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Similarity of Dissolution Curves

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1.0 ABSTRACT

Dissolution testing of pharmaceutical products is important as it is a surrogate measure of in-vivo dissolution. In vivo dissolution affects the bio-availability, which may affect pharmaco kinetics (blood levels) and as a result may affect safety and efficacy. In case a change is proposed with respect to the manufacturing process, the manufacturing site, or the test method, 'equivalence' needs to be demonstrated to obtain a bio-waiver.
Similarity of curves may be tested using the mathematical f_2 metric. However, in case the variability is too high, a multivariate distance based statistic needs to be used instead. Some options will be shown for model dependent and model independent approaches. Use of JMP will be illustrated, with standard functionality and with a dedicated script, for the Mahalanobis distance.

2.0 INTRODUCTION

A solid dosage form of a drug, like a tablet, contains next to the active ingredient (the molecule with the desired therapeutic properties) additional substances, or excipients. The powder mixture is compressed and often coated with one or two layers to form the final drug product, i.e. the tablet[2].

When the tablet is administered, the active ingredient is released and dissolved at a certain place and at a certain speed in the body of the patient, this allows absorption through the intestinal wall. This is necessary for the active entity to become 'available' for its intended task, as measured by concentrations in the blood.

Where and how fast the active ingredient is released and dissolved is dependent on many factors:

- Physical properties of the active ingredient, solubility, salt form and particle size
- Physical properties of the tablet, hardness and disintegration time

Changes in the 'availability' of a drug relates to its efficacy and safety. Dissolution testing is a means to assess the 'availability' of a drug *in vitro* under conditions which mimic places in the human body where the drug should be released *in vivo*. The drug is placed in a certain solvent, and the concentration of the active ingredient is measured over time at regular intervals. The dissolution curve describes the increase in concentration over time (accumulative profile).

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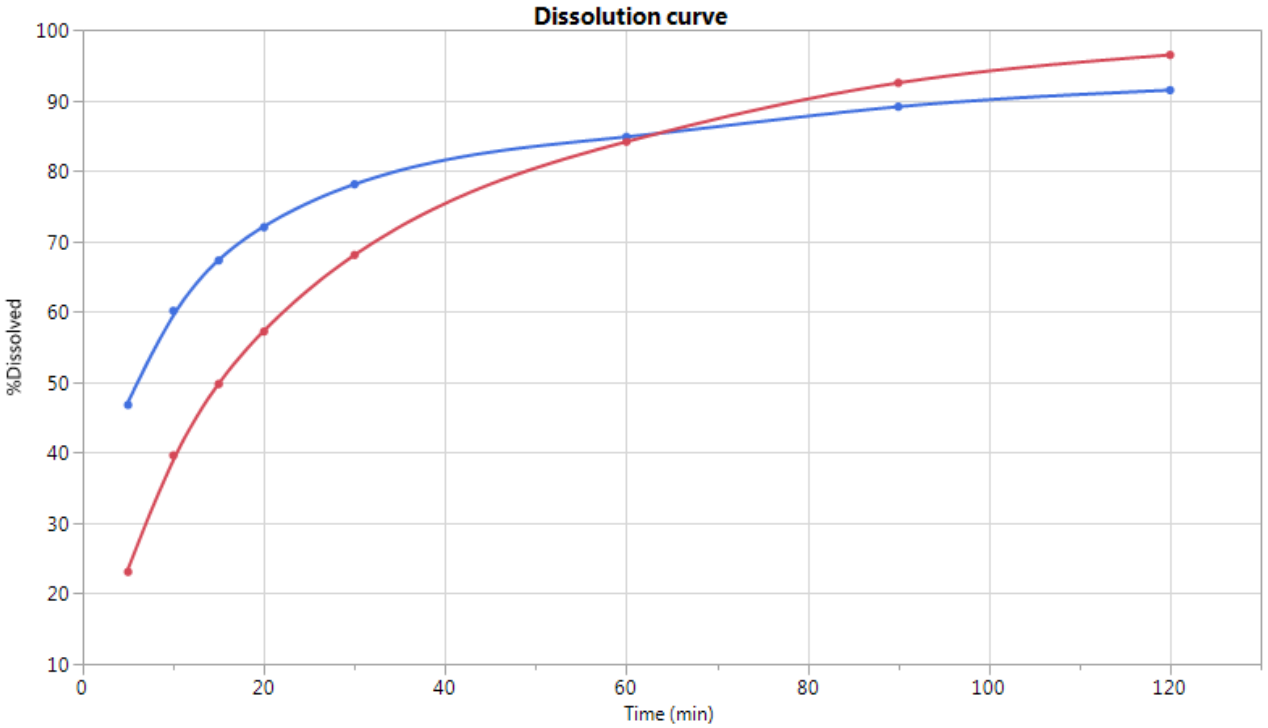
[2] This paper is focused on tablets, but for other solid dosage forms, like capsules, dissolution testing is equally relevant.



Dissolution testing is used

- in drug development
  - to optimize the dosage form with respect to location and speed of release.
- in quality control
  - compendial requirement for most solid oral dosage forms
  - one or more time-points are selected, where the measured amount of dissolved drug should comply with specified acceptance levels.

Dissolution testing often comes with a rather high variability, especially at the early time points. Common practice, endorsed by regulations, is to test at least 6 units (tablets).

Dissolution "equivalence" needs to be demonstrated to validate changes, with respect to

- Tablet composition
- Manufacturing process
- Manufacturing facility

Dissolution "equivalence" is demonstrated in terms of similarity of dissolution curves.

3.0 SIMILARITY METRICS

3.1 F_2 METRIC

The default similarity metric in comparing dissolution curves is the f_2 quantity[3], which should have a value > 50 to conclude 'equivalence':

$$f_2 = 50 \cdot \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}} \right) > 50$$

Rearranging this equation gives: $\sqrt{1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}} < 10$

Apparently, dissolution curves are regarded 'similar' if 'on average' they do not differ more than 10% per time point.

Note that the f_2 metric

- is a point estimate
- based on Euclidean distances per time-point
- without a measure of uncertainty.

Use of the f_2 metric is allowed, provided that the following constraints are met:

- ≥ 3 time-points
- 85% rule
  (not more than 1 time-point should be included with an average dissolution above 85%
- CV $\leq$ 20% first time-point(s), CV $\leq$ 10% other points

If the variability is too high, one should consider a multivariate statistical distance (MSD) metric.

However, there is no clear guidance given on which metric and what acceptance limit to use.

The approach, i.e. metric and acceptance limits and whether to use f2 or not, does not only depend on what is most appropriate from the scientist's point of view, but also on the view of a particular regulatory body.

Many proposals have been published, a few will be discussed, some in more detail.

It is convenient to have several tools available and to know something about their merits.

