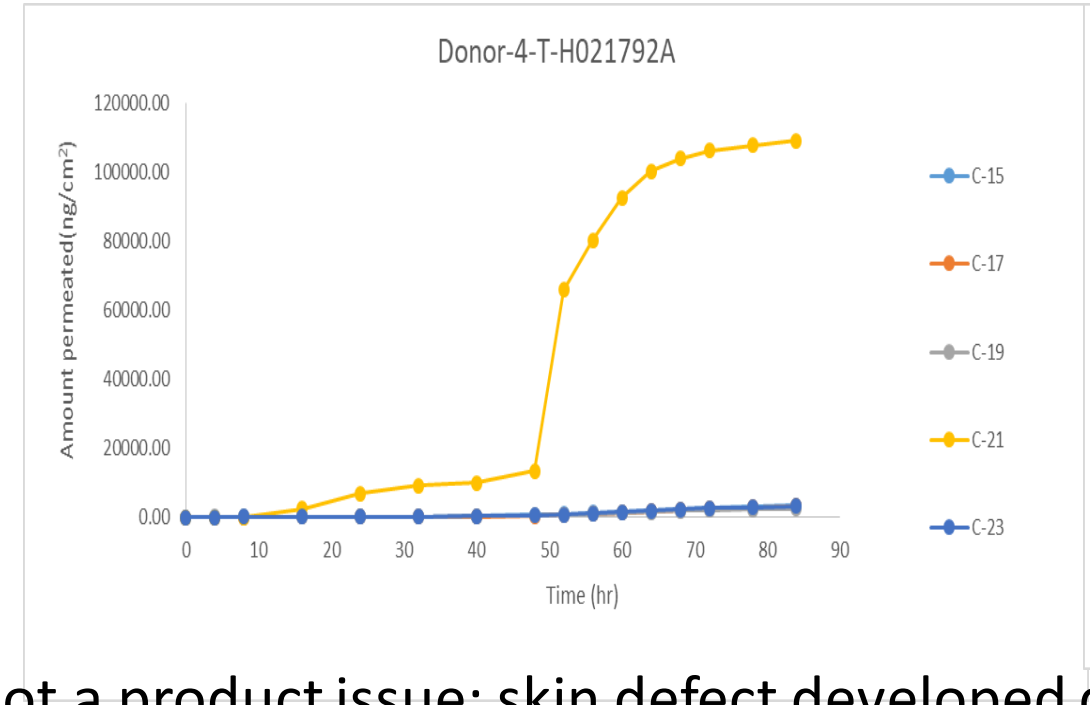
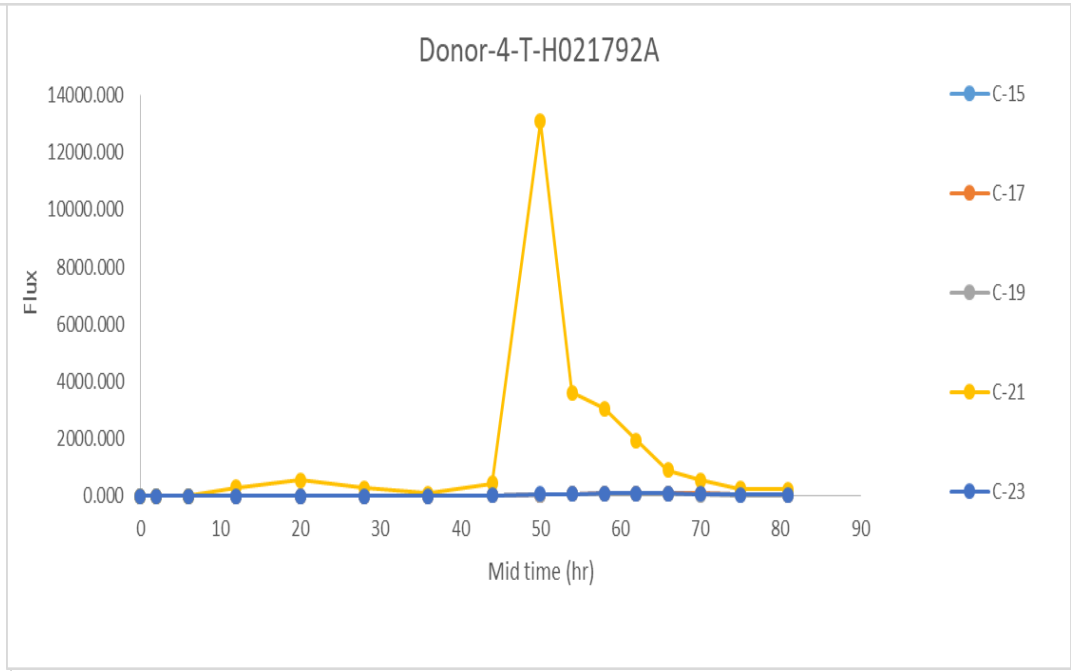
FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop

4th May 2020

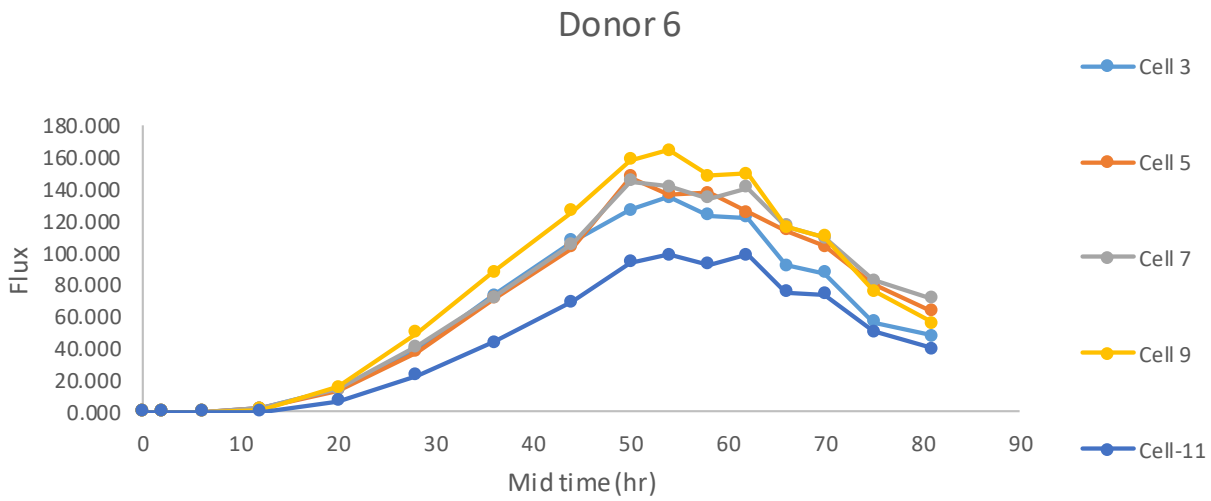
One cell gives abnormally high J_{max} and AUC

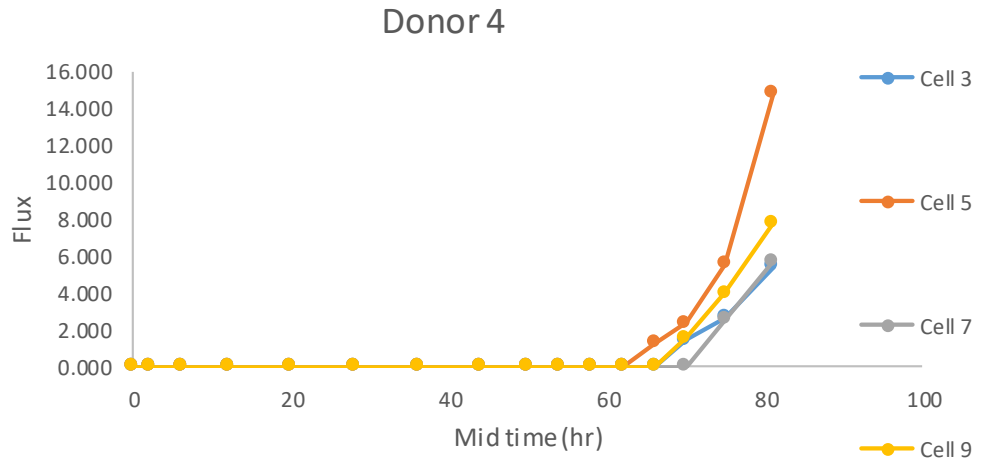




- Not a product issue; skin defect developed during the experiment
- Request the Agency to conduct research on how to address this type of outlier:
  - Eliminate this data considering it as an outlier?
  - Replace the cell?
- One suggestion: based on the Pilot study data, use a SD multiplier to establish as experimental outliers

