SUBSTANTIAL EQUIVALENCE SCIENTIFIC CONTENT

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CENTER FOR TOBACCO PRODUCTS

AGENDA

Background

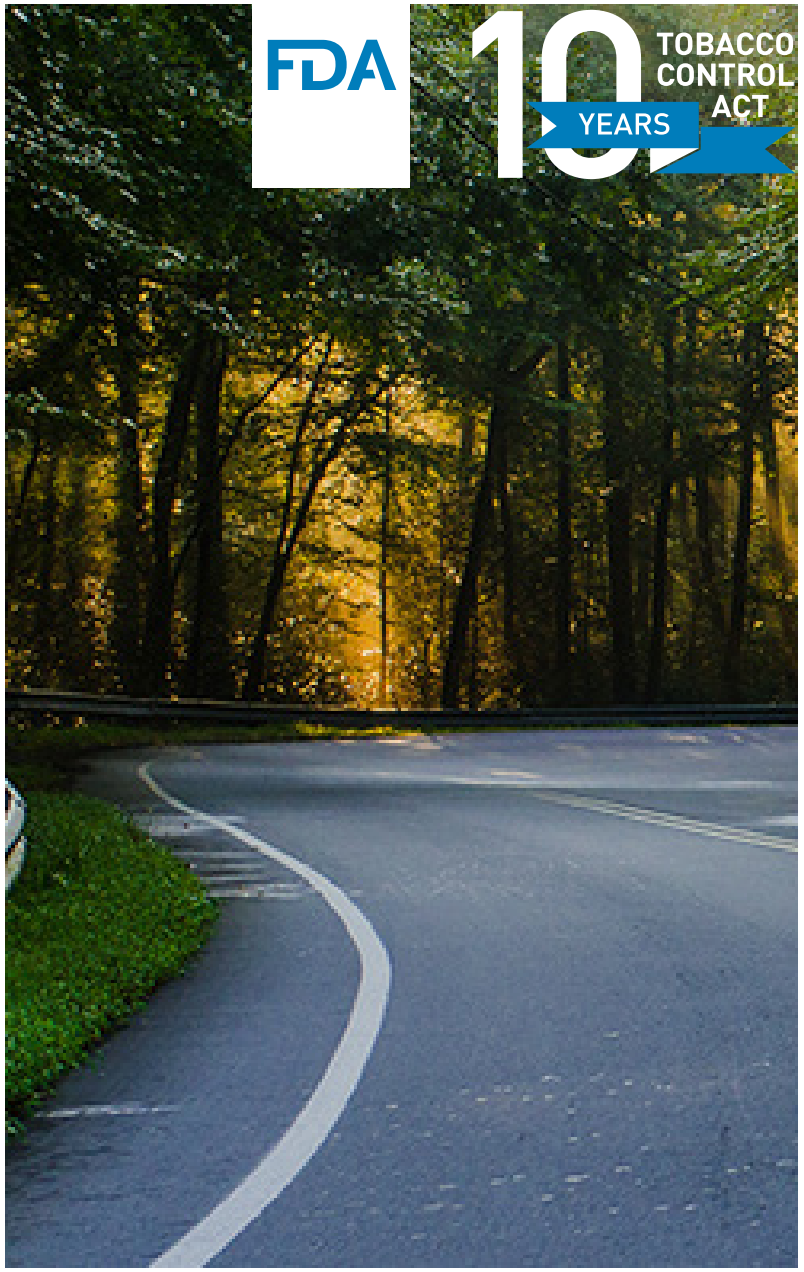
- Overview of the scientific review process

Scientific Content

- Overview of SE data
- Data by tobacco product category
- Data formatting
- Common issues

