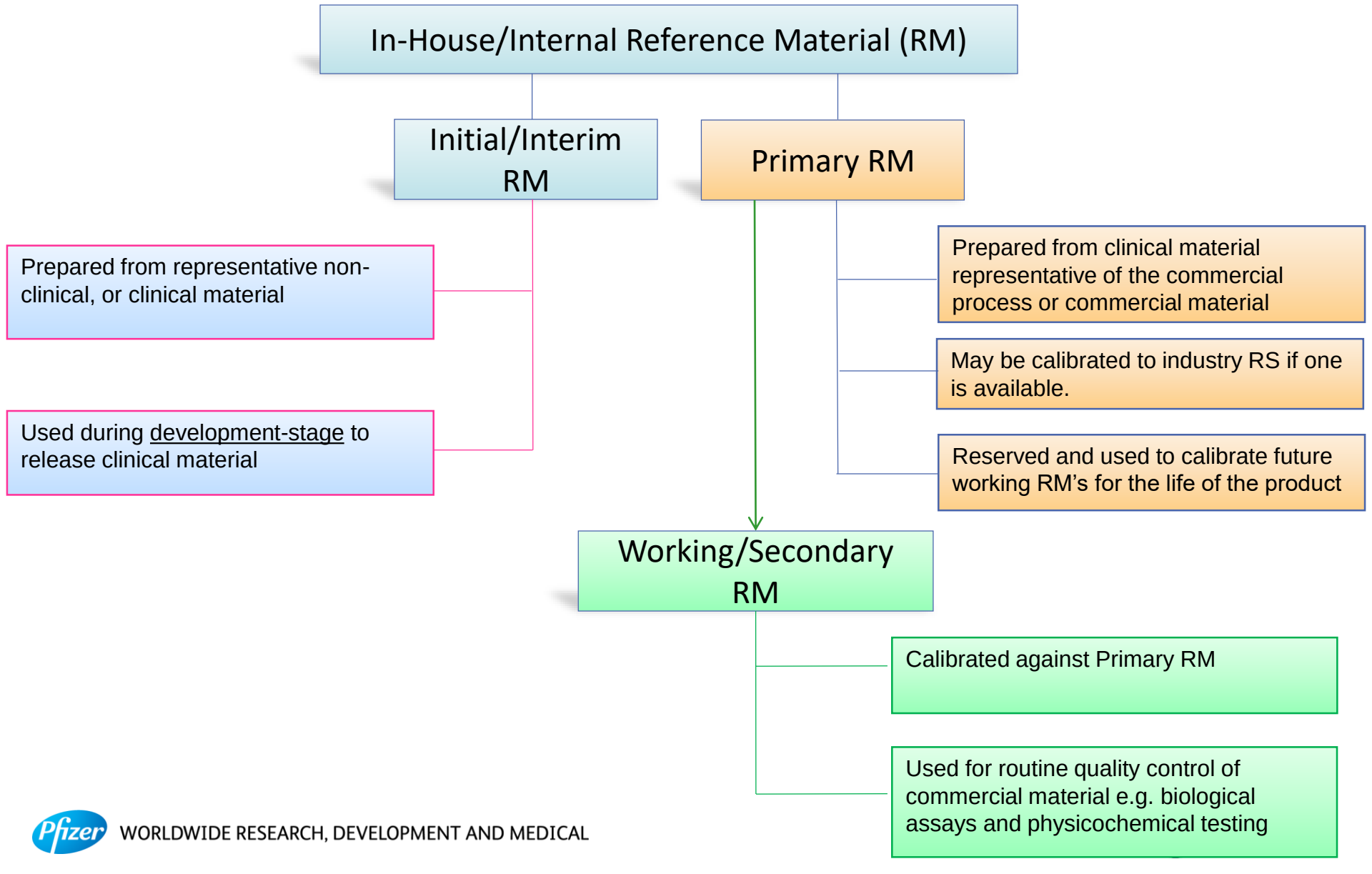
   - Characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing (***ICH Q6A***)
2. How is the reference standard/reference material used?
   - Analytical tests are used to assess the product quality in a number of activities
     - Characterization, Comparability, Lot release and Stability
   - Reference Standard and Reference Material play a critical role in calibrating and confirming the suitability of such tests.