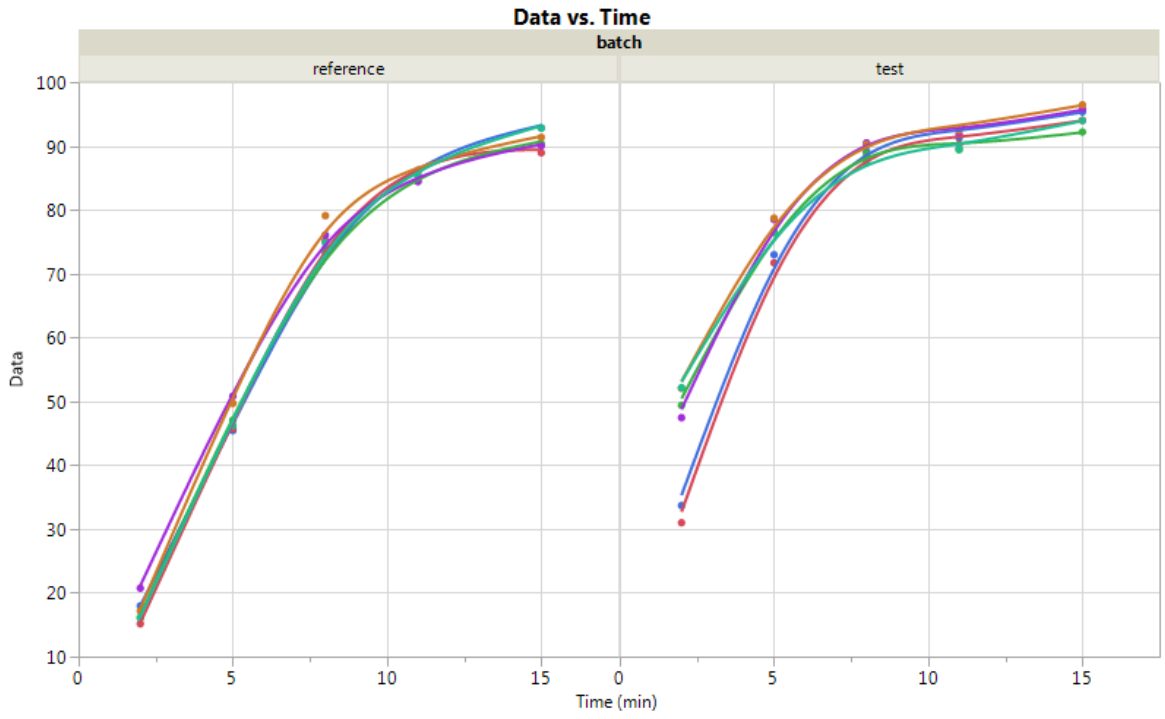
[3] Moore, J.W., Flanner, H.H. (1996).
Mathematical comparison of dissolution profiles, Pharmaceutical Technology 20 (6) 64:74

Example:

- Exclude 15 h time-point (85% rule)
- 4 time-points left (≥ 3)
- CV > 20% for 1st time-point
  f_2 metric not allowed → use multivariate statistical distance metric

Table 1: **Dissolution data for a reference and a test batch**

%dissolved		Time point (h)									
		02		05		08		11		15	
batch	tablet	Mean	CV	Mean	CV	Mean	CV	Mean	CV	Mean	CV
reference	1	17.97	.	45.42	.	73.90	.	86.18	.	92.83	.
	2	15.16	.	45.76	.	75.15	.	86.17	.	88.94	.
	3	16.11	.	47.04	.	73.39	.	84.51	.	90.35	.
	4	20.74	.	50.82	.	76.05	.	84.43	.	90.02	.
	5	17.16	.	49.68	.	79.09	.	85.42	.	91.37	.
	6	16.11	.	46.20	.	74.83	.	85.38	.	92.85	.
	All	17.21	11.5	47.49	4.7	75.40	2.7	85.35	0.9	91.06	1.7
test	1	33.69	.	72.97	.	89.18	.	91.28	.	95.36	.
	2	30.99	.	71.71	.	88.12	.	90.27	.	94.03	.
	3	49.37	.	76.61	.	88.82	.	89.42	.	92.20	.
	4	47.45	.	78.48	.	90.50	.	91.83	.	95.77	.
	5	52.05	.	78.71	.	90.24	.	92.47	.	96.46	.
	6	52.14	.	76.43	.	87.40	.	89.55	.	94.01	.
	All	44.28	21.3	75.82	3.8	89.04	1.3	90.80	1.4	94.64	1.6



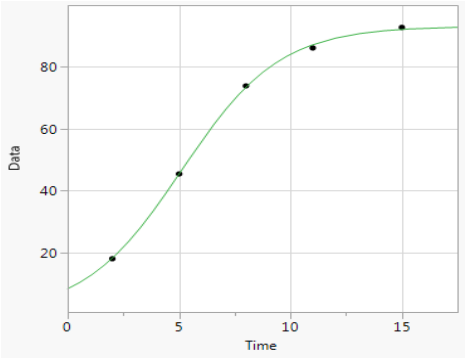
The multivariate statistical distance metric (MSD) is not based on a (transformed) Euclidean distance, but on a Mahalanobis distance, and depends on the covariance structure of the data, i.e. on the pooled variances per time-point and on correlations across time-points. Further statistical details are described elsewhere[4]. The MSD can be computed either using a model free or a model based approach.

- In a model free approach, each *time-point* forms a variable.
- In a model based approach, the dissolution curves are fit, using a pre-defined function, and each *parameter* of the model subsequently forms a variable.

For the example given, non-linear models were fitted, per tested unit (tablet). Two functions have been selected (out of many candidates), a graph of the fit for the first unit is shown:

three-parameter *logistic* model (built-in)

$$f(t) = F_{\max} \times \frac{1}{1+e^{-k(t-\gamma)}}$$



three-parameter *Weibull* model (added)