HPHC Testing & Reporting

Presented by Melis Coraggio

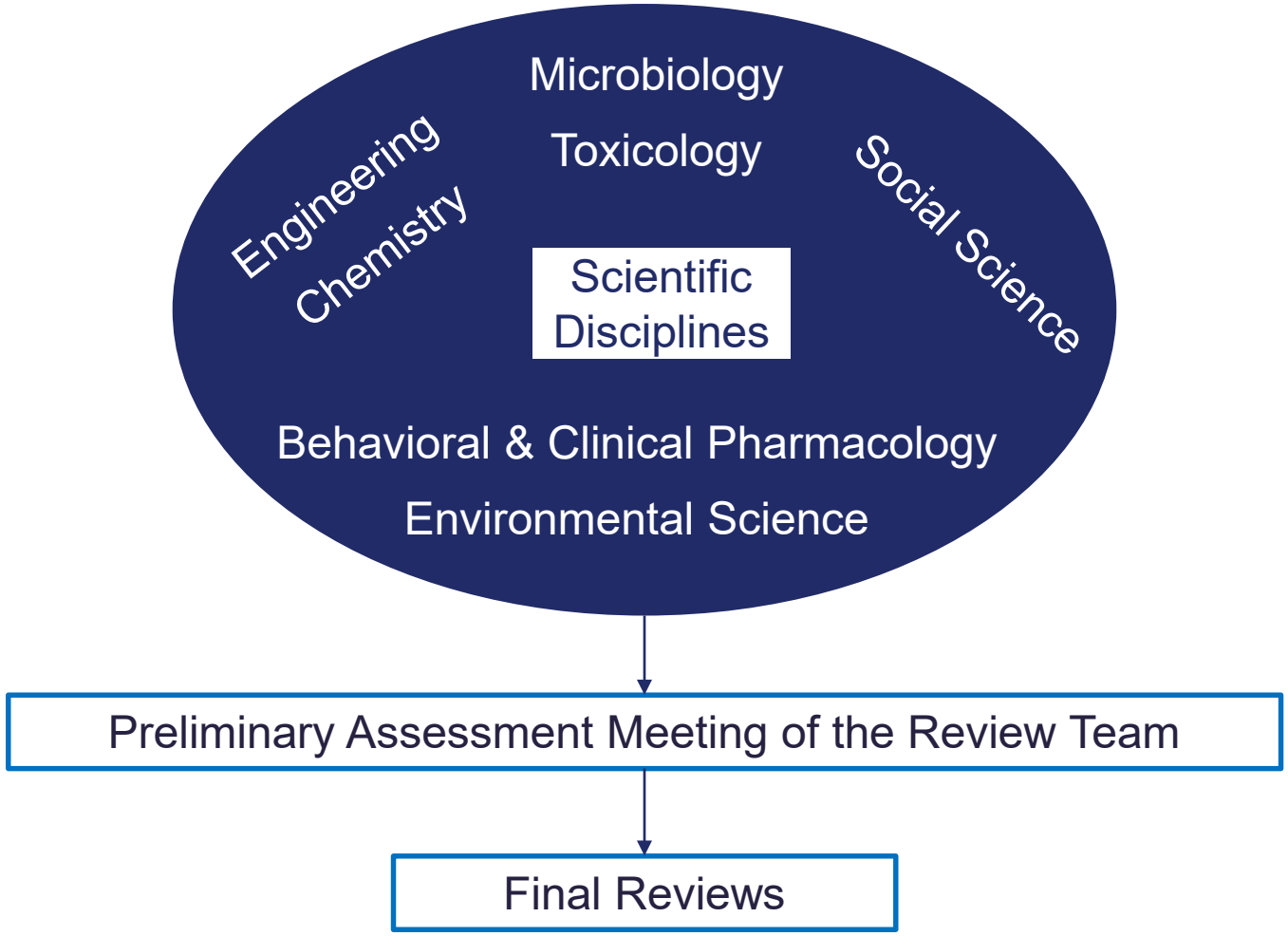


A BRIEF NOTE

- The examples presented is this talk are based on the SE Proposed Rule and our application review experience
  - SE Proposed Rule comment period closed on June 17, 2019-- SE Final Rule may change based on comments
  - Applicants may find this information useful because it reflects our thinking as of April 2, 2019 for the items in the proposed rule and our review experience to the present date.

