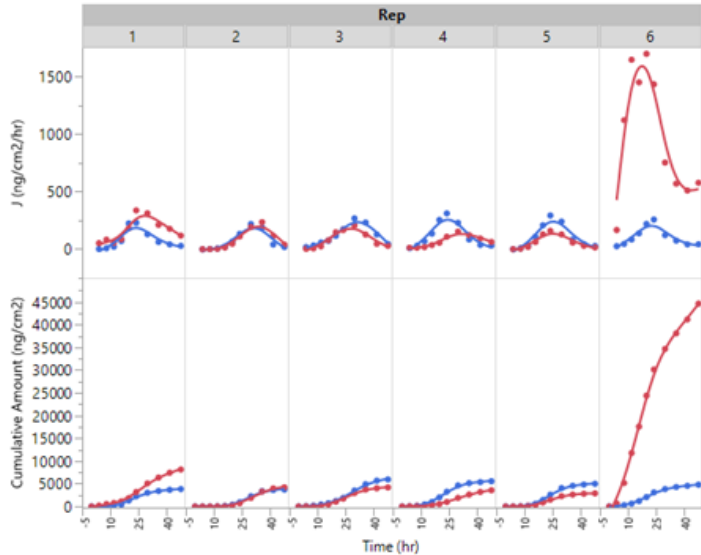


REPLICATE VARIABILITY IN IVPT – ABERRANT DATA/OUTLIERS



IVPT Data Analysis

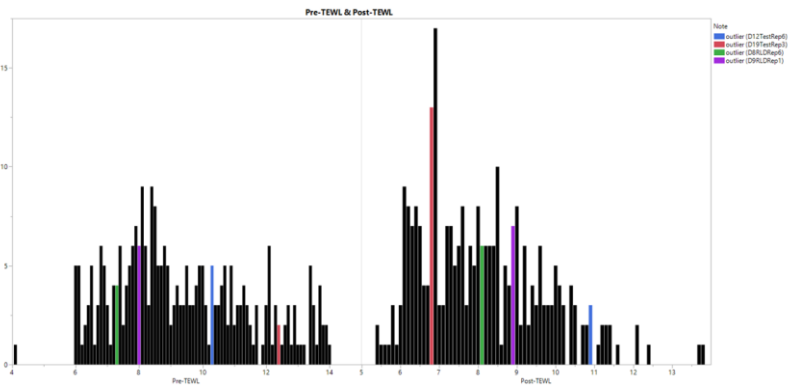
Problem Statement on Outliers/Aberrant Data: As illustrated by the data certain replicates demonstrate different PK parameters when compared to other replicates within the same donor even when using optimized assay parameters. In these instances, the entire replicate was excluded for further calculations and comparisons for both flux and cumulative amount.

Question: What can be done to reduce the incidence?

REPLICATE VARIABILITY IN IVPT– PREDICTOR PARAMETERS

IVPT Data Analysis

Problem Statement on Outliers/Aberrant Data: An investigation of which critical parameters may help predict outliers could not conclusively identify either TEWL or skin thickness as factors



TEWL distribution with outliers identified

NIS	product	Donor	Rep	Cell	Dose	Pre-TEWL	Thick	Post-TEWL	Jmax	AUC	Note
1	Test	12	6	30	26.3	10.3	251.29	10.9	25473.94984	285063.4405	outlier (D12TestRep6)
2	Reference	17	4	45	27.6	10	251.7	6.4	219.5321011	5099.807005	
3	Test	12	4	26	25.1	10	253.53	13.7	550.0349399	15558.26266	
4	Reference	12	2	20	27.5	10.9	253.9	10.7	561.7517743	5643.112064	
5	Non-Dosed	17	NA	42	ND	14	254.63	10			•
6	Test	11	1	2	27	11.7	256.71	8.7	677.0479679	9749.494721	
7	Test	17	5	46	28.3	13.7	256.88	7.8	354.2394597	5105.066429	
8	Non-Dosed	20	NA	42	ND	7.8	257.16	6.4			•
9	Reference	11	2	6	23.8	13.9	257.41	10.5	449.6695322	6083.685997	
10	Test	17	3	38	24.5	11.2	258.02	5.9	151.763329	2841.35693	
11	Non-Dosed	11	NA	8	ND	13.5	259.45	9.2			•
12	Reference	12	5	28	28.5	10.7	259.9	8.8	248.3884822	6685.350111	

