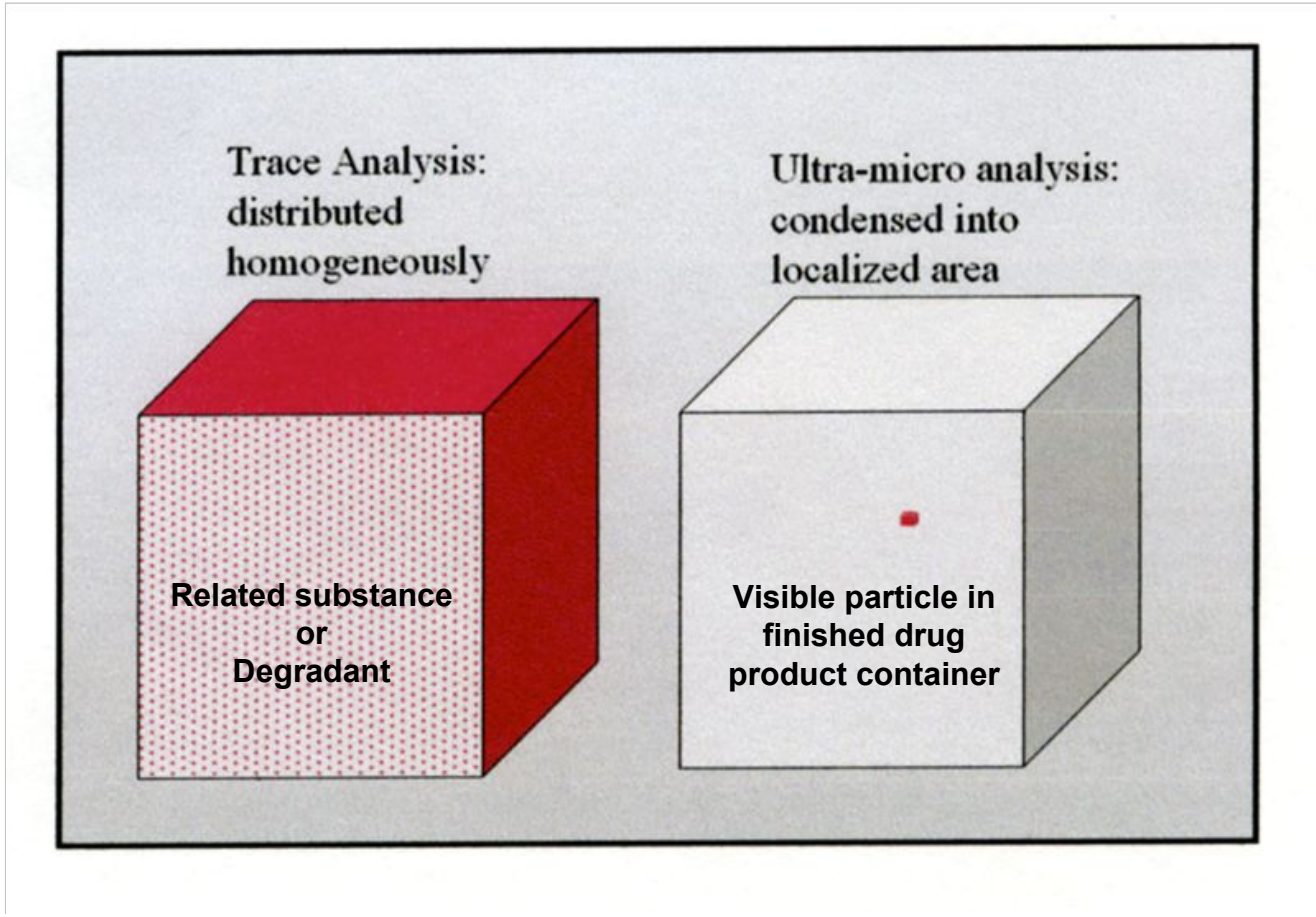
Problem Solving During Trace Foreign Matter Investigations: Points to Consider