Reference Standard

Reference Standard (RS)

- Refers to international, industry wide standards
- Obtained from Pharmacopeias (USP and Ph.Eur), Other authorities (WHO) or Commercial suppliers (NIST)
- Used throughout development phase and commercialization
- Standard against which all in-house references are calibrated

Reference *Material*



Establishing Reference Material

1. FDA Compliance Program Guidance Manual 7356.002 requires written and approved procedures that detail the "**tests to establish equivalency to current official reference standards as appropriate**" for pharmaceutical reference standards.
2. Orthogonal Analytical methods should be used to confirm potency
   - Strength, Identity, Purity, Homogeneity and Stability
3. Statistical methodology should be applied, where appropriate, to confirm equivalency
   - The goal is "results equivalency"
4. The target product attribute(s) and testing purpose determines the reference material choice and the type of required characterization tests
5. At all stages, the established RM should be "representative of production and clinical materials" (ICH Q6B)

Analytical Characterization

1. Primary Structure e.g. Molecular Mass by LC/MS
2. Higher Order Structure (HOS) e.g. Secondary and Tertiary Structures by FTIR and Near-UV CD
3. Post-Translational Modifications e.g. N-Glycosylation by HPLC-FLR
4. Aggregation
   - Leverage orthogonal tools e.g. SE-HPLC, SEC-MALLS
5. Product Isoforms/Degradation Products/Impurities e.g. Fragments by RP-HPLC
6. **Biological Activity**

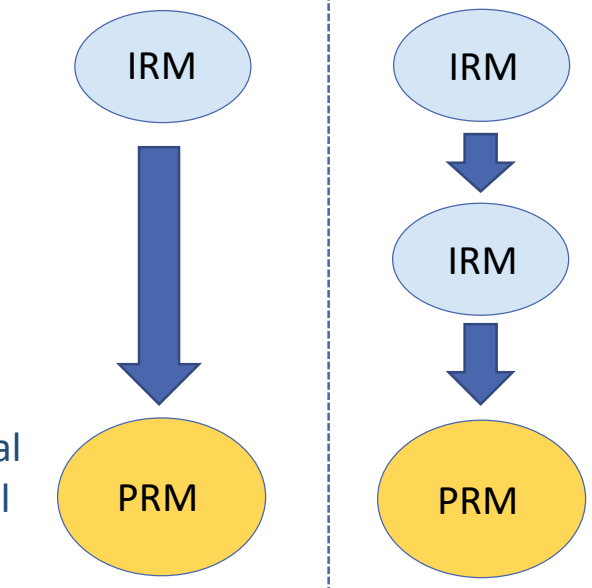
Reference Material Replacement

1. Ensure to keep sufficient stock of the RS or first primary RM (your *gold* standard) for calibration purposes during the whole product life cycle.
2. The number of **primary** RM replacements should be **kept to a minimum** in order to ensure that the historical link to the clinical material is maintained without disruption.
3. Keeping the RS or primary RM (if stability is ensured) as the calibrator each time another secondary/working material is developed:
   compare A→B, A→C, A→D and **not** A→B→C→D.
4. Recommend a meeting with agency to gain agreement on RM or primary RM replacement if necessary

Scenarios for Bridging

1) Clinical Typical (ideal)

2) Clinical Atypical



Key:

IRM = Initial or Interim RM

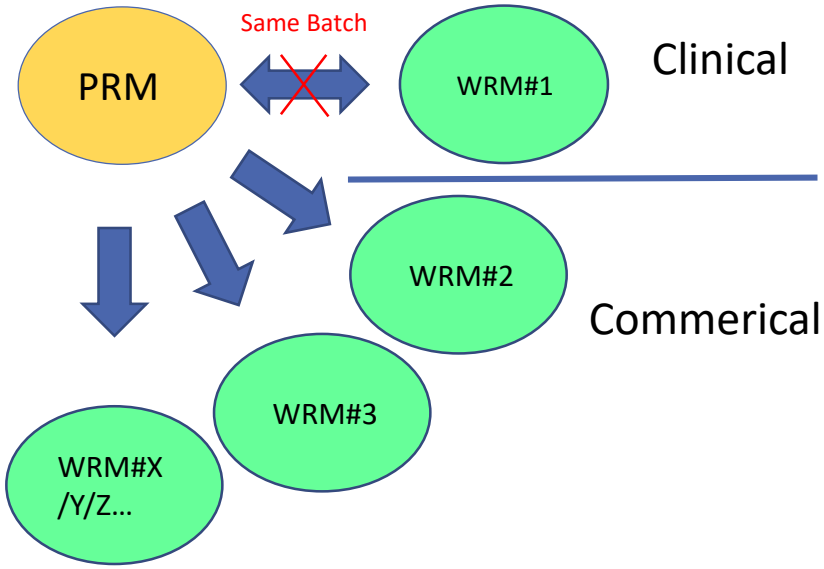
PRM = Primary RM (Pivotal Material)