BACKGROUND

SCIENTIFIC REVIEW PROCESS



SCIENTIFIC CONTENT

SE PATHWAY: TOBACCO PRODUCTS

Examples of tobacco products for the SE pathway

- Cigarettes
- Smokeless products
- Roll your own products
- Cigars
- Waterpipes
- Pipes

OVERVIEW OF SE DATA

- Physical design parameters
- Tobacco blend
- Ingredients other than tobacco
- Stability
- Harmful and Potentially Harmful Constituents (HPHCs)
- Other studies (e.g., dissolution studies, nonclinical studies)

DATA BY TOBACCO PRODUCT CATEGORY

EXAMPLE SCIENTIFIC CONTENT: CIGARS

Engineering

- Assessment of design parameters such as length (mm), minimum diameter (mm), maximum diameter (mm), tobacco filler mass (mg), tobacco rod density (g/cm^3), tobacco moisture (%), tobacco cut size (mm), wrapper porosity (CU)

Chemistry

- Identification, quantification and description of all tobaccos and ingredients in the cigar wrapper, binder, and filler
- Smoke HPHC data, ground cigar HPHC data

Microbiology

- Container closure system, tobacco processing methods (e.g., curing, fermentation) including description and process parameters
- Stability data, measured at several time points post-manufacture, which may include: water activity (a_w), microbial counts (Total aerobic microbial count [TAMC] and total yeast and mold count [TYMC]), N-Nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and total tobacco specific nitrosamines (TSNAs)) yields

Toxicology

- Discussion of changes and scientific rationale on the resulting impact on exposure
- Relevant references

EXAMPLE SCIENTIFIC CONTENT: PIPES & WATERPIPES

Engineering

- Assessment of design parameters such as hose/pipe length (mm), hose/pipe internal diameter (mm), hose/pipe permeability (CU), stem length (mm), bowl diameter (mm), bowl volume (cm^3); bowl shape, pressure drop (mm H_2O), and ventilation (%)

Chemistry

- Identification, quantification and description of all tobaccos and ingredients in the tobacco
- Smoke HPHC data, unburned pipe/waterpipe tobacco HPHC data

Microbiology

- Container closure system, tobacco processing methods (e.g., curing, fermentation, heat-treatment) including description and process parameters
- Stability data, measured at several time points post-manufacture, which may include: pH, a_w, nitrate, nitrite, microbial counts (TAMC and TYMC), NNN, NNK, total TSNAs, and stability testing conditions (temperature and humidity)

Toxicology

- Discussion of changes and scientific rationale on the resulting impact on exposure
- Relevant references

DATA FORMATTING

DATA FORMATTING: DESIGN PARAMETERS

Example Table

Comparison of design parameters for new and predicate cigar tobacco product

		Overall Cigar					Tobacco					
		Package Quantity	Rod Length		Diameter		Filler Mass		Rod Density		Rod Moisture	
			Target Value	Range Limit	Target Value	Range Limit	Target Value	Range Limit	Target Value	Range Limit	Target Value	Range Limit
			mm	mm	mm	mm	mg	mg	g/cm^3	g/cm^3	%	%
[New Tobacco Product (TP) STN]	New TP	1	103	100.75-105.25	9.57	9.21-9.93	2418	1555-3274	0.3766	0.2319-0.5498	17.26	11.98-22.54
	Predicate TP	1	106	103.75-108.25	9.62	9.19-10.05	2829	1798-3842	0.4205	0.2492-0.6306	19.04	13.76-24.32
	% Change		↓ 2.8		↓ 0.5		↓ 14.5		↓ 10.4		↓ 9.3	

Note: STN is Submission Tracking Number

DATA FORMATTING: TOBACCO BLEND

Example Table
Comparison of tobacco blends between the new and predicate tobacco product

SE Report	Component	Type	Target Quantity (mg/unit)		% Change
			New TP	Predicate TP	
[New Tobacco Product (TP) STN]	Tobacco	Total tobacco	646.1	732.5	↓12
	Bright	Leaf	204.8	143.6	↑43
	Burley	Leaf	286.6	346.8	↓17
	RCBD	Reconstituted	122.3	122.3	0
	EX	Expanded	32.4	N/A	Added
	ISB	Stem	N/A	119.8	Removed

Notes:
- *STN is Submission Tracking Number*
- *Units may be per gram of product or per product such as mg/cigar*

DATA FORMATTING: OTHER INGREDIENTS

Example Table
Summary of ingredient changes between the new and predicate tobacco product

