2021 CRCG IVRT/IVPT Workshop

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IVPT Data Challenges in the Real World:

IVPT Outlier, Anomalous or Aberrant Data: Examples

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Outline of Presentation

1. “Outlier” Data Examples
2. Those pesky Zero values
3. What about that elusive J_{max}?

Foundation of Topic: Outliers

Within a set of replicate skin sections mounted onto Diffusion Cells, one may encounter one or more skin sections that are quite different in permeation kinetics from the other replicates. These could be identified as outliers, or anomalous or aberrant data, with the consideration for being **Highly Improbable** rather than **Natural Extremes,** where causality has not been identified or documented.

- Where a single sample time point for one replicate diffusion cell within a flux profile is clearly different from the other replicate values at the same time point.

- Where one flux profile from one diffusion cell is parallel in profile to its replicates but considerably higher or lower than the other replicate diffusion cells.

- Where the flux profile from one or more diffusion cells is clearly different from the profile of the other replicate diffusion cells (e.g. substantially different T_{max}).

Foundation of Topic: Outliers

FDA's current opinion on outliers:

"In general, the Agency does not recommend excluding data from a bioequivalence study analysis without documented protocol violations (e.g., errors that occur while conducting the study)."

Documented vs Undocumented.

Documented at the time of occurrence, or are found during an investigation or QC review:

- Analytical: missed injection, system malfunction, mislabeled sample, etc.
- IVPT/IVRT: incomplete dosing, missed sample collection, lost or spilled sample, mislabeled sample, damaged diffusion cell, etc.

Undocumented

- Analytical: samples incorrectly sequenced in tray, power fluctuations, etc.
- IVPT/IVRT: membrane damage during dosing, localized physiological differences in stratum corneum, incomplete sampling, etc.

Outlier Frequency in Pivotal Studies – Our Experience

Drug	# Donors	# Replicates	# Outliers	Percent
Drug A	13	6	None	0
Drug A	12	6	1	0.7 %
Drug B	12	8	None	0
Drug C	14	6	None	0
Drug D	20	6	3	1.3 %
Drug D	12	6	2	1.4 %
Drug E	14	6	None	0
Drug E	10	6	None	0
Drug F	12	6	3	2.1 %

- 4 out of 9 studies had 1 or more outliers (3-fold or greater AUC then other replicates).
- Potential influence on BE outcome (particularly if all outliers are with one test article by chance).
- Anecdotally suggests it may be drug or formulation related:
  - 2 studies with Drug “D” had outliers.
  - 2 studies with Drug “E” did not have outliers.

Study Design

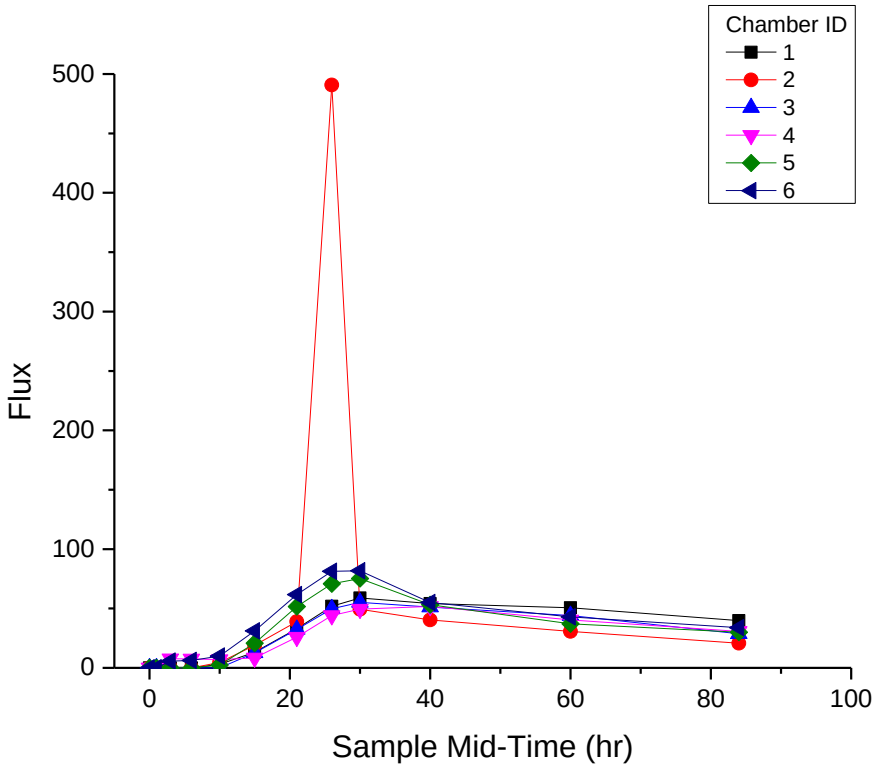
Examples are real data obtained from different studies with different APIs from well controlled studies.