WRM = Working Reference Material

PV = Process Validation (PPQ)

3) Post Establishing PRM

WRM#1: No biological activity bridging required, confirmatory testing only as from same batch as PRM



Commercial Stage

3 Scenarios:

- For 1 & 2 use Clinical stage bridging criterion
- For 3 use Commercial bridging criterion
- For WRM#1 only bioassay *testing* is required not *bridging*

BTx Pharm Sci

Bridging Approach

Establish two Equivalency Acceptance Criterion (EAC) that are based on the stage of product development (Equivalence testing vs. difference testing)

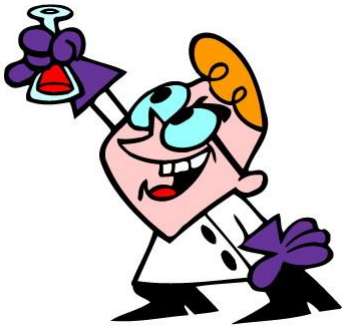
1. To appropriately balance consumer and producer risks (project stage)
   - Clinical Phase: Equivalence Acceptance Criterion (EAC): 80-120% IRM to PRM bridging
   - Commercial Phase: Equivalence Acceptance Criterion (EAC): 90-110% for clinical RM bridging (typically PRM to WRM #2 or replacement RM lot)
2. Powered study to confirm they have the same potency
   - Confidence level (95%)
   - Sample size (n) based on variability in assay, confidence level and EAC
3. Study design and criteria to be specified before testing begins
4. Equivalency confirmed if both the following are true
   - The entire confidence interval range is within the EAC (equivalence test)
   - The confidence interval includes 100% (difference test)

Case Study

Mock study outline

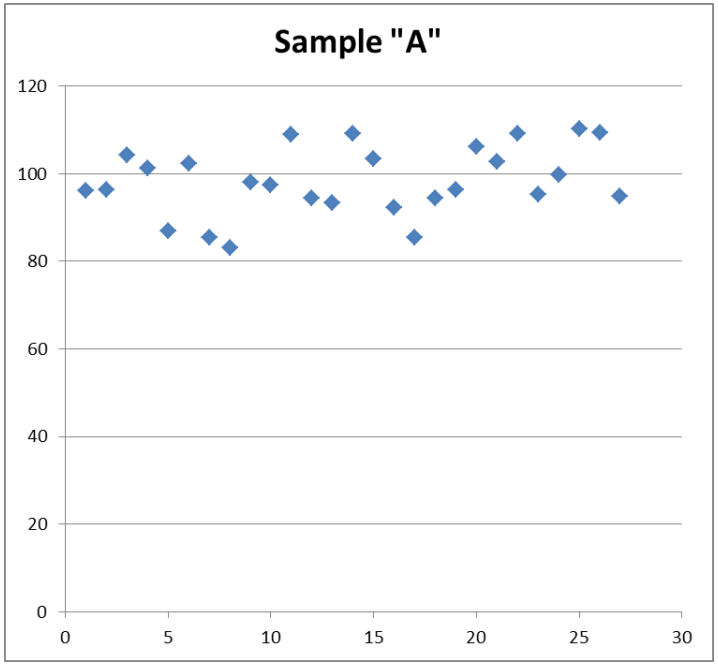
1. 2 RM samples provided for replicate testing
    - Sample A concentration is 100% of target (10 mg/mL)
    - Sample B concentration is 90% of target (9 mg/mL)

2. 2 labs, multiple analysts
    - True RM sample concentration is blinded to the analysts



