



An International Pharmaceutical
Supply Chain Consortium

Highlights from June 2011 Glass Container Delamