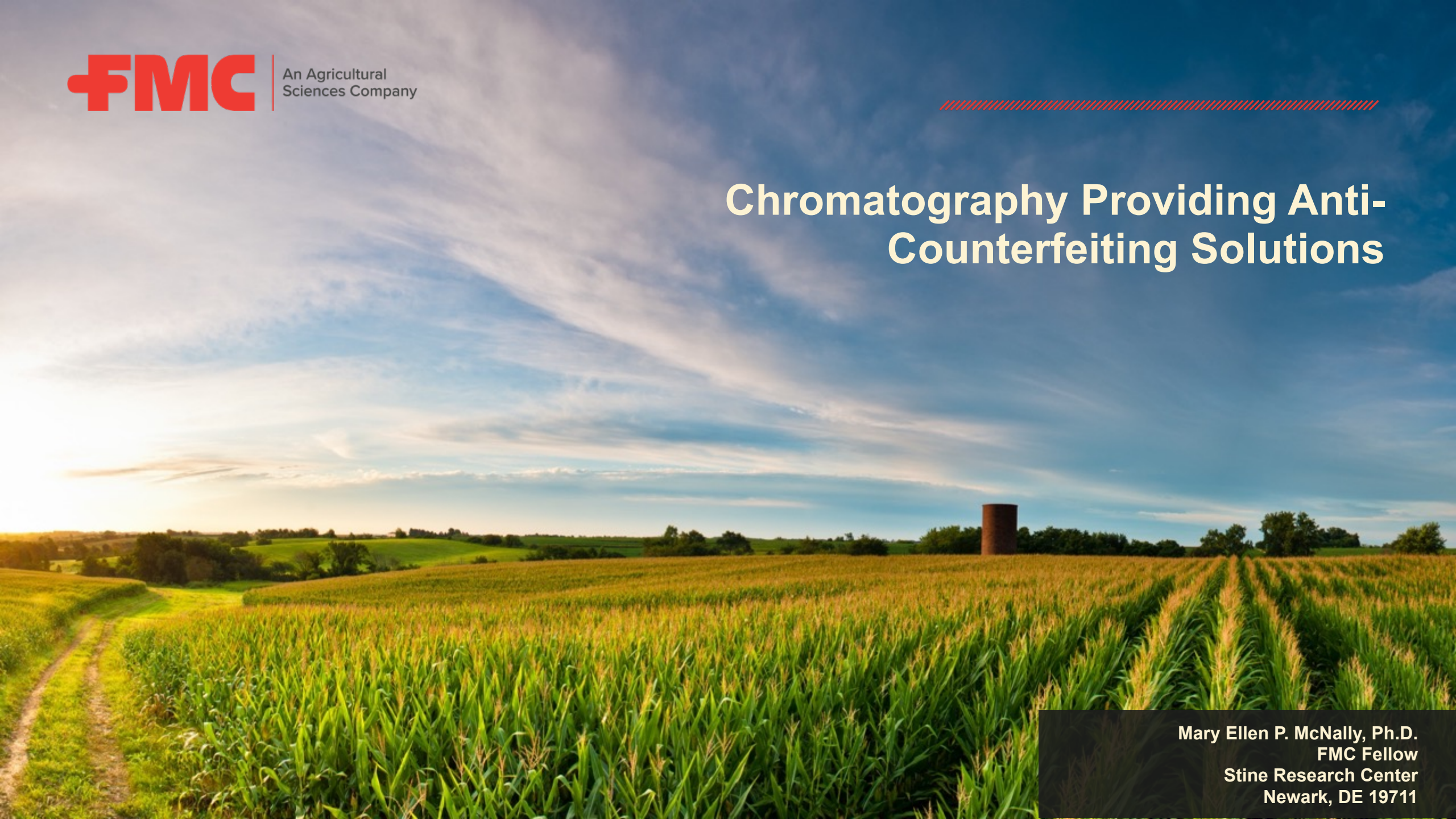

Chromatography Providing Anti-Counterfeiting Solutions

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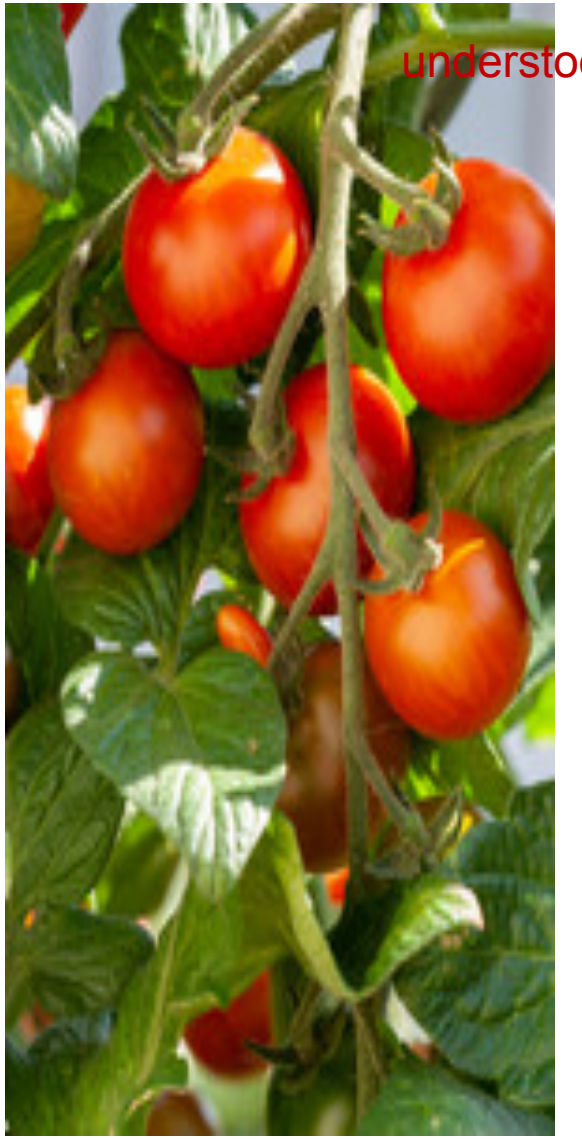
Outline

- Background
  - The Issue
  - UN Sustainable Development Goals
  - Examples
  - Suspect Products
- Regulatory Analytical Methodology
  - Registered and Enforcement Methods
  - MAIM, Tolerance
  - Questions Answered
- Specifications & Additional Methodology
  - Counterfeit, Knock-offs, Replica's
- Conclusions

Background

The Issue



Over the last two decades…

trafficking of pesticides has quietly grown into one of the world's most lucrative and least understood criminal enterprises.

Impact of counterfeit and illegal material goes beyond loss of sales into:

- Brand integrity damage
- Trademark dilution
- High Cost of enforcing intellectual property rights and protection.
- Residual effects of counterfeit and illegal products being introduced into the food chain if not manufactured correctly or used according to registered specifications and labeling.
  - Potential to affect the environment as well as the health and well being of consumers.
- Multinational corporations that sell food say their products are safe.
  - Bunge, a U.S. producer that sources crops, said its contracts with farmers include clauses that "require the responsible use of pesticides," and it conducts "chemical analyses on its products to ensure their safety."
  - Citrosuco, the world's largest producer of orange juice concentrate, said it trains fruit growers to use only "approved" pesticides.
  - Cargill said it "performs constant monitoring" to guarantee producers "respect social and environmental legislation."