Case Study: Sample A (100%) Data

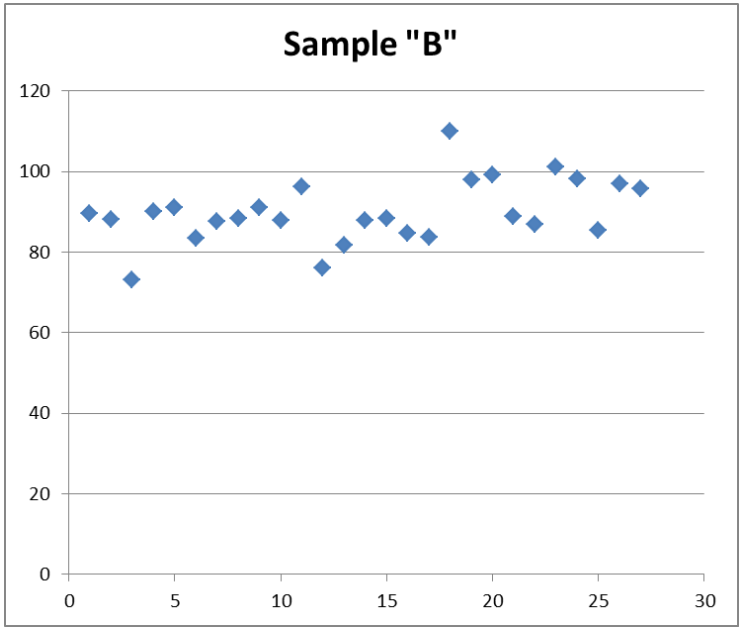
Lab	Analyst	Date of Test	Replicate % RP	Reportable Mean % Relative Potency	%CV
Lab 1	1	20-Jan-15	96.06	99	4.67
	1	20-Jan-15	96.23		
	1	20-Jan-15	104.13		
	1	20-Jan-15	101.27	97	8.84
	1	20-Jan-15	87.02		
	1	20-Jan-15	102.37		
	2	20-Jan-15	85.42	89	9.07
	2	3-Feb-15	82.99		
	2	3-Feb-15	97.99		
	1	4-Feb-15	97.32	100	7.66
	1	4-Feb-15	108.99		
	1	4-Feb-15	94.5		
	1	4-Feb-15	93.34	102	7.86
	1	4-Feb-15	109.2		
	1	4-Feb-15	103.27		
	3	2-Apr-15	92.32	91	5.20
	3	2-Apr-15	85.37		
	3	2-Apr-15	94.37		
Lab 2	4	5-May-15	96.39	102	4.89
	4	5-May-15	106.2		
	4	5-May-15	102.74		
	4	6-May-15	109.15	101	6.95
	4	6-May-15	95.35		
	4	6-May-15	99.75		
	4	13-May-15	110.26	105	8.23
	4	13-May-15	109.28		
	5	9-Jun-15	94.86		
			average	98	
			stdev	5.38	
			%CV	5.47	



