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An Investigation of Distribution Distance Measures

James Blum, University of North Carolina Wilmington;
Charity del Sol, Biostudy Solutions

ABSTRACT

Draft FDA guidance proposes utilizing Earth Mover's Distance (EMD) as a means of assessing similarity of distributions of parameters such as globule size. For a univariate distribution, EMD can be easily calculated from the empirical cumulative distribution function (CDF), making it readily comparable to the Cramer-von Mises and Kolmogorov-Smirnov metrics. This paper will explore the sensitivity of each of these metrics under a variety of simulated scenarios for equal and unequal distributions, and the effects on subsequent population bioequivalence tests.

INTRODUCTION

In order to determine bioequivalence of globule size distributions, draft FDA guidance for Cyclosporine suggests use of Earth Mover's Distance (EMD). This distance metric can be formalized as follows: Let a pair of distributions be represented by:

$$D_1 = \{(c_{11}, w_{11}), (c_{12}, w_{12}), \dots , (c_{1m}, w_{1m})\},$$

$$D_2 = \{(c_{21}, w_{21}), (c_{22}, w_{22}), \dots , (c_{2n}, w_{2n})\}$$

Where the value c_{kl} represents the l^{th} cluster of distribution k, most commonly as a centroid, and w_{kl} represents the distributional weight assigned to that cluster. Defining the distance between clusters as

$$d_{ij} = d(c_{1i}, c_{2j}),$$

for some distance metric $d(.,.)$, and the movement of weights as the flow, f_{ij}, EMD minimizes the work done to match the distributions:

$$W = \sum_{i=1}^{m} \sum_{j=1}^{n} d_{ij} f_{ij}.$$

The minimization is considered subject to the following constraints:

$$i)\ f_{ij} \geq 0, \text{ for all } i,j$$

$$ii)\ \sum_{j=1}^{n} f_{ij} \leq w_{1i}, \text{ for each } i$$

$$iii)\ \sum_{i=1}^{m} f_{ij} \leq w_{2j}, \text{ for each } j$$

$$iv)\ F = \sum_{i=1}^{m} \sum_{j=1}^{n} f_{ij} = \min\left(\sum_{i=1}^{m} w_{1i}, \sum_{j=1}^{n} w_{2j}\right).$$

For the minimum work, the Earth Mover's Distance is then defined as $EMD = \frac{W}{F}$. For bioequivalence testing, D_2 will represent the distribution of the reference product (typically via the "average" distribution across all samples) and will serve as the "target" distribution with the flows constructed to make D_1 match D_2.

For univariate distributions with the same set of bin centroids and normalized to a total weight of one, which is common for the bioequivalence testing on globule distributions, the statement of the problem can be altered somewhat from the above specification. First, note that if the flows are normalized to total one via $f_{ij}^* = f_{ij}/F$ then $EMD = \frac{W}{F}$ becomes

$$EMD = \frac{\sum_{i=1}^{m} \sum_{j=1}^{n} d_{ij} f_{ij}}{F} = \sum_{i=1}^{m} \sum_{j=1}^{n} d_{ij} f_{ij}^*.$$

Also, the problem at this point can be viewed as finding a joint distribution in two variables with marginal distributions that match the starting and target distributions in question. Therefore, constraint iv) is modified to having $F = 1$ and constraints ii) and iii) are now equalities rather than inequalities.