Reference: "In agricultural giant Brazil, a growing hazard: The illegal trade in pesticides", T. McCoy, The Washington Post (on-line), February 2020

Source: Tracit.org

UN Sustainable Development Goal Descriptions

1 NO POVERTY	Precludes agricultural productivity that can reduce poverty, create jobs and drive higher incomes and productivity.
2 ZERO HUNGER	Destabilizes food security and undermines sustainable food production and access to food.
3 GOOD HEALTH AND WELL-BEING	Presents significant risks to human health via direct exposure to unsafe chemicals, food toxicity, and safety hazards associated with transportation and handling.
6 CLEAN WATER AND SANITATION	Jeopardizes water quality and the protection of water-related ecosystems from contamination.
8 DECENT WORK AND ECONOMIC GROWTH	Drains farmer profitability through spending on ineffective pesticides, causing reductions in crop yields and knock-on effects on GDP, jobs and tax revenues.
12 RESPONSIBLE CONSUMPTION AND PRODUCTION	Prevents environmentally sound, life-cycle management of chemicals and wastes.
14 LIFE BELOW WATER	Exacerbates prevention of harmful run-off and releases of toxic chemicals to water bodies.
15 LIFE ON LAND	Renders agricultural land infertile due to soil degradation, increase pest resistance and contaminated ground water.
16 PEACE, JUSTICE AND STRONG INSTITUTIONS	Undermines governments' capacity to enforce policy, promote the rule of law, eradicate corruption and combat other forms of criminal activity.

Counterfeit Manufacturing Conditions

Common Transport & Transactions In the Criminal Network

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Consequences of using a Counterfeit Pesticide

Source: CROPLIFE, LI

Lithuanian grower sprayed a counterfeit pesticide that resulted in the yellowing of the crop in the field.

What are suspect products?