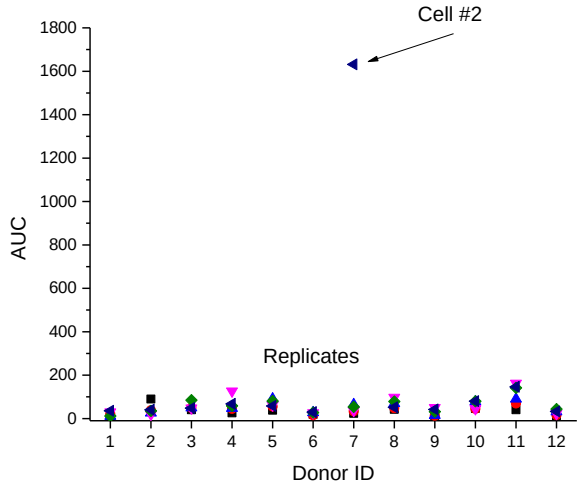
Basic study design:

- Cryopreserved dermatomed skin
- Static Franz Diffusion Cells
- Dosed and sampled following the FDA guidance recommendations
- Acceptable Integrity Test (TEWL)
- Well controlled room temperature and humidity environment
- Standardized GLP procedures
- Validated Analytical Method

Example #1

Example 1: Single point anomaly within a permeation curve profile



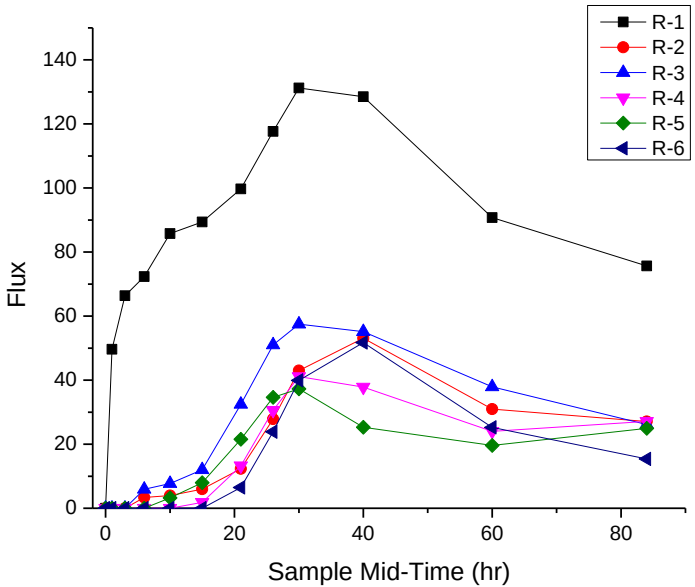


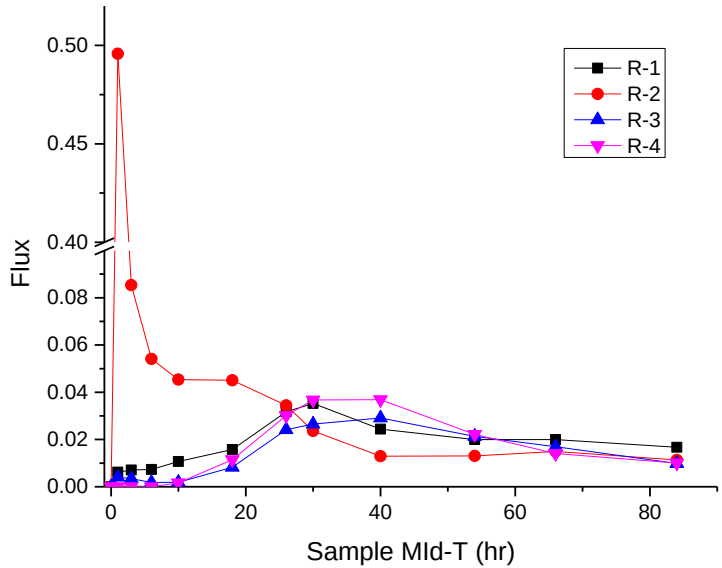
Most likely a sampling error or an analytical issue.

Review study records, log books, and analytical results for a documented or identifiable cause.

Example #2

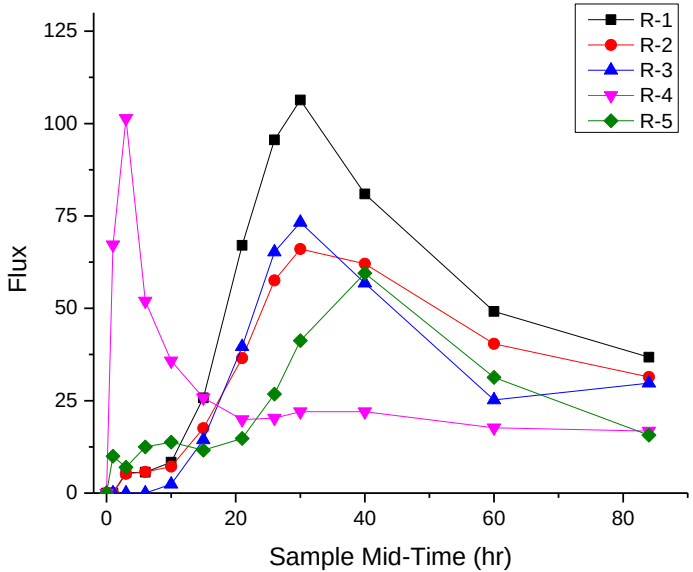
Example 2: Different Permeation Profile with Different AUC and/or J_{max} values

