Equivalence Margin Evaluations for Analytical Method Transfer

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janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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Outline

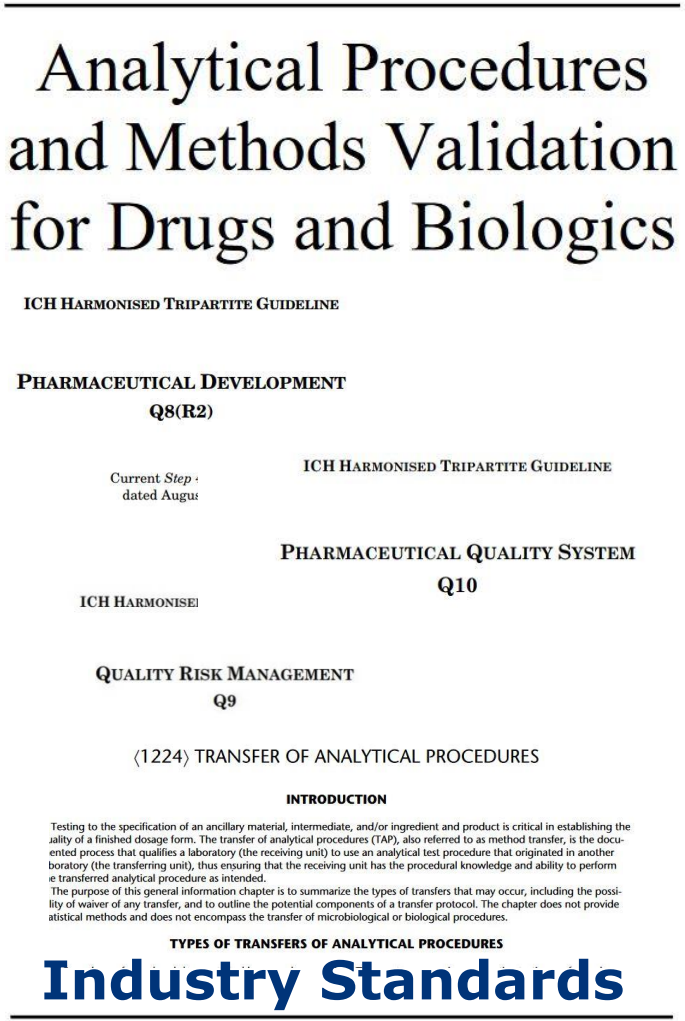
- Analytical Method Transfer (AMT)
- Study Designs
- Statistical Methodology
- Equivalence Acceptance Criteria (EAC)
- EAC Using Historical dataset
- Conclusions

Analytical Method Transfer

Method transfer is the process of transferring a validated analytical method from sending laboratory to a receiving laboratory, after demonstrating experimentally that it also masters the method.

Protocol driven study with pre-determined acceptance criteria

Demonstration of a laboratory's proficiency in running a particular method



Analytical Procedures and Methods Validation for Drugs and Biologics

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step* 4 version
dated August 2009

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

⟨1224⟩ TRANSFER OF ANALYTICAL PROCEDURES

INTRODUCTION

Testing to the specification of an ancillary material, intermediate, and/or ingredient and product is critical in establishing the quality of a finished dosage form. The transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended.

The purpose of this general information chapter is to summarize the types of transfers that may occur, including the possibility of waiver of any transfer, and to outline the potential components of a transfer protocol. The chapter does not provide statistical methods and does not encompass the transfer of microbiological or biological procedures.

TYPES OF TRANSFERS OF ANALYTICAL PROCEDURES

Industry Standards

FDA (2006) ICH 2005
The guidance introduces the concept of *quality by design* for a product lifecycle, ICH guidance for industry, Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System

FDA (2015)
The guidance recommends method transfer studies to evaluate *precision and accuracy* with regards to the assessment of interlaboratory variability

USP 1224
The aim of analytical method transfer is to evaluation of the analytical procedure's performance at the receiving site

Study Design

STUDY DESIGNS

Possible method transfer study designs, along with the proposed statistical analysis focuses on three objectives:

"Equivalence between Laboratories"

Demonstrate equivalence between laboratory mean responses.

"Laboratory Consistency"

Demonstrate consistency within laboratories through equivalence between mean responses for the analysts within each laboratory

"Laboratory and Analyst Proficiency"

Demonstrate the proficiency of each laboratory and each analyst through a test of equivalence to reproduce the expected result of the method transfer.

Independent Replicate Samples

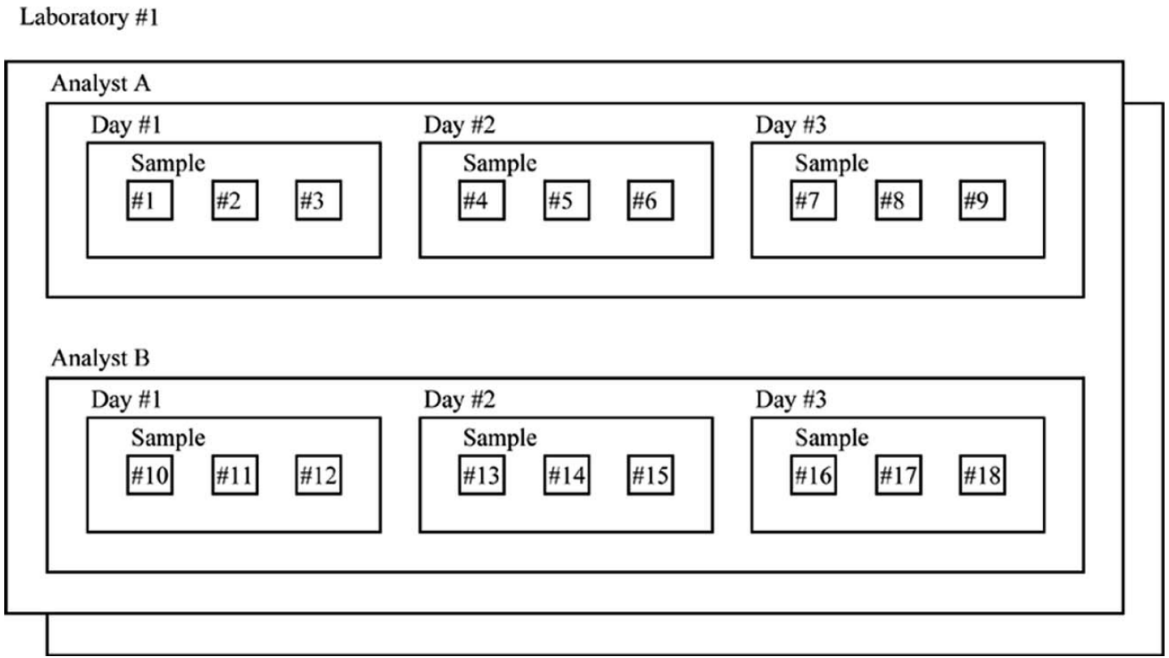


Figure 1 Independent replicate samples (Design #1). Total sample size = 36.

ANOVA table

Table 1 Analysis of variance (ANOVA) table: Design #1: 2 laboratories, 2 analysts, 3 days, 3 samples

Source	Effect	df	Test denominator
Laboratory	Fixed	1	Day(Laboratory*Analyst)
Analyst(Laboratory)	Fixed	2	Day(Laboratory*Analyst)
Day(Laboratory*Analyst)	Random	8	$\sigma_\varepsilon^2 + 3\sigma_{D(L*A)}^2$
Residual error	Random	24	σ_ε^2

