

# A 'Smart' Substantial Equivalence approach

**Katherine Ciambrone**

SVP, Product Integrity & Compliance

Chief Compliance Officer

ITG Brands

# Agenda

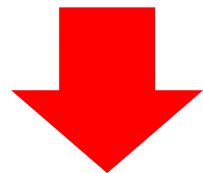
- Examples of the current burden and future opportunities
- Principles of 'Smart' Regulation
- Control challenges for Cigars
- 'Smart' regulatory pathway for Cigars

# Examples of current Regulatory Burden:

What can we learn and *improve*?

## Lack of Transparency

- Risk-based strategy was discussed but not put into practice
- FDA Reviewer Guides not made available
- Unclear science requirements



Intent should be transparent

What **Drug** Manufacturers have to reference:

**-VS-**

What **Tobacco** Manufacturers have to reference:

MANUAL OF POLICIES AND PROCEDURES  
CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 6010.3 Rev. 1

1, Recommendations/Risk-Benefit Analysis, section 5, Sources of Clinical Data, section 6, Review of Efficacy, and section 7, Review of Safety.

- Additional subheadings may be created under any of the higher-numbered template subsections, but should not be sequentially numbered below the numbers given in the current template (e.g., do not use *section 7.4.2.1* or *section 7.4.2.1.1*). The current template is organized so that the review flows logically and is not fragmented into an excessive number of subsections. Unnumbered subheadings can be used instead (such as the above heading, General Instructions).

The template may be modified by individual clinical review divisions when necessary to accommodate unique application issues or division-specific procedures. Divisions may choose to review individual studies/clinical trials under section 5.3, Discussion of Individual Studies/Clinical Trials, for some applications and under section 6, Review of Efficacy, for other applications, based on the number of studies or clinical trials to be covered, how data were integrated in the submission, and division preferences. Reviewers may find that for applications that rely on a single study/clinical trial for safety and efficacy the single study or clinical trial may be discussed completely within section 5.3, Discussion of Individual Studies/Clinical Trials. The same information would not need to be repeated in section 6, Review of Efficacy, and section 7, Review of Safety. These sections provide a more logical format for integrating efficacy and safety data, respectively. In general, reviewers should avoid repeating information within the review to keep the review concise. Reviewers may refer the reader to previous sections and use hypertext links wherever necessary.

### JOINT REVIEWS

Occasionally, several clinical reviewers are assigned to review different parts of an application (i.e., joint reviews). The clinical review template can accommodate joint reviews with the following recommendations:

Chemistry SE Reviewers' Guide

April 1, 2016

If menthol is listed as one of the ingredients in a cigarette SE Report, consider the following: menthol is considered a characterizing flavor in menthol cigarettes. All characterizing flavors in cigarettes with the exception of menthol have been banned under section 907(a)(1)(A) of the FD&C Act. Menthol is known to have addictive and physiological properties. Two boilerplate deficiencies exist for: a) an increase in menthol or change in menthol location (24); or b) changes in tobacco blend or design parameters that could affect menthol delivery (25). A non-mentholated tobacco product containing (b) (5) mg/cigarette of menthol is unlikely to raise different questions of public health even if the tobacco product is labeled as a non-mentholated tobacco product (Ai 2015). Additionally, if an applicant uses a predicate tobacco product that is non-mentholated and a new tobacco product that is mentholated the utility of requiring smoke yields has minimal benefits and should not be a deficiency and this should be therefore deferred to addition for a review. The scientific reviewer should consider the following product modifications that can potentially impact menthol delivery, however you should consider other factors that may also increase or decrease menthol yields and whether it is necessary to seek further information from the applicant:

- Any significant increase (b) (5) in the pack menthol content (i.e., the total menthol level in the product including tobacco rod, cigarette paper, filter, and pack foil) (See Boilerplate 24)
- Any change in the menthol application method that results in a significant (b) (5) change in the quantity of menthol applied to any cigarette component (b) (5) (See Boilerplate 24)
- Any product design modification that can alter the cigarette mainstream smoke delivery, (e.g., significant decrease in ventilation (b) (5) or decrease in cigarette paper porosity). (See Boilerplate 25)
- Any significant change in tobacco types (e.g., addition of reconstituted tobacco that constitutes (b) (5) of the total tobacco weight). (See Boilerplate 25)
- Any significant decrease in humectants (e.g., propylene glycol or glycerol) that can impact the menthol vapor pressure. (See Boilerplate 25)

# Examples of current Regulatory Burden:

*What can we learn and **improve**?*

## Not Defined or Understood

- Evolving Expectations
  - Surrogate & predicate remanufacture
  - HPHC requirements unclear across products
- No standard glossary of terms
  - Accept/reject and/or upper and lower limits for specifications
  - Everything is a “specification” →
- FDA Reviewers understanding of products



**Expectations should be clearly defined and understood**

**Total regulatory response was 2,674 pages, and the following text appeared 45 times:**

Furthermore, FDA CTP has not provided in any guidance or regulations on accepted manufacturing practices for the tobacco industry or product standards for cigarettes, including process control parameters, design parameter specifications, key design parameters, upper and lower process control limits, or upper and lower design specification limits. Without such guidance, [redacted] has provided FDA with the information for design characteristics and process parameters as "specifications", "control parameters", "machine parameters", and "characteristics", depending on the parameter.