SE Report	Component	Function	Ingredient	CAS #	mg per Unit	New TP	Predicate TP	% Change
[New Tobacco Product (TP) STN]	Additive	Flavor / Processing Aid	Ammonium Hydroxide	1336-21-6	mg	1.4	0	Added
	Additive	Flavor	Vanillin	121-33-5	µg	36	2.4	↑1400
	Seam Adhesive	Defoamer	[IUPAC Name]	31069-81-5	µg	0.0028	0	Added

Notes:
- *STN is Submission Tracking Number*
- *Units may be per gram of product or per product such as mg/cigar*

DATA FORMATTING: HPHCs

Example Table

HPHC changes between the new and predicate tobacco product

SE Report	Smoking regimen	Constituent	Units	New Product	Std. Dev	N	Predicate Product	Std. Dev	N	% Change
[New Tobacco Product STN]	Non-intense	Tar	mg/cigarette	1.23	0.05	7	1.56	0.07	7	↓21.2
		CO	mg/cigarette	15.6	1.1	7	16.5	0.95	7	↓5.5
		Acrolein	µg/cigarette	17.2	0.5	7	15.8	0.7	7	↑8.9
		B[a]P	ng/cigarette	65.1	0.9	7	81.2	0.9	7	↓19.8
		Formaldehyde	µg/cigarette	62.1	1.3	7	72.9	1.6	7	↓14.8
	Intense	Tar	mg/cigarette	2.43	0.07	7	2.61	0.09	7	↓6.9
		CO	mg/cigarette	36.4	0.95	7	39.1	0.4	7	↓6.9
		Acrolein	µg/cigarette	33.4	0.7	7	33.4	1.5	7	0
		B[a]P	ng/cigarette	129	0.9	7	132.2	0.9	7	↓2.4
		Formaldehyde	µg/cigarette	72.1	1.6	7	N/P	N/A	7	N/A

N = number of replicates

DATA FORMATTING: MICROBIOLOGY

Example Tables: Product Stability
Comparison of pH, Moisture (OV%), Water Activity (a_w) NNN, NNK, and Total TSNAs Over Time

		pH (pH units)			Moisture (OV%)			Water Activity (a_w)		
SE Report	Storage Time (# months)	New Product	Predicate Product	% Change	New Product	Predicate Product	% Change	New Product	Predicate Product	% Change
[New Tobacco Product STN]	0	7.89	7.83	↑1	56.86	55.28	↑3	0.865	0.845	↑2
	6	7.56	7.56	0	56.56	54.92	↑3	0.854	0.851	↑0.4
	12	7.42	7.36	↑1	56.53	54.97	↑3	0.864	0.869	↓1
	% Change Over Time	↓6	↓6		↓1	↓1		↓0.1	↑3	
		NNN (ng/g)			**NNK (ng/g)**			**Total TSNAs (ng/g)**		
[New Tobacco Product STN]	0	2064	3047	↓32	890	977	↓9	6965	7234	↓4
	6	2883	3346	↓14	796	998	↓20	6841	7643	↓10
	12	2758	3220	↓14	755	801	↓6	6854	6981	↓2
	% Change Over Time	↑34	↑6		↓15	↓18		↓19	↑19	

COMMON ISSUES

COMMON ISSUES: ENGINEERING

- Not *all* of the design parameters' target specifications and upper and lower range limits for the new and predicate tobacco products are provided

- Discrepancies between the information provided by the applicant and the data presented from the manufacturer (e.g., in a certificate of analysis)

- Multiple or alternative materials for a component

COMMON ISSUES: CHEMISTRY

- Missing complete ingredient information: ingredient functions, CAS#
- Complex ingredients: the composition (individual ingredients with quantities) of complex ingredients are often missing from submissions
- Based on ingredient changes, specific HPHC concerns may need to be addressed (e.g., changes in sugars)

COMMON ISSUES: MICROBIOLOGY

- Lack of stability data for the new and/or predicate tobacco product
- Incomplete stability data for the new and/or predicate tobacco product
- Lack of information on the specific time points (dates) of the stability study
- Lack of an adequate justification on the exclusion of attributes that are likely to influence the microbiological stability of the product during storage in a stability study
- Inadequate justification on the lack of established shelf life for the new and/or predicate products

COMMON ISSUES: TOXICOLOGY

- Lack of an adequate rationale and justification why the changes do not cause the new tobacco product to raise different questions of public health

- Lack of bridging information or rationale/justification to show relevance of supporting literature/documents to the new tobacco product in comparison to the predicate product

THE END

Next:

HPHC Testing & Reporting

Presented by Melis Coraggio

HPHC TESTING AND REPORTING IN PREMARKET APPLICATIONS

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Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.