$$g(t) = G_{\max} \times \left(1 - e^{-\frac{1}{\alpha}t^{\beta}}\right)$$

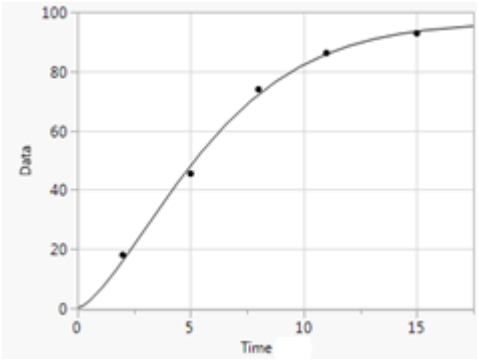


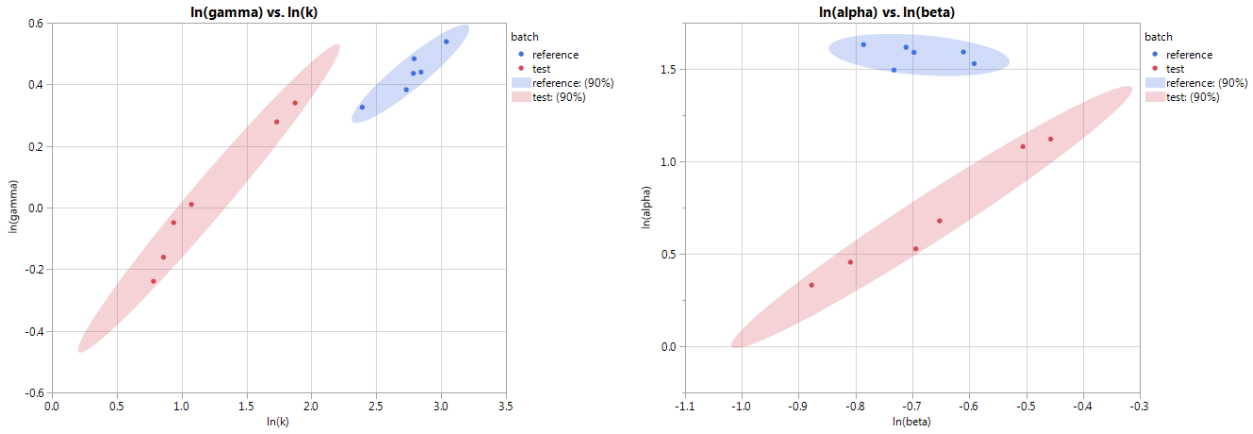
Table 2: fitted parameters to data of Table 1

Estimated parameters		logistic			Weibull		
batch	tablet	F_{max}	k	γ	G_{max}	α	β
reference	1	93.1974	0.4556	5.1152	96.5290	15.3411	1.4666
	2	89.3004	0.5432	4.9141	90.4384	20.9004	1.7143
	3	89.7674	0.4979	4.9053	92.1197	16.2077	1.5463
	4	89.5467	0.4807	4.4580	92.1449	10.9267	1.3856
	5	90.1870	0.5535	4.6155	91.6883	16.3046	1.6218
	6	92.0337	0.4910	5.0412	94.7421	17.1919	1.5526
test	1	93.6921	0.6031	2.9459	94.4331	5.6521	1.3212
	2	92.3985	0.6333	3.0688	92.9860	6.5125	1.4049
	3	91.6527	0.4995	1.6948	92.5505	2.5537	0.9528
	4	94.3803	0.5209	1.9713	95.4384	2.9293	1.0106
	5	95.4131	0.4452	1.5769	97.3731	2.3614	0.8515
	6	92.9477	0.4159	1.3927	95.4919	2.1862	0.7874

A graph of the fitted parameters per unit and per batch (on a log scale) is shown on the next page.

[4] Dave Leblond et al., "In Vitro Dissolution Curve Comparisons: A Critique of Current Practice", Dissolution Technologies, February 2016

logistic	Weibull



3.2 MULTIVARIATE DISTANCE BASED STATISTICS

For two groups of univariate data, the standardized mean difference or Cohen's d is commonly used, defined as:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s_p}, \text{ where } s_p = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

and the confidence interval is based on Student's t-distribution with (n_1+n_2-2) degrees of freedom.

For two groups of multivariate data, the Mahalanobis distance gives a multivariate extension:

$$D^2 = (\bar{X}_1 - \bar{X}_2)^t \hat{\Sigma}^{-1} (\bar{X}_1 - \bar{X}_2), \text{ where } \hat{\Sigma} \text{ is the pooled covariance matrix.}$$

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \rho_{12}\sigma_1\sigma_2 & \rho_{13}\sigma_1\sigma_3 & \rho_{14}\sigma_1\sigma_4 & \rho_{15}\sigma_1\sigma_5 \\ \rho_{12}\sigma_1\sigma_2 & \sigma_2^2 & \rho_{23}\sigma_2\sigma_3 & \rho_{24}\sigma_2\sigma_4 & \rho_{25}\sigma_2\sigma_5 \\ \rho_{13}\sigma_1\sigma_3 & \rho_{23}\sigma_2\sigma_3 & \sigma_3^2 & \rho_{34}\sigma_3\sigma_4 & \rho_{35}\sigma_3\sigma_5 \\ \rho_{14}\sigma_1\sigma_4 & \rho_{24}\sigma_2\sigma_4 & \rho_{34}\sigma_3\sigma_4 & \sigma_4^2 & \rho_{45}\sigma_4\sigma_5 \\ \rho_{15}\sigma_1\sigma_5 & \rho_{25}\sigma_2\sigma_5 & \rho_{35}\sigma_3\sigma_5 & \rho_{45}\sigma_4\sigma_5 & \sigma_5^2 \end{pmatrix}$$

Due to the cumulative nature of the profiles, results obtained for one unit at a certain time point is correlated with results at previous and subsequent time points. The covariance matrices for Table 1 data are shown in Table 3. The off-diagonal elements show the correlations to be non-zero and the matrices seem to show a different structure.

Table 3: Covariance matrices for data listed in Table 1

Time-point	test					reference				
	02	05	08	11	15	02	05	08	11	15
02	89.3763	24.9013	2.1372	0.2705	0.1668	3.9327	3.1065	0.8641	-0.6821	0.1633
05	24.9013	8.2877	1.9119	1.3047	1.2818	3.1065	5.0059	3.0846	-1.1415	-0.9540
08	2.1372	1.9119	1.4351	1.2832	1.2132	0.8641	3.0846	4.1432	-0.0237	-0.2501
11	0.2705	1.3047	1.2832	1.5656	1.8054	-0.6821	-1.1415	-0.0237	0.5838	0.2719
15	0.1668	1.2818	1.2132	1.8054	2.3661	0.1633	-0.9540	-0.2501	0.2719	2.5026

The Mahalanobis distance can be corrected for bias using:

$$D_u^2 = \left(\frac{n_1 + n_2 - p - 3}{n_1 + n_2 - 2}\right) D^2 - p\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

However, in comparing distances, this is not relevant.

A confidence interval for the Mahalanobis distance is based on the F distribution, where:

$$\frac{(n_1 + n_2 - p - 1)}{(n_1 + n_2 - 2)} \cdot \frac{n_1 n_2}{(n_1 + n_2)} D^2 = \frac{(n_1 + n_2 - p - 1)}{(n_1 + n_2 - 2)} T^2 \approx F_{p, n_1 + n_2 - p - 1}(\lambda),$$

and where the non-centrality parameter

$$\lambda = \frac{n_1 n_2}{n_1 + n_2} \delta^2,$$

and T^2 represents Hotelling's statistic[5].

The interval inversion approach seeks the values of non-centrality that correspond to the target percentiles of the appropriate F-distribution[6].
For $\lambda=0$ (assuming the profiles are the same), the Lagrange multiplier method is used and for $\lambda>0$, a root finding algorithm is applied.