Mary Lee Ciolkowski
Senior Principal Scientist
Bausch+Lomb

Particle Characterization = Ultra-Microanalysis



Particle Classification
USP Informational chapters: <1790>, <1787>

Extrinsic	Intrinsic	Inherent
- Hairs	- Formulation ingredients	- Protein aggregates
- Celluloses	- Packaging component related	- API particles in a suspension
- Skin Flakes	Si oil, slip agents, shavings	
- Fibers, Lint	- Changes on stability	
- Insect parts	product/pkg interaction	
- Glass	precipitation of actives or inactives	
- Soil	- Particle generation during filling process (abrasion)	
- Cleanliness of pkg components		

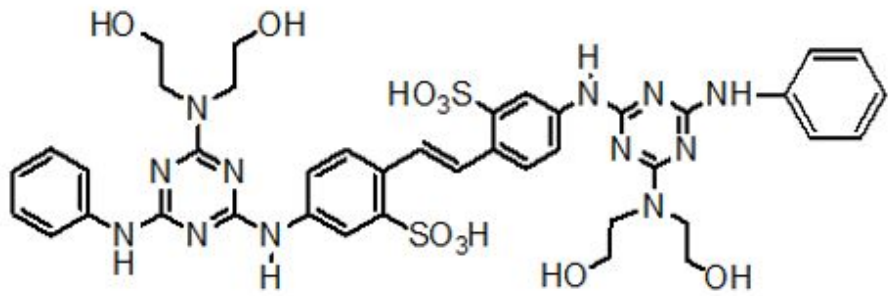
- Quickly assigning the category of the foreign material provides valuable directional information for the investigation
- Intrinsic of most concern during development
- Debris addition is a continual challenge; Minimize and control

"The Unknown Unknowns": unexpected or unforeseeable, they cannot be anticipated based on past experience or investigation

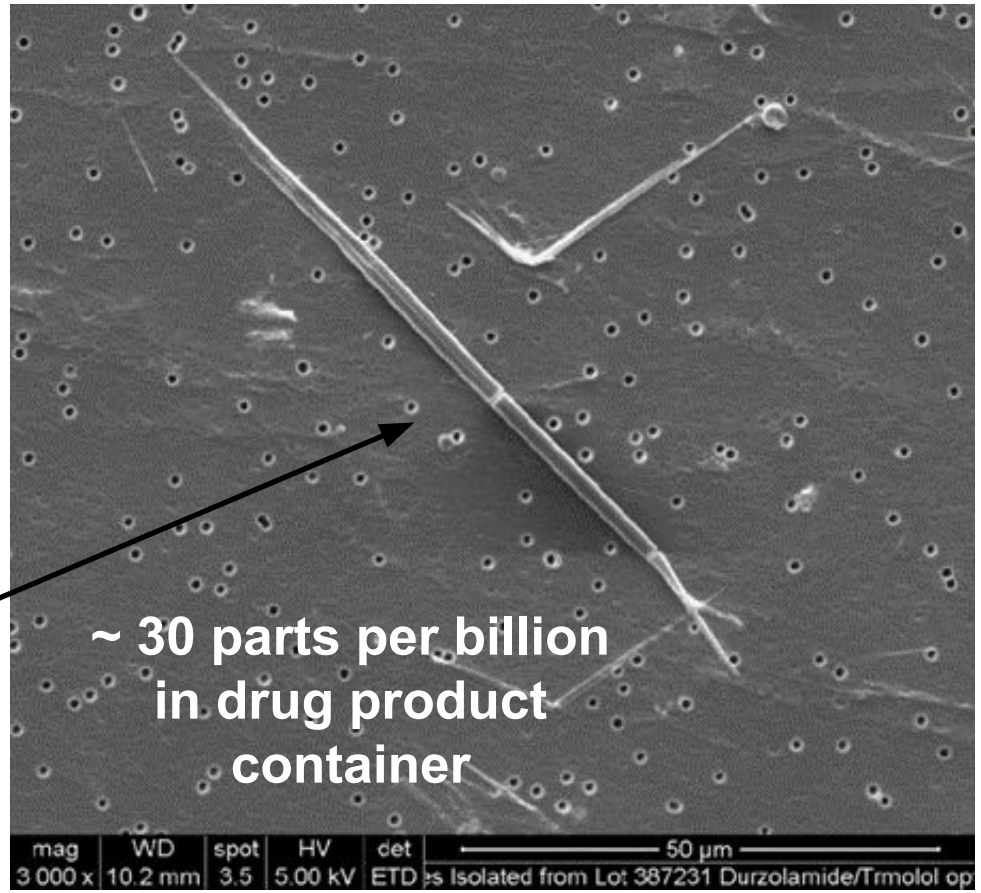
Topical Ophthalmic Solution: (Active 1 & Active 2)
Indication: reduces intra-ocular pressure due to glaucoma

