



## An Introduction to Pharmaceutical Forensics

*"...Physical evidence cannot be wrong; it cannot perjure itself; it cannot be wholly absent – only its interpretation can err. Only human failure to find it, study and understand it, can diminish its value."*

*(Harris v. United States, 331 US 145, 1947)*

### Background on Forensic Science

Forensic science is generally defined as the application of multiple fields of scientific investigation to answer questions related to the legal system. The field of forensic science encompasses a broad range of scientific disciplines such as chemistry, biology, physics, materials science and toxicology, among others. Forensic science can be subdivided into several sub-specialties including trace evidence, serology, DNA testing, drug chemistry, questioned documents, impression evidence, crime scene evaluation and medical investigations. Significant differences between forensic science and conventional scientific fields lie not only in the legal arena in which forensic science resides, but in the evaluation of the resulting scientific data.

Where most scientific disciplines conclude with the summarization of scientific data, forensic science must go further, applying the conclusions of analytical testing to: 1) identify unknown materials, 2) compare questioned and known samples to determine the likelihood that the questioned and known sources may have originated from a common source and 3) evaluate the significance of such associations. The levels of association may range from similarities in class characteristics (such as a common shoe size, racial origin of a hair or generic polymer classification of a synthetic fiber) to the identification of a questioned sample to a known source (such as physical matching of tape and plastics, or identification of a fingerprint). The forensic scientist is trained in the evaluation of physical evidence to not only yield a scientific conclusion based on the analytical testing protocols, but to apply problem solving tactics to evaluate the significance of the data. This evaluation of data must then be communicated to a trier of fact (judges and juries) to explain the significance of scientific data in laymen terms.

### What Is Pharmaceutical Forensics?

Pharmaceutical forensics is a specialized field of examination that applies forensic expertise, analysis and problem solving principles to pharmaceutical deviation investigations. Often times, particulate contamination occurs in products, processes and customer-related investigations. In other instances, the need for detailed problem solving methodologies are required to determine the source of stains, discolorations, product defects and to understand the nature of similar products through reverse engineering and reformulation. The field of forensic trace evidence analysis is uniquely positioned as an investigative science that has historically dealt with these problems in a criminal environment. However, the methods of material isolation, testing, comparison and ultimate source determination commonly used in forensic investigations are easily transferrable across industries (as in pharmaceutical investigations) where detailed material characterization and source apportionment is critical.



## Forensic Evaluation for Pharmaceutical Investigations

The most significant aspect of a pharmaceutical investigation occurs in the initial evaluation, where the overall purpose is defined. Here, relevant questions are addressed through establishing a scientific protocol. In pharmaceutical forensics, typical questions include: What is this material? Where did it come from? What are common sources of this material? Does a questioned material "match" a known source material?

The identification of the foreign material relies on basic analytical testing methods utilized in most laboratories. The ability to take that information and interpret its relevance in the overall product lifecycle is the foundation of a pharmaceutical forensic investigation. To answer any questions established, it is imperative at this phase to not only understand the analytical testing protocols but the environment in which a foreign or unknown material originated. The investigator needs to understand the types of product materials inherent to the manufacturing and production process, as well as the main components present. For instance, if a particulate is found in the parenteral product, it is important to understand the environment in which it was produced to create a population of known exemplar samples for comparison. The basic flow to pharmaceutical forensic analysis includes:

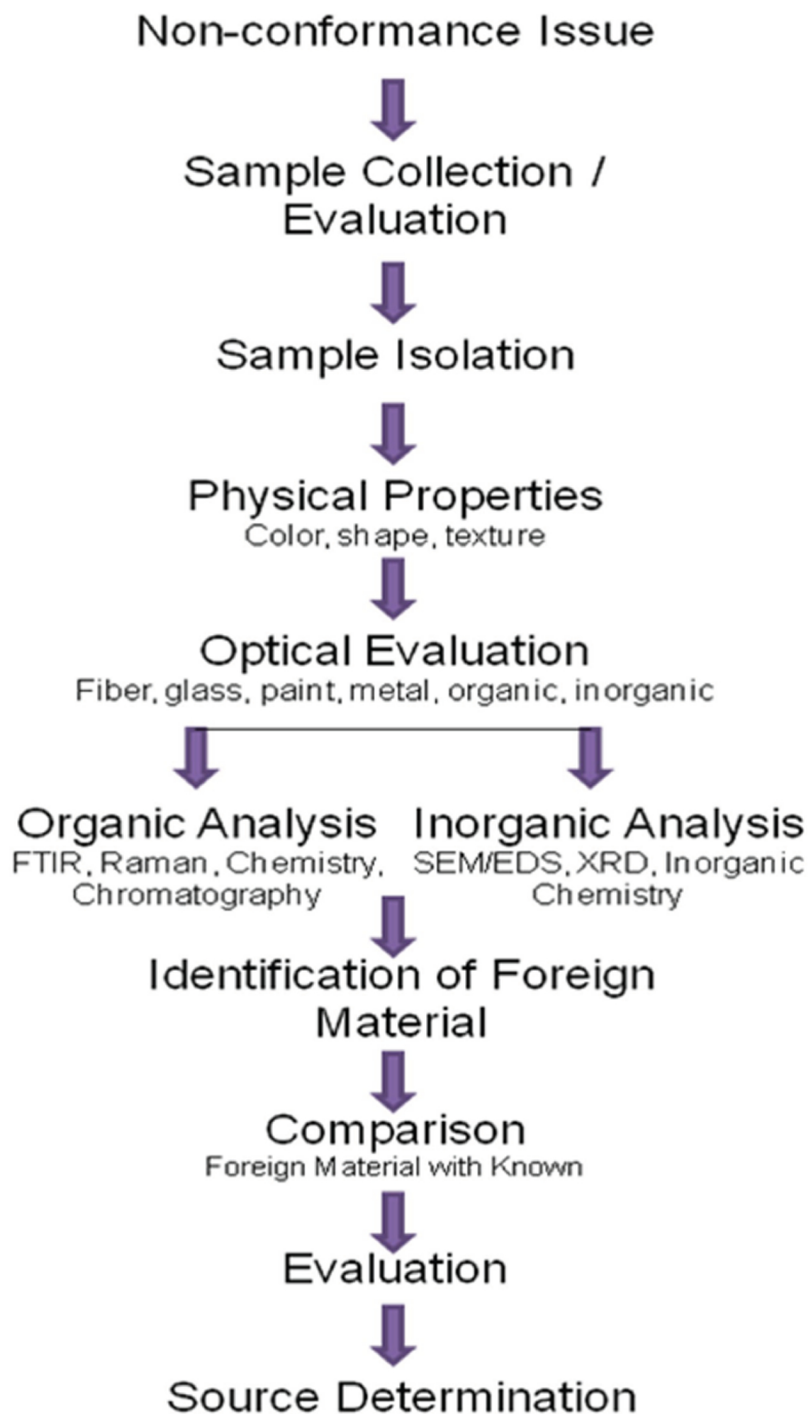
- Evaluation of the problem
- Laboratory/client communication
- Investigation of related process materials
- Investigation of related product/process materials
- Specialized analytical testing
- Forensic approach to materials characterization