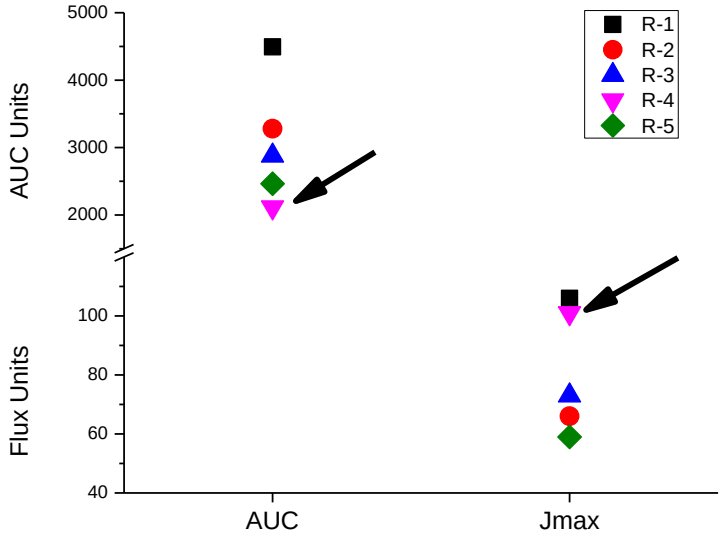




Example #3

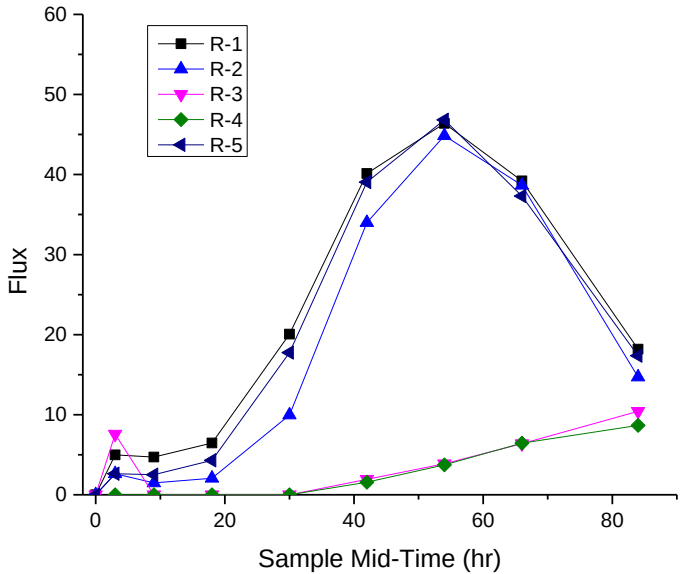
Example 3: Different Permeation Profile with <u>Similar</u> AUC and J_{max}

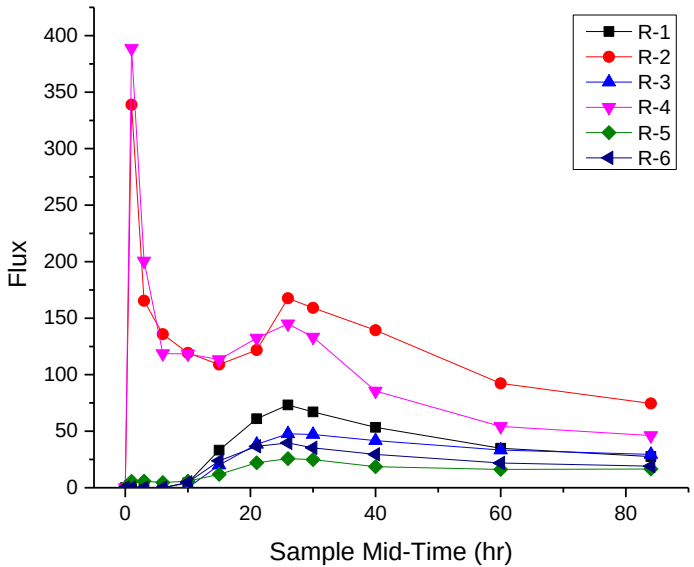




Example #4

Example 4: More than one replicate demonstrates a Different Permeation Profile. Should Low Outliers be as important as High Outliers?





Discussion Points

FDA's current response to outliers:

"In general, the Agency does not recommend excluding data from a bioequivalence study analysis without documented protocol violations (e.g., errors that occur while conducting the study)."

As related to IVPT:

"The Agency does not currently have specific recommendations relating to appropriate (objective and pre-specified) criteria for identifying experimental outliers for an IVPT study, although the Agency is currently studying this matter."

For Consideration and Discussion:

- How to objectively identify an anomalous data point, chamber or permeation profile?
- Will its removal need a scientific justification for its removal, or just a statistical demonstration of difference?
- Only high outliers to be considered, or also low outliers?
- Remove, replace, or include anomalous data? – Influence on Study Outcome?
- Should similar criteria, or consideration, be applied to Donor data, or keep just for replicates within a donor?

Foundation of Topic: Zero Values

With very low permeating compounds when coupled with lower limit of detection limitations, zero permeation results may be encountered.