- A product purposely sold under an accepted tradename but containing another product.
- A product purposely sold under an accepted tradename with no active ingredient present.
- A product sold with an incorrect active ingredient present.
- A product purposely manufactured to mimic a registered and trademarked material under patent
- A product purposely sold in a container to mimic a registered product’s container and label

Regulatory Analytical Methodology

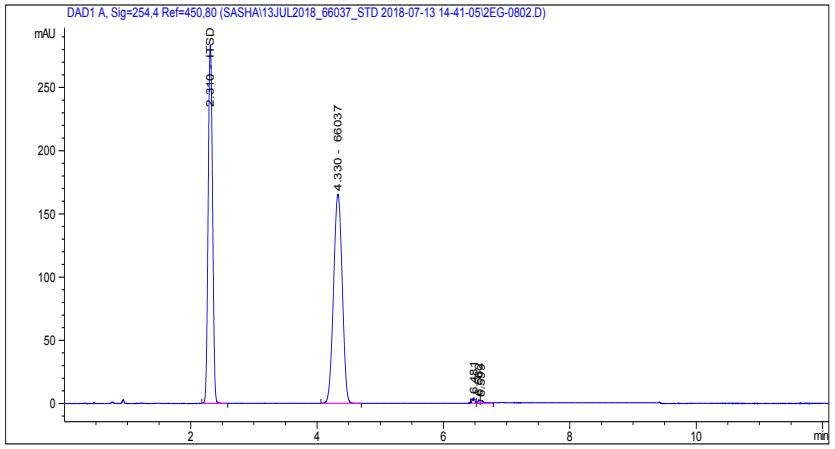
Legitimate Commercial Pharma and Agricultural Producers

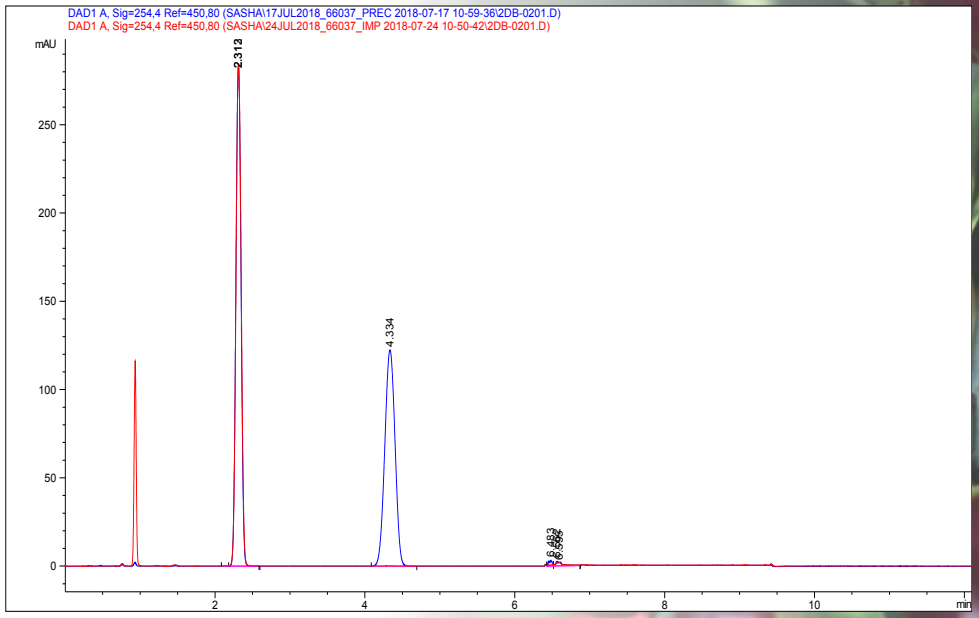
- Submit to regulatory bodies
  - Analytical methods for the identification and quantitation of technical active ingredients.
  - Generally, these methods also include the analysis of the a.i. in commercial formulations.
  - These methods are called "Enforcement Methods"
    - The methods verify that products sold meet the registered labeled requirements.
    - They identify the a.i.
    - They quantify the a.i.
  - The methods are used by:
    - Regulatory Agencies to bring legal action when suspect samples are found.
    - By the commercial producer, to verify that what is being manufactured meets registered specifications.
  - The methods are typically LC or GC based.