90% confidence region Mahalanobis distance, for **$\lambda = 0$**:

$$k \times \left(\left(y - \left(x_{test} - x_{ref} \right) \right)^t \times S_{pooled}^{-1} \times \left(y - \left(x_{test} - x_{ref} \right) \right) \right) \leq F_{p, n_1 + n_2 - p - 1, 0.90}$$

where $k = \frac{n_1 n_2}{n_1 + n_2} \cdot \frac{n_1 + n_2 - p - 1}{(n_1 + n_2 - 2) \times p} = \frac{n_1 n_2}{n_1 + n_2} \cdot k_2 = k_1 \cdot k_2$

$$\Rightarrow \begin{cases} y_1^* = \left(x_{test} - x_{ref} \right) \left\{ 1 + \sqrt{\frac{F_{p, n_1 + n_2 - p - 1, 0.90}}{k \left(x_{test} - x_{ref} \right)^t \times S_{pooled}^{-1} \times \left(x_{test} - x_{ref} \right)}} \right\} \\ y_2^* = \left(x_{test} - x_{ref} \right) \left\{ 1 - \sqrt{\frac{F_{p, n_1 + n_2 - p - 1, 0.90}}{k \left(x_{test} - x_{ref} \right)^t \times S_{pooled}^{-1} \times \left(x_{test} - x_{ref} \right)}} \right\} \end{cases}$$

$$\Rightarrow \begin{cases} D_M^{upper} = \max\left(\sqrt{\left(y_1^* \right)^t \times S_{pooled}^{-1} \times y_1^*}, \sqrt{\left(y_2^* \right)^t \times S_{pooled}^{-1} \times y_2^*} \right) \\ D_M^{lower} = \min\left(\sqrt{\left(y_1^* \right)^t \times S_{pooled}^{-1} \times y_1^*}, \sqrt{\left(y_2^* \right)^t \times S_{pooled}^{-1} \times y_2^*} \right) \end{cases}$$

[5] B.S. Everitt and G. Dunn, "Applied Multivariate Data Analysis, 2nd Ed.", Arnold, London (2001)

[6] K.Y. Hogerty et al, "A Macro for Computing Point Estimates and Confidence Intervals for Mahalanobis Distance" SAS SUGI 30 Proceedings (2005), Paper 163-30

90% confidence region Mahalanobis distance, for **λ > 0**:

$$y = k \times D^2 = k \times \left(\left(x_{test} - x_{ref} \right)^t \times S_{pooled}^{-1} \times \left(x_{test} - x_{ref} \right) \right) \approx F_{p,n_1+n_2-p-1}(\lambda)$$

(where $\lambda = k_1 \delta^2$ and δ^2 = population mean of the Mahalanobis distance)

now using an iterative root finder for a monotonic function, find λ_0 for

$$y - F_{p,n_1+n_2-p-1,0.90}(\lambda) = 0$$ (JSL function 'F noncentrality')

then the critical distance **d** is obtained from

$$d = \sqrt{\frac{\lambda_0}{k \times sum\left(S_{pooled}^{-1}\right)}}$$

acceptance limits

A statistically significant difference between two groups of multivariate data, i.e. between two sets of dissolution curves, now can be assessed using the Mahalanobis confidence interval. However, this leaves the question open whether observed differences are relevant from a practical point of view, comparable to the f_2 criterion. Therefore, other limits have been proposed:

λ=0	An acceptance limit is derived from the reference profile and a profile which is shifted by 10% relative to the reference profile[7,8]. The Mahalanobis distance between the reference and the shifted profiles is taken as the acceptance limit. The Mahalanobis distance between test and reference profile should be less than the acceptance limit. $dmc = \sqrt{D_g^{\,t} \times S_{pooled}^{-1} \times D_g}$ where D_g represents a p×1 vector with all elements equal to D_g, the difference specified as the 'global similar limit'.
λ>0	Based on simulations, an acceptance limit of 6% has been proposed[9].

[7] Tsong Y, Hammerstrom Th, Sathe PM, Shah, VS, "Statistical Assessment of Mean Differences between two Dissolution Data Sets", Drug Inf. Journal (1996), Vol. 30, 1105-1112

[8] Instead of 10%, one could define a different number, 15% has been proposed as well.

[9] Saranadasa H, "Defining the Similarity of Dissolution Profiles Using Hotelling's T² Statistic", Pharm.Tech.Europe, June 2003, 23-28

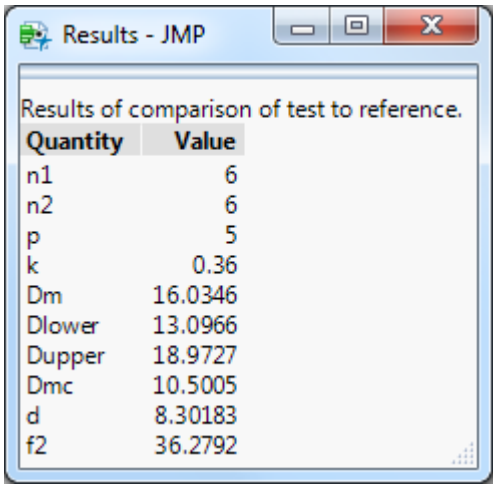
Mahalanobis and JMP

For a single group of multivariate data, the Mahalanobis distance of each observation to the mean of the remaining group can be evaluated in the JMP multivariate platform, in screening on outliers.

For two groups of multivariate data, the Mahalanobis distance between the means of the groups is not available in standard JMP, and needs to be defined in a JSL script. The fundaments for this script plus most of the implementation were kindly provided by Diane K. Michelson (SAS Institute) and is included as Attachment 1. As she suggested, the script was extended to include the confidence interval estimation. This extension includes both the $\lambda=0$ and $\lambda>0$ approaches and is listed as Attachment 2.

3.3 SOME RESULTS

For the data listed in Table 1, the output is shown:


Results - JMP

Results of comparison of test to reference.

Quantity	Value
n1	6
n2	6
p	5
k	0.36
Dm	16.0346
Dlower	13.0966
Dupper	18.9727
Dmc	10.5005
d	8.30183
f2	36.2792

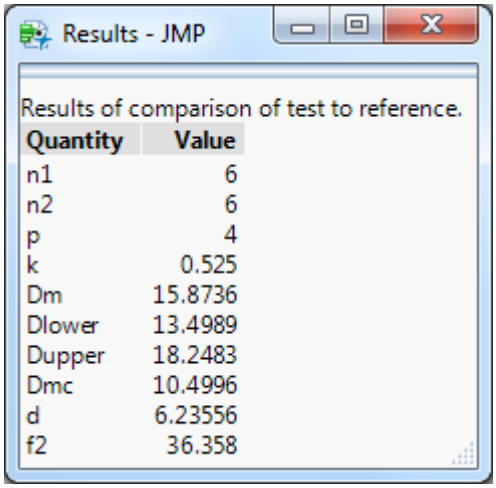
For both the $\lambda=0$ and the $\lambda>0$ approach the conclusion is the same: the dissolution curves are not sufficiently similar.

The conclusion is in line with the f_2 value (which is not applicable here, and is for illustration only).

$\lambda=0$: Dm > Dmc

$\lambda>0$: d >6%

For the data listed in Table 1, the last time-point should be excluded, and this results in:


Results - JMP

Results of comparison of test to reference.

Quantity	Value
n1	6
n2	6
p	4
k	0.525
Dm	15.8736
Dlower	13.4989
Dupper	18.2483
Dmc	10.4996
d	6.23556
f2	36.358

In this case, the 85% rule does not change the conclusions.