- Function of analytical sensitivity.
- Less of an issue if one out of multiple replicates within a donor show no measurable permeation, where a cross replicate mean can still be obtained for that donor.
- Becomes an issue if one or more donors show no measurable permeation due to the log transformation requirement for BE analysis.

Example

	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8
AUC	167.088	801.928	719.241	204.987	685.718	439.572	0.000	32.015
Receptor (%)	6.127	29.339	26.272	7.532	25.116	16.127	0.000	1.174
Jmax (Curve Mean)	3.290	21.447	16.111	3.887	16.032	9.274		1.677
Ln Jmax	1.328	3.066	2.784	1.479	2.775	2.233		0.700
Ln AUC	5.119	6.687	6.578	5.323	6.530	6.086		3.466

Undefined

Options for consideration:

- Remove Donor 7 from BE calculations?
- Replace with Geometric mean of other donors?
- Replace with Lower Limit of Detection value?
- Disqualify it as being an Outlier and replace with another Donor?
- What if no permeation from one formulation, but measurable for the other formulation?

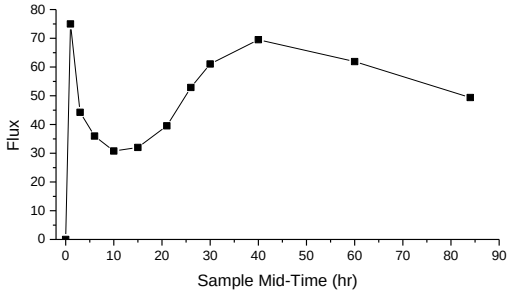
Foundation of Topic: J_{max}

J_{max} can be an illusive and poorly defined parameter.

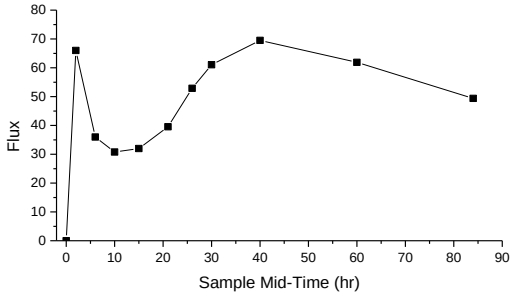
- Sensitive to sampling schedule (particularly for static chambers).
- Which J_{max} best represents the permeation profile?

