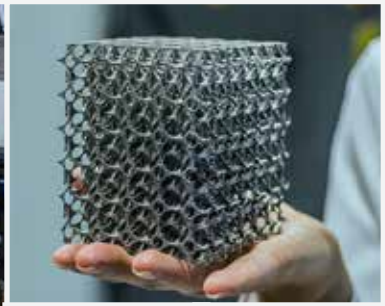
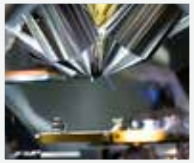




HOW DO YOU LEVERAGE THE POWER OF MATERIALS SCIENCE TO GET **GENERIC DRUGS** TO MARKET SMARTER, FASTER AND WITH LESS RISK?

eurofins | EAG Laboratories

How does Eurofins | EAG Laboratories expedite the generic drug development process?

Eurofins | EAG Laboratories' Material Sciences division has been performing investigative analytical chemistry for the pharmaceutical industry for over 25 years, performing failure investigations, unknown particle identifications and material characterizations. However, with the development of the FDA's guidance for the generic industry, our role has evolved into full reverse engineering of Reference Listed Drugs (RLDs) and Reference Standards (RSs).

Our primary focus is qualitative and quantitative analysis of excipients, two of the critical factors that must be addressed when demonstrating Q1/Q2 equivalence to the RLD (Qualitative Equivalence and Quantitative Equivalence). Since the issuance of the FDA's guidance document for acyclovir ointment, EAG has analyzed over 210 different RLD systems.

What is RLD Reverse Engineering?

Reverse engineering is the process of completely understanding the RLD from excipient grade and quantity to API polymorphism and the exact location of each component. Although the API and excipients of a formulation are provided with a product insert, this information is rarely sufficient to develop a comparable formulation.

At EAG Laboratories, we develop programs to answer our customers' questions about RLD products, including:

- **How much of each excipient is present?**
- **What grade of an excipient is present in the RLD?**
- **What is the polymorph of the API in a semi-solid?**
- **Is the API in our product equivalent to the RLD? Is it changing during formulation?**
- **How is the API distributed throughout the microbeads in an extended release capsule?**

The EAG Difference

As a premier scientific services provider, we recognize the importance of delivering results and answers to critical questions within a time frame to make an impact. We foster a proper sense of urgency with our scientists and engineers, accomplished by:

Capital resource management: In most cases within EAG, we have multiple instruments for our techniques. This capacity allows back-up instrumentation in the event an instrument is out of service. Additionally, the multiple pieces of equipment increase our overall capacity for throughput, allowing delivery of results within a reasonable time frame.

Efficient scientific services process: We have developed a proprietary, in-house LIMS system, resulting in efficient sample management and throughput in the lab.

Laboratory culture: Our scientists embrace an efficient laboratory culture and are passionate about delivering results to make a meaningful impact for our client's commercial success.

We leverage our size and knowledge base to support generic pharmaceutical companies. We have been supporting generic companies for many years and understand the unique needs of this industry.

When you work with EAG, you can expect:

- A dedicated team including a Ph.D. technical specialist, program director, and scientists
- A program kick-off discussion
- Weekly progress updates
- An easy to understand report with a chance to review prior to finalization. We want to make sure you are satisfied with the final product.

"Telling a customer that an RLD has 10% PVP in it is just not very helpful. They also need to know the exact grade/MW of PVP that was used."

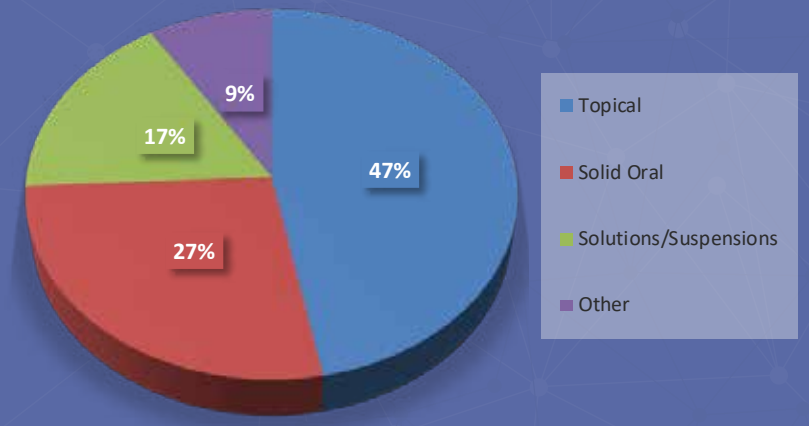
— An EAG scientist

EAG LABORATORIES' REVERSE ENGINEERING AT A GLANCE:

EAG has over 20 years of experience in supporting the generic drug industry.

