

ONLINE EXCLUSIVE - Lab Microscopy | Solve Vial Delamination Before it Starts

By Kristie J. Diebold

Manufacturers becoming more proactive in testing for product-packaging compatibility

After years of research and millions of dollars invested in shepherding a drug to market, a manufacturer has rigorously tested every aspect of a new drug's safety and efficacy. But what about the packaging?

Packaging is a vital and critical step in the drug development process and should be tested just as rigorously as the drug in order to establish product compatibility. Otherwise, there could be perilous consequences, both for the consumers' well being and for the manufacturer's good name.

With this risk in mind, progressive manufacturers are moving away from reactive quality testing and toward proactive pre-testing for product-packaging compatibility—testing how drug solutions will react with packaging before the product is brought to market.

These quality control issues are particularly important for injectables and liquid solutions supplied in glass vials, products that are often overlooked for packaging testing. Made of common borosilicate and soda lime glasses, the vials are chosen for their strong barrier properties, cost effectiveness, and perceived stability. Glass vials are presumed to be safe because of their longevity in the industry, but long history does not equal safety. Because glass vials can pose contamination risks that are often invisible to the naked eye, they should be pre-tested to ensure product compatibility.

Glass Delamination a Risk

Glass vials used for pharmaceutical products must withstand attack from many chemicals and processes during the manufacturing process, including heat treatment, sterilization, product filling, and storage of potent drug mixtures. In rare instances, chemicals from the product solution or manufacturing process can cause a vial to delaminate and discolor, posing serious contamination risk to the drug product and potential liability for the drug manufacturer.

When glass delaminates, the top layers of a glass surface separate and flake off at a scale that is typically invisible to the naked eye. Delamination is often correlated with pitting, extremely localized corrosion that creates small holes in the glass surface.

Delamination can occur at any point during the vial's life, whether it is during manufacturing (e.g., fusion at the neck or base where delamination and/or pitting are frequently found), during heat treatment or sterilization, or after the manufacturing process due to the vial's adverse reactions to its contents (e.g., etching due to an acidic or basic solution, or one with a high sodium or salt content).

There are many ways to investigate glass delamination in pharmaceutical vials, ranging from examining the chemical nature of the vial's contents to evaluating manufacturing conditions. Because most pharma quality control departments are not equipped for extensive microanalytical testing, they must turn to independent laboratories to discover whether glass delamination is occurring.

Recently, a leading manufacturer of branded injectable pharmaceutical products decided to pre-test product-package compatibility because it determined that delamination could occur in one of its drug candidates. The injectable company predicted that the drug, which had a high pH level, would react unfavorably with its traditional glass vial packaging, but the company did not have the equipment or expertise to further examine the issue. The injectable company consulted with McCrone Associates, the microanalysis division of The McCrone Group, to compare vials from three different manufacturers for glass delamination and corrosion potential. For confidentiality purposes, we will refer to them as companies A, B, and C.

Prior to sending the vials to McCrone Associates, the drug company stored them at varying temperatures for different time frames to determine the conditions under which the vials were least likely to corrode. Vials from all three companies were stored at 55°C for two weeks, while additional sets of vials from the three companies were stored at 40°C, 30°C, 25°C, and 4°C for four weeks. A third set of vials, from company B, was studied at these temperatures for eight weeks. These vials warranted additional study because they exhibited numerous striations along the inner vial wall, a characteristic that, while likely a byproduct of their manufacture, was a potentially harmful variable (see Table 1).

At First Sight

Researchers first examined the empty vials using a stereomicroscope. The scientists noticed some pitting and striations on a few of the vials across each set but could make no definitive assessments of delamination. The vials were then submitted to McCrone's ISO Class 5 cleanroom for further sample preparation and more rigorous examination.

Although the manufacturer sent empty vials, McCrone recommends that pharmaceutical manufacturers submit their vials filled with the original drug solution for drug compatibility testing and vial evaluation. With proper illumination and microscope set-up, an examination of the vial can reveal any particulate matter floating in the solution. Often particulates are not noticeable with visual

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Four Ways to Avoid Delamination Disasters

When pre-testing your glass vials for product compatibility, do not limit your examinations to the vials themselves. Remember that if the stopper and seal materials will touch the solution, they also require testing.