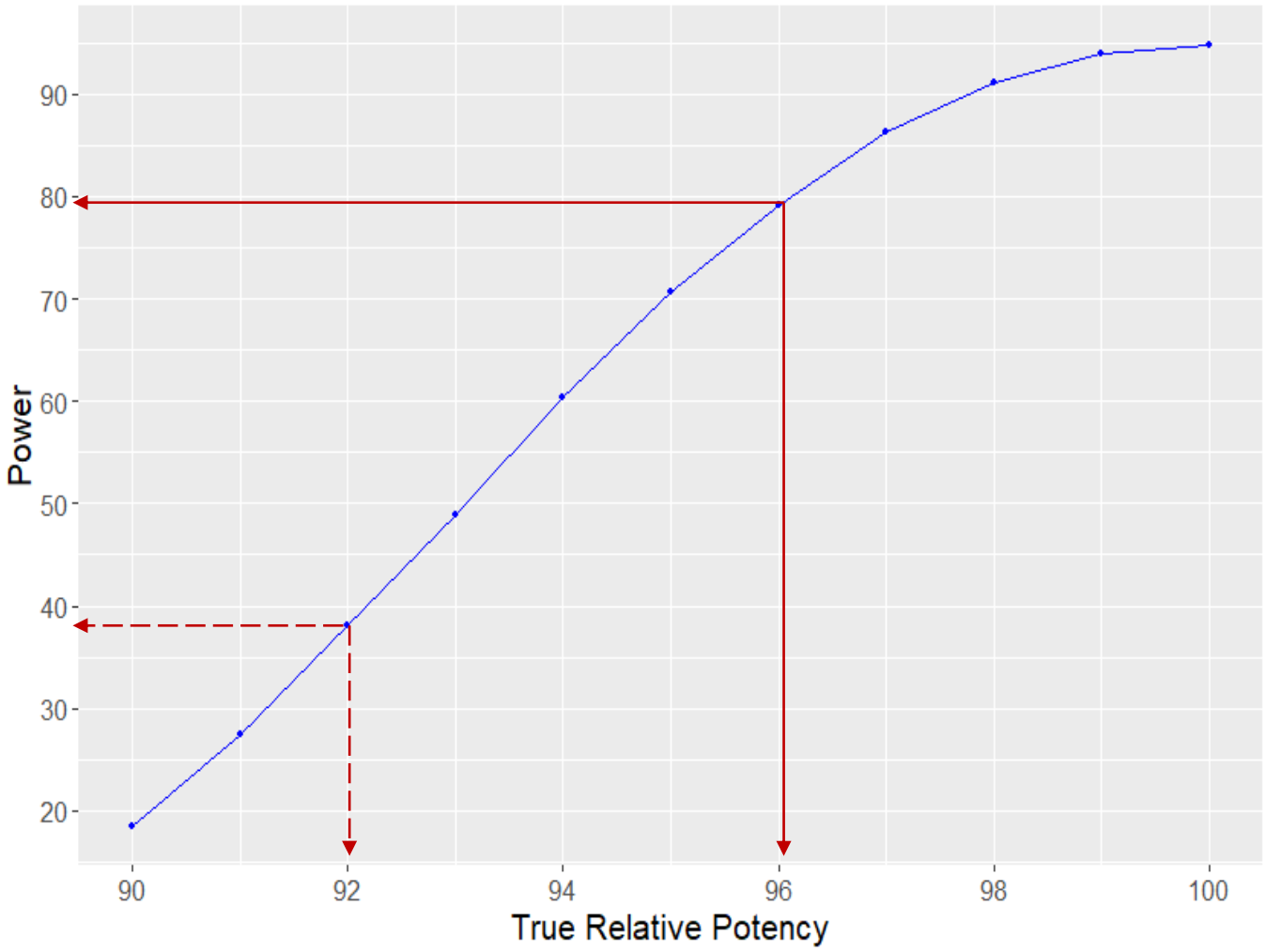
Case Study: Sample B (90%) Data

Lab	Analyst	Date of Test	Replicate % RP	Reportable Mean % Relative Potency	%CV
Lab 1	1	13-Jan-15	89.45	84	10.87
	1	13-Jan-15	88.17		
	1	13-Jan-15	73.12		
	2	14-Jan-15	90.03	88	4.68
	2	14-Jan-15	91.12		
	2	14-Jan-15	83.48		
	2	20-Jan-15	87.54	89	2.00
	2	20-Jan-15	88.34		
	2	20-Jan-15	90.95		
	2	20-Jan-15	87.84	87	11.67
	2	20-Jan-15	96.16		
	2	20-Jan-15	76.03		
	2	4-Feb-15	81.75	86	4.30
	2	4-Feb-15	87.9		
	2	4-Feb-15	88.39		
	3	27-May-15	84.73	93	15.99
	4	29-Apr-15	83.77		
	3	19-May-15	109.95		
Lab 2	5	15-May-15	97.8	95	5.90
	5	15-May-15	99.08		
	5	15-May-15	88.78		
	5	19-May-15	86.93	95	7.84
	6	13-May-15	101.15		
	5	13-May-15	98.07		
	7	19-May-15	85.36	93	6.85
	7	19-May-15	96.86		
	7	19-May-15	95.78		