Common Replicates Sets Shared among Laboratories

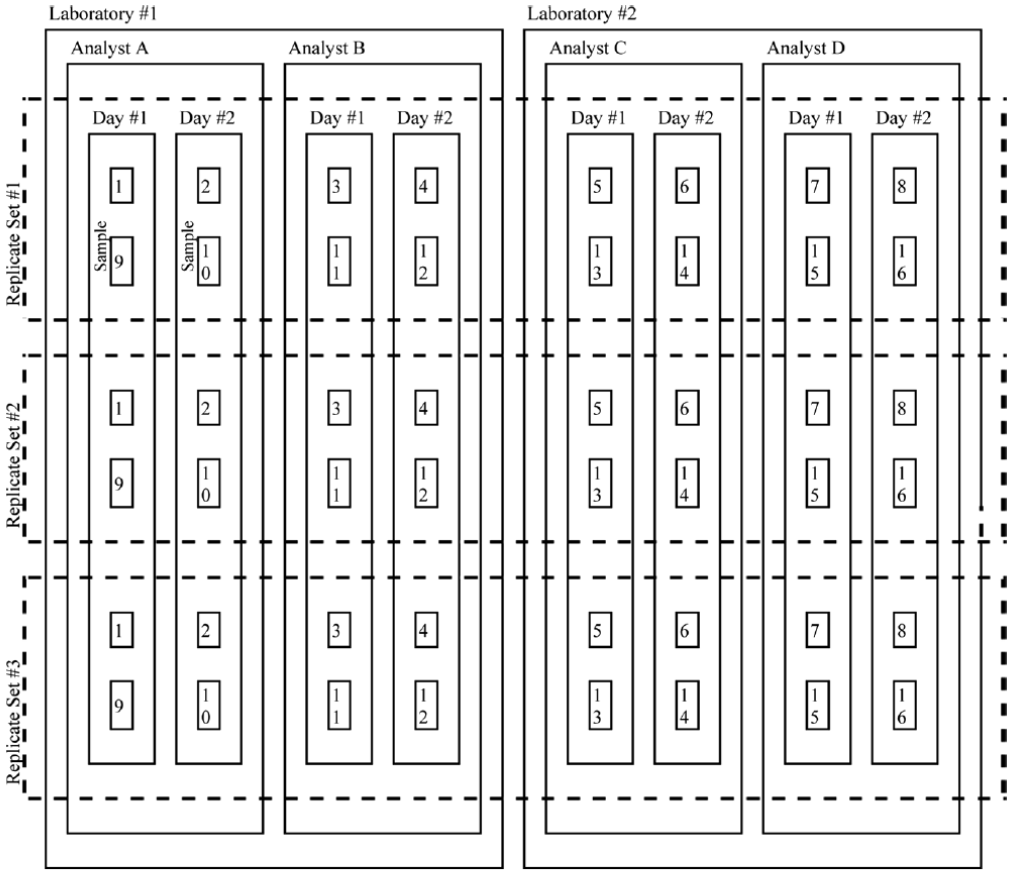


Figure 3 Common replicate sample sets shared among laboratories and analysts (Design #3). Total sample size = 48.

ANOVA table

Table 2 Analysis of variance (ANOVA) table: Design #3: 2 laboratories, 2 analysts, 3 replicate sets, 2 days, 2 samples

Source	Effect	df	Test denominator
Laboratory	Fixed	1	Function of mean squares
Analyst(Laboratory)	Fixed	2	Function of mean squares
Replicate	Random	2	$\sigma^2_\varepsilon + 2\sigma^2_{D*R(L*A)} + 4\sigma^2_{R*A(L)} + 8\sigma^2_{R*L} + 16\sigma^2_R$
Replicate*Laboratory	Random	2	$\sigma^2_\varepsilon + 2\sigma^2_{D*R(L*A)} + 4\sigma^2_{R*A(L)} + 8\sigma^2_{R*L}$
Replicate*Analyst(Laboratory)	Random	4	$\sigma^2_\varepsilon + 2\sigma^2_{D*R(L*A)} + 4\sigma^2_{R*A(L)}$
Day(Laboratory*Analyst)	Random	4	$\sigma^2_\varepsilon + 2\sigma^2_{D*R(L*A)} + 6\sigma^2_{D(L*A)}$
Day*Replicate(Laboratory*Analyst)	Random	8	$\sigma^2_\varepsilon + 2\sigma^2_{D*R(L*A)}$
Residual error	Random	24	σ^2_ε

Statistical Methodology

Statistical Methodology

A method transfer is successful when the originator and destination laboratories demonstrate equivalent results.