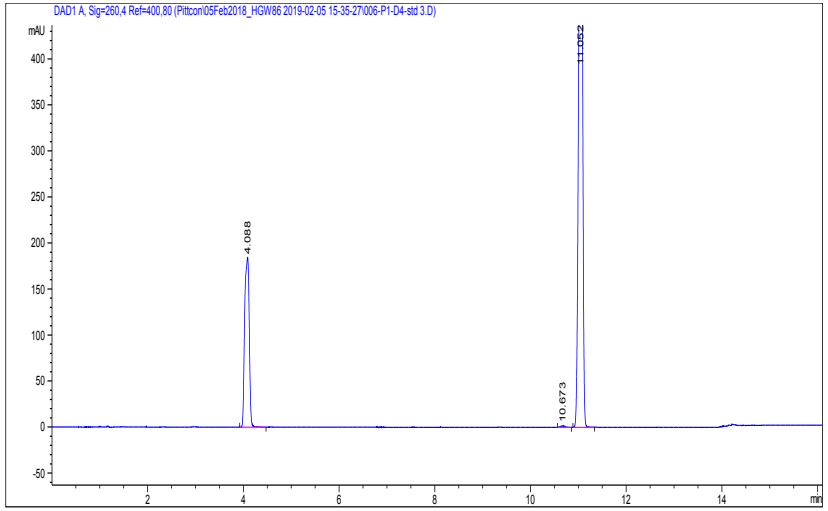
Typical Enforcement Method Conditions

Column Type	Length	Diameter	Particle Size	Flow Rate	Detection	Sample Concentration	Diluent
Ace ® 3 C18	150 mm	4.6 mm	3.0 µm	1.8 mL/min	275 nm	1.0 mg/mL	50:50 ACN/0.005 M NaH_2PO_4
Zorbax ® SB C8	150 mm	4.6 mm	5.0 µm	2.0 mL/min	254 nm	1.0 mg/mL	50:50 ACN/0.01N NH_4OH
Zorbax ® SB C8	75 mm	4.6 mm	3.5 µm	2.0 mL/min	254 nm	0.7 mg/mL	ACN
Zorbax ® SB C8	150 mm	4.6 mm	3.5 µm	1.0 mL/min	240 nm	0.375 mg/mL	ACN
Zorbax ® SB C8 Solvent Saver	250 mm	3.0 mm	5.0 µm	0.65 mL/min	280 nm	0.5 mg/mL	ACN

Typical Enforcement Method Chromatograms

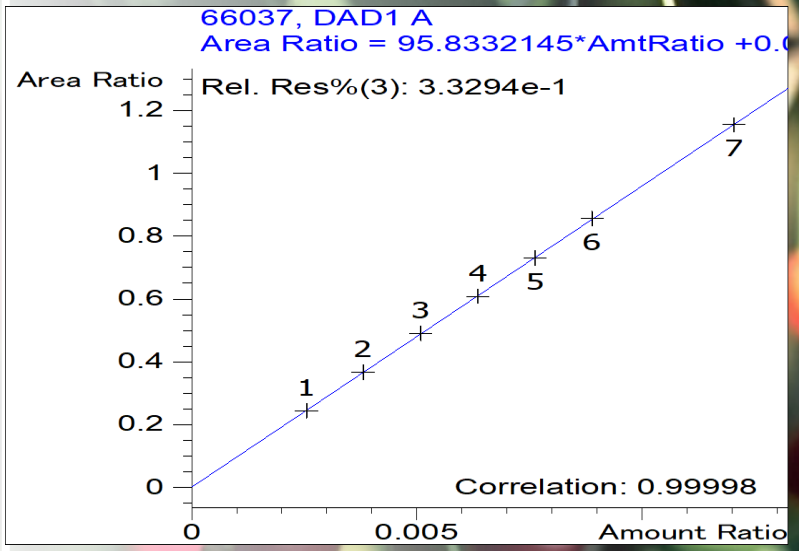






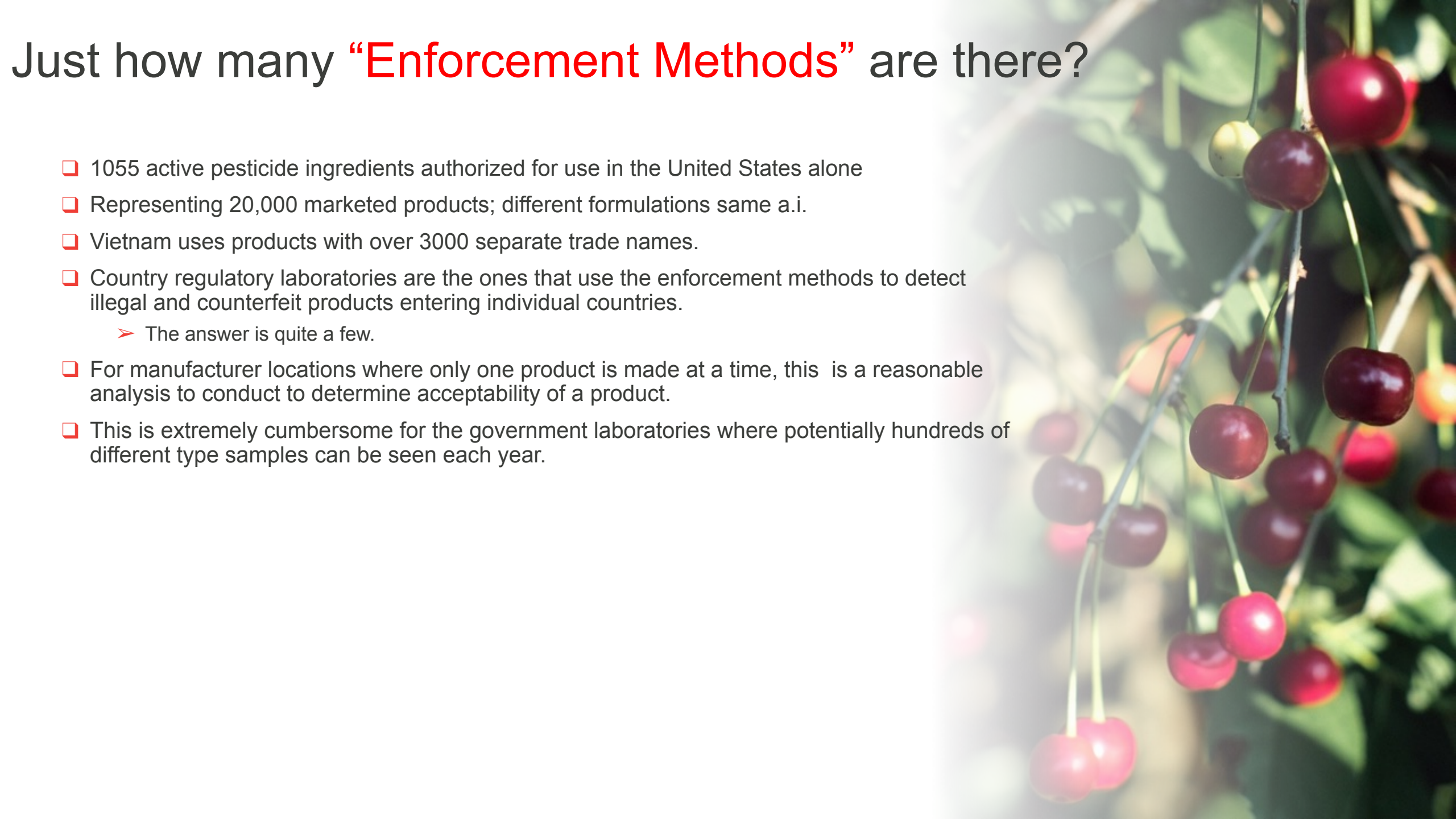
Typical Enforcement Method Regulatory Acceptance Criteria