214	The number of independent drug products on which we have performed reverse engineering studies.
105	The number of topical formulations we have reverse engineered.
3,000+	The total number of excipients that we have quantified in these studies.
300+	The number of discreet excipients that we have encountered.
19.2	The average number of days to completion of draft report for these studies.

PRODUCT TYPES



Topical creams, lotions, ointments and gel analysis

Roughly half of all the RLDs EAG has analyzed are topical creams, lotions, ointments and gels. With complex excipients, these systems require extensive analytical instrumentation and expertise. We are experienced in the separation and characterizations of RLD systems containing several excipients. A representative topical reverse engineering program will use a combination of techniques, including but not limited to: LC/MS, GC-MS, HPLC, GC, GPC, IC, ICP-MS, TGA, DSC, and Viscosity.

Examples of complex excipients in topicals include:

- Hydrocarbons
- Mineral oils
- Waxes
- Polyols
- Modified celluloses
- Carbomers
- Siloxanes
- Mono-, Di-, and Triglycerides
- Surfactants

EAG knows how to perform quantitation of excipients, from low-level single components to complex excipients experiencing major matrix effects or overlapping signals. After identifying the grade of material used as the excipient in the RLD, we then obtain reference standards of this material to use for quantitation. Whenever possible, we perform spiked additions to confirm the accuracy of our methodology. Some clients prefer to prepare their own formulations for our scientists to compare side-by-side with the RLD to further validate the data.

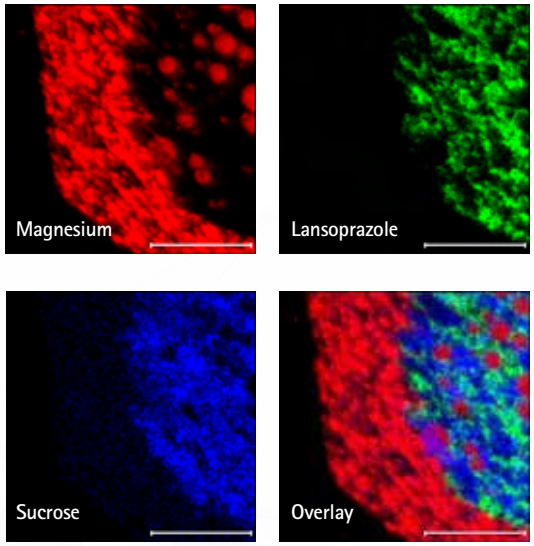
Polymer analysis for transdermals

Having been in the polymer analysis business for nearly 30 years, EAG Laboratories combines our knowledge and experience with pharma expectations to successfully reverse engineer many transdermal patches. We are well equipped with the polymer analysis techniques required for transdermals, such as MALS-GPC, DSC, TGA, DMA, TMA, Raman and FTIR. In addition to these, we also offer a wide range of cross-sectional analysis and mapping techniques (TOF-SIMs, Raman, FTIR, SEM-EDS, and X-Ray) to understand the 3D structure of the system, depth of layers, and the pinpoint location of each component in the product.

Solid oral dosage analysis

From tablets to extended release capsules, we investigate many different dosage systems to see how they are put together. We perform excipient characterizations and quantitations using a similar approach as other delivery systems. We also perform many cross-sectional studies to ascertain the location of the excipients within the capsule/tablet/bead to gain insight as to how the delivery system was constructed. We answer questions such as:

- Is there a sugar sphere core?
- Are there multiple applications of API or excipient form layers?
- Is there a disintegrant dispersed throughout the drug product with the API?



TOF-SIMS cross-sectional images of an antacid drug product show the presence of Mg, both in the talc exterior and $MgCO_3$ particles in the core; the API lansoprazole, and sucrose present with the lansoprazole. TOF-SIMS is extremely useful for APIs with an elemental makeup similar to the excipients present. While SEM-EDS data provides an elemental map, TOF-SIMS presents a molecular map from observing ions evolved from a surface.

Particle Identification

In addition to reverse engineering and characterization work, we also perform a wide variety of emergency contamination investigations and particle identifications. Particulate material commonly shows up in pharmaceutical raw materials, in-process samples and finished products. Understanding the identity of the species is required to determine root cause and evaluate potential corrective action plans.