average	88
stdev	3.32
%CV	3.77

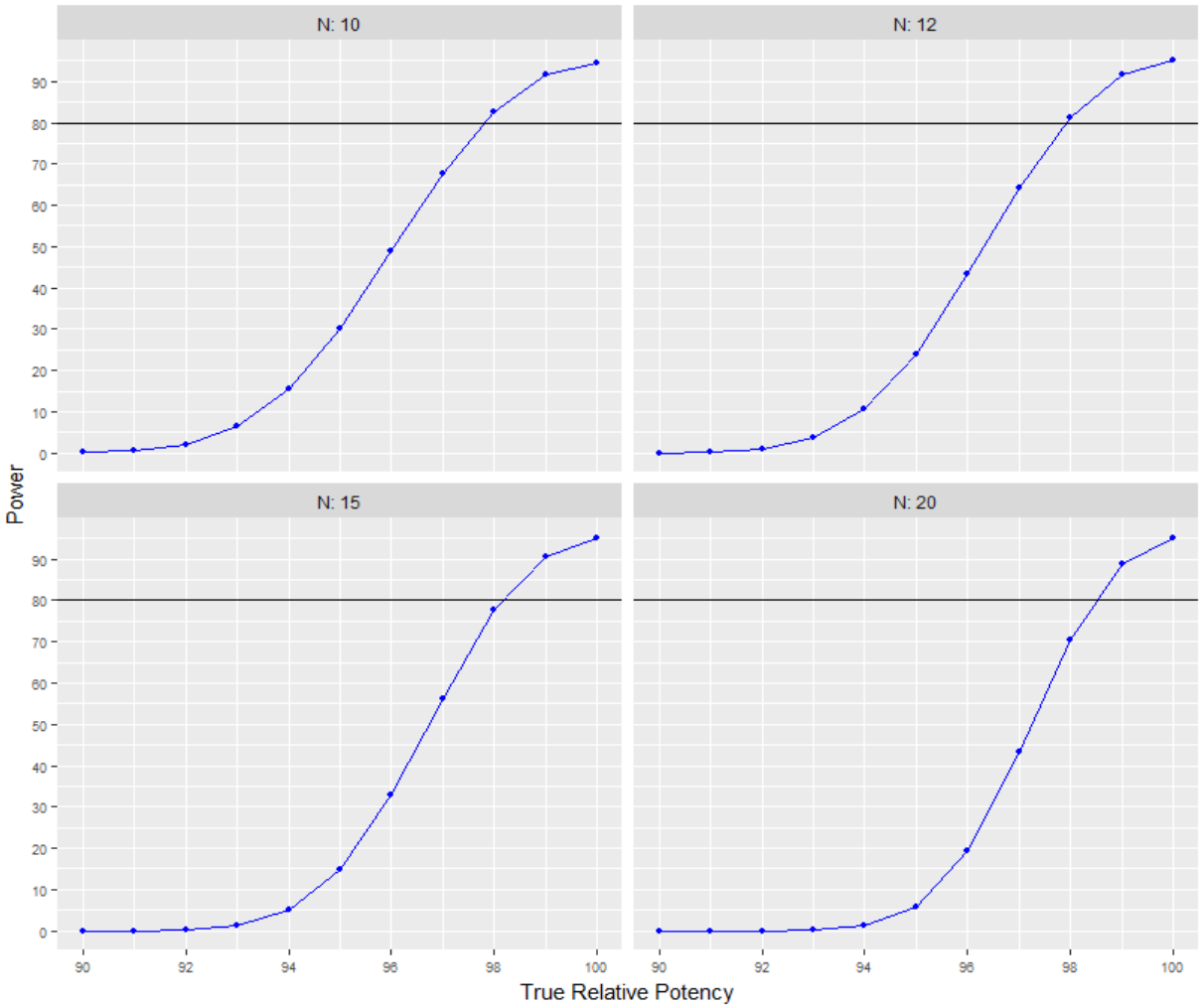


Power of the Study



- High probability to claim the equivalency when the two reference materials have small true mean differences
- Low probability to claim the equivalency when the two reference materials have large true mean differences