- Precision
  - 8 to 10 individual samples for method precision.
  - 1 sample run 8 to 10 times to ensure instrument precision.
- Accuracy
  - 3 samples prepared at 3 different concentrations. Most commonly 75%, 100% and 125% of the concentration of the sample solution.
- Linearity
  - Calibration curve of 7 points with a correlation of 0.99 or greater, standard solutions as specified by the method or adjusted when necessary.
- Specificity
  - Qualitative analysis for impurity interference for the technical active ingredient versus any impurity at 3% or greater in the technical specification
  - For formulations, this is versus the is versus the formulation blank also.



Just how many “Enforcement Methods” are there?

- 1055 active pesticide ingredients authorized for use in the United States alone
- Representing 20,000 marketed products; different formulations same a.i.
- Vietnam uses products with over 3000 separate trade names.
- Country regulatory laboratories are the ones that use the enforcement methods to detect illegal and counterfeit products entering individual countries.
  - The answer is quite a few.
- For manufacturer locations where only one product is made at a time, this is a reasonable analysis to conduct to determine acceptability of a product.
- This is extremely cumbersome for the government laboratories where potentially hundreds of different type samples can be seen each year.



Multi-Analyte Methods

- Methods are for GC, LC and UPLC
  - 113 agricultural compounds have been analyzed with these methods thus far.
  - Developed by Dr. Jim Garvey and his team from the Ireland Department of Agriculture and Food Laboratories.
  - Supported by CIPAC, Collaborative International Pesticides Analytical Council
    - CIPAC is a world-wide recognized organization that establishes standardized methods through round-robin trials to support FAO specifications.
- In these MAM's,
  - One set of conditions have been investigated for active ingredients and products from a wide variety of manufacturers.
  - Eliminates the need for multiple conditions, multiple set-ups and numerous columns in the regulatory laboratories.

Key Pieces of Information Obtained from the Enforcement Method

- Retention Time on a Known Method for Confirmation of ID
  - Further Confirmation Possible with UV or MS
- Whether the amount of a.i. fits the Specification range.
  - Example:

  Product with 20% a.i. as the nominal value

  Tolerance is the limits that define an acceptable range of variability around a declared value.

  EPA tolerances are different than FAO tolerances.

	EPA	FAO
Acceptable Tolerance Level	+/- 5%	+/- 6%
Acceptable Tolerance Range for 20% a.i.	19 to 21 wt%	18.8 to 21.2 wt%

Solved Suspect products with Enforcement Methods?

- ~~A product purposely sold under an accepted tradename but containing another product.~~
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- A product purposely manufactured to mimic a registered and trademarked material under patent.
- A product purposely sold in a container to mimic a registered product's container and label.

Counterfeit?

Definitions:

Counterfeit Products: Counterfeit products are unauthorized copies of branded goods that illegally use a trademark or logo identical or very similar to the genuine brand with the intent to deceive consumers.

Key Characteristics:

- Violate intellectual property laws (e.g., trademarks).
- Often sold as if they are the original brand.
- Quality may vary, but deception is the goal.