Whether pre-testing or doing a regular quality control examination, make sure to look for pitting. Although pitting is usually invisible to the naked eye, a simple stereomicroscope can often detect it. Pitting

inspection alone, and only a stereomicroscope exam will reveal them suspended in solution.

Using a combination of transmitted light, coaxial illumination, and fiber optic oblique illumination, the nature of the particulate can be characterized. Microscopists look for a “twinkling effect” that results when light reflects off particulate contaminants in solution. Thus, an initial examination with a stereomicroscope can lead to early identification of delamination problems, saving both time and money on additional testing.

Next, whether the vials are filled or empty, they must be prepared for microanalysis. To prevent cross-contamination, sample preparation must be performed in a cleanroom environment. When performing microanalysis, even tiny amounts of introduced contaminants can lead to confusion and potentially incorrect conclusions.

In this case, the scientists carefully broke the empty vials into smaller pieces to examine the interior surfaces, then mounted the individual fragments on different substrates for various analyses.

For drug-filled vials, scientists opened the vials in an ISO Class 5 cleanroom hood and filtered the liquid onto a polycarbonate membrane filter to aid with characterization and isolation of the particulates. Microscopists then used finely pointed tungsten needles, only a few micrometers thick at the tip, to isolate the suspected contaminant(s) and prepare samples for analysis. These needles, far smaller than commercial dissecting needles, are essential for small particle isolation. McCrone typically manufactures its needles in house to maximize quality and utility.

Once isolated, the filtered particulate and vial pieces were mounted on various substrates for further analysis. The substrates varied depending on the analytical technique and instrumentation available. For instance, for elemental analysis in an electron microprobe, a polished carbon substrate was typically used; for infrared analysis, a polished salt crystal was used. Subsequent analysis of the small particles using additional analytical techniques often requires carefully moving the particles to different substrates. Therefore, each particle must be treated uniquely, and proper control in a cleanroom environment is the only way to ensure its integrity.

Vial Microanalysis

For this case study, after further examination in the cleanroom, scientists mounted particulate from the filtered solutions and residues from the inner vial walls on potassium bromide crystals for micro-Fourier transform infrared (FTIR) spectrometry analysis. They used infrared spectroscopy to identify organic—and some inorganic—materials present, including glass. The micro-FTIR instrument shines a beam of infrared radiation through the sample and records the different frequencies at which the sample absorbs the light.

Company A’s vials showed an unusual pink and brown discoloration in all temperature ranges, so scientists isolated a portion of the discoloration from the vial wall of the 55°C set for FTIR analysis, along with delamination flakes, to search for a similarity between them. Both IR spectra showed a broad band at ~1100 cm⁻¹, characteristic of silica. This suggested that the discoloration was a property of the glass and not a foreign contaminant.

The scientists then mounted particulate filtered from the glass vials on a carbon substrate for scanning electron microscopy/energy dispersive spectroscopy (SEM/EDS) analysis. These analyses can confirm whether the contaminant is glass and can provide clues to the conditions under which delamination is most likely to occur. The SEM/EDS method yields two types of information: high-resolution electron images showing the features of the contaminant and X-ray spectra of the elemental constituents present in the sample. SEM/EDS is commonly used to analyze inorganic materials to identify particulate matter such as metals and glass fragments. SEM/EDS analysis can also be performed directly on large fragments of glass from vials.

For some of the company C vials, SEM/EDS captured images of glass pieces flaking off the interior walls; this was confirmed to be glass delamination (see Figure 1). Imaging of the glass fragments in the SEM/EDS also revealed pitting on the glass surface, and further examination at higher magnification demonstrated tapering and enlargement of the pits (see Figures 2 and 3), indicating that as pitting increased, the pits’ borders overlapped and caused pieces of glass to flake off or delaminate.

Finally, the scientists examined the vial fragments using X-ray photoelectron spectroscopy (XPS, also known as electron spectroscopy for chemical analysis, or ESCA). XPS is the method of choice for analysis of very thin surface films. In the XPS instrument, an X-ray beam generates photoelectrons in the sample; these, in turn, provide analytical information from only the outermost (~5 nm) surface of the sample. This technique is well suited for analyzing thin surface layers and residues on the surface of solid samples, and it is often essential for determining the chemical nature of glass delamination.

is often a precursor to or an indicator of delamination, so examine the inside of your empty vials under the scope early and often.