AGENDA

- HPHC Data for Premarket Applications
  - Examples HPHCs per product type
  - Example of data formatting
- HPHC Testing: Methods and Validation
  - Method Development and Validation
  - Common issues seen with methods

TYPICAL MATRICES FOR REPORTING HPHCS

Filler	
Cigarette	Cigar[1]
Smokeless	Pipe Tobacco
Roll-Your-Own Tobacco	Waterpipe Tobacco
ENDS[2]	

[1] *includes tobacco rod, binder, and wrapper*

[2] *e-liquid*

Mainstream Smoke/Aerosol	
Cigarette	Cigar
Roll-Your-Own	Waterpipe
ENDS[3]	

[3] *aerosol*

SOME HPHCS REPRESENTATIVE OF CHARACTERISTIC CHANGES, BLENDS, AND INGREDIENTS

Cigarette and Cigar Smoke	**Nicotine** (total)	**TSNAs** (NNN, NNK)	**Carbonyls** (Acetaldehyde, Acrolein, Crotonaldehyde, Formaldehyde)	**Gases** (Carbon Monoxide)	**Polyaromatic Hydrocarbons** (Benzo[a]pyrene)	**Aromatic Amines** (1-Animonapthlanene, 2-Aminonapthalene, 4-Aminobiphenyl)	**Acyclic Hydrocarbons** (Acrylonitrile, 1,3,-Butadiene, Isoprene)	**Aromatic Hydrocarbons** (Benzene, Toluene)	**Acyclic Amines** (Ammonia)
Smokeless Tobacco	**Nicotine** (total and freebase)	**TSNAs** (NNN, NNK)	**Carbonyls** (Acetaldehyde, Crotonaldehyde, Formaldehyde)	**Polyaromatic Hydrocarbons** (Benzo[a]pyrene)	**Metals** (Arsenic, Cadmium)				
RYO and Tobacco Product Filler	**Nicotine** (total)	**TSNAs** (NNN, NNK)	**Metals** (Arsenic, Cadmium)	**Acyclic Amines** (Ammonia)	Glycerol[1]	Propylene Glycol[1]			

[1] applicable for waterpipe tobacco

SOME HPHC REPRESENTATIVE OF CHARACTERISTIC CHANGES, BLENDS, AND INGREDIENTS

ENDS Aerosol	**Nicotine** (total)	**TSNAs** (NNN, NNK)	**Carbonyls** (Acetaldehyde, Acrolein, Crotonaldehyde, Formaldehyde)	**Aromatic Hydrocarbons** (Benzene, Toluene)	Acrylonitrile	**Metals** (Cadmium, Chromium, Nickel, Lead)	Diethylene Glycol	Ethylene Glycol
Closed ENDS and Closed e-liquids	**Nicotine** (total)	Glycerol, Propylene Glycol	**Carbonyls** (Butyrlaldehyde, Acetic Acid, Acetoin, Benzyl Acetate, Ethyl Acetate, Isobutyl Acetate)	Diacetyl	2,3-Pentanedione	Propionic Acid		
ENDS e-liquids	**Nicotine** (total)	**TSNAs** (NNN, NNK)	Diethylene Glycol	Ethylene Glycol				