Knockoff products: Knockoff products are imitations of popular branded products that do not use the actual trademarked names or logos but closely mimic the design or style.

Key Characteristics:

- Do not directly infringe trademarks but may infringe on design or trade dress rights.
- Often legal in some jurisdictions, though ethically questionable.
- Sold under different brand names, usually at lower prices.

Replica: Replica products are copies made to closely resemble original branded items, sometimes marketed openly as replicas rather than authentic goods.

Key Characteristics:

- Can be high-quality or low-quality.
- May or may not use logos — some sellers disclose them as replicas.
- Legality depends on use of trademarks and intent to mislead.

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- Sold under different brand names, usually at lower prices.

Not illegal but can be challenged in court by the brand that owns the trademark.

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Key Characteristics:

- Can be high-quality or low-quality.
- May or may not use logos — some sellers disclose them as replicas.
- Legality depends on use of trademarks and intent to mislead.

When replicas are identical to existing products, they are illegal.

Counterfeit?

- A product purposely manufactured to mimic a registered and trademarked material under patent. Counterfeit!
- A product purposely sold in a container to mimic a registered product's container and label. Counterfeit!

Which one is Counterfeit?

Specifications and Additional Methodology

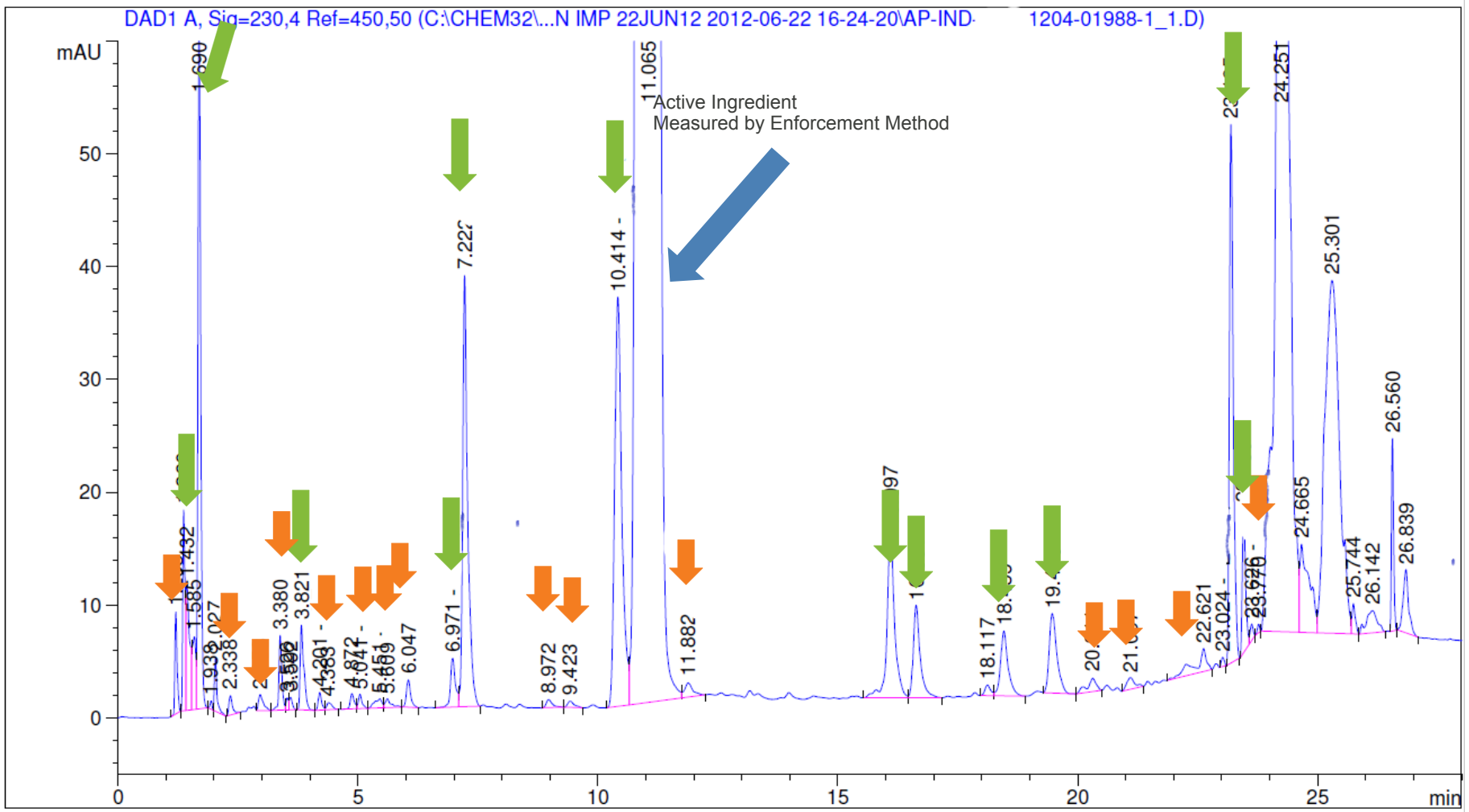
Other Required Regulatory Testing

- **Mass Balance: 98% or 980 g/kg**
  - Identify all impurities to 0.1 weight % or 1 g/kg
  - Includes
    - Organic Impurities
    - Inorganic Impurities
    - Water
    - Solvents
- **This is required but not public information.**
  - It is used to determine and submit specifications for each compound.
  - Every commercial batch of material is monitored for each component above the trigger level.