Example #1 – Early Time Point Sample Schedule Influence

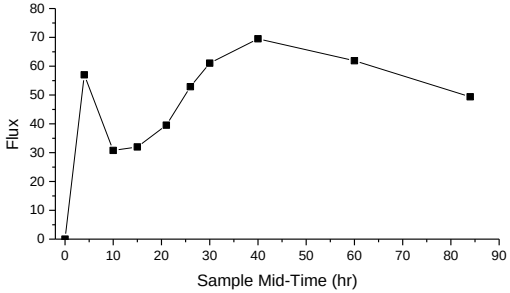
Original Data



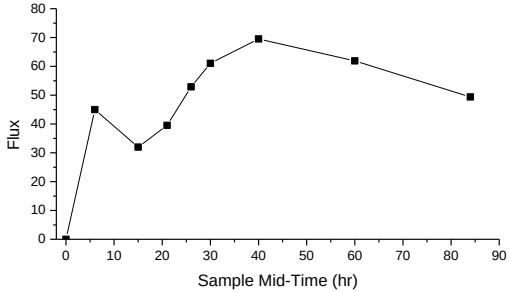
If first sample was collected at 4 hrs



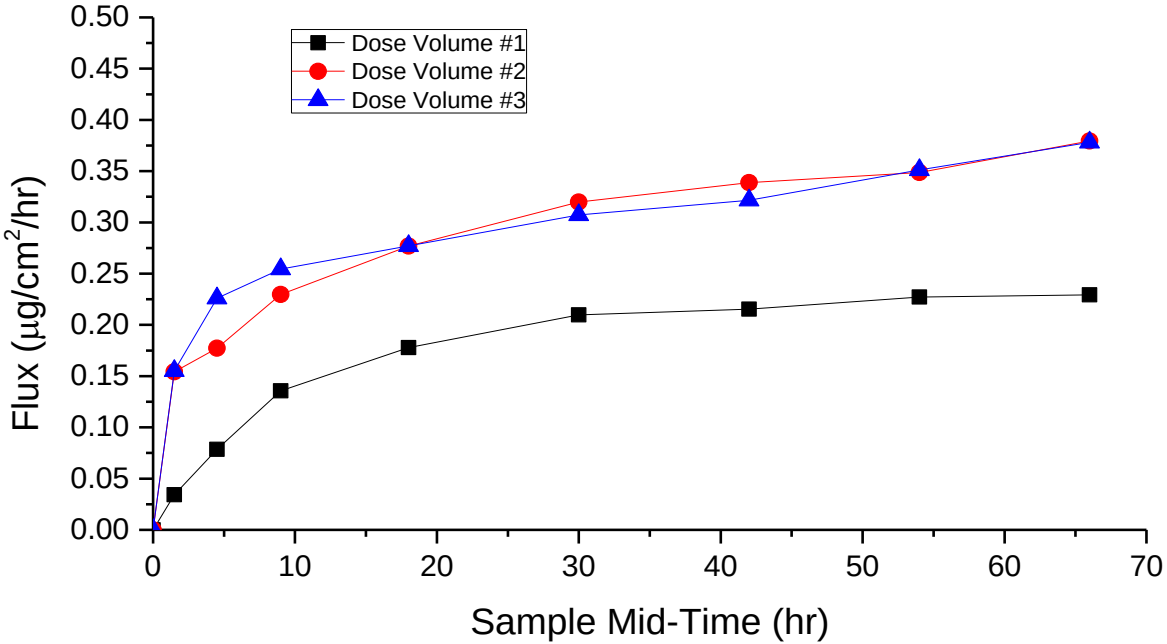
If first sample was collected at 8 hrs



If first sample was collected at 12 hrs



Example #2 – No J_{max} seen



Which J_{max}?

J_{max} across replicates within a donor.

Product A												
Sample flux (ng/hr-cm²)	74	76	78	80	82	84			Average	SD	%CV	Mid-T (hr)
1	2.607	35.648	**79.599**	0.000	6.587	18.515			23.826	30.311	127.217	1.5
2	3.784	35.329	60.632	3.927	9.732	9.470			20.479	22.901	111.825	4.5
3	4.626	28.378	34.263	5.144	11.213	10.720			15.724	12.524	79.651	9.0
4	9.676	24.991	23.646	6.955	14.885	12.770			15.487	7.365	47.554	18.0
5	27.282	52.355	32.539	16.659	30.290	38.797			32.987	11.962	36.263	28.0
6	52.244	74.280	47.069	47.178	49.902	75.513			57.698	13.465	23.337	40.0
7	**82.765**	**83.203**	65.827	92.988	**79.259**	**108.622**			**85.444**	14.349	16.793	52.0
8	74.664	67.308	65.210	**94.907**	75.206	81.040			76.389	10.736	14.055	64.0
9	51.042	45.110	52.649	82.218	75.489	49.729			59.373	15.444	26.013	84.0
10												
11												
12												
Receptor (ng)	8292.695	9867.974	9176.214	10126.977	9615.499	9990.683			9511.674	684.722	7.199	
Receptor (ng/cm²)	4298.961	5115.590	4756.980	5249.858	4984.707	5179.203			4930.883	354.962	7.199	
Receptor (%)	2.291	2.719	2.523	2.783	2.643	2.754			2.619	0.186	7.091	
Jmax	82.765	83.203	79.599	94.907	79.259	108.622			**88.059**	11.579	13.149	
AUC	4298.961	5115.590	4756.980	5249.858	4984.707	5179.203			4930.883	354.962	7.199	
Ln Jmax	4.416	4.421	4.377	4.553	4.373	4.688			4.471	0.125	2.789	
Ln AUC	8.366	8.540	8.467	8.566	8.514	8.552			8.501	0.075	0.878	

#1

#2

Which J_{max}?