# FDA's New Strategy:

*“Strike the **right balance** between ‘**smart**’ regulation & encouraging innovation of satisfying, less harmful products.”*

*Mitch Zeller, J.D., Director, FDA Center for Tobacco Products, 23Aug17*

## What might we consider to be ‘**smart**’ for any regulation?

1. Intent is transparent
2. Clearly defined and understood expectations
3. Does not produce unintended consequences
4. Controls are relative to risk
5. Controls are designed to achieve intended outcome
6. Total benefits exceed total costs

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# Smart regulations:

*Controls are **relative** to risk*

# Smart regulations:

Controls are *relative* to risk

Is there...	Pharma	Cigarettes	Machine Made Cigar	Hand Rolled Cigar
History of regulation?				
Significant Public Health Risk?				
Standardized Design?				
Product Complexity?				
Complex Supply Chain?				
Standardized Manufacture?				



# Smart regulations:

Controls are *relative* to risk

Is there...	Pharma	Cigarettes	Machine Made Cigar	Hand Rolled Cigar
History of regulation?	Yes			
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Standardized Design?	Yes	Yes	~	
Product Complexity?	Yes	~	~	
Complex Supply Chain?	Yes	Yes	~	
Standardized Manufacture?	Yes	Yes	~	

\* Relative to total population

# Smart regulations:




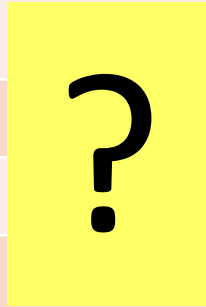



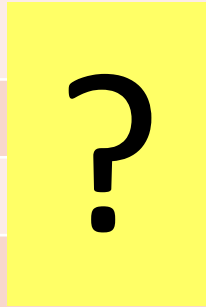



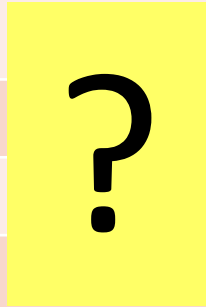



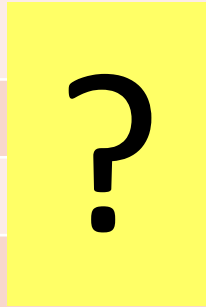
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\* Relative to total population

# Smart regulations:









Controls are *relative* to risk

Is there...	Pharma	Cigarettes	Machine Made Cigar	Hand Rolled Cigar
History of regulation?	Yes	Yes	No	No
Significant Public Health Risk?	Yes 	Yes 	~* 	* 
Standardized Design?	Yes 	Yes 	~ 	No 
Product Complexity?	Yes 	~ 	~ 	No 
Complex Supply Chain?	Yes 	Yes 	~ 	No 
Standardized Manufacture?	Yes	Yes	~	No

\* Relative to total population

# Smart regulations: Does an SE make sense?

Controls are *relative* to risk

Is there...	Pharma	Cigarettes	Machine Made Cigar	Hand Rolled Cigar
History of regulation?	Yes	Yes	No	No
Significant Public Health Risk?	Yes 	Yes 	~*	*
Standardized Design?	Yes 	Yes 	~	No
Product Complexity?	Yes 	~ 	~	No
Complex Supply Chain?	Yes 	Yes 	~	No
Standardized Manufacture?	Yes	Yes	~	No