Other Required Regulatory Testing

- **Mass Balance: 98% or 980 g/kg**
  - **Identify all impurities to 0.1 weight % or 1 g/kg**
  - **Includes**
    - **Organic Impurities by LC or GC**
    - **Inorganic Impurities by IC**
    - **Water**
    - **Solvents by GC**
- **This is required but not public information.**
  - **It is used to determine and submit specifications for each compound.**

Typical Impurity profile chromatogram of an A.I. by LC/UV



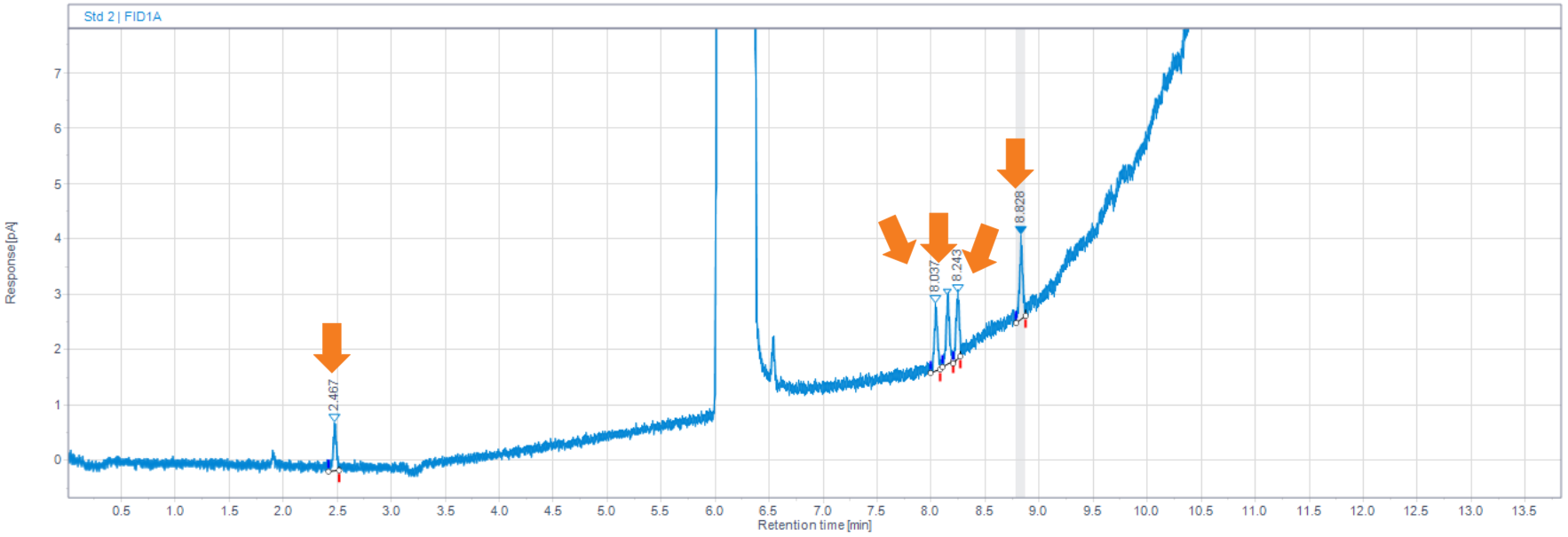
Other Required Regulatory Testing

- **Every commercial batch of material is monitored for each component in the specification.**
  - **For some products, this is thousands of batches/year.**
  - **Material is not released unless specifications are met.**

Terminology

- **Identify all impurities to 0.1 weight % or 1 g/kg**
  - **Any impurity above this level is considered a significant impurity**
  - **Any impurity below this level is considered an insignificant impurity.**
- **Significant and insignificant impurities are tracked to make sure everything is in the acceptable range as set by specifications.**