Power Plot Used to Determine Sample Size for Bridging

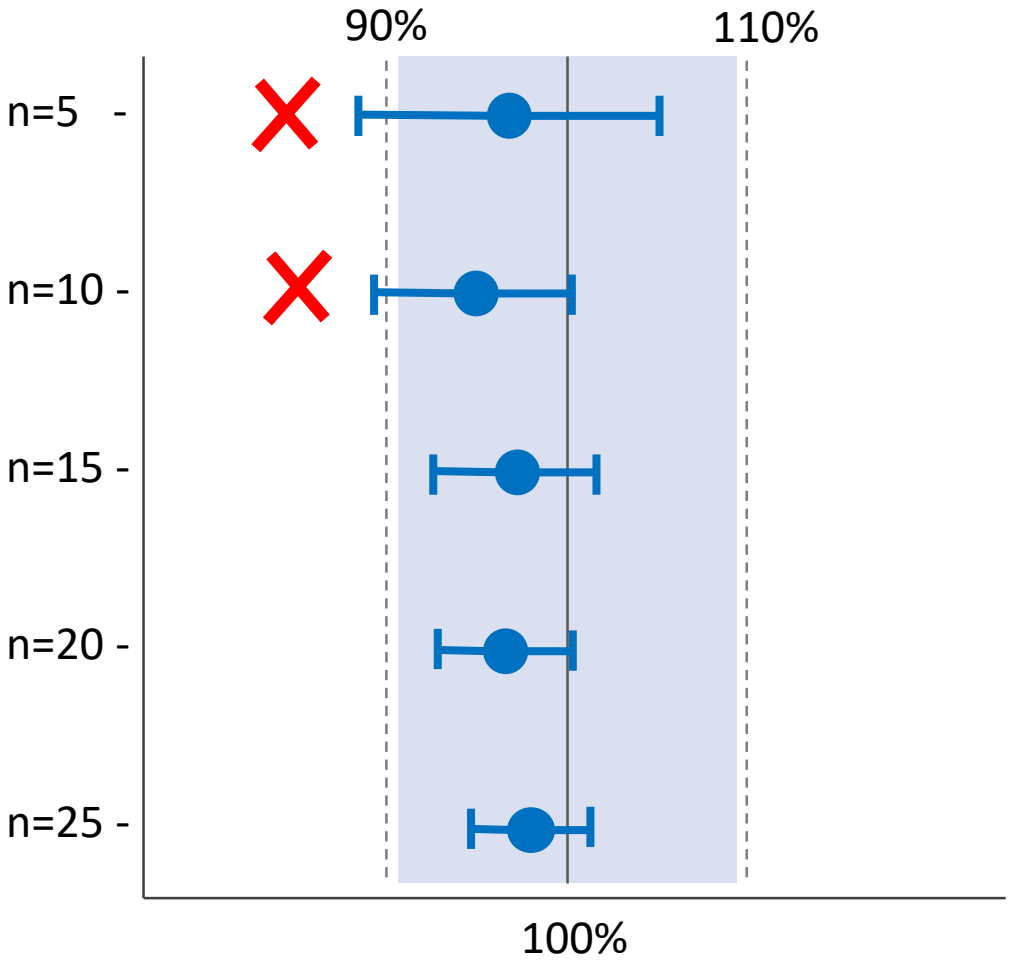


Significance
Level=2.5%
SD=6%
EAC=90-110%

n=10, power 80%, 2% true mean diff.
n=20, power 70%, 2% true mean diff.

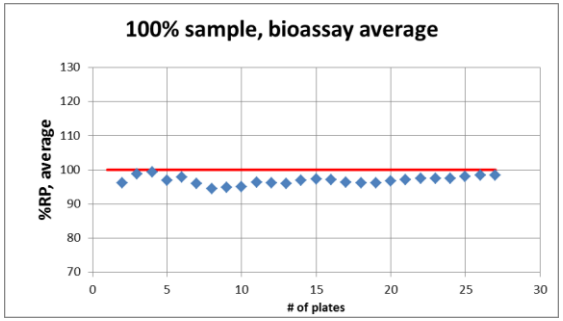
Conclusion: With two equivalent criteria (95% CI within EAC and covers 100%), power does not improve with larger sample size. The statistical power calculation helps select the appropriate sample size

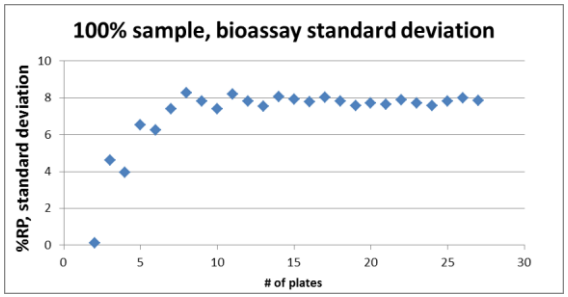
Sample A (100%)



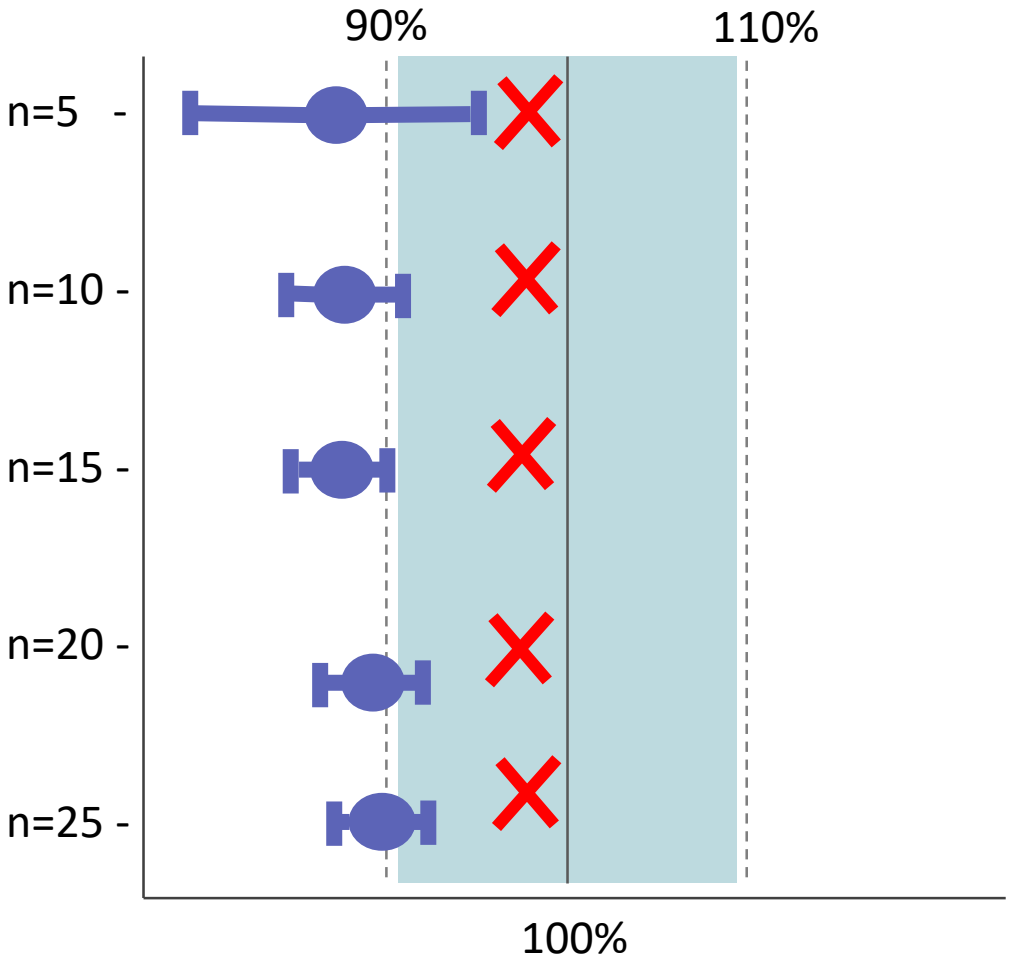
5 analysts, 2 labs, over period of months