\* Relative to total population

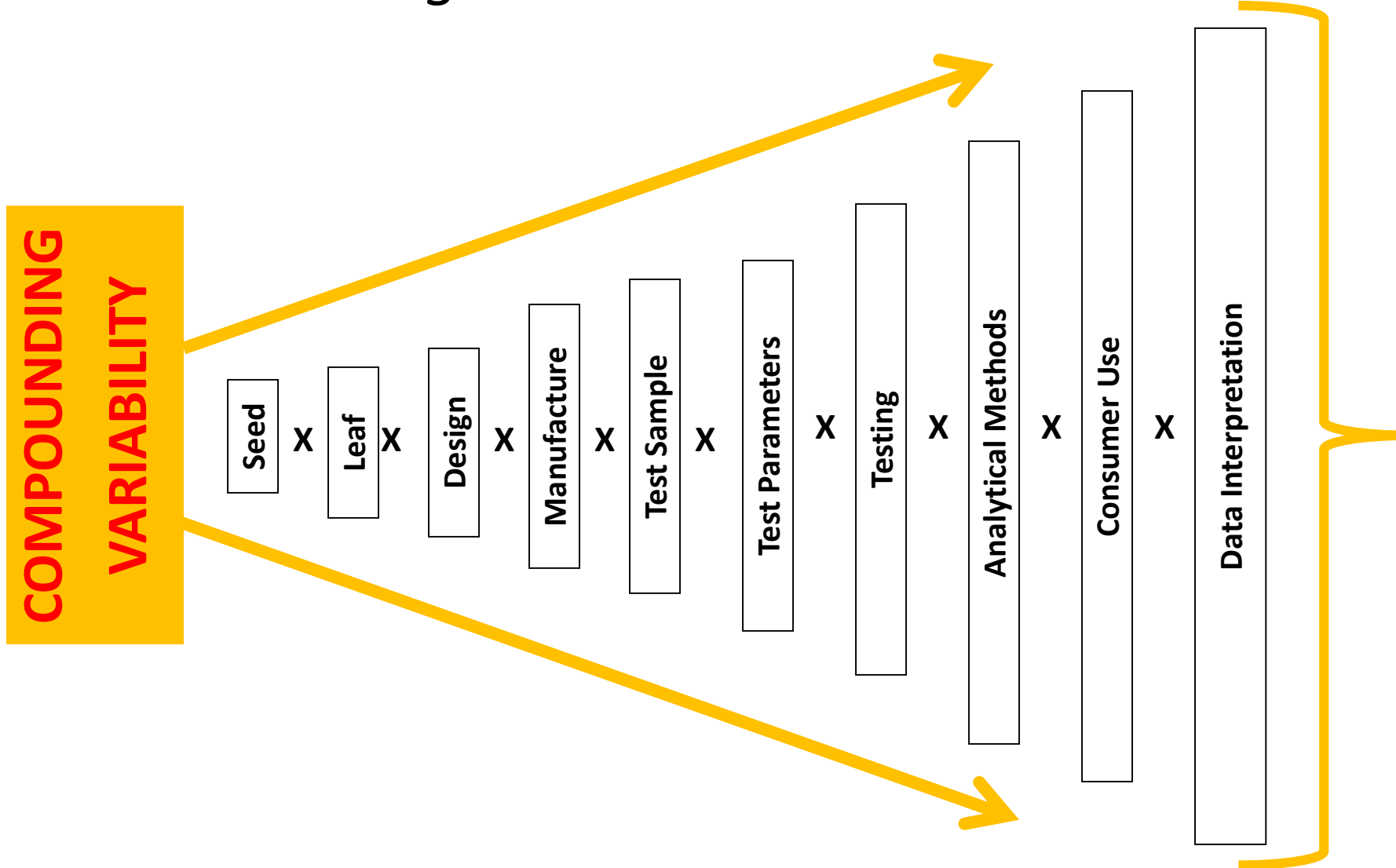
# Smart regulations:

*Controls are designed to achieve intended outcome*

What  
**SHOULD** be  
or **CAN** be  
***controlled***  
then ask  
**HOW?**

# Smart regulations:

*Controls* are designed to achieve intended outcome

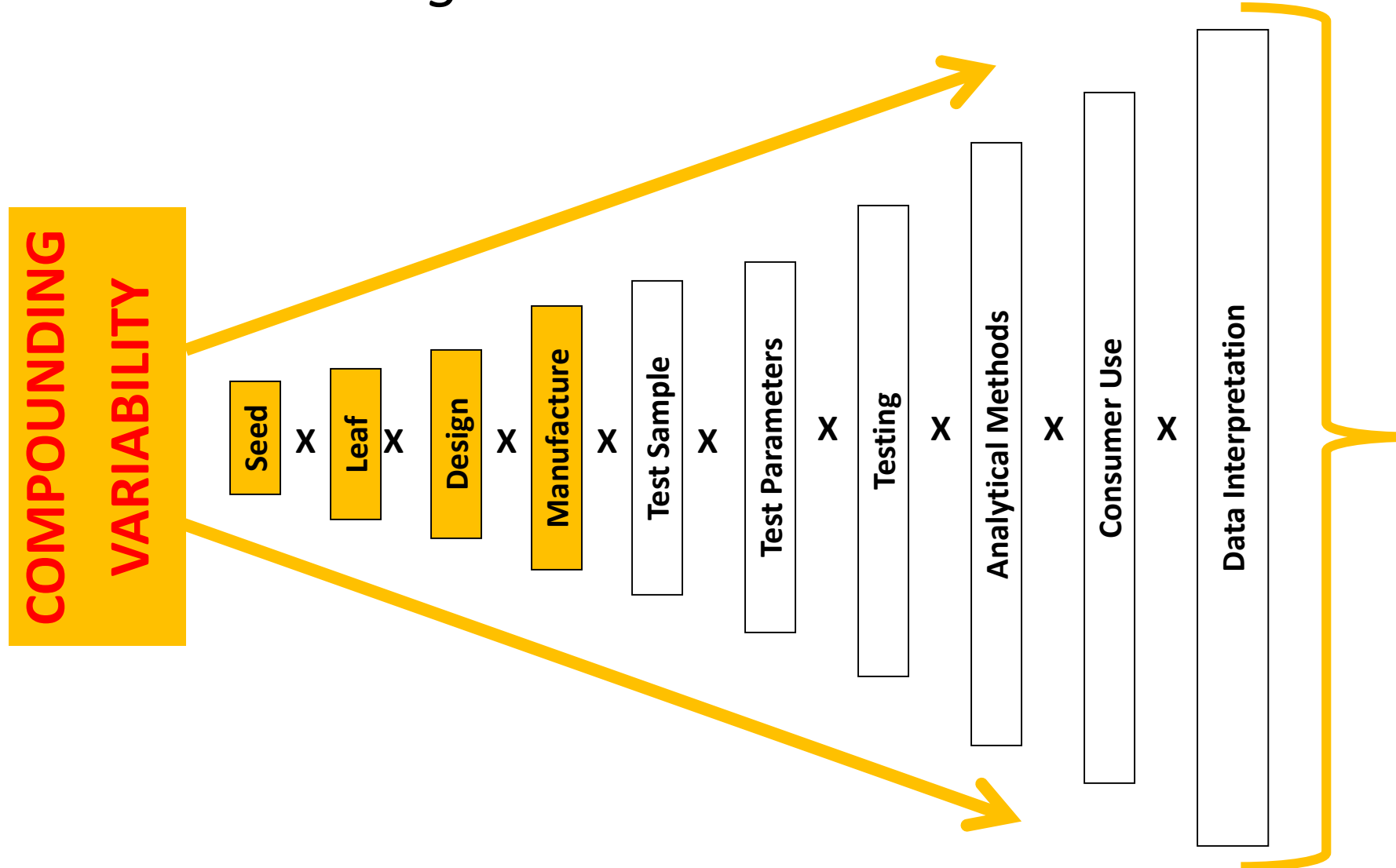


What  
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What **SHOULD** be or **CAN** be *controlled* then ask **HOW?**

# Smart regulations:

*Controls are designed to achieve intended outcome*

## Seed:

- Cigarettes: 4 types, male-sterile  
- vs -
- Cigars: **Over 12 seed types with various sub-types, not controlled**



# Smart regulations:

*Controls are designed to achieve intended outcome*

Leaf:



1 Seed  
Type

X  
Grow



# Smart regulations:

*Controls* are designed to achieve intended outcome

Leaf:



1 Seed  
Type

X  
Grow



X  
Cure



# Smart regulations:

*Controls are designed to achieve intended outcome*

Leaf:



1 Seed Type

X  
Grow



X  
Cure



X  
Ferment



X  
Age



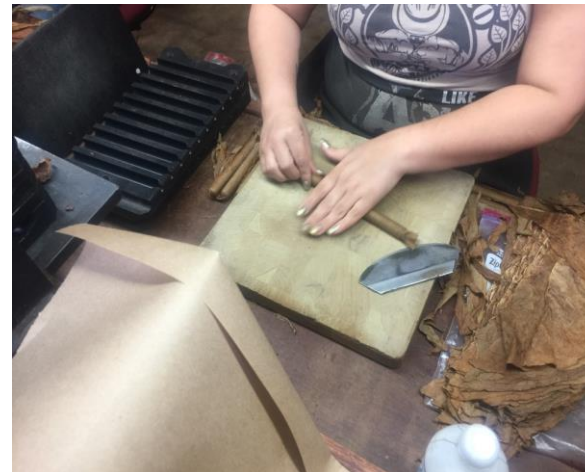
An example of the many  
= Leaf Chemistry VARIATIONS  
from 1 Seed

# Smart regulations:

*Controls are designed to achieve intended outcome*

## Design & Manufacture:

- **Different** techniques
- **Different** natural & reconstituted wrappers and binders
- **Different** manual & semi-manual, machine
- **Different** local test equipment



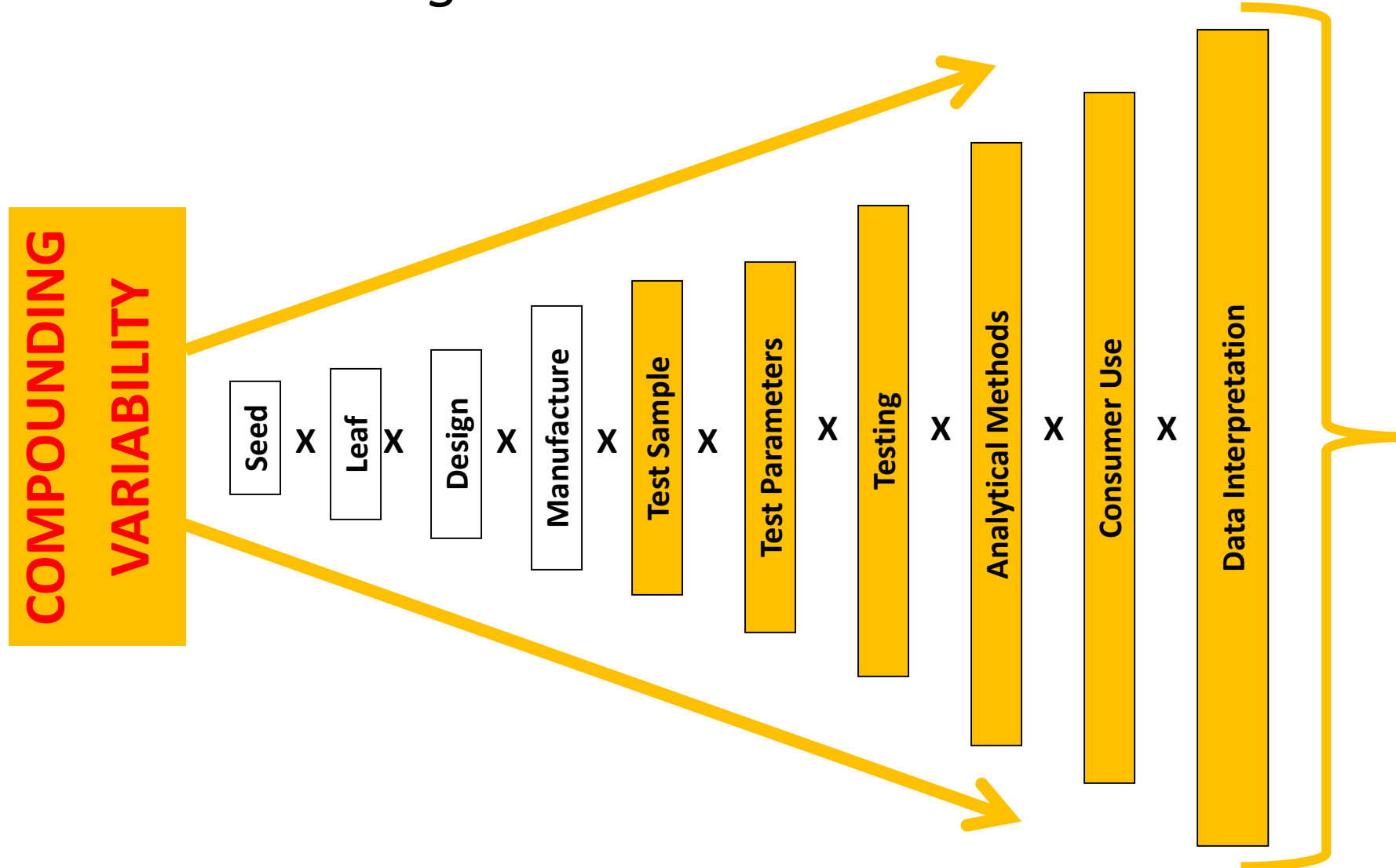
Ref: Cigar Tobacco and its required quality