Most pharmaceutical manufacturers are not equipped with the specialized skills and expertise available at independent analytical laboratories. Consider outsourcing your vial testing and contamination analyses to a trusted laboratory, especially if you discover pitting in your routine checks.

Think about introducing barrier coatings to the inside of your vials. Typical coatings include ceramics, polymers, and silicones to protect the glass from the drug solution.

Table 1: RESULTS OF DELAMINATION STUDIES

	COMPANY A	COMPANY B	COMPANY C
55°C for two weeks	Pitting at base; delamination bands at product fill line. Pink/brown residue below delamination band.	Pitting throughout; no delamination.	Pitting at base and fine pitting at neck; delamination at fill line and base.
48°C, 30°C, 25°C, and 4°C for four weeks	Pitting at base and fine pitting at neck at all temperatures; no delamination.	Pitting at base at all temperatures except 4°C; no delamination.	Pitting at base in every temperature; delamination at every temperature.
48°C, 30°C, 25°C, and 4°C for eight weeks	Not tested.	Pitting at base for all temperatures except 25°C; delamination at 42°C and 30°C.	Not tested.

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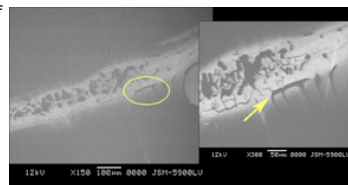


IMAGE COURTESY OF THE MCCRONE GROUP

Figure 1: Glass pieces flaking off the interior walls of company C vials, captured by scanning electron microscopy/energy dispersive spectroscopy analysis, confirmed glass delamination was occurring.

In the vials from all three companies, XPS analysis revealed the chemical composition of the glass surfaces of the vials and showed changes in the relative amounts of glass component elements sodium (Na), calcium (Ca), magnesium (Mg), and silicon (Si) in the fragments. These chemical changes are indicators of chemical attack on the glass by the drug product solution, which in turn produced preferential leaching of reactive components. The XPS therefore revealed that this chemical attack was the cause of pitting and, eventually, the delamination of the vials.

Drug Company Case Study Findings

Using a combination of light microscopy, micro-FTIR, SEM/EDS, and XPS analyses, we found that the highly basic drug in this compatibility study produced glass delamination in all three tested vials and that the delamination often occurred near the fill line. McCrone also found that as the storage temperature and time increased for these vials, their vulnerability to delamination increased.

Pitting is often indicative of and a precursor to delamination. Our analytical results in this study showed that as pits grow larger and/or appear in greater number, they may begin to consolidate to produce the flat flakes typical of glass delamination. (For complete study results, see Table 1)

The drug company discontinued the development of the highly basic drug after reviewing the analytical results. "Patient safety comes first—and this particular drug reacted with packaging in volatile ways," said the company's lead product developer. "Even if we could solve the delamination problem with new kinds of vials or different packaging, there might still be a risk for extractables or leachables due to the drug's high pH level and the way the drug reacts with its packaging. We saved money on additional testing and decided the drug was not worth the potential risk of letting it go to market."

When bringing a product to market, packaging is a critical step. Unfortunately, it is often the last step, and companies can easily overlook potential packaging problems until very late in product development. As this case study illustrated, the wrong packaging can delay or even shut down a developing project. Therefore, the package's stability, functional performance, and integrity must be tested early in the development process.

Manufacturers should select packaging components for their physiochemical compatibility with the product, for proper fit and package functionality, and for their ability to withstand processes such as sterilization and the anticipated product distribution cycle. Whenever possible, manufacturers should challenge the integrity and functional performance of the package at the limits of component specifications and the operational extremes of filling, assembly, shelf life, and distribution. Laboratories specializing in microanalysis can provide invaluable information in the assessment of packaging integrity, drug compatibility, and possible failure mechanisms.

Pharmaceutical industry quality control personnel face considerable challenges in keeping abreast of not only evolving regulatory requirements but also of the various microanalytical capabilities available to resolve their problems. Many educational institutions cater to this growing need.

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Figure 2 and Figure 3: Fine pitting on the glass surface of vials demonstrates tapering and enlargement of pits.

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