It can be further shown that the EMD solution is directly related to common distance metrics on the empirical cumulative distribution functions (empirical CDF). Using a variation on the previous conventions, define

$$F_k = \{(c_{k1}, W_{k1}), (c_{k2}, W_{k2}), \dots , (c_{km}, W_{km})\}, W_{kl} = \sum_{i=1}^{l} w_{ki}$$

So W is the cumulative weight and F_k is the k[th] cumulative distribution and the EMD between two distributions is given by

$$EMD = \sum_{i=1}^{m-1} d\left(c_{1(i+1)}, c_{1i}\right)||W_{1i} - W_{2i}||_p$$

Which, for distances defined as simple differences and presuming the bin centroids are listed in increasing order, becomes:

$$EMD = \sum_{i=1}^{m-1} \left(c_{1(i+1)} - c_{1i}\right)|W_{1i} - W_{2i}|$$

Thus, EMD is related to several metrics used to measure distances between empirical CDFs, and a comparison among several of these, including Kolmogorov-Smirnov and Cramer-von Mises, seem warranted. What follows is a simulation study of the performance of these metrics under various conditions of distribution shape and similarity to determine sensitivity and specificity of bioequivalence testing under a variety of conditions.

SIMPLE CASES AND NON-UNIQUENESS OF THE EMD SOLUTION

Simple examples will help in showing how the EMD calculation works and that, while the set of flows chosen is not unique, the optimal distance is. Consider a simple pair of distributions given in Table 1 and Table 2 below:

c	1	3	4	5	7
w	0.1	0.2	0.2	0.3	0.2

Table 1. Target Distribution

c	1	3	4	5	7
w	0.2	0.2	0.3	0.2	0.1

Table 2. Distribution

In each of these, while the set of centroids is the same, the centroids are not equally spaced. Using simple absolute differences for the distances between centroids, Table 3 describes the full set of distances.

c	1	3	4	5	7
1	0	2	3	4	6
3	2	0	1	2	4
4	3	1	0	1	3
5	4	2	1	0	2
7	6	4	3	2	0

Table 3. Distances

Note that for any element of this matrix d_{ij}, for $i < k < j$, $d_{ij} = d_{ik} + d_{kj}$. For example, the distance between the first and third centroids is 3, which is the sum of the distance from the first to the second (2) and the second to third (1). This is important in showing that different sets of flows can produce the same distance.

SOLUTIONS

The flow set in Table 4 below shows the two distributions across the five centroids in the first row and column, with the set of flows as a 5x5 joint distribution with row and column totals that match the original and target distributions. However, even following the constraints given in the EMD algorithm, other joint distributions are possible.

Target->	0.1	0.2	0.2	0.3	0.2
0.2	0.1	0.1	0	0	0
0.2	0	0.1	0	0.1	0
0.3	0	0	0.2	0	0.1
0.2	0	0	0	0.2	0
0.1	0	0	0	0	0.1

Table 4. Flow Set A

While the flow sets are quite different, each does produce the correct marginal distributions and, when matching with the distance matrix, both produce the same EMD of 0.7. Flow Set B in Table 5 below only moves weights to adjacent bins, following the EMD calculation given in the first section, which is based on adjacent differences in the empirical CDF. Though no complete proof is given here, there is always a minimizer for EMD that uses only adjacent flows under the condition of using simple differences as the distance between centroids.

Target->	0.1	0.2	0.2	0.3	0.2
0.2	0.1	0.1	0	0	0
0.2	0	0.1	0.1	0	0
0.3	0	0	0.1	0.2	0
0.2	0	0	0	0.1	0.1
0.1	0	0	0	0	0.1

Table 5. Flow Set B

IVBE EXPLANATION

To assess whether the variability of distances is equivalent for the test and reference products, in-vitro bioequivalence (BE) assessments are computed. In-Vitro bioequivalence assessments were calculated as per the Budesonide Draft Guidance. Values were log-transformed prior to statistical analysis.

The geometric mean of each population, difference between means, variance of each population, point estimates for the linearized population BE statistic, and the 95% upper confidence bound for both the reference-scaled and constant-scaled linearized statistics were calculated. As life stage was not being considered in the simulations, all equations are simplified reflecting the removal of life stage.

Let μ_T and μ_R represent the geometric means for the test (T) and reference(R) products, and let σ_T^2 and σ_R^2 represent the total variance of the test and reference products estimates using

$$\sigma_k = \frac{\sum_1^{n_k}(X_{ij} - \bar{X}_j)^2}{n_k - 1}.$$

Where n_k represents the number of samples for each product, x_{ik} represents the i^{th} sample of product k, and $\bar{x}_{.k}$ represents the population mean for product k.