Hartley M, Universal Leaf Tobacco Company, Inc., 198 W. Liberty ST, Lancaster, PA, USA

CORESTA OCT2017

# Smart regulations:

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What  
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# Smart regulations:

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## Test Sample

- How many? How often?
  - Hand Rolled 300/day/team of 2
  - Machine made natural wrapper 20-150/minute
  - Machine made reconstitute wrapper 200-2,000 /minute
  - Cigarettes - 16,000/minute
- Statistically relevant and at what cost?
- No standardized approach means **variable interpretation** of any testing results.





# Smart regulations:

*Controls are designed to achieve intended outcome*

## Test Parameters

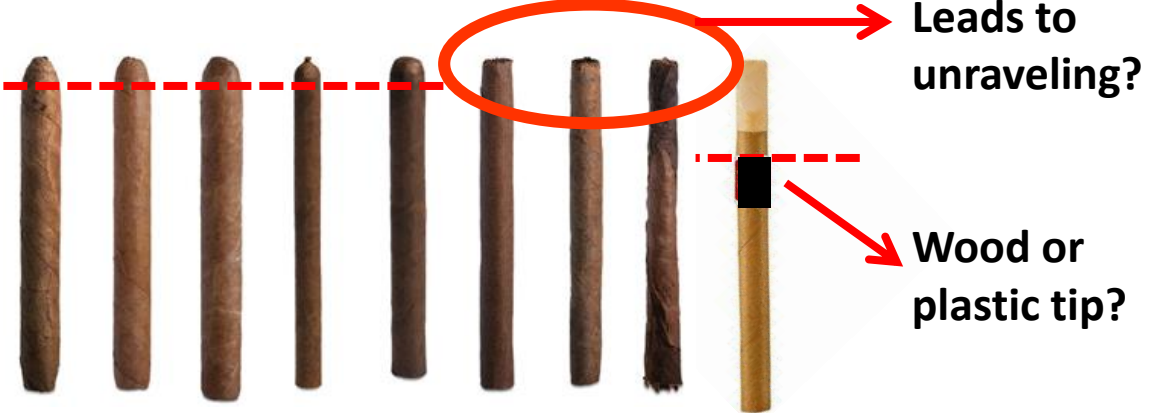
- How to condition?
- Where and how to cut?

**Where and how to cut? No standard practice**  
*Lab procedure variability can result in data variability*



Leads to unraveling?

Wood or plastic tip?



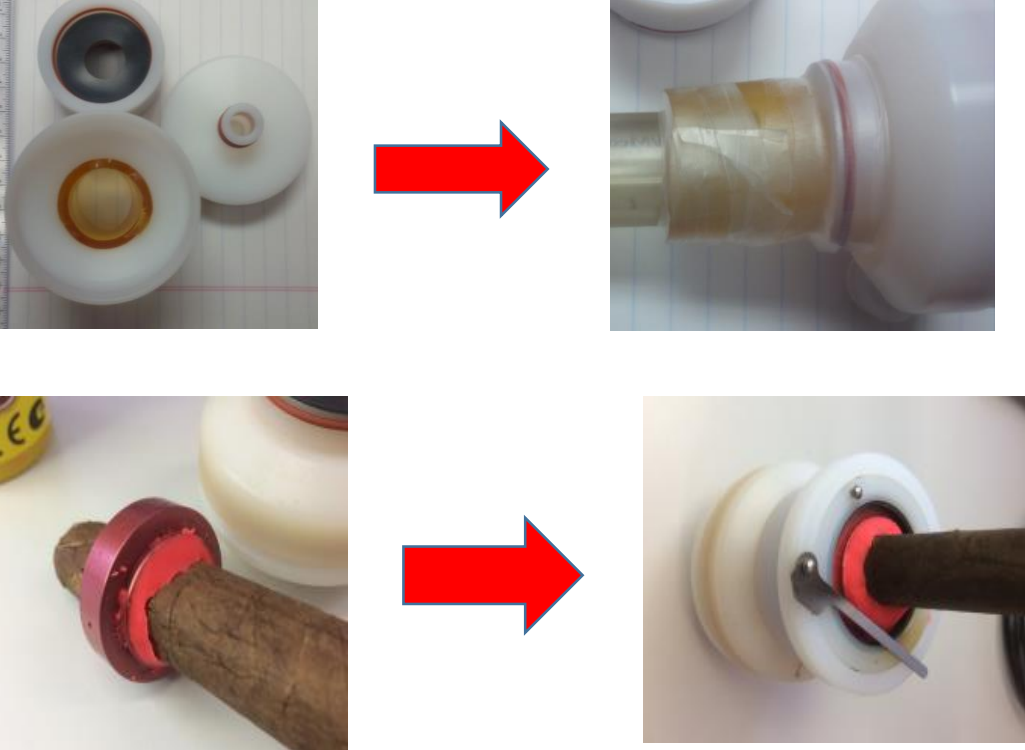
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## Testing