- During development: No particulate matter issues observed for registration stability/process validation lots

- A drug product lot (post scale up for commercial launch) failed USP<789> stage 1 LO for particles/mL ≥ 10 µm at 3-month stability timepoint

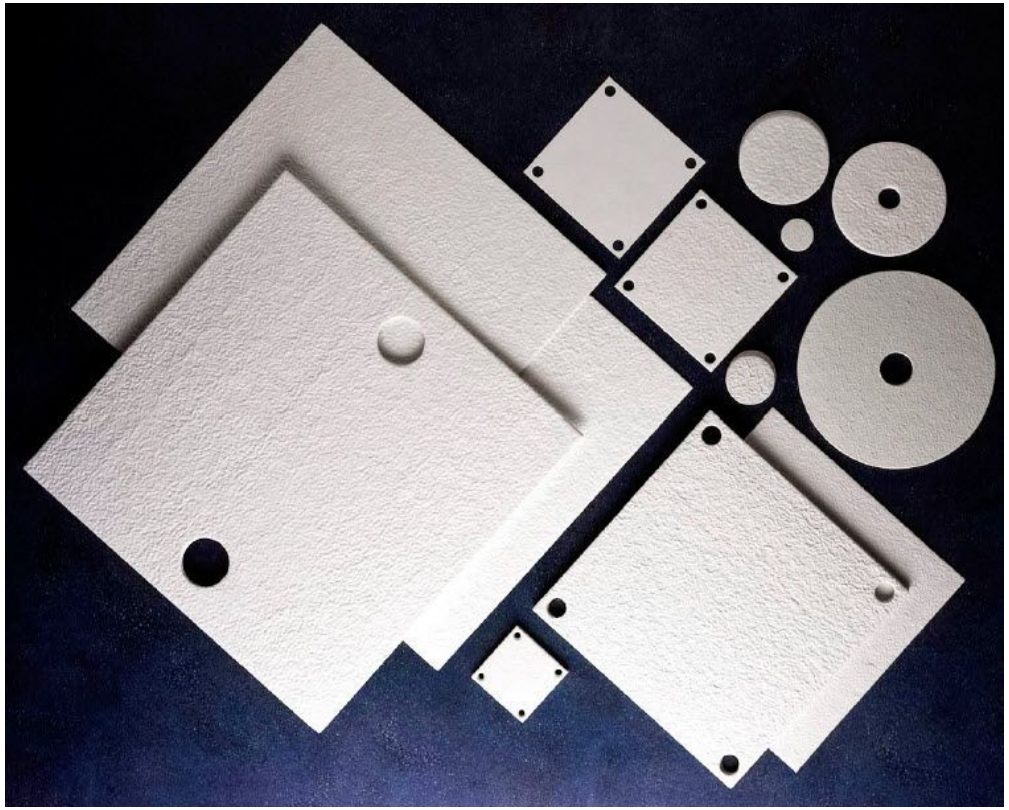


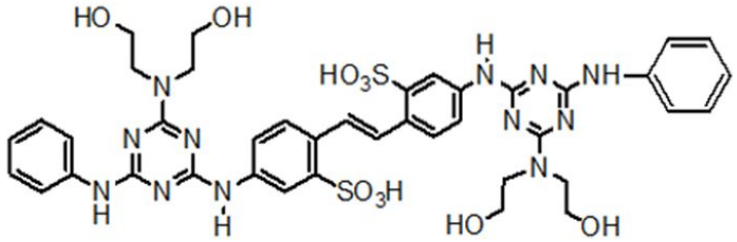
sulfonated stilbene: optical brightener



Optical Brightener Source: Cellulose-based filtration support (Steri-Mat)

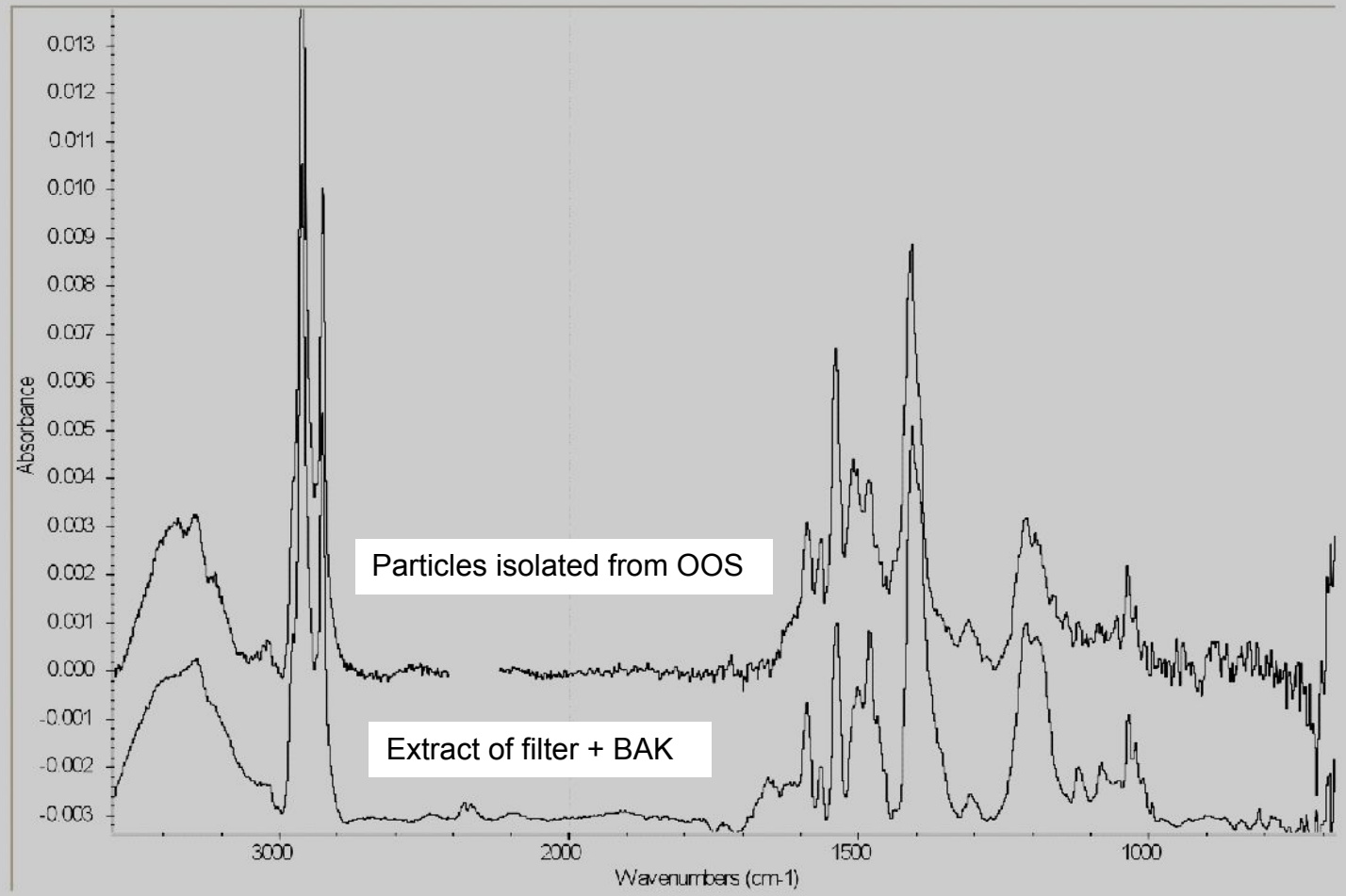
- Contaminant had fluorescent properties; provided a key “analytical hook” for tracking
- Generally optical brighteners absorb in the UV range and fluoresce in visible λ range (minimize yellow discoloration)
- Used fluorescence properties of contaminant to track back to specific API lots during investigation
- Elevated temperatures used in final crystallization step (API) caused fluorescent optical brightener to leach from the filter support and incorporate into drug substance lots