## Pharmaceutical Particulate Examination

The main goals in any forensic investigation are to identify the questioned material of interest and compare this particulate to known source samples to determine possible origins of the unknown sample. In addition, the forensic scientist must understand the significance of various sample types and communicate that information in layman's terms to investigative teams, so that they can focus the investigation. This type of contamination identification and tracking is valuable to demonstrate efforts pharmaceutical companies make to identify contaminants and take corrective action as required by the FDA. This approach is also beneficial when validating new process methods and eliminating particulate contamination in manufacturing and packaging processes.

Due to the minute size of typical particulate contaminants (e.g. hair, fiber, paint, metal, glass, polymers), experience working with microscopic particulate is critical. Forensic trace evidence examiners specialize in the area of microscopic evidence analysis. They apply experience and training in identifying and comparing microscopic particulate in the following pharmaceutical areas: environmental particle contamination, particulate contamination from manufacturing process materials, particulate contamination from manufacturing product materials, and identification of customer-returned contaminants.

An understanding of various analytical testing methods, sample preparation and isolation of particulate is critical to the investigative approach. The flow of information and testing methods typically used in forensic particulate investigations is shown below.







## Other Critical Pharmaceutical Forensic Analyses

### Parenterals

The 100% inspection process is typical for parenteral manufacturing. Filled vials of product are visually inspected to identify potential contaminants. If a contaminant is identified, the product is removed for additional testing. Forensic trace evidence analysis focuses on the examination of these types of particulate. Numerous 483 Warning Letters have been issued over the years to manufacturers that have not adequately characterized these contaminant materials, identified their sources and implemented a solid plan to address this issue.

### Tablets

The presence of particulate in tablet manufacturing is also an important issue that is effectively addressed with solid forensic analysis. Whether it be a piece of stainless steel from production equipment or cross contamination from products manufactured in cross contaminating environments, the identification and source determination on a microscopic scale is imperative for complete contaminant investigation.

### Particle-free environments

Often times, manufacturers go to great lengths with filtration points to ensure a particle free environment, but neglect to account for peripheral sources of particulate contamination in the downstream process. Contamination can arise from the bottle washing process or shedding covering material that is used to protect the product containers. It can also occur through inherent particulate in downstream containers. An evaluation of the entire process and potential introduction points are important aspects of a thorough pharmaceutical forensic investigation.

### Sterile products

Another thing to note is that sterile does not mean particulate free. In instances where sterile materials are used, caution should always be taken in evaluating the potential source of particulate from containers. Routine rinse studies of vial lots and other downstream containers can ensure a particle free environment.

A forensic investigation of particulate imparts information beyond simply identifying the unknown material. Peripheral facts are taken into consideration to determine how and where potential sources of contamination may have occurred. An example of this is when dry, brittle cellulose particles are present. Typical laboratory testing may indicate the presence of a hair, but further examination of its physical properties may provide additional information such as exposure to dry or wet heat (autoclaving) to determine if it was in fact present in certain stages of the manufacturing process.

Pharmaceutical forensic analysis is not limited to particulate contamination investigations. In many cases, the experience of forensic investigation can help solve issues related to glass fracture of vials and bottles (thermal vs. mechanical fracturing and exposure to product), sources of stained regions on filtration devices, failure analysis of materials, packaging related issues such as ink, paper and adhesive investigation and product counterfeiting. A thorough investigative process is vital not only to understanding the circumstances surrounding non-conformance issues, but is critical in addressing the peripheral factors that are important in providing a final solution.