- Seal?
- With what type of lighter?  
Pre-light? Re-light?
- Ash Removal?

**No standard Cigar holder for each size and shape**  
*Smoke collection variability results in data variability*



The image block contains two rows of photographs. The top row shows a white plastic holder with a red ring on the left, and a red arrow pointing to a close-up of a cigar being inserted into the holder on the right. The bottom row shows a red plastic holder with a white ring on the left, and a red arrow pointing to a close-up of a cigar being inserted into the holder on the right. The text above the images states 'No standard Cigar holder for each size and shape' and 'Smoke collection variability results in data variability'.

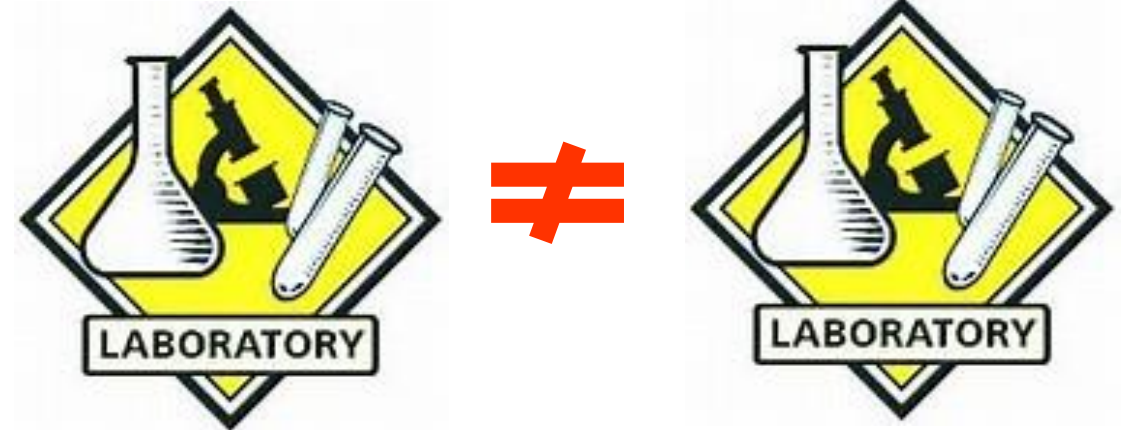
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## Analytical Methods

- No standard length of time to smoke
- No agreed best way to trap the gas
- Lack of reference product
- No international standard (ISO)

Currently, there is **not a way** to prove that scientific data from different labs is **Comparable, Repeatable and Reliable.**