When the reference product total variance exceeded the regulatory constant ($\sigma_{T_0}^2 = 0.01$), in-vitro population bioequivalence was evaluated using the upper 95% confidence bound for the reference-scaled criterion. The point estimate for the reference-scaled criterion is defined as

$$(\mu_T - \mu_R)^2 + (\sigma_T - \sigma_R)^2 - \theta_p \sigma_R^2 \leq 0.$$

When the reference product total variance was less than or equal to the regulatory constants ($\sigma_R^2 \leq \sigma_{T0}^2$), in-vitro population bioequivalence was evaluated using the upper 95% confidence bound for the constants scaled criterion. The point estimate from the constant-scaled criterion is defined as

$$(\mu_T - \mu_R)^2 + (\sigma_T - \sigma_R)^2 - \theta_p \sigma_{T0}^2 \leq 0.$$

Where θ_p is the bioequivalence limit given by:

$$\theta_p = \frac{ln(1.11)^2 + 0.01}{\sigma_{T0}^2}.$$

A negative or zero value for the upper 95% confidence bound on the linearized statistic indicates a passing result.

SIMULATION SCENARIO DESCRIPTIONS

To assess the performance of various distance metrics for both equivalent and different distributions a simulation study was undertaken. Each case uses two groups, test and reference, and is based on 10,000 simulated sample data sets. Three distribution types are considered: unimodal distributions simulated from a triangular distribution, unimodal distributions with heavier tails simulated from a mixture of a triangular and uniform distributions, and a bimodal distribution simulated from a mixture of triangular distributions. All observations are simulated from distributions with support on the interval 0 to 100 and are binned into histograms of bin width five, with the first bin starting at zero. Cases for distributions that are not equivalent are built by moving the mode between the two groups or by moving the mixture weight for the two mixture distributions. Quartile summaries of the test-to-reference ratio of the average distance are reported along with proportions of IVBE confidence bounds above and below zero.

RESULTS

Simulation Case 1

The first simulation case is based on a triangular distribution on 0 to 100 with a base mode of 50, shifted in non-equivalent scenarios by 0.5 or 1.0 in the reference group for certain cases. Samples of 10, 20, and 40 per group are considered. The distribution of Test-to-Reference ratios for Case 1 is presented in Table 6 below.

Shift of Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
0	10	Cramer	0.586	0.988	1.107	1.237	2.165
		EMD	0.560	0.985	1.106	1.239	2.182
		Kolmogorov	0.609	0.988	1.106	1.236	1.950
	20	Cramer	0.634	0.970	1.048	1.137	1.623
		EMD	0.628	0.969	1.049	1.138	1.601
		Kolmogorov	0.673	0.972	1.050	1.135	1.574
	40	Cramer	0.761	0.969	1.025	1.084	1.387
		EMD	0.760	0.969	1.025	1.084	1.401
		Kolmogorov	0.770	0.970	1.025	1.082	1.403
0.5	10	Cramer	0.580	1.047	1.186	1.345	2.461
		EMD	0.546	1.046	1.181	1.344	2.411
		Kolmogorov	0.601	1.046	1.185	1.338	2.580

Shift of Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
	20	Cramer	0.697	1.038	1.132	1.237	1.727
		EMD	0.686	1.033	1.129	1.234	1.745
		Kolmogorov	0.711	1.037	1.129	1.229	1.744
	40	Cramer	0.810	1.040	1.105	1.176	1.559
		EMD	0.799	1.036	1.102	1.172	1.542
		Kolmogorov	0.769	1.039	1.102	1.171	1.595
1	20	Cramer	0.769	1.242	1.368	1.511	2.456
		EMD	0.773	1.228	1.353	1.495	2.440
		Kolmogorov	0.787	1.233	1.353	1.489	2.234
	40	Cramer	0.894	1.250	1.344	1.443	1.968
		EMD	0.882	1.237	1.330	1.427	1.938
		Kolmogorov	0.897	1.241	1.330	1.423	1.893

Table 6. Distribution of Test-to-Reference Ratios for Case 1

The percentages of confidence bounds below zero are presented below in Table 7.