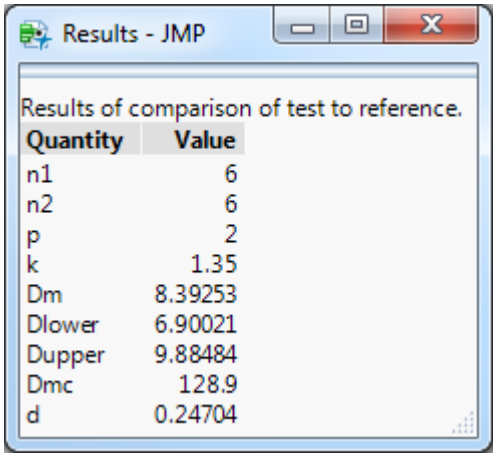
$\lambda=0$: Dm > Dmc

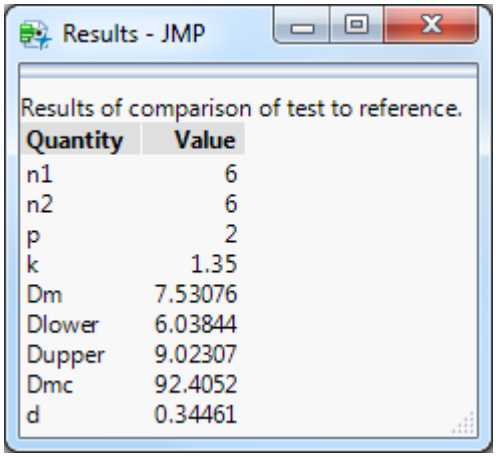
$\lambda>0$: d >6%

In our view, the 85% rule should also be applied to this multivariate approach, as later time points (approaching the assymptote) only add ‘noise’ and no ‘signal’.

For the data listed in Table 2, the Mahalanobis distance was calculated for the log transformed parameters (excluding F_{max}). Note that the Dmc and d values here have no meaning, acceptance limits should be defined in a different way[10].

Left the results for the logistic model, and right for the Weibull model:





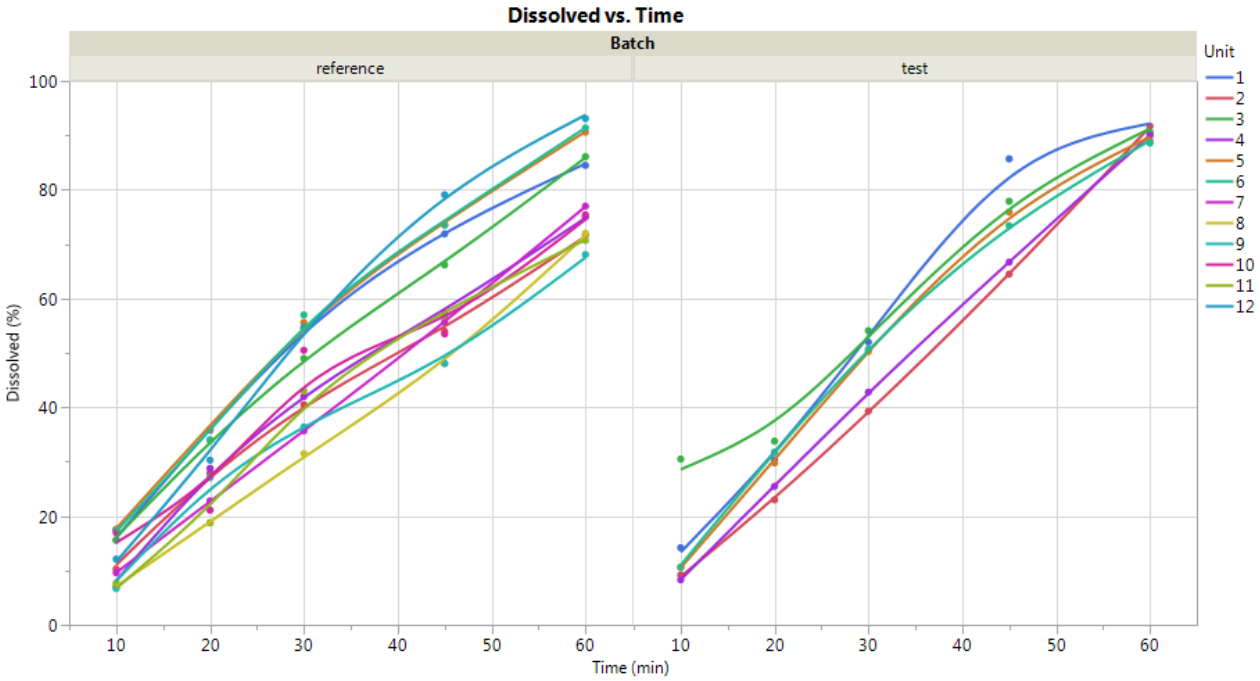
For these two models, the Mahalanobis distance is comparable, but the model selection has some impact on the results.

A second data set is shown in Table 4, where again the variability is too high to allow using f_2.

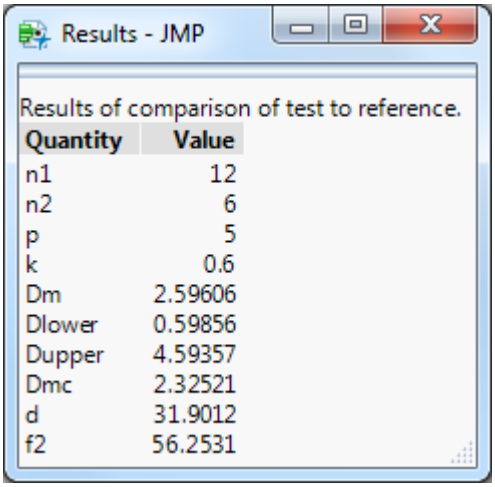
Table 4: Dissolution data for a reference and a test batch

		Time point (min)									
		10		20		30		45		60	
Batch	**Unit**	**Mean**	**CV**	**Mean**	**CV**	**Mean**	**CV**	**Mean**	**CV**	**Mean**	**CV**
reference	1	15.6	.	35.8	.	54.6	.	71.9	.	84.5	.
	2	10.3	.	27.9	.	40.5	.	54.0	.	71.7	.
	3	15.6	.	34.0	.	49.0	.	66.2	.	86.1	.
	4	7.0	.	28.8	.	42.0	.	57.3	.	75.0	.
	5	17.6	.	36.0	.	55.6	.	73.6	.	90.6	.
	6	17.5	.	34.0	.	57.0	.	73.5	.	91.4	.
	7	9.6	.	22.8	.	35.7	.	55.7	.	77.0	.
	8	7.1	.	18.8	.	31.5	.	48.0	.	72.0	.
	9	6.7	.	27.1	.	36.4	.	48.1	.	68.1	.
	10	17.0	.	21.1	.	50.5	.	53.5	.	75.4	.
	11	7.7	.	18.8	.	43.0	.	56.8	.	70.7	.
	12	12.1	.	30.3	.	54.7	.	79.1	.	93.1	.
	All	12.0	37.0	28.0	22.8	45.9	19.2	61.5	17.6	79.6	11.3
test	1	14.2	.	30.4	.	52.0	.	85.7	.	90.5	.
	2	9.2	.	23.0	.	39.3	.	64.5	.	91.7	.
	3	30.5	.	33.8	.	54.1	.	77.9	.	90.5	.
	4	8.3	.	25.5	.	42.8	.	66.7	.	90.0	.
	5	10.6	.	29.8	.	50.3	.	75.9	.	89.0	.
	6	10.6	.	31.8	.	50.7	.	73.4	.	88.6	.
	All	13.9	60.3	29.1	13.9	48.2	12.0	74.0	10.5	90.1	1.2