# Smart regulations:

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## Consumer Use

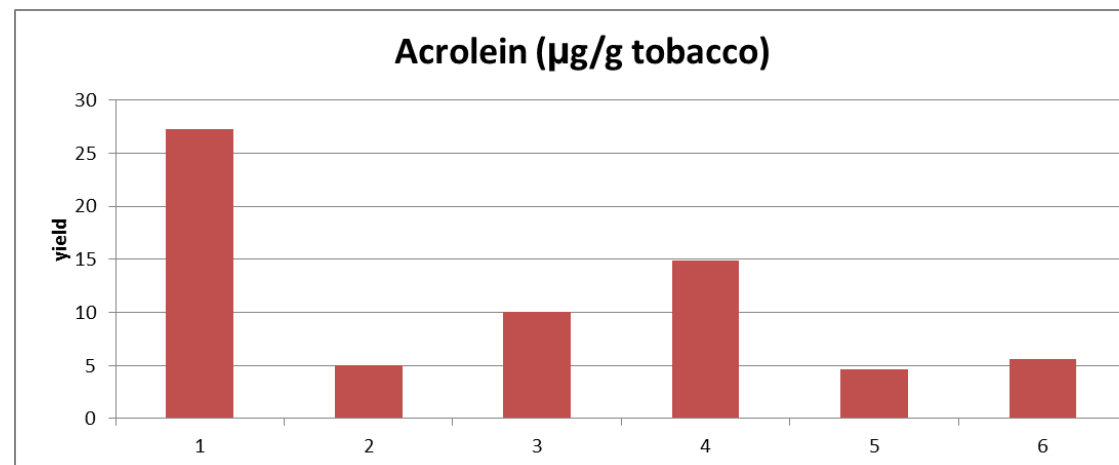
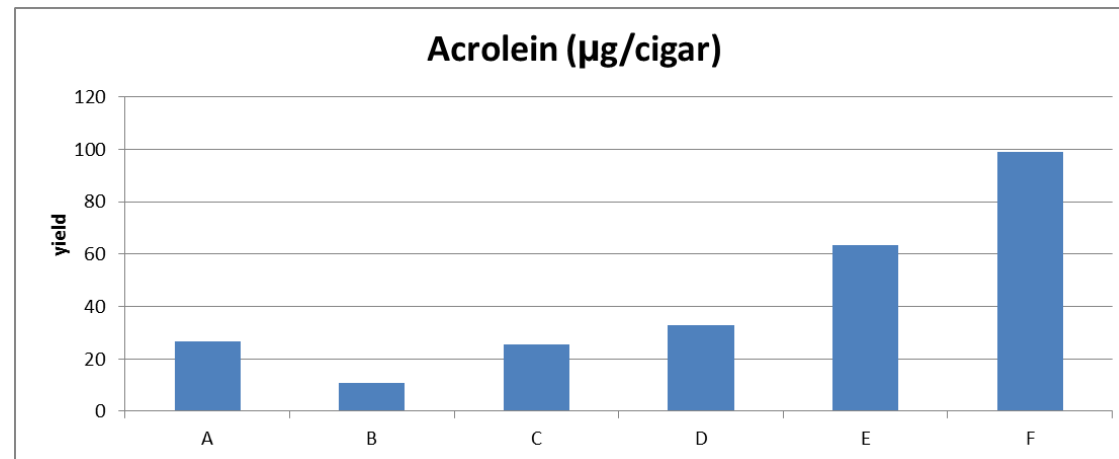
- High variability in consumer use and behavior impacting ability to reliably predict risk via existing risk models
  - Quantitative Risk Assessment (QRA) – use point estimates
  - Probabilistic Risk Assessment – use a population distribution approach
- No standardized or validated model leads to **interpretation variability**

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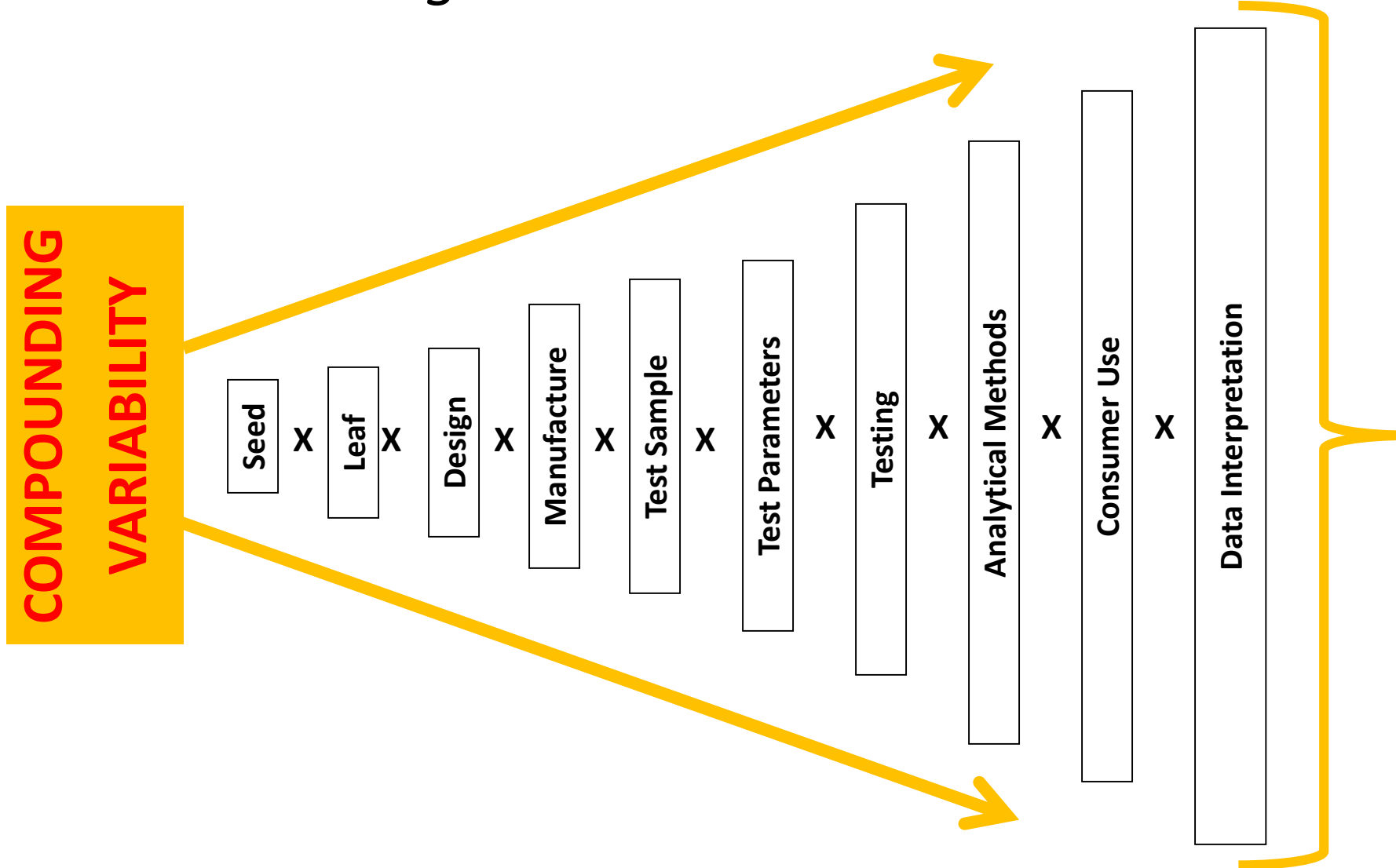
## Data Interpretation