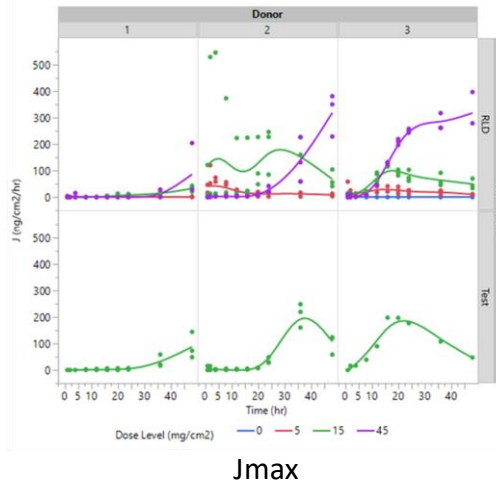
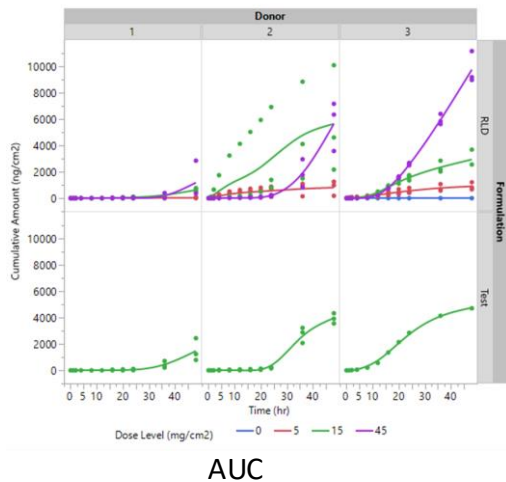
Replicates in Thickness Range (250-260 μm)

Question: Are there other barrier integrity parameters that could be evaluated to improve inter-replicate consistency?

DONOR VARIABILITY IN IVPT – UNCONVENTIONAL FLUX PROFILES

IVPT Method Development and Validation

Problem Statement: Unconventional flux profiles have been observed for certain donors which impact the pharmacokinetic endpoints (J_{\max} and AUC)



Question: While this may reflect the “true population” and the flux profile is similar for the test and RLD, does this impact the sensitivity/outcome of the methodology?

DONOR VARIABILITY IN IVPT – HIERARCHY OF VARIABLES

IVPT Method Development and Validation

Problem Statement on how to establish Donor Criteria: Trying to establish criteria and hierarchy of variables to help minimize inter-donor variability

Donor Criteria	Proposed Limits for a Cream Product	Rationale
TEWL	8 - 14 (g/m ² h)	TEWL is a critical factor that governs the integrity of the skin.
Thickness	250 to 400 μm	Keeping thickness criteria more stringent helps minimize variability.
Age	18 – 75 years	Age criteria can be broader; the rationale being that TEWL is a better indicator of skin integrity than age.

Questions: Is the hierarchy of variables product specific and to be re-established for each dosage form?

Potential areas for FY 2021 research priorities

Inclusion criteria for **donors**; can this be further improved with a systematic evaluation of the parameters? Is there a hierarchy to them?

Are there barrier integrity measurements that are more sensitive or a better predictor of **replicate** outliers? Is there a hierarchy to them?

Handling donors that have unconventional profiles?

Is there a greater incidence of such for certain formulation types – e.g., ointments vs. gels?

Can these be minimized with a better understanding of the considerations above?