Alternate Materials and their potential impact on HPHCs

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Alternate Materials

- For supply security and other reasons, it is common to have more than one supplier for a variety of cigarette materials and the materials are typically used interchangeably
  - The FDA considers each combination of materials to be a different product.
- Part of supporting the use of alternate materials is to verify that the HPHCs are comparable when using the different materials
- A designed experiment can provide an efficient and powerful tool for estimating the differences (if any) among HPHC yields resulting from use of the materials.

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Alternate Materials (cont.)

- All are commercially available materials
  - Two plug wraps
  - Two base tipping papers
  - Two cigarette seam adhesives
  - Two tipping adhesives
  - Three filter tow materials
  - 2 x 2 x 2 x 2 x 3 = 48 possible combinations
- Employed a fractional factorial design with 16 runs

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Other design and analysis considerations

- Smoke analytes
  - 18 HPHCs on the FDA abbreviated list in addition to tar
  - ISO and Health Canada Intense (HCI) smoking regimens
  - 20 replicates for tar, nicotine, and carbon monoxide
  - 7 replicates for the remaining analytes
- ISO 17025 accredited laboratories carried out the analyses
- Replicates were interleaved
  - This mitigates confounding effects of lab drift
- A single design was used for all cigarettes
- All cigarettes constructed using the same batch of tobacco filler
- Multiplicity Effects
  - Carried out analysis with and without adjustment for the number of comparisons being made

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Experimental Alternatives

- One-at-a-time experiment
  - Have a “base design” and change one material at time from that base
  - 7 combinations

	Run No.						
	1	2	3	4	5	6	7
Plug wraps	A	B	A	A	A	A	A
Tipping papers	A	A	B	A	A	A	A
Seam adhesives	A	A	A	B	A	A	A
Tipping adhesives	A	A	A	A	B	A	A
Filter tow	A	A	A	A	A	B	C

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Experimental Alternatives

- One-at-a-time experiment
  - Have a “base design” and change one material at time from that base
  - 7 combinations
- Designed Experiment
  - 16 combinations
- A designed experiment was chosen because it more efficiently estimates the potential effects.

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Why are designed experiments more efficient?

- More of the data points are used in each estimated effect. For example:

Factor Levels in Experiment			Effect Estimates		
A	B	C	A2-A1	B2-B1	C2-C1
A1	B1	C1	-0.25	-0.25	-0.25
A2	B1	C2	0.25	-0.25	0.25
A1	B2	C2	-0.25	0.25	0.25
A2	B2	C1	0.25	0.25	-0.25
A2	B2	C1	0.25	0.25	-0.25
A1	B2	C2	-0.25	0.25	0.25
A2	B1	C2	0.25	-0.25	0.25
A1	B1	C1	-0.25	-0.25	-0.25

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Standard Errors of Difference Estimates

- Comparison of standard errors of estimates comparing the alternate materials, where σ is the standard deviation of a test result:

	Designed Test	One Factor at a Time
Tow	0.65σ	1.41σ
Plug wrap	0.51σ	
Tipping Adhesive	0.51σ	
Sideseam adhesive	0.51σ	
Base tipping	0.51σ	

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Results with Testing Multiplicity Effects

- 7 comparisons/analyte x 19 analytes x 2 regimens = 266 total comparisons
  - With α=0.05, on average, one expects 0.05 x 266 = 13.3 statistically significant effects.
  - There were 11 statistically significant differences prior to adjustment
  - After adjusting for multiple comparisons (using either Bonferroni or Benjamini-Hochberg) there were no statistically significant differences
  - The adjustment for multiple comparisons reduces power to detect differences – examining estimated differences is a way to mitigate the risk of having missed large estimated differences

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Nominally Statistically Significant Results
(Prior to Adjusting for Multiple Testing)

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Least Squares Means Estimated Values

Tip Adhesive		Seam Adhesive		Base Tipping		Plug Wrap		Filter Tow		
A	B	A	B	A	B	A	B	A	B	C
HCI Acrylonitrile (ug/cig)										
25.9	25.9	25.7	26.1	25.9	25.9	26.3	25.5	26.1	25.7	25.9
HCI Benzene (ug/cig)										
95.0	94.4	94.1	95.3	94.5	94.9	96.2	93.1	95.4	93.6	95.0
HCI Toluene (ug/cig)										
165	165	165	166	165	165	167	163	166	164	165
ISO 2-Aminonaphthalene (ng/cig)										
15.7	16.1	15.7	16.0	16.2	15.5	16.0	15.8	15.8	16.3	15.5
ISO Acetaldehyde (ug/cig)										
804	798	805	797	787	814	799	803	805	794	803
ISO Acrolein (ug/cig)										
79.3	78.9	79.4	78.8	77.7	80.4	79.0	79.1	79.3	77.9	80.0
ISO Ammonia (ug/g)										
18.9	19.4	19.1	19.2	19.2	19.0	19.1	19.1	19.7	18.8	18.8
ISO Benzo[a]pyrene (ng/cig)										
10.7	10.4	10.5	10.5	10.5	10.6	10.6	10.5	10.9	10.1	10.6
ISO Crotonaldehyde (ug/g)										
21.2	21.3	21.3	21.2	20.7	21.8	21.3	21.2	21.3	20.7	21.7
ISO Toluene (ug/cig)										
82.7	83.1	83.2	82.5	81.8	83.9	83.2	82.6	82.9	82.8	82.9

Blue indicates statistical significance prior to adjustment for multiple testing

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Conclusions

- A designed study is an efficient approach for evaluating the effects on HPHC yields of different materials
- Care should be taken to mitigate potential confounding effects such as lab drift, tobacco and other material differences
- When large numbers of comparisons are made some allowance must be made for testing multiplicity
  - One has to balance the risk of falsely claiming differences against the risk of missing important effects.
- In this instance after adjusting for testing multiplicity there were no statistically significant differences and all of the estimated differences were numerically small

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Questions?

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