Shift of Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
0	10	Cramer	1.2	30.1
		EMD	1.3	30.4
		Kolmogorov	1.0	29.0
	20	Cramer	2.9	66.9
		EMD	3.3	66.7
		Kolmogorov	2.6	67.1
	40	Cramer	5.9	95.2
		EMD	6.3	95.1
		Kolmogorov	5.8	95.4
0.5	10	Cramer	0.8	21.2
		EMD	0.9	22.4
		Kolmogorov	0.7	21.2
	20	Cramer	1.7	50.3
		EMD	1.6	51.1
		Kolmogorov	1.3	51.9
	40	Cramer	1.7	83.6
		EMD	1.9	84.1
		Kolmogorov	1.8	86.6
1	20	Cramer	0.1	16.9
		EMD	0.2	19.2

Shift of Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
		Kolmogorov	0.1	18.8
	40	Cramer	0.0	33.9
		EMD	0.1	38.0
		Kolmogorov	0.0	39.0

Table 7. Percentages of Confidence Bounds Below Zero for Case 1

Simulation Case 2

The second simulation case is based on a mixture of triangular distributions, one on 45 to 100 with a base mode of 75 and ¾ weight and the second on 0 to 55 with base mode 25 and weight ¼. Each mode was shifted in non-equivalent scenarios by 0.5 in the reference group for certain cases. Samples of 10, 20, and 40 per group are considered. The distribution of Test-to-Reference ratios for Case 1 is presented in Table 6 below.

Shift of Primary Mode	Shift of Secondary Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
0	0	10	Cramer	0.585	0.981	1.102	1.247	2.081
			EMD	0.553	0.975	1.102	1.250	2.144
			Kolmogorov	0.610	0.989	1.104	1.237	2.004
		20	Cramer	0.665	0.966	1.051	1.144	1.775
			EMD	0.643	0.964	1.052	1.149	1.781
			Kolmogorov	0.697	0.971	1.051	1.137	1.668
		40	Cramer	0.744	0.970	1.027	1.090	1.455
			EMD	0.731	0.968	1.027	1.093	1.474
			Kolmogorov	0.748	0.973	1.027	1.086	1.367
	0.5	10	Cramer	0.585	0.996	1.122	1.262	2.248
			EMD	0.558	0.992	1.123	1.272	2.323
			Kolmogorov	0.591	1.000	1.119	1.251	2.300
		20	Cramer	0.660	0.980	1.064	1.158	1.815
			EMD	0.655	0.979	1.064	1.163	1.797
			Kolmogorov	0.657	0.983	1.062	1.147	1.744
		40	Cramer	0.758	0.980	1.040	1.102	1.437
			EMD	0.737	0.980	1.042	1.106	1.465
			Kolmogorov	0.742	0.979	1.036	1.093	1.427
	1	10	Cramer	0.548	1.034	1.167	1.320	2.453
			EMD	0.552	1.033	1.172	1.332	2.478
			Kolmogorov	0.623	1.030	1.153	1.289	2.402
		20	Cramer	0.668	1.021	1.112	1.205	1.746