J_{max} across donors.

Product A															
Sample flux (ng/hr-cm²)	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Donor 9	Donor 10	Donor 11	Donor 12	Average	SE	Mid-T (hr)
1	23.826	5.715	0.674	58.292	11.766	31.873	**32.390**	4.396	**128.595**	30.962	46.851	4.596	31.661	10.263	1.5
2	20.479	5.631	0.000	**65.839**	18.167	18.142	22.181	4.660	68.530	9.396	26.916	4.227	22.014	6.554	4.5
3	15.724	5.316	0.000	55.836	16.507	14.631	14.629	4.731	42.568	6.165	18.028	3.597	16.478	4.804	9.0
4	15.487	7.688	0.163	51.752	13.857	17.250	13.685	8.434	34.194	5.813	17.317	3.471	15.759	4.138	18.0
5	32.987	16.331	0.169	51.047	14.820	21.045	16.452	19.429	34.382	6.852	29.171	6.362	20.754	4.104	28.0
6	57.698	27.722	1.498	56.251	23.432	27.273	18.932	40.552	32.558	11.342	55.060	17.648	30.830	5.284	40.0
7	**85.444**	**41.400**	3.570	62.461	38.837	34.339	24.286	**56.856**	41.154	21.132	**72.311**	**22.547**	**42.028**	6.809	52.0
8	76.389	39.043	6.118	47.568	**43.521**	36.926	20.730	49.438	45.116	30.674	60.722	13.125	39.114	5.686	64.0
9	59.373	38.550	**9.942**	33.428	33.607	**38.991**	15.104	38.938	52.743	**34.517**	37.196	7.525	33.326	4.529	84.0
10															
11															
12															
Receptor (ng)	9511.674	5041.394	760.720	9066.021	5135.378	5499.330	3353.938	6059.733	8429.721	3766.089	7897.972	1917.322	5536.608	810.408	
Receptor (ng/cm²)	4930.883	2613.475	394.360	4699.855	2662.197	2850.871	1738.693	3141.386	4369.995	1952.353	4094.335	993.946	2870.196	420.118	
Receptor (%)	2.619	1.392	0.209	2.493	1.412	1.523	0.922	1.668	2.323	1.035	2.170	0.528	1.525	0.223	
Jmax (Donor Mean)	88.059	49.249	10.402	88.227	57.015	65.971	41.087	68.219	143.309	57.713	99.722	22.789	**65.980**	10.338	
Jmax (Curve Mean)	85.444	41.400	9.942	65.839	43.521	38.991	32.390	56.856	128.595	34.517	72.311	22.547	**52.696**	9.247	
AUC	4930.883	2613.475	394.360	4699.855	2662.197	2850.871	1738.693	3141.386	4369.995	1952.353	4094.335	993.946	2870.196	420.118	
Ln Jmax	4.478	3.897	2.342	4.480	4.043	4.189	3.716	4.223	4.965	4.055	4.602	3.126	4.010	0.203	
Ln AUC	8.503	7.868	5.977	8.455	7.887	7.955	7.461	8.052	8.383	7.577	8.317	6.902	7.778	0.212	

#1

#2

#3

Which J_{max}?

J_{max} options.

Source	Jmax	Consideration
From Overall Population Mean Flux Profile	42.03 +/- 6.81	Analogous to mean blood level curve from a BE study
Mean across Donor Profiles (Across replicate means)	65.98 +/- 10.34	Analogous to how the mean AUC is derived
Mean across each Donor's Flux Profile	52.70 +/- 9.25	Mean across donors
Geometric Mean	63.07 +/- 2.05	Per FDA recommended calculations for BE

Open for Discussion

1. “Outlier” Data Examples
2. Those pesky zero values
3. What about that elusive J_{max}?