[10] Sathe PM, Tsong Y, Shah VS, "In-Vitro Dissolution Profile Comparison: Statistics and Analysis, Model dependent Approach" (1996), Pharmaceutical Research, Vol. 13, No. 12, 1799-1803



For the data listed in Table 4, the output is shown:



For both the λ=0 and the λ>0 approach the conclusion is the same: the dissolution curves are not sufficiently similar.
Here, the conclusion is not in line with the f_2 value.

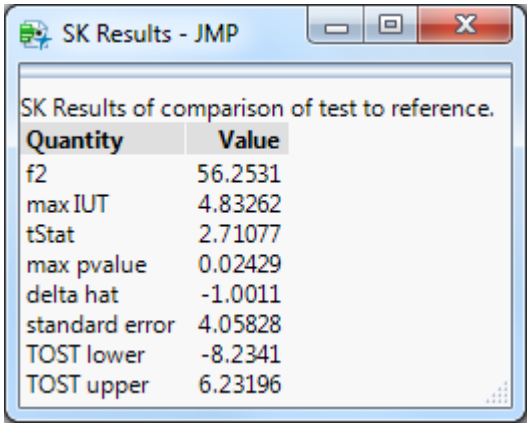
λ=0: Dm > Dmc

λ>0: d >6%

3.4 DELTA TEST AND IUT

An alternative test is offered by assuming that the dissolution curves for the reference and test batches have shifted in a strict parallel sense[11]. This approach is not discussed here, but the JSL script is included as Attachment 3. The same script also evaluates the Intersection Unit Test (IUT) approach[12], which should give a p value < 0.05 to conclude similarity.

For the data shown in Table 4 the result is shown:



Here, similarity is concluded to be sufficient:

- The 90% two-one-sided-t (TOST) confidence interval for the average (parallel) shift is completely embedded in the acceptance interval [-10 ; 10]%.
- The IUT p value is less than 0.05.

3.5 MANOVA

Comparing two groups of multivariate data is also amenable to MANOVA, supported by JMP. Although useful in examining the data, and deciding on a statistically significant difference between groups, MANOVA does not help in telling whether the difference is acceptable from a practical point of view, in line with the f_2 criterion.

4.0 DISCUSSION

Several multivariate statistical approaches have been described, for testing similarity of dissolution curves. The Mahalanobis distance between two groups of multivariate data is an important metric, applied in both model free and model based evaluations. A JSL script has been developed to calculate this distance and its confidence interval (supported by JMP). Next to this, a script was developed to calculate 'delta' and 'IUT' statistics.

Having available these tools, enables evaluating their merits and to select the most appropriate tool. To meet regulatory requirements and due to new insight, this set may need further expansion in future. One alternative approach is a bootstrap[13] confidence interval for f_2 and another a Bayesian approach[14].

---

[11] Saranadasa H, Krishnamoorthy K (2005) "A Multivariate Test for Similarity of Two Dissolution Profiles", J. of Biopharm. Stat., 15: 265-278

[12] Berger RL, Hsu JC (1996) "Bioequivalence trials, intersection-unt tests and equivalence confidence sets", Stat Sci 11(4):283-319

[13] Ma M-C, Wang BBC, Liu J-P, Tsong Y (2000) "Assessment of Similarity between Dissolution Profiles", J. of Biopharm. Stat., 10(2), 229-249

[14] Novick S, Shen Y, Yang H, Peterson J, LeBlond D, Altan S (2015) "Dissolution Curve Comparisons Through the F_2 Parameter, a Bayesian Extension of the f_2 statistic", J. of Biopharm. Stat. 25(2), 351-371

5.0 CONCLUSION

- Dissolution testing is important for pharmaceutical products, as it is related to safety and efficacy, and is widely applied in support of
  - Development
  - Quality control
  - Changes
- Comparing dissolution curves
  - gives insight in 'equivalence' of products produced using
    - different processes,
    - different formula, or
    - at different sites
  - preferably makes use of the f_2 metric
  - is based on MSD (multivariate statistical distance) metric, where f_2 is not applicable
- Application of MSD metrics is hampered by
  - Lack of guidance
  - Lack of calibration
  - Regulatory acceptance
- JMP supports comparing dissolution curves by
  - standard functionality
    - MANOVA
    - Outlier testing
    - Non-linear curve fitting
    - Graph builder
  - and dedicated JSL scripts