Shift of Primary Mode	Shift of Secondary Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
			EMD	0.660	1.022	1.117	1.216	1.778
			Kolmogorov	0.616	1.015	1.101	1.185	1.658
		40	Cramer	0.784	1.024	1.085	1.148	1.517
			EMD	0.795	1.026	1.090	1.157	1.578
			Kolmogorov	0.781	1.014	1.070	1.130	1.459
0.5	0	10	Cramer	0.636	1.064	1.205	1.369	3.078
			EMD	0.594	1.046	1.190	1.353	3.014
			Kolmogorov	0.661	1.090	1.231	1.392	2.929
		20	Cramer	0.701	1.055	1.152	1.261	1.887
			EMD	0.697	1.040	1.137	1.247	1.877
			Kolmogorov	0.671	1.079	1.178	1.287	1.944
		40	Cramer	0.788	1.065	1.133	1.203	1.585
			EMD	0.765	1.048	1.118	1.190	1.558
			Kolmogorov	0.809	1.090	1.157	1.228	1.652
1	0	10	Cramer	0.748	1.317	1.499	1.702	2.894
			EMD	0.663	1.257	1.432	1.629	2.743
			Kolmogorov	0.820	1.419	1.618	1.845	3.326
		20	Cramer	0.869	1.309	1.437	1.571	2.372
			EMD	0.817	1.249	1.369	1.500	2.294
			Kolmogorov	0.915	1.414	1.557	1.705	2.624
		40	Cramer	0.983	1.324	1.413	1.506	2.044
			EMD	0.913	1.262	1.346	1.436	1.977
			Kolmogorov	1.085	1.432	1.530	1.633	2.327

Table 8. Distribution of Test-to-Reference Ratios for Case 2

The percentages of confidence bounds below zero are presented below in Table 9.

Shift of Primary Mode	Shift of Secondary Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
0	0	10	Cramer	1.1	30.0
			EMD	1.2	30.4
			Kolmogorov	1.0	29.3
		20	Cramer	2.7	67.8
			EMD	2.6	68.2
			Kolmogorov	2.5	67.0
		40	Cramer	5.1	95.4
			EMD	4.5	95.3

Shift of Primary Mode	Shift of Secondary Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
			Kolmogorov	6.2	95.8
	0.5	10	Cramer	1.1	29.9
			EMD	1.0	30.6
			Kolmogorov	1.0	29.8
		20	Cramer	3.2	68.7
			EMD	3.0	68.6
			Kolmogorov	3.0	69.7
		40	Cramer	6.1	95.5
			EMD	5.8	95.4
			Kolmogorov	7.0	95.9
	1	10	Cramer	1.3	30.2
			EMD	1.1	29.9
			Kolmogorov	1.1	30.4
		20	Cramer	3.7	68.2
			EMD	3.3	67.3
			Kolmogorov	3.7	70.9
		40	Cramer	7.3	95.2
			EMD	6.7	94.4
			Kolmogorov	8.8	96.8
0.5	0	10	Cramer	0.9	26.8
			EMD	1.1	28.9
			Kolmogorov	0.5	20.1
		20	Cramer	2.0	59.8
			EMD	2.3	63.0
			Kolmogorov	1.1	48.7
		40	Cramer	3.7	90.5
			EMD	4.5	92.5
			Kolmogorov	1.2	83.0
1	0	10	Cramer	0.2	13.1
			EMD	0.5	18.9
			Kolmogorov	0.0	4.1
		20	Cramer	0.4	31.0
			EMD	1.0	43.2
			Kolmogorov	0.0	8.8
		40	Cramer	0.2	55.2

Shift of Primary Mode	Shift of Secondary Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
			EMD	0.8	72.8
			Kolmogorov	0.0	15.3

Table 9. Percentages of Confidence Bounds Below Zero for Case 2

Simulation Case 3

The third simulation case is based on a mixture of a triangular distribution, on 0 to 100 with a base mode of 75 and ¾ weight, and a uniform on 0 to 100 with weight ¼. The mode was shifted in non-equivalent scenarios by 0.5 in the reference group for certain cases. Samples of 10, 20, and 40 per group are considered. The distribution of Test-to-Reference ratios for Case 1 is presented in Table 10 below.