Mean (n=27): 98.38%
stdev: 7.8%



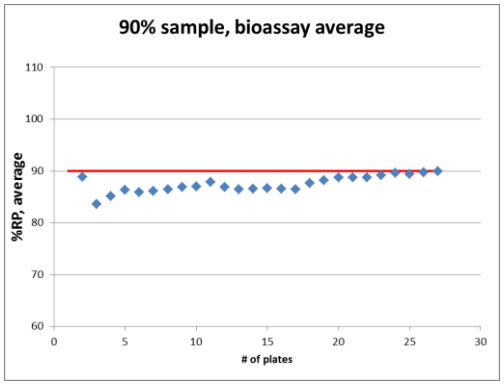


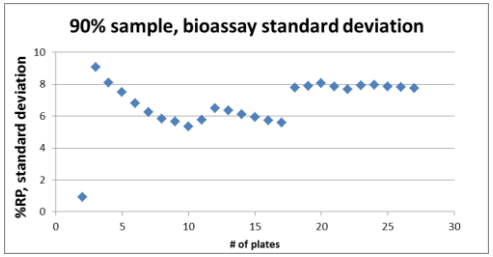
Sample B (90%)



5 analysts, 2 labs, over period of months

Mean (n=27): 89.9%
stdev: 7.8%





Case Study Results

Sample	95% CI	Interim to PRM	WRM to PRM
A (100%)	94.24, 102.43	Equivalent (within 80-120% and spans 100%)	Equivalent (within 90-110% and spans 100%)
B (90%)	86.69, 93.20	Not Equivalent (within 80-120%, but does not span 100%)	Not Equivalent (not within 90-110% and does not span 100%)

*calculation arithmetic mean is used since the reported value is the average of three individual values so the normal distribution (not log-normal) is used for analysis

Failure to meet Equivalency

If the RM fails equivalency, choose approach based on the stage of product development.

1. Bridging IRM to PRM
   - Discuss with project team, investigate potential cause, etc.
     - If assignable cause non-material related, i.e. analyst errors, repeat the equivalence testing.
   - Select a different batch that is equivalent.
   - If no equivalent lot is available, and PRM is representative of future batches, assign 100% relative potency to PRM.

2. Bridging secondary or new WRM lot back to PRM
   - Select a different batch that is equivalent.
   - If no equivalent lot is available, apply correction factor.
     - i.e. If mean value of replacement lot is 96%, use this value in test method to calculate sample reportable result.

Summary

1. Determine the bridging approach based on the stage of product development.
   - Clinical Phase: Equivalence Acceptance Criterion (EAC): 80-120% IRM to PRM bridging
   - Commercial Phase: Equivalence Acceptance Criterion (EAC): 90-110% for commerical RM bridging (typically PRM to WRM #2 or replacement RM lot)
2. Powered study to confirm the materials have the same potency
   - Confidence level (95%)
   - Sample size (n) based on variability in assay, confidence level and EAC
3. If the RM fails equivalency – depending on phases specific approach
   - Identify an equivalent lot
   - Apply a correction factor
   - Assign 100% relative potency if representative lot

Acknowledgements

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Backup

References

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