END OF DOCUMENT

Attachment 1: JSL script for Mahalanobis distance, provided by SAS Institute

```
/*
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Note: please read the disclaimer at the end of this script.

Purpose
This script implements the comparison procedure in Tsong, et al, 1996,
"Statistical Assessment of Mean Differences Between Two Dissolution Data Sets,"
Drug Information Journal, Vol. 30, pp. 1105--1112.

Author
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Contact
di.michelson@sas.com

Usage
Simply run this script by any one of these methods:

	Edit > Run Script
	Control-R
	Click "Run Script" button in tool bar
*/

//choose data table
numTables = N Table();
lstTables = List();
lstTables[1] = "None of these, launch the OPEN TABLE dialog.";
For( iTable = 1, iTable <= numTables, iTable++,
	lstTables[iTable + 1] = Data Table( iTable ) << get name
);
nwTable = New Window( "Choose a data table",
	Text Box( "Choose a data table containing columns for analysis." ),
	cbTable = Combo Box( lstTables ),
	bbGo = Button Box( "OK", exprGo )
);

exprGo = Expr(
	If( (cbTable << get selected) == "None of these, launch the OPEN TABLE dialog.",
		dt = Open(),
		dt = Data Table( cbTable << get selected )
	);
//pick grouping column, pick analysis columns
	nw1 = New Window( "Select Columns",
		Text Box( "Select grouping column. Select analysis columns." ),
		H List Box(
			Panel Box( "Select Columns", colListData = Col List Box( all ) ),
			Panel Box( "Cast Selected Columns into Roles",
				Lineup Box( N Col( 2 ),
					Button Box( "Grouping Column",
						colListGroup << append( colListData << get
selected );
						groupCol = colListGroup << get items;
					),
					colListGroup = Col List Box( minitems( 1 ), maxitems(
1 ), nlines( 1 ) ),
					Button Box( "Analysis Columns",
```

```
                                        colListY << append( colListData << get selected
);
                                        yCol = colListY << get items;
                                ),
                                colListY = Col List Box( numeric, minitems( 2 ),
nlines( 5 ) )
                        )
                ),
                Panel Box( "Action",
                        Button Box( "OK", exprOK ),
                        Button Box( "Cancel", nw1 << close window() ),
                        Text Box( " " ),
                        Button Box( "Remove",
                                colListGroup << remove selected;
                                colListY << remove selected;
                        ),
                        Button Box( "Help", exprHelp )
                )
        )
    );
    nwTable << close window();
);

exprOK = Expr(
//pick reference and group
    lstGroups = Associative Array( Column( dt, groupCol[1] ) << get values ) << get
keys;
    nw1 << close window();
    nw2 = New Window( "Select groups",
        Text Box(
                "Select reference and test groups in column " || (Column( dt,
groupCol[1] ) <<
                get name) || "."
        ),
        H List Box(
                Panel Box( "Select Groups", lbGroups = List Box( lstGroups ) ),
                Panel Box( "Identify Reference and Test Groups",
                        Lineup Box( N Col( 2 ),
                                Button Box( "Reference Group",
                                        lbRef << append( lbGroups << get selected );
                                        refGroup = lbRef << get items;
                                ),
                                lbRef = List Box( {}, max selected( 1 ), nlines( 1 )
),
                                Button Box( "Test Group",
                                        lbTest << append( lbGroups << get selected );
                                        testGroup = lbTest << get items;
                                ),
                                lbTest = List Box( {}, max selected( 1 ), nlines( 1 )
)
                        )
                ),
                Panel Box( "Action",
                        Button Box( "OK", exprOK2 ),
```

```
                        Button Box( "Cancel", nw2 << close window() ),
                        Text Box( " " ),
                        Button Box( "Remove",
                                lbRef << remove selected;
                                lbTest << remove selected;
                        )
                )
        )
    );
);

exprOK2 = Expr(
//setup
    ref = (lbRef << get items)[1];
    test = (lbTest << get items)[1];
    colGroup = Parse( ":" || (Column( dt, groupCol[1] ) << get name) );
    dt << clear select;
    dt << select where( colGroup == ref );
    dtREF = dt << subset( selected rows );
    dt << clear select;
    dt << select where( colGroup == test );
    dtTEST = dt << subset( selected rows );
    dt << clear select;
    matREF = J( N Row( dtREF ), N Items( yCol ), . );
    For( iCol = 1, iCol <= N Items( yCol ), iCol++,
        matREF[0, iCol] = (Column( dtREF, yCol[iCol] ) << get values)
    );
    matTEST = J( N Row( dtTEST ), N Items( yCol ), . );
    For( iCol = 1, iCol <= N Items( yCol ), iCol++,
        matTEST[0, iCol] = (Column( dtTEST, yCol[iCol] ) << get values)
    );

//find mean and cov of reference group
    meanREF = J( 1, N Items( yCol ), 0 );
    For( iRow = 1, iRow <= N Row( matREF ), iRow++,
        meanREF = meanREF + matREF[iRow, 0]
    );
    meanREF = meanREF / N Row( matREF );
    sREF = Covariance( matREF );

//find mean and cov of test group
    meanTEST = J( 1, N Items( yCol ), 0 );
    For( iRow = 1, iRow <= N Row( matTEST ), iRow++,
        meanTEST = meanTEST + matTEST[iRow, 0]
    );
    meanTEST = meanTEST / N Row( matTEST );
    sTEST = Covariance( matTEST );

    sPOOL = (sREF + sTEST) / 2;

//find distance of test group to reference group
    //dm = sqrt(round((meanTEST-meanREF),2)*round(inverse(sPOOL),2)*round((meanTEST-
meanREF),2)`);
    dm = Sqrt( (meanTEST - meanREF) * Inverse( sPOOL ) * (meanTEST - meanREF)` );
```

```
//find confidence region
	n = N Row( matREF );
	p = N Items( yCol );
	k = n * n * (2 * n - p - 1) / (2 * n * (2 * n - 2) * p);

//display results
	nw2 << close window();
	Close( dtREF, nosave );
	Close( dtTEST, nosave );
	nw3 = New Window( "Results",
		Text Box( "Results of comparison of " || test || " to " || ref || "." ),
		Table Box(
			String Col Box( "Quantity", {"n", "P", "K", "Dm"} ),
			Number Col Box( "Value", {n, p, k, dm[1]} )
		)
	);
);


/*
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*/
;
```

Attachment 2: Extension of JSL script, to include confidence regions

```
exprOK2 = Expr(
//setup
	ref = (lbRef << get items)[1];
	test = (lbTest << get items)[1];
	colGroup = Parse( ":" || (Column( dt, groupCol[1] ) << get name) );
	dt << clear select;
	dt << select where( colGroup == ref );
	dtREF = dt << subset( selected rows );
	dt << clear select;
	dt << select where( colGroup == test );
	dtTEST = dt << subset( selected rows );
	dt << clear select;
	matREF = J( N Row( dtREF ), N Items( yCol ), . );
	For( iCol = 1, iCol <= N Items( yCol ), iCol++,
		matREF[0, iCol] = (Column( dtREF, yCol[iCol] ) << get values)
	);
	matTEST = J( N Row( dtTEST ), N Items( yCol ), . );
	For( iCol = 1, iCol <= N Items( yCol ), iCol++,
		matTEST[0, iCol] = (Column( dtTEST, yCol[iCol] ) << get values)
	);

//find mean and cov of reference group
	meanREF = J( 1, N Items( yCol ), 0 );
	For( iRow = 1, iRow <= N Row( matREF ), iRow++,
		meanREF = meanREF + matREF[iRow, 0]
	);
	meanREF = Transpose(meanREF / N Row( matREF ));
	sREF = Covariance( matREF );

//find mean and cov of test group
	meanTEST = J( 1, N Items( yCol ), 0 );
	For( iRow = 1, iRow <= N Row( matTEST ), iRow++,
		meanTEST = meanTEST + matTEST[iRow, 0]
	);
	meanTEST = Transpose(meanTEST / N Row( matTEST ));
	sTEST = Covariance( matTEST );

	sPOOL = (sREF + sTEST) / 2;

//find distance of test group to reference group
	//dm = sqrt(round((meanTEST-meanREF),2)*round(inverse(sPOOL),2)*round((meanTEST-
meanREF),2)`);
	meanDIFF = meanTEST - meanREF;
	p = N Items( yCol );
	dm = Sqrt( Transpose(meanDIFF) * Inverse( sPOOL ) * meanDIFF );

//calculate f2
    mu_inprod = Transpose(meanDIFF)*meanDIFF;
    f2 = 50*log10(100/sqrt(1+mu_inprod/p));
```

```
//find confidence region, lamda = 0
	n1 = N Row( matREF );
	n2 = N Row( matTEST );
	k = n1 * n2 * (n1 + n2 - p - 1) / ((n1 + n2) * (n1 + n2 - 2) * p);
	df2 = n1 + n2 - p - 1;
	Fp = F Quantile(0.90,p,df2,0);
	y1p = meanDIFF*(1 + sqrt(Fp/(k*dm*dm)));
    y2p = meanDIFF*(1 - sqrt(Fp/(k*dm*dm)));
    Dupper =
max(sqrt(Transpose(y1p)*Inverse(sPOOL)*y1p),sqrt(Transpose(y2p)*Inverse(sPOOL)*y2p));
    Dlower =
min(sqrt(Transpose(y1p)*Inverse(sPOOL)*y1p),sqrt(Transpose(y2p)*Inverse(sPOOL)*y2p));

//find critical distance for shift of 10% relative to reference group
	critDIFF = J( N Items( yCol ), 1, 10 );
	dmc = Sqrt( Transpose(critDIFF) * Inverse( sPOOL ) * critDIFF );

//find confidence region, lambda > 0
    ncp = n1 * n2 / (n1 + n2);
    y = k*dm*dm;
    root = F noncentrality(ncp, p, df2, 0.10);
    d = sqrt(root/(k*sum(Inverse(sPOOL))));

//display results
	nw2 << close window();
	Close( dtREF, nosave );
	Close( dtTEST, nosave );
	nw3 = New Window( "Results",
		Text Box( "Results of comparison of " || test || " to " || ref || "." ),
		Table Box(
			String Col Box( "Quantity", {"n1", "n2", "p", "k", "Dm", "Dlower",
"Dupper", "Dmc", "d"} ),
			Number Col Box( "Value", {n1, n2, p, k, dm[1], Dlower, Dupper,
dmc[1], d} )
		)
	);
);
```