- Same constituent reported by different units across same cigars by different units.
- No standardized collection or reporting units leads to **interpretation variability.**



# Smart regulations:

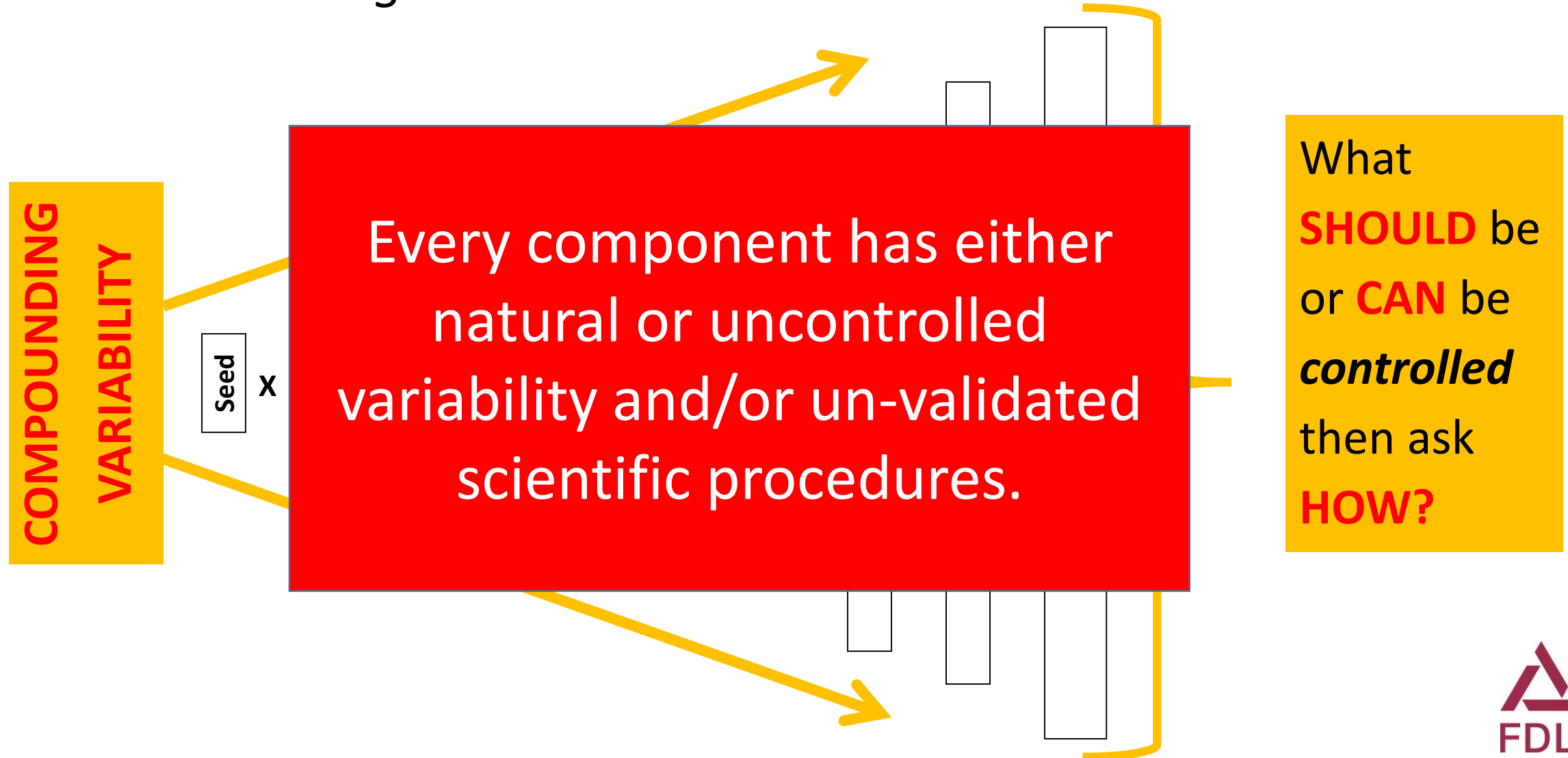
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# Cigar Regulation in other Countries

- Majority of Cigar Regulation focuses on:
  - Adulteration
  - Contamination
  - Mislabeling



Propose that is  
fit-for-purpose  
**“Smart”**  
risk-based regulation



# Is regulating Cigars by SE 'smart'?



=



It's like **pretending** that the GRAPES grown in 2016 climate conditions, from the same vineyard, from same undefined hybrid grape vines, are **from 2007...**

then pretend to **scientifically prove**, by using un-validated science, that a **"2007" vintage = 2018 vintage**