EXAMPLE OF HPHC DATA REPORTING: CIGARETTE

Smoking Regimen	Constituent	Units	Data					
			New Product			Predicate Product		
			Mean Quantity	Standard Deviation	N	Mean Quantity	Standard Deviation	N
ISO 3308:2012	Acrolein	µg/cigarette	52.1	6	7	50.7	7.3	7
ISO 3308:2012	Benzene	µg/cigarette	48.3	5.1	7	49.1	6.1	7
ISO 3308:2012	Carbon Monoxide	mg/cigarette	18.7	0.8	12	17.8	1.3	12
ISO 3308:2012	Formaldehyde	µg/cigarette	17.51	2.4	7	17.5	3.4	7
ISO 3308:2012	Nicotine	mg/cigarette	2.7	0.1	12	2.9	0.2	12
ISO 3308:2012	NNK	ng/cigarette	173	13.7	7	176.8	24.1	7
ISO 3308:2012	NNN	ng/cigarette	204	14	7	235	14.2	7
ISO 20778:2018	Acrolein	µg/cigarette	248	6	7	229	12	7
ISO 20778:2018	Benzene	µg/cigarette	123.5	2.4	7	120.8	8.1	7
ISO 20778:2018	Carbon Monoxide	mg/cigarette	47.7	3.4	12	45.1	2.4	12
ISO 20778:2018	Formaldehyde	µg/cigarette	101.7	5	7	85.4	8.2	7
ISO 20778:2018	Nicotine	mg/cigarette	2.7	0.1	12	2.9	0.2	12
ISO 20778:2018	NNK	ng/cigarette	173	13.7	7	176.8	24.1	7
ISO 20778:2018	NNN	ng/cigarette	203.7	13.9	7	234.9	14.2	7

EXAMPLE OF HPHC DATA REPORTING: CIGAR

Smoking Regimen or Tobacco Filler	Constituent	Units	Data					
			New Product			Predicate Product		
			Mean Quantity	Standard Deviation	N	Mean Quantity	Standard Deviation	N
CRM 64	Tar	mg/cigar	92.1	13.7	12	96.5	12.7	12
CRM 64	Nicotine	mg/cigar	6.2	1.29	12	5.8	1.1	12
CRM 64	Carbon Monoxide	mg/cigar	55	5.6	12	80.1	1.8	12
CRM 64	NNK	ng/cigar	111	13.7	7	122	22	7
CRM 64	NNN	ng/cigar	117	13.6	7	142	24.2	7
N/A	Ammonia	µg/cigar	2902	17	7	2911	20.5	7
N/A	Arsenic	ng/cigar	277	6.95	7	298	7.27	7
N/A	Cadmium	ng/cigar	1237	37.3	7	1412	51.3	7
N/A	Nicotine	mg/cigar	25	0.1	7	26	0.11	7
N/A	NNK	ng/cigar	2538	59.1	7	2500	45.8	7
N/A	NNN	ng/cigar	6076	165	7	6345	165	7

N/A: Measurement of ground cigar (includes tobacco rod, binder, and wrapper)

EXAMPLE OF HPHC DATA REPORTING: ENDS

Aerosol Generating Regimen or e-liquid	Constituent	Units	Data					
			New Product			Comparator Product		
			Mean Quantity	Standard Deviation	N	Mean Quantity	Standard Deviation	N
ISO 20768:2018	Nicotine	µg/puff	70	13.7	15	81.5	12.7	15
ISO 20768:2018	Acrolein	µg/puff	25.1	3.29	15	32.4	4.1	15
ISO 20768:2018	Formaldehyde	µg/puff	35	5.6	15	42	6.8	15
ISO 20768:2018	Acetaldehyde	µg/puff	85.3	13.7	15	102	22	15
ISO 20768:2018	Nickel	pg/puff	2.1	0.6	15	3.2	0.2	15
N/A	Nicotine	mg/mL	15	3.2	7	18	2.5	7
N/A	Acrolein	µg/mL	57.3	6.95	7	59.1	7.27	7
N/A	NNN	ng/mL	32	7.3	7	38	5.3	7
N/A	NNK	ng/mL	25	1.1	7	26	2.11	7
N/A	Propylene Glycol	mg/mL	700	59.1	7	820	45.8	7
N/A	Glycerol	mg/mL	300	45	7	280	65	7