Attachment 3: Extension of JSL script, to implement delta approach

```
exprOK2 = Expr(
//setup
	ref = (lbRef << get items)[1];
	test = (lbTest << get items)[1];
	colGroup = Parse( ":" || (Column( dt, groupCol[1] ) << get name) );
	dt << clear select;
	dt << select where( colGroup == ref );
	dtREF = dt << subset( selected rows );
	dt << clear select;
	dt << select where( colGroup == test );
	dtTEST = dt << subset( selected rows );
	dt << clear select;
	matREF = J( N Row( dtREF ), N Items( yCol ), . );
	For( iCol = 1, iCol <= N Items( yCol ), iCol++,
		matREF[0, iCol] = (Column( dtREF, yCol[iCol] ) << get values)
	);
	matTEST = J( N Row( dtTEST ), N Items( yCol ), . );
	For( iCol = 1, iCol <= N Items( yCol ), iCol++,
		matTEST[0, iCol] = (Column( dtTEST, yCol[iCol] ) << get values)
	);

//find mean and cov of reference group
	meanREF = J( 1, N Items( yCol ), 0 );
	For( iRow = 1, iRow <= N Row( matREF ), iRow++,
		meanREF = meanREF + matREF[iRow, 0]
	);
	meanREF = Transpose(meanREF / N Row( matREF ));
	sREF = Covariance( matREF );

//find mean and cov of test group
	meanTEST = J( 1, N Items( yCol ), 0 );
	For( iRow = 1, iRow <= N Row( matTEST ), iRow++,
		meanTEST = meanTEST + matTEST[iRow, 0]
	);
	meanTEST = Transpose(meanTEST / N Row( matTEST ));
	sTEST = Covariance( matTEST );

	sPOOL = (sREF + sTEST) / 2;

//find distance of test group to reference group
	//dm = sqrt(round((meanTEST-meanREF),2)*round(inverse(sPOOL),2)*round((meanTEST-
meanREF),2)`);
	meanDIFF = meanREF - meanTEST;
	p = N Items( yCol );
	dm = Sqrt( Transpose(meanDIFF) * Inverse( sPOOL ) * meanDIFF );

//calculate f2
    mu_inprod = Transpose(meanDIFF)*meanDIFF;
    f2 = 50*log10(100/sqrt(1+mu_inprod/p));
```

```
//compute SK delta statistics
	n1 = N Row( matREF );
	n2 = N Row( matTEST);
	maxDIFF = max(abs(meanDIFF));
	e = J(1,p,1);
	V = sPOOL*(n1+n2-2);
	invsP = Inv(V);
	deltaHAT = (e*invsP*meanDIFF)/(e*invsP*Transpose(e));
	qt = t Quantile(0.95,n1+n2-2,0);
	IUT = sqrt((Vec Diag(sREF)*(n1-1) + Vec Diag(sTEST)*(n2-1))/((n1+n2-2)^2)*qt +
abs(meanDIFF));
	maxIUT = max(IUT);
	// Matrix A
	a11 = 1;
	a21 = Transpose(J(1,p-1,1));
	a12 = J(1,p-1,0);
	a22 = -1*Identity(p-1);
	// Matrix V
	v11 = V[1,1];
	v12 = V[1,2::p];
	v21 = V[2::p,1];
	v22 = V[2::p,2::p];
	// AVA'
	wyy = a11^2*v11;
	wyx1 = a11*v11*Transpose(a21);
	wyx2 = a11*v12*Transpose(a22);
	wyx = wyx1 + wyx2 ;
	wxy = a21*v11*a11+a22*v21*a11;
	wxx =
v11*a21*Transpose(a21)+a22*v21*Transpose(a21)+a21*v12*Transpose(a22)+a22*v22*Transpose(
a22);
	ybar = meanDIFF[1];
	xbar = Transpose(meanDiff[1]-meanDIFF[2::p]);
	Q = 1/(1/n1+1/n2)*xbar*Inv(wxx)*Transpose(xbar);
	sigmayyx = (wyy-wyx*Inv(wxx)*wxy)/(n1+n2-p-1);
	se = sqrt(sigmayyx*(1+Q)*(1/n1+1/n2));
	delta0 = 10;
	t1 = (deltaHAT-delta0)/se;
	t2 = (deltaHAT+delta0)/se;
	pvalue1 = t Distribution(t1,n1+n2-p-1,0);
	pvalue2 = 1 - t Distribution(t2,n1+n2-p-2,0);
	pvalue = max(pvalue1,pvalue2);
	qt2 = t Quantile(0.95,n1+n2-p-1,0);
	upperCI = deltaHAT[1]+qt2*se;
	lowerCI = deltaHAT[1]-qt2*se;
	tStat = (abs(deltaHAT-delta0))/se;
```

```
//display results
	nw2 << close window();
	Close( dtREF, nosave );
	Close( dtTEST, nosave );
	nw3 = New Window( "SK Results",
		Text Box( "SK Results of comparison of " || test || " to " || ref || "."
),
		Table Box(
			String Col Box( "Quantity", {"f2", "max IUT", "tStat", "max
pvalue", "delta hat", "standard error", "TOST lower", "TOST upper"} ),
			Number Col Box( "Value", {f2[1], maxIUT, tStat[1], pvalue,
deltaHAT[1],se[1],lowerCI[1],upperCI[1]} )
		)
	);
);
```