Shift of Primary Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
0	10	Cramer	0.471	0.981	1.103	1.243	2.114
		EMD	0.489	0.979	1.104	1.246	2.188
		Kolmogorov	0.472	0.986	1.102	1.237	1.966
	20	Cramer	0.678	0.967	1.051	1.136	1.639
		EMD	0.681	0.965	1.050	1.139	1.661
		Kolmogorov	0.680	0.973	1.048	1.134	1.540
	40	Cramer	0.757	0.970	1.025	1.086	1.453
		EMD	0.730	0.968	1.025	1.087	1.484
		Kolmogorov	0.780	0.972	1.025	1.082	1.357
0.5	10	Cramer	0.589	1.015	1.146	1.289	2.217
		EMD	0.606	1.009	1.144	1.293	2.195
		Kolmogorov	0.588	1.020	1.145	1.282	2.154
	20	Cramer	0.718	1.006	1.092	1.190	1.737
		EMD	0.715	1.001	1.092	1.192	1.757
		Kolmogorov	0.732	1.009	1.092	1.184	1.723
	40	Cramer	0.761	1.008	1.069	1.137	1.578
		EMD	0.752	1.005	1.068	1.137	1.596
		Kolmogorov	0.780	1.009	1.067	1.134	1.511
1	10	Cramer	0.649	1.115	1.275	1.458	2.584
		EMD	0.648	1.107	1.267	1.455	2.599
		Kolmogorov	0.602	1.126	1.274	1.444	2.482
	20	Cramer	0.748	1.114	1.222	1.347	2.028
		EMD	0.734	1.107	1.215	1.341	2.007
		Kolmogorov	0.790	1.117	1.219	1.334	1.997
	40	Cramer	0.812	1.121	1.197	1.279	1.674
		EMD	0.777	1.114	1.191	1.274	1.682
		Kolmogorov	0.855	1.121	1.194	1.270	1.631

Shift of Primary Mode	Samples	Distance Metric	Min	Q1	Median	Q3	Max
1.5	10	Cramer	0.717	1.292	1.489	1.709	3.248
		EMD	0.688	1.273	1.472	1.693	3.299
		Kolmogorov	0.693	1.302	1.482	1.688	3.367
	20	Cramer	0.864	1.293	1.424	1.572	2.568
		EMD	0.828	1.275	1.404	1.555	2.582
		Kolmogorov	0.867	1.298	1.422	1.558	2.344
	40	Cramer	0.869	1.303	1.400	1.501	2.120
		EMD	0.840	1.286	1.381	1.486	2.120
		Kolmogorov	0.913	1.308	1.395	1.491	2.002
2	10	Cramer	0.769	1.523	1.751	2.018	3.739
		EMD	0.736	1.487	1.713	1.983	3.694
		Kolmogorov	0.840	1.538	1.753	1.993	3.260
	20	Cramer	1.026	1.535	1.690	1.867	2.982
		EMD	0.979	1.499	1.655	1.832	2.827
		Kolmogorov	1.022	1.547	1.695	1.851	3.016
	40	Cramer	0.996	1.555	1.668	1.786	2.395
		EMD	0.973	1.519	1.632	1.751	2.461
		Kolmogorov	1.070	1.563	1.666	1.777	2.335

Table 10. Distribution of Test-to-Reference Ratios for Case 3

The percentages of confidence bounds below zero are presented below in Table 11.

Shift of Primary Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
0	10	Cramer	1.0	30.1
		EMD	1.1	30.1
		Kolmogorov	1.0	28.4
	20	Cramer	3.0	67.2
		EMD	3.1	67.2
		Kolmogorov	3.0	67.4
	40	Cramer	5.7	95.4
		EMD	5.4	95.2
		Kolmogorov	6.2	95.7
0.5	10	Cramer	1.0	26.2
		EMD	1.0	26.8
		Kolmogorov	0.8	25.0
	20	Cramer	2.5	61.0
		EMD	2.6	61.9