We have developed microanalytical methods using a combination of organic characterization and surface analysis techniques to provide insight into the chemistry of the unknown material. Whether the offending material is organic or inorganic based, EAG has the equipment needed for full characterization. Typically, we will use FTIR microscopy, Raman microscopy, XPS/ESCA, and/or TOF-SIMS for organics and XPS/ESCA, Auger Electron Spectroscopy, SEM/EDS or XRF to provide elemental information and additional speciation of inorganics.

Contamination Identification

In addition to particle identification work, we also analyze hazes, films, oils and residues appearing in final products as well as on equipment, containers or from any other point in the manufacturing process. EAG Laboratories is fully equipped with the necessary instrumentation, from FTIR, NMR, and Raman to GC-MS and LC/MS. By performing unknown characterizations for over 15 years, we have developed our own internal LC/MS library of mass spectral data of common contaminants. This information is extremely useful for quickly identifying impurities and helping our customers make informed decisions about their products.

Impurity Identification

During stability studies, new impurity peaks can arise that do not match those identified and profiled during forced degradation or extractable/leachable studies. Our team is experienced in performing rapid method transfers to replicate our client's chromatographic conditions. EAG can also convert HPLC methods to conditions compatible with LC/MS instrumentation. Once a suitable method is in place, we use LC with high resolution mass spectrometry (LC-HRMS) to identify the impurity and propose a structure. EAG can either acquire or synthesize a standard to confirm the incident peak. This material can then also serve as a reference standard for future stability tests.

CMC Analytical Support

EAG Laboratories offers comprehensive CMC analytical support including multi-disciplinary, multi-technique analytical method development and validation, complete stability program management and in-depth extractables and leachables expertise. Our analytically focused CRO has deep experience in method development, program design and complex study execution.

Custom Synthesis

Our synthesis team brings unparalleled expertise to custom synthesis and small-scale manufacture of intermediates, impurities, analogs, metabolites, analytical standards, DEA-controlled substances, and other chemical compounds. We have extensive experience with multi-step and other complex synthesis projects, and our full suite of analytical services ensures quick turnaround of purity and structural confirmation. We can generate material from mg to kg scale to meet your current and future needs. Our custom synthesis teams have expertise in:

- Small molecule synthesis
- Heterocycles chemistry
- Steroids
- Opioids
- Radiolabeled synthesis (^{14}C, ^{3}H)
- Impurity reference standards

Other Services

EAG Laboratories also performs API characterization ranging from XRD for polymorph characterization to DSC, TGA, Raman and other techniques. We also perform particle size investigations of APIs or excipient particles in semi-solid matrixes using microscope Raman with mapping. Additional services our generic pharmaceutical clients have found helpful include:

- Glass delamination investigations using SIMS
- Elemental analysis
- Physical characterizations
- Polymer analysis

We understand urgency

We recognize the importance of urgency in product investigations, with a highly efficient and cost-effective approach to contaminant and particle identification. EAG's dedicated team guarantees same-day response from a technical specialist.

	Organic Techniques										Elemental					Thermal		Imaging							XRD	Surface Analysis		Physical	
	LCMS	HPLC	GCMS	GC	Pyro-GCMS	FTIR	NMR	Raman	GPC	Ion Chromatography	ICP-OES	ICP-MS	GDMS	IGA	XRF	TGA	DSC	Optical Microscopy	Optical Profilometry	SEM-EDS	TEM/STEM	Raman Microscopy	AFM	TOF-SIMS	XRD	SIMS	XPS/ESCA	Tensiometry	Viscometry
Grade Determination	✓	✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	✓			✓		✓		✓			✓		
Excipient Quantitation	✓	✓	✓	✓			✓		✓	✓	✓	✓		✓		✓									✓				
RLD Construction	✓		✓			✓	✓	✓	✓	✓								✓		✓		✓		✓			✓	✓	✓
Microstructure Analysis (Morphology)																		✓	✓	✓		✓	✓	✓				✓	✓
API Polymorph and Characterization	✓					✓	✓	✓								✓	✓			✓		✓			✓				
Unknown Compound Investigation	✓		✓			✓		✓	✓	✓										✓		✓		✓					
Particle/Contaminant Investigation	✓		✓			✓		✓			✓	✓			✓			✓		✓		✓		✓					
Glass Delamination												✓			✓			✓		✓						✓	✓		
Elemental Analysis											✓	✓	✓	✓	✓					✓							✓		
Physical Characterization																												✓	✓
Polymer Analysis	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓		✓	✓	✓	✓	✓			✓	✓	✓
Metallurgical Analysis											✓	✓	✓		✓			✓		✓	✓						✓		

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