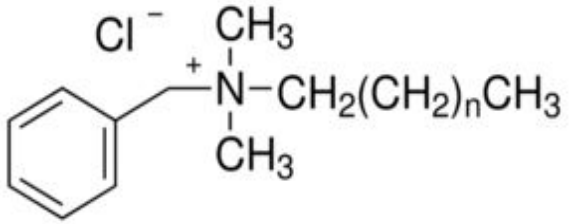


Sulfonic acid stilbene derivatives absorb in the UV and emit fluorescence in the visible wavelength range causing a white appearance “whitening” effect

Infrared Spectrum of Optical Brightener+BAK Precipitate Correlates with Particles from OOS Drug Product Lot



Benzalkonium chloride preservative (BAK)

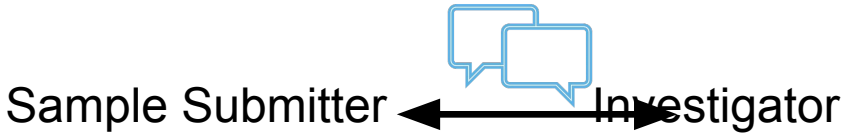


- Anionic optical brightener leached from a cellulose filter support at the API supplier in India;
- Formed a complex with BAK preservative in the formulation and precipitated as a particle

Points to consider during trace contaminant investigations:

1. Keep an open mind: First hypothesis is usually incorrect (be humble)

2. Openly share information: Product and process knowledge is imperative to effective problem solving



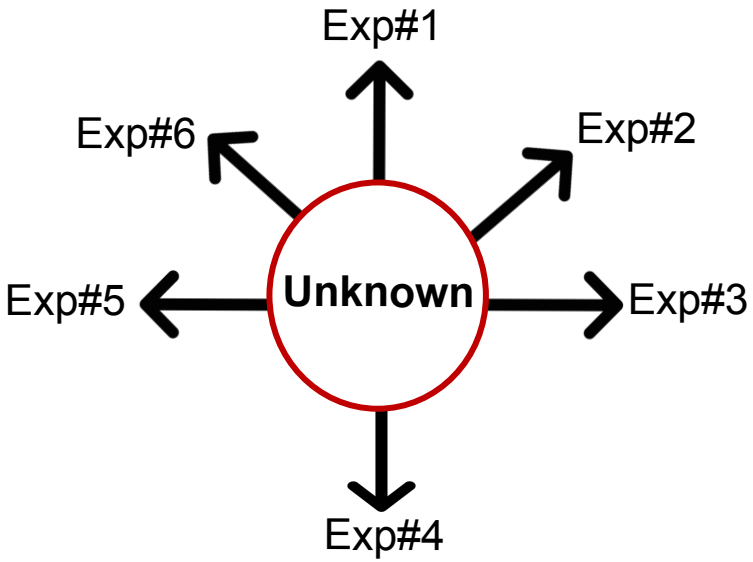
3. Try to clearly establish the goal of the investigation (What is the problem statement?)
   Has there been a test failure? OOS, non-conformance?