Shift of Primary Mode	Samples	Distance Metric	C-S 95% Upper Bound Below 0 (%)	R-S 95% Upper Bound Below 0 (%)
		Kolmogorov	2.2	61.7
	40	Cramer	3.8	91.7
		EMD	4.0	91.6
		Kolmogorov	3.8	93.2
1	10	Cramer	0.6	18.6
		EMD	0.7	19.4
		Kolmogorov	0.4	17.1
	20	Cramer	0.7	41.0
		EMD	1.0	42.9
		Kolmogorov	0.5	40.9
	40	Cramer	0.8	73.1
		EMD	1.0	75.2
		Kolmogorov	0.6	75.5
1.5	10	Cramer	0.1	8.7
		EMD	0.2	10.3
		Kolmogorov	0.1	7.0
	20	Cramer	0.1	19.5
		EMD	0.2	22.7
		Kolmogorov	0.1	17.1
	40	Cramer	0.1	36.5
		EMD	0.1	42.3
		Kolmogorov	0.0	34.1
2	10	Cramer	0.0	2.9
		EMD	0.0	4.1
		Kolmogorov	0.0	1.6
	20	Cramer	0.0	5.1
		EMD	0.0	8.0
		Kolmogorov	0.0	3.0
	40	Cramer	0.0	7.4
		EMD	0.0	11.6
		Kolmogorov	0.0	4.4

Table 11. Percentages of Confidence Bounds Below Zero for Case 3

CONCLUSION

One of the most important characteristics to note from these simulations is how the median test-to-reference ratio differs from one in the cases where it is expected to be one, those where the distributions

are the same. It is also useful to note that the deviation from one is roughly of the same percentage as the ratio of one to the number of samples in each group: *i.e.* for 10 samples the median test-to-reference ratio is about 1.10 or 10% = 1/10 above one, for 20 samples it is about 1.05, or 1/20 = 5% more than expected. It is theorized that this is a reflection of the fact that variability is calculated around the reference sample mean, effectively corresponding to one less degree of freedom in the reference group than the test group.

As can be seen in the simulation results, even in the null case the behavior of the test-to-reference ratio for small samples results in a low probability of demonstrating bioequivalence with the R-S bound. However, this difference becomes much less important for the R-S bound as the number of samples increases. The R-S bound appears to behave as expected in the unimodal case, quickly decreasing with a minor shift in the mode. In the bimodal case, a minor shift in the primary mode has a greater effect than similar shift in the secondary mode, but each has a lower effect than the corresponding shift in the unimodal case. The Kolmogorov metric shows as the most sensitive to large shifts in the primary mode. For the heavy-tailed unimodal distributions, larger shifts in the mode are required to lessen the likelihood of declaring bioequivalence. The C-S bound shows little chance of finding bioequivalence even when true. Overall, the three distance metrics show similar performance, with the Kolmogorov metric detecting the shift in the primary mode of the bimodal case more often.

Future work is expected to focus on making an adjustment for the measurement of distances in both groups from a centroid that comes from one group. While some scale adjustment to the statistics themselves may be possible, investigation will focus instead on basing distances within the reference group on the jackknife sample for each observation, with the test group still using the mean from the full reference sample. In that case, no centroid depends on the observation its distance is measured from which should make for a more equal comparison.

REFERENCES

US Department of Health and Human Services, U.S. Food and Drug Administration. “Draft Guidance on Cyclosporine”, Issued June 2013; Revised February 2016; October 2016. Available at https://www.fda.gov/downloads/Drugs/.../Guidances/UCM319977.pdf, verified March 12, 2018.

US Department of Health and Human Services, U.S. Food and Drug Administration. “Draft Guidance on Budesonide”, Issued September 2012. Available at https://www.fda.gov/downloads/Drugs/.../Guidances/UCM319977.pdf, verified March 12, 2018.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

James Blum
University of North Carolina Wilmington
blumj@uncw.edu

Charity del Sol
Biostudy Solutions
charity@biostudysolutions.com