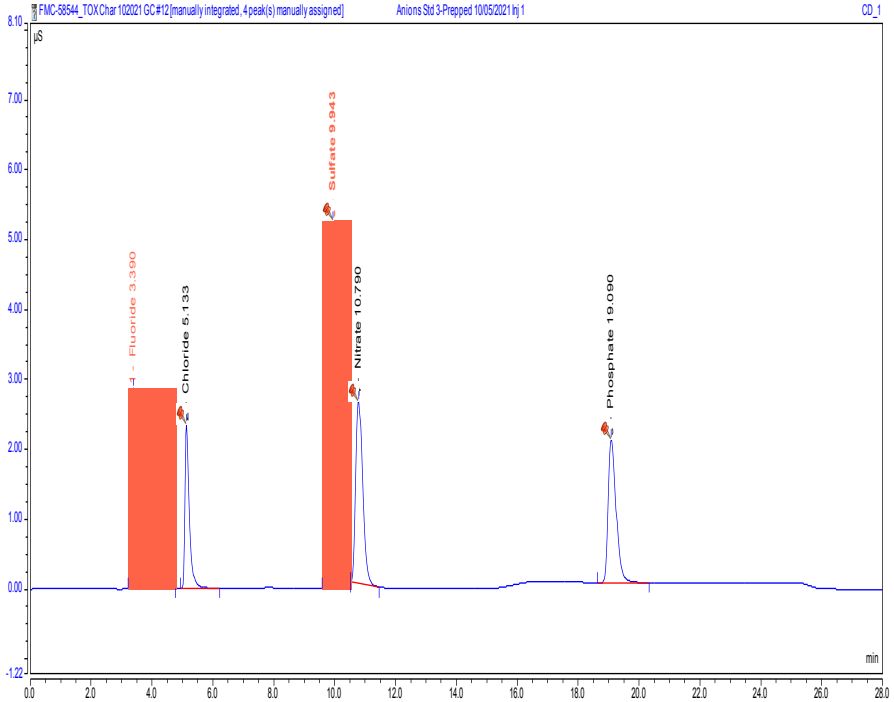
Typical Solvent Analysis Chromatogram by GC/FID

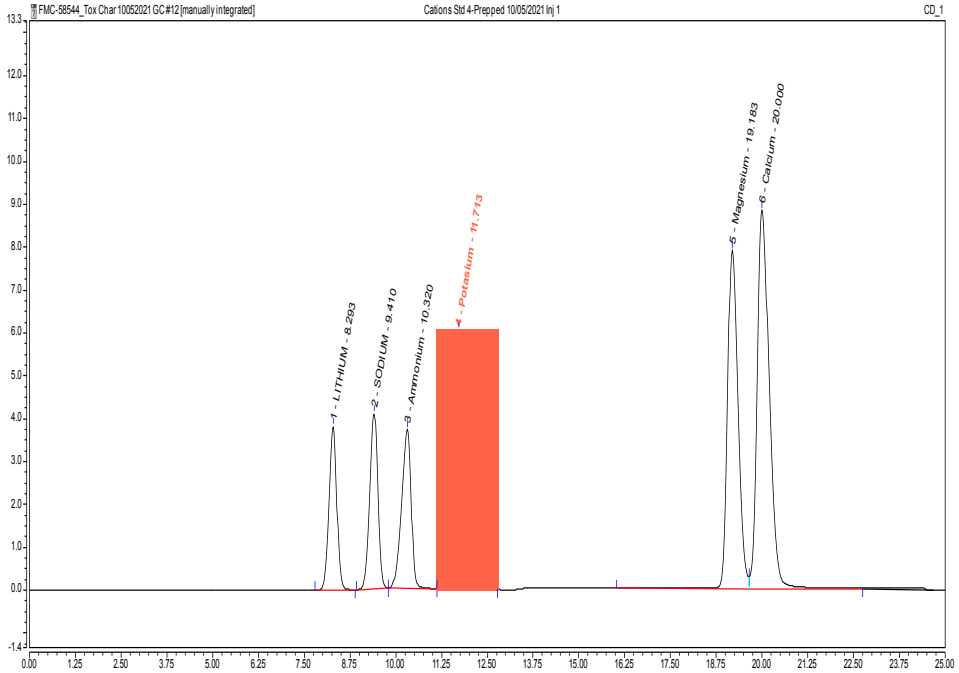


Residual Solvents are not always significant impurities, but they are always monitored.

Typical Ion Chromatography Standard Chromatogram using conductivity detection

Anion Standards





Anions and cations are typically insignificant impurities, but they are monitored.

There will also be a specification on H_2O

What does all of this required regulatory testing mean?

- **We know our products:**
  - Active ingredient
    - Tolerance level of active ingredient
    - And it is met with every production batch!
  - Identification of Significant impurities
      - Registered levels
      - Typical Manufactured levels
  - Identification of Insignificant impurities
      - Registered levels are < 0.1 wt%
      - Typical Manufactured levels
  - Solvent, inorganic content
      - Typical levels < 0.1 wt%
- And we maintain databases of our products analyses so that we can confirm the material meets specification when it enters into the chain of commerce.

.

Additional required registration testing…allows us to determine counterfeit material.

- ~~A product purposely manufactured to mimic a registered and trademarked material under patent.~~
- ~~A product purposely sold in a container to mimic a registered product's container and label.~~

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