

FDA NEWS & INFORMATION

A Comprehensive Weekly Guide to the Agency and Related Activities, Policies and Releases

Volume 8, Number 41

October 12, 2007

Method Comparability

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Regulatory agencies often include recommendations with their observations in the course of reviewing submissions and in performing audits. These recommendations are generally well received by the company since they provide insight into what the reviewer is thinking and often simplifies the response. A difficulty arises when the recommendation is not correct or could be better. The company doesn't want to antagonize the reviewer but wants to use the most correct methods available, particularly when the more correct approach is also to the benefit of the company.

This problem surfaced recently when a company received this observation in relation to transferring analytical methods

from a developing laboratory to the QC receiving laboratory at the production site.

"The transfer of the several analytical methods has not been confirmed by the use of a statistically valid application of the t-test to the results."

In the situation under review, the company had taken twenty random samples from a typical lot of product and had ten samples tested in the two labs. The method was a state-of-the-art HPLC and had excellent reproducibility.¹ That is, the standard deviation from the validation study was smaller than that typically seen. When the company used the classic two sample t-test as suggested, they found, surprisingly, that there was a statistically significant² difference between the two laboratories. However, the actual difference between the two averages was very small and experienced laboratory analysts all agreed that the difference was not of any practical importance and in fact, the transfer had been a success. Now the laboratory manager and the regulatory staff faced the task of explaining why the statistical significance was not a failure of the method transfer.

"It is ironic that on one hand research statisticians have been meticulously using advanced mathematics to consolidate the

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¹ See ICH Q2 for the definition.

² P=0.001.

foundations of statistical science; while on the other hand scientific articles still contain massive misuses of the Student t-test.”

Wang 1993

The basic problem with using the usual two sample t-test for method validation, transfer and comparability is that the better the method is for precision, the more we find statistical significances that are not of any practical importance. This is further compounded when we have large sample sizes. Thus, we find ourselves in the position of the regulatory staff of trying to explain why this statistical significance does not have any practical meaning.

This is just the opposite of what would be logically expected. In a sense the company is being punished because the test method has good precision and a small standard deviation. This leads to the realization that there is a strong disincentive to have good precision or to collect more data since it actually works against the company. It is ironic that a poor method with poor precision is less likely to show a statistically significant difference between two averages. A company should be rewarded for good precision and large sample sizes.

Part of the problem is that the two sample t-test is the right answer to the wrong question. The question is not are the averages of the two samples equal, but rather is the difference between the two sample averages small enough to not be of any practical importance?

This issue was recognized in 1979 by biostatisticians in the context of bioequivalence. See Westlake, 1979. The issue has been further addressed in the literature by Schurimann, 1987, Stein and Doganaksoy, 2000, Chambers, et al, 2005 and the USP Chapter <1010>, 2007.

In the example, the results of the t-test were not informative, in that a relatively small difference between the two averages was shown to be statistically significant but not necessarily shown to be practically significant or of any practical importance. We expect to find differences between any two locations or laboratories, but we also expect that any observed difference not be large enough to be of scientific concern.

Because of this problem, statisticians have developed an approach that rewards for good precision and larger sample sizes. See USP 2007. It is called comparability or comparison of methods. First, we first establish a range for a difference that is considered of practical importance or we calculate a range based on historical data and the current specifications. Second, we find the difference between the two averages and then calculate a confidence interval for that difference. Third, we require the confidence interval on the difference of the averages to lie within the predetermined practical range. If it does, then the methods are considered comparable. With this approach, better precision gives a smaller confidence interval as does a larger sample size. More precise methods and more data are rewarded.

The authors of USP chapter <1010>, Appendix E, (including this author) are members of the USP Expert Committee for Statistics and are all professional statisticians working in the pharmaceutical industry. This USP method gives a statistically valid approach that is accepted by industry statisticians and is based on the FDA approved approach to bioequivalence. It is recommended that this USP approach be used to meet the requirement of confirming analytical method validations, transfers and comparability in place of the usual two sample t-test.

References:

1979. Westlake, W. J.; "Statistical Aspects of Comparative Bioavailability Trials," *Biometrics*, 35, 273-280, March.

1981. Westlake, W. J.; "Response," *Biometrics*, September, page 591.

1987. Schurimann, D. J.; "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability," *J of Pharmacokinetics and Biopharmaceutics*, Vol. 15, No. 6.

1993. Wang, C., Sense and Nonsense of Statistical Inference, Marcel Dekker, page 1.

2000. Stein, J. and Doganaksoy, N.; "Sample Size Considerations for assessing the Equivalence of Two Process Means," *Quality Engineering*, 12(1), 105-110.

2005. Chambers, D., Kelly, G., et all; "Analytical Method Equivalency – An Acceptable Analytical Practice," *Pharmaceutical Technology*, September.

2007. USP Expert Committee for Statistics; "Chapter <1010> Analytical Data – Interpretation and Treatment, Appendix E: Comparison of Methods – Determining the Largest Acceptable Difference, δ , Between Two Methods, USP 30, NF 25, Volume 1, page 396.

About the Author:

Mr. Lynn Torbeck is a consultant specializing in applied statistics and designed experiments for CGMPs, QA/QC, SPC, OOS, QbyD, PAT, validation and manufacturing. He has been in the pharmaceutical industry since 1975 and president of Torbeck and Assoc since 1988.

Regulatory Documents

A compilation of regulatory significance from government authorities and industry experts, offered by Kendle Regulatory Affairs on a subscription basis. The list is sorted numerically, and contains the Document ID number, title, an executive summary, author, issue date, and document length.

Doc.# 001-2065

Electronic FOI LOG

This diskette contains a listing of the requests filed with the Food and Drug Administration under the Freedom of Information Act. The diskette covers the time period of October 1 through October 5, 2007. The following fields are included: agency file number, date requested, date agency is required to respond, responding office, name of requestor, firm name, and information requested.

Author: FOI, FDA

Date: 10/5/2007

Doc.# 009-4207

Citizen Petition: Auto Injectors

This petition requests FDA to approve ANDAs and 505(b)(2) applications that reference drug products containing auto-injectors and to make therapeutic equivalence designations, only in accordance with the standard required by law and described in the petition.

Author: King Pharmaceuticals, Inc.

Date: 9/26/2007 **Page(s):** 32

Doc.# 009-4208

Citizen Petition: Namenda Tablets 15 mg and 20 mg

This petition requests FDA to determine whether Namenda Tablets 15 mg and 20 mg were voluntarily withdrawn from sale for reasons related to safety efficacy.

Author: Lachman Consultant Services, Inc.

Date: 9/27/2007 **Page(s):** 29

Doc.# 009-4209

Citizen Petition: Dronibinol

This petition requests FDA to prevent false and misleading labeling and ensure the safe and efficacious use of dronibinol.

Author: Unimed Pharmaceuticals, Inc.

Date: 9/28/2007 **Page(s):** 47

Doc.# 009-4210

Letter: Metal/Metal Semiconstrained Hip Joint Prostheses with Cemented or Uncemented Acetabular Components

This letter to the Orthopedic Surgical Manufacturers