N/A: Measurement in E-liquid

METHOD DEVELOPMENT AND VALIDATION

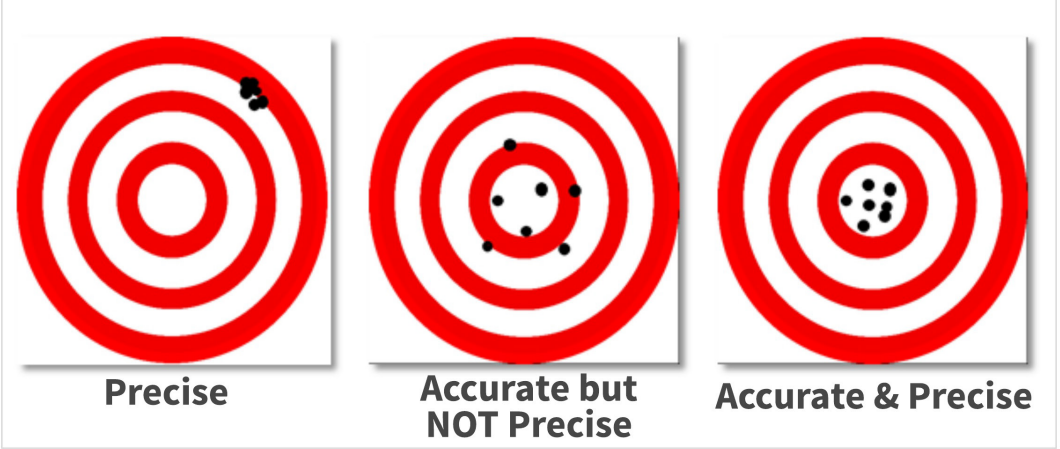
METHOD VALIDATION

- Process of demonstrating or confirming that the analytical test method is suitable for its intended purpose.
- Analytical method validation considers the entire analytical method, including analytical procedure and sampling procedure.
  - Precision
  - Accuracy
  - Selectivity
  - Sensitivity

- Validation is conducted relative to a reference product similar to the product that is tested.

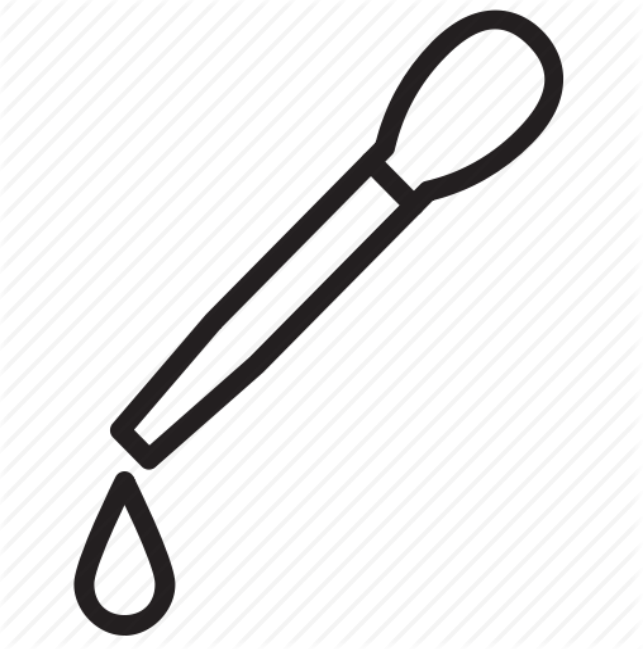
METHODS AND VALIDATION PARAMETERS

- Accuracy: the closeness of mean test results obtained by the analytical method to the true value of the analyte.
- Precision: closeness of individual measurements of an analyte when the procedure is applied repeatedly to multiple aliquots of a single, homogenous solution of an analyte.
- Selectivity: the ability of an analytical method to differentiate and quantify the analyte of interest in the presence of other matrix components present in the sample.
- Sensitivity: the limit of quantification and the limit of detection.



VERIFICATION

- A validated method can be extended to other products within the same category through a verification process.
- Verification is the demonstration of a laboratory's ability to successfully meet performance criteria established for an analytical test method previously validated in the laboratory performing the validation.
- Any substantial changes to a method result in a new method and should be independently validated.



COMMON ISSUES SEEN WITH METHODS

- Deviations to standardized methods not reported
- Inappropriate reference standard used for method development
- Inadequate number of replicates analyzed
- Limit of quantitation not reported


FDA
10
YEARS
TOBACCO
CONTROL
ACT