An Example of Method Transfer and Controls:
The USP Dissolution Test #2 Using the 10 mg Prednisone
"NCDA Tablet #2" As a Process Control Sample.

The successful transfer of analytical methods among laboratories is a major on-going concern for all analytical laboratory managers. These transfers are especially problematic in the highly regulated pharmaceutical industry where there is considerable outside scrutiny of all aspects of the process. If methods transfers are not effected well a plethora of Out-of-Specification (OOS) test findings may result, the investigations of which will markedly reduce productivity and increase stress.

To effect an orderly and successful transfer of methods several major quality system aspects must be well-delineated:

1. identification in the method of the "process critical control points" ("PCCP"),
2. development of training aids to help assure staff competence in controlling the variance which can occur at each of these "PCCP,"
3. identification of an appropriate "PCCP" control test sample, and
4. identification of an appropriate procedural test sample.

I have attached some documents which present an example of a successful method transfer where these issues were well addressed and a related within laboratory on-going repeatability[1] study which demonstrates how controls and training can impact repeatability as well as reproducibility. The key article in this series is a collaborative study conducted by the FDA National Center for Drug Analysis (NCDA)[2] in the early 1980s. A copy of that document and the transmittal memo with the study protocol are included here as Attachments 1 and 2. This study was the culmination of a major effort undertaken by the staff in the late 1970s to identify and control the "PCCP" elements which affected the "repeatability" and "reproducibility" issues associated with the performance of the "USP Dissolution Test # 2, the Paddle Method." The USP "Paddle Method" was evolved from the "Poole Method" for determining solid dosage forms drug release rates.[3] Although the NCDA staff members had demonstrated through extensive testing the repeatability of this procedure and had successfully applied it to certify that all Digoxin tableted products marketed in the US, there was concern in the FDA and the regulated industry that the method transfer would pose a major challenge. To address this issue analysts at NCDA undertook a program to identify the "PCCP" in the technology and to confirm their control through a AOAC modeled collaborative study process.[4]

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[1] The terminology "repeatability" meaning within laboratory and "reproducibility" meaning among laboratory measurements is taken from the AOAC International-International Union of Pure and Applied Chemistry harmonized nomenclature. See http://www.iupac.org/publications/compendium/index.html for definitions.

[2] The National Center for Drug Analysis (NCDA) was established in 1967 and over the subsequent 20 years the name was changed to Center for Drug Analysis (CDA), Division of Drug Analysis (DDA), Division of Testing and Applied Analytical Development (DTAAD) and Division of Pharmaceutical Analysis (DPA). Throughout these reorganizations and name changes the staff and mission of the organization evolved with the technology but not with the names.

[3] The apparatus for the "Poole Method" is described in the Code of Federal Regulations, 21 CFR 310.500. See http://frwebgate1.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=55183018860+1+0+0&WAISaction=retrieve

[4] The full AOAC official methods process was not undertaken at the time because we believed it would have required too much time. The AOAC has subsequently streamlined their protocols to speed their adoption processes. See http://www.iupac.org/publications/pac/2002/7405/7405x0835.html for a discussion on these validation issues.

This attached documents are copies of materials prepared by staff members at NCDA as a part of their official duties and that were either submitted for publication in the open literature or were widely disseminated to the public. Attachment 1 presents the results of the 11-laboratory collaborative study which was published.[5] The transmittal letter and protocol for that collaborative study presented in Attachment 2 was distributed widely to interested parties upon request. Attachment 3 summarizes the dissolution test data obtained on the "NCDA Tablet #2, 10 mg Prednisone"[6] over a number of years which demonstrates its suitability as a control sample and also the reproducibility of the USP Dissolution Test Method #2.[7]

The 11-FDA laboratory USP Apparatus 2 Dissolution Test collaborative study used five lots of prednisone tablets that disintegrated within 5 minutes. The results obtained were unexpectedly good; the repeatability (% rsd) and reproducibility (%RSD) obtained by the 11 laboratories for the four lots still dissolving[8] at the end of the test were 1.6 % and 2.6 % of label claim, respectively. These values compare remarkably well with the values reported by Horwitz in his extensive retrospective survey of pharmaceutical analysis collaborative study results which are presented in the table below. This indicates that in this method transfer study that the "PCCP" associated with the performance of the USP Dissolution Test #2 were controlled to a level to make this test procedure comparable to all other pharmaceutical analyses.

A Retrospective Analysis of AOAC Published Pharmaceutical Product Collaborative Studies[9]				
Methods of Analyses[a]	Number of Compounds	Number of Studies	Repeatability (% rsd)	Reproducibility (% RSD)
LC	26	18	1.8	2.9
GC	8	4	1.3	2.6
SPCTR	5	5	1.1	2.5
AUTO	10	7	1.3	2.2
Total/Average[b]	49	34	1.5	2.6
[a] LC= Liquid Chromatography including HPLC, GC=Gas Chromatography, SPCTR=Spectrophotometric Methods, AUTO=Automated methods of analysis.				
[b] The average % rsd and % RSD are weighted for the number of reported compounds				

It should be noted that protocols required to address the "PCCP" presented here are not necessary at this time because, as is noted in Attachment 3, the dissolution testing equipment has been markedly refined and improved to eliminate or reduce the variance associated with many of these test elements so the very careful and tedious alignment procedures discussed here are no longer necessary.

[5] Cox, DC and Furman, WF, J. Pharm. Sci., **1984**, 73(5), 670

[6] Our thanks to the late Milton Blitz of Danbury Pharmaceutical for his assistance in developing this control sample; his assistance and scientific tenacity were essential to its characterization and development.

[7] These data were published: Moore, T, Hamilton, J. and Kerner, C, Pharm. Forum, **1995**, 21(3), 1383-86.

[8] The lots that were still dissolving continued to be dominated by the variability of the dissolution test and the content uniformity. Those which had completely dissolved at the end of the test period would reflect content uniformity variability.

[9] William Horwitz, JAOAC, **1977**, 60, 1355-1363