The test to demonstrate equivalence of the mean responses between laboratories is the primary comparisons of interest for the method transfer study

Statistical Methodology

Consider the hypotheses in terms of the equivalence delta

$$H_0: |\mu_T - \mu_R| \geq \Delta;\ H_a: |\mu_T - \mu_R| < \Delta$$

$$H_{01}: \mu_T - \mu_R \leq -\Delta;\ H_{a1}: \mu_T - \mu_R > \Delta,$$
$$H_{02}: \mu_T - \mu_R \geq \Delta;\ H_{a2}: \mu_T - \mu_R < \Delta$$

Confidence Interval Approach by Schuirmann, 1987

The $(1-2\alpha)100\%$ confidence interval of $\mu_T - \mu_R$ is given by $\left(\bar{X}_T - \bar{X}_R - t_{1-\alpha,2n-2}s\sqrt{2/n}, \bar{X}_T - \bar{X}_R + t_{1-\alpha,2n-2}s\sqrt{2/n}\right)$ where $n = n_T = n_R$

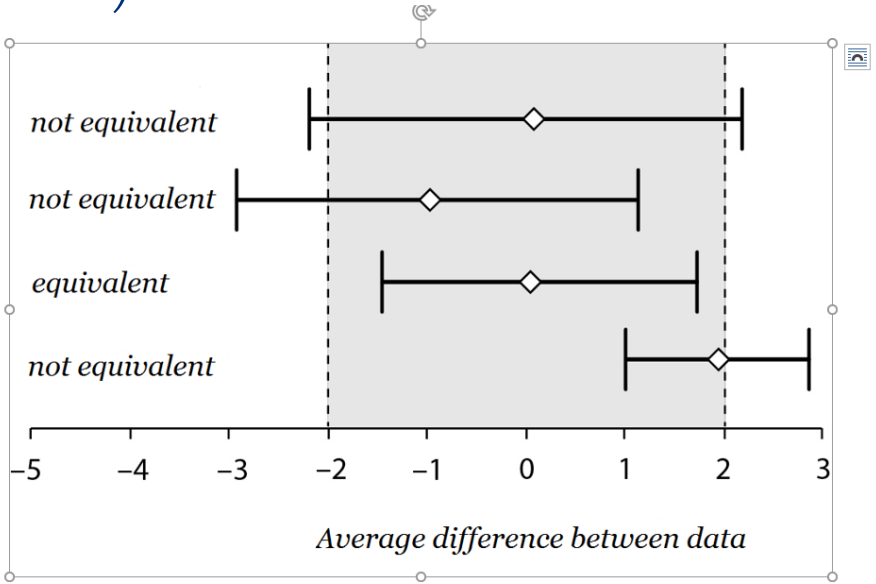
Equivalence Acceptance Criteria (EAC)

Under H_a: the power of the equivalence test can be calculated from a central t-distribution

$$\Phi_{2n-2}\left(\frac{\Delta-\theta}{s\sqrt{2/n}}-t_{1-\alpha,2n-2}\right)\text{-}\Phi_{2n-2}\left(\frac{\Delta-\theta}{s\sqrt{2/n}}+t_{1-\alpha,2n-2}\right)$$

where $\Phi_v(x)$ is the cumulative probability at x of a central t-distribution with v degrees of freedom

For a given AMT design and α level, an EAC (Δ) that ensures desired power $(1-\beta)$ can be obtained from the power function