4. Have a clear exit strategy (root cause definitions; do we need to know the exact source?) When do we

5. Every experiment should test a hypothesis: Start simple and progress to complex; A progressive problem-solving approach is preferred over a “shot gun” approach
   Goal: maximize data from a minimum amount of sample

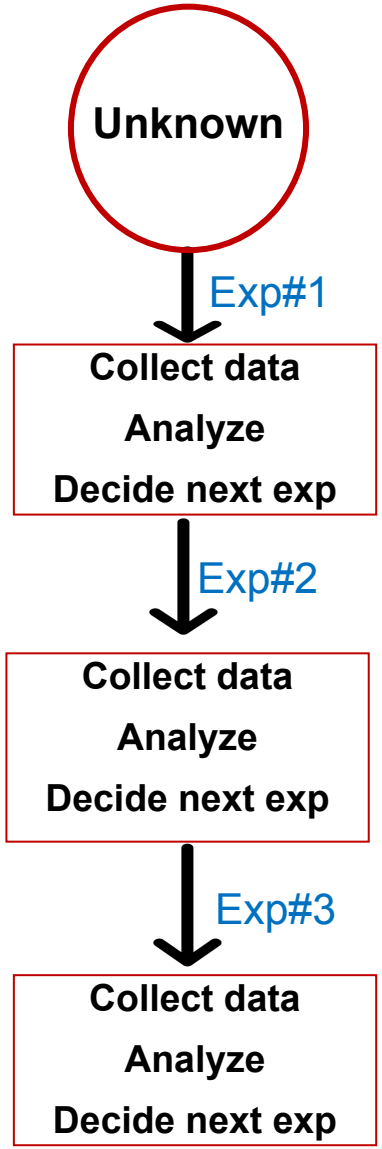
6. Verify conclusions using multiple orthogonal microanalytical techniques where possible