Flux profiles completely different with two different donors





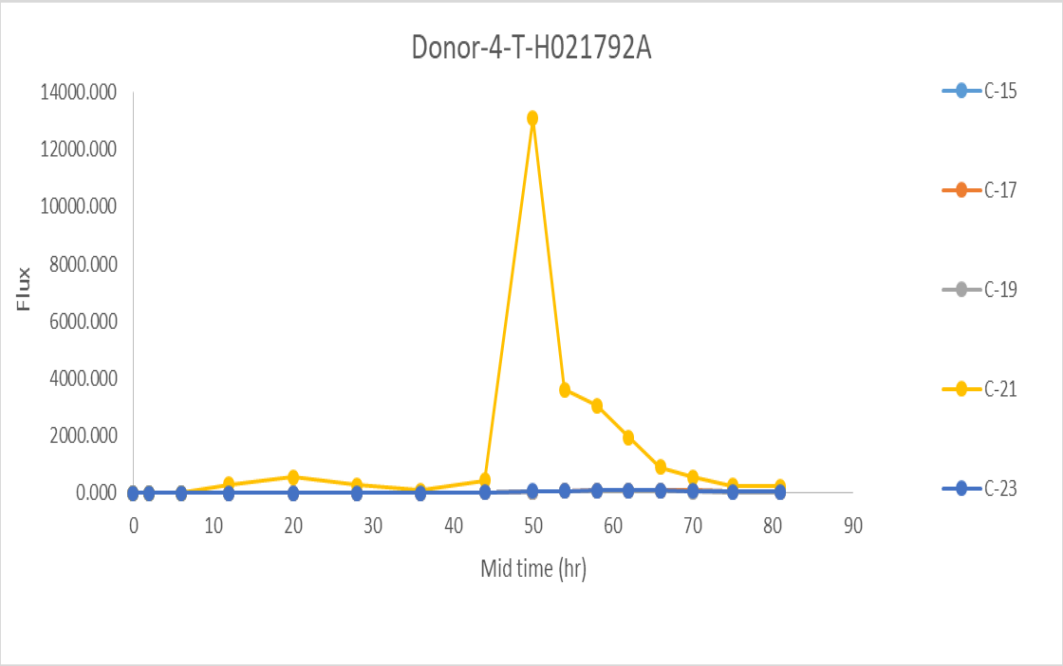
- Test product – two different donors flux data for the same lot of test product. Reference product behaves similarly;
- The duration of the study was established during method development to be 84h .
- Not enough data points to establish Jmax and more variability is expected during the lag time period.
- Request the Agency to conduct research on establishing guidelines for such behavior

Mean cumulative amount of drug permeated for two lots of Reference products

	Amount released (ng/ml)			SD		
Time	DA7435		CG9189	DA7435		CG9189
0	0.0		0	0.0		0
1	2.5		4.5	2.5		5.9
2	5.6		9.8	6.7		12.6
4	13.4		20.6	16.3		19.5
8	29.5		43.4	28.1		30.3
12	47.5		71.6	41.5		41.2
16	68.0		106.8	55.4		54.7
20	88.8		142.0	67.5		60.9
24	114.4		182.8	81.3		68.0
28	138.4		221.0	93.9		71.8
32	163.5		260.2	107.3		74.3
36	187.0		298.2	117.8		76.4
40	213.3		339.5	129.1		77.6
44	237.3		377.5	140.5		81.1
48	259.4		413.3	149.1		83.6
52	283.4		451.0	159.3		87.5
56	303.5		483.0	167.1		90.2
60	322.9		514.3	174.5		91.6
64	343.2		545.6	181.6		93.8
GM	311.353		538.956			
R1/R2			1.73			

- Lot to lot variability of RLD is significant
- The election of the Reference product becomes even more difficult when only couple of lots of RLD are available in market!
- Request the Agency codnuct research on how to address selection of RLD.
- One suggestion is to evaluate use of multiple of RLDs in the IVT experiments instead of one lot.

Unbalanced data analysis



- How do we treat unbalanced number of replicates used in the analysis?
- If one replicate of either Test or Reference product is removed from the analysis or replaced due to experimental outlier, should a cell from the other product also be removed from data analysis or replaced?
- Request the Agency provide clarity in the Guidance.