Equivalence Acceptance Criteria (EAC)

EAC can be defined as a function of the

- **AMT study design**
- **allowable mean difference**
- **method variability**
- α **level and**
- **target power** $(1-\beta)$

Appropriate Choice of Δ

01

Scientific Decision, not statistical

02

Specific to the compound, method and process

03

Review development and historical data

Risk-based approach if no historical data

04

Assess in relation to specification bounds

05

Example: Assay, content uniformity acceptance criteria is $\pm 2\%$

EAC using Historical data

Challenges

- Limited data with proper design
- Limited data with no design/limited design
- Good data with no design/limited design
- No data/no design

Approaches

Fit a linear mixed model effect accounting for fixed lab effects, and depending on your design, homogenous random components due to between-assay and within-assay variability

$y_{ij(k)} = \mu + L_i + \delta_{j(k)} + \varepsilon_{ij(k)}$

$y_{ij(k)}$ = the i^{th} result from the j^{th} assay run at the k^{th} lab

μ = overall mean

L_i = the fixed effect of the k^{th} lab,

$\delta_{j(k)}$= the random effect of the j^{th} assay run at the k^{th} lab, $\delta_{j(k)} \sim N(0, \sigma_w^2)$,

$\varepsilon_{ij(k)}$= the residual deviation of the i^{th} result from the j^{th} assay run at the k^{th} lab, $\varepsilon_{ij(k)} \sim N(0, \sigma_\varepsilon^2)$

Approaches: Bayesian simulation

- **Output**: Posterior summaries, prediction interval for the variability
- **Simulation**:
  - Generate i samples from the mixed model
  - For each posterior sample, compute the $(1-\alpha)100\%$ CI of the mean differences given by $TR_i = \mu_T - \mu_R \pm z_{1-\alpha/2} \times \sqrt{2 * \left(\frac{\sigma_{w,i}}{n_w} + \frac{\sigma_{\varepsilon,i}}{n}\right)}$
  - Compute the 90% CI with pre-specified probability (say 95%)

Approaches: Probability of Study design EAC

- **Output**: probability of study design being able to meet the acceptance criteria
- **Scenario assumptions**
  - between-assay and within-assay variability based on the AMT design
  - True Mean Difference
  - Sample size, assays per site and replication in each assay

  - Compute estimated probability of study design meeting proposed acceptance criteria

Simulated Capillary Isoelectric Focusing Study

Analytical Method: cIEF (Sum of Acidic Peaks)

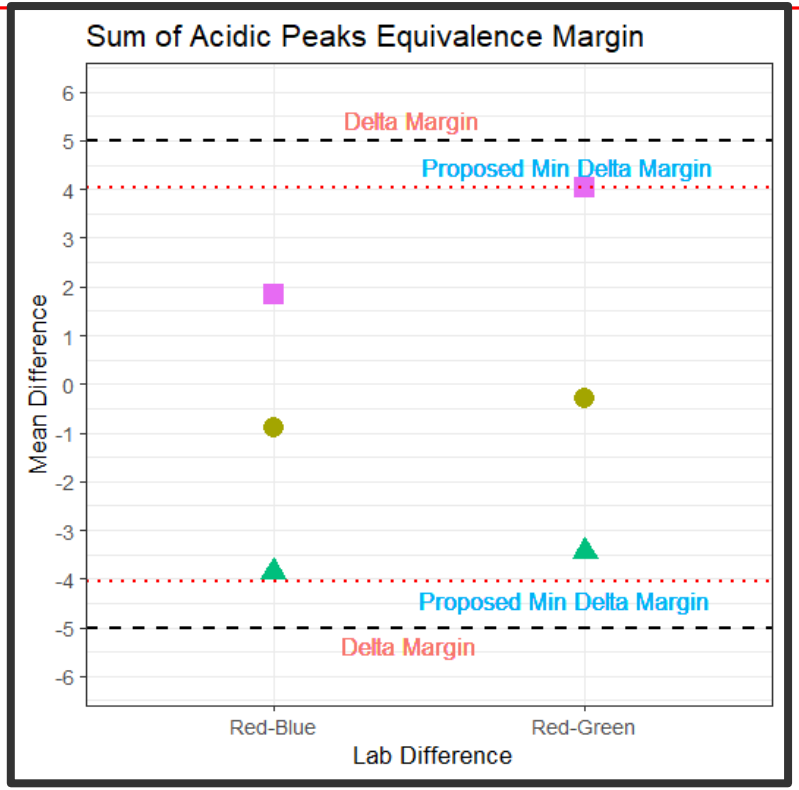
Data and Design:
- Three labs (Red, Blue, Green)
- 1 Analyst, 2 days, 6 samples per day