Typical Problem-Solving Approaches



Shot Gun Approach

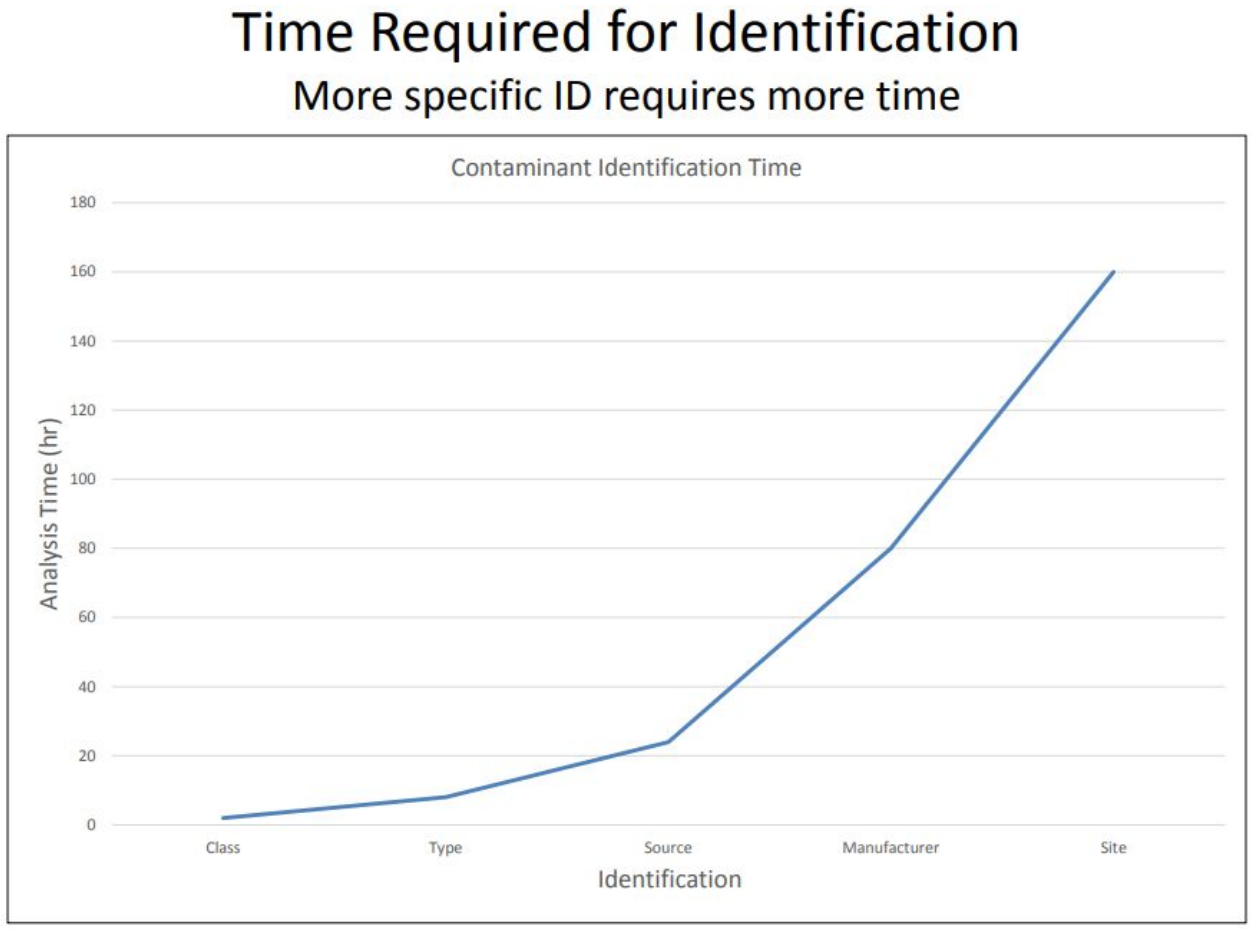
- Experiments done in parallel covering a wide range of analytical techniques
- Significant sample consumption
- Quickly generates lots of data
- Conflicting results from different exps can lead to confusion; inefficiency
- Goal is to quickly find “analytical hook” to identify contaminant and track it to the source: IR spectrum, molecular weight, autofluorescence



Progressive Approach

- Maximize data while consuming a minimal amount of sample
- Results from each experiment guide the next experiment
- Progress seems slow however a “body of evidence” is being created that builds with each exp.

Think about the exit strategy for the investigation?



Root Cause Definitions:

Definitive vs Proximate

Definitive: Thorough understanding of how the failure occurred and the cause/event can be replicated

Proximate: Good understanding of how failure occurred. Narrowed it down to a small set of factors (raw material lot, drug product lot, manufacturing process, container/closure)

Can identify possible corrective/preventative actions

Image: Robert Carlton presentation, Hooke College of Applied Sciences

Extrinsic vs Intrinsic Particle Types "in-process or out of process?"

- Unless obvious filth (e.g., hair, insect parts, etc.) proceed with caution when classifying as extrinsic. Extrinsic could imply "adulterated" by Regulatory Authorities

- Assigning particulate matter source "within the process" may be difficult due to trace levels

- Evaluation of the potential impact of identified particles may be enhanced by conducting a clinical risk assessment

Conclusions

- Contaminant identification (particles) typically involves ultra-trace analysis approaches
- Starting simple and progressing to increasingly complex analysis techniques conserves sample and builds a body of evidence towards identification
- Think about the exit strategy for the investigation. Knowing when to stop is sometimes challenging. May be dependent on product/process risk assessment

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Thank you!