Objective:
- Statistical assessment of the equivalence margin based on historical data

Limitations: No analyst-to-analyst information available

Equivalence Margin

Bayesian Simulations

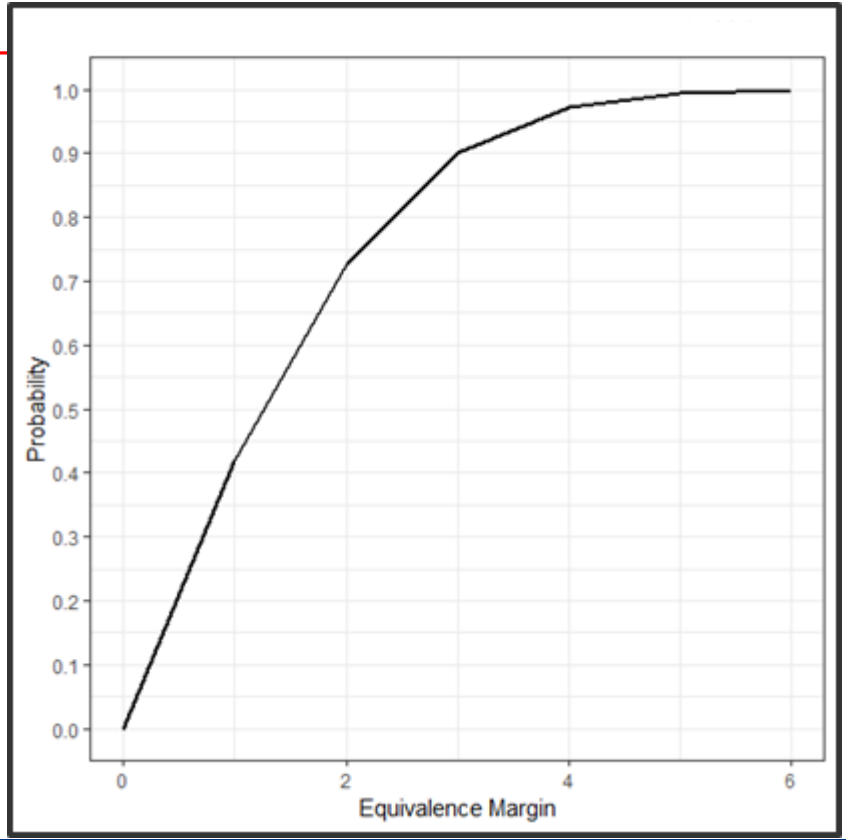


Equivalence Margin

- Estimated Probability of Study design meeting acceptance criteria

Scenario assumptions

- between-assay and within-assay variability based on the AMT design
- Mean Difference



Conclusion

Take Away

1

Equivalence Testing is a statistical tool for method transfer

2

Setting an equivalence margin is difficult. Historical data plays a role.

3

Studies can be powered if an equivalence margin is pre-specified

4

Risk based approach and method precision should determine the number of samples needed

5

The criterion is an assay/ situation specific proposal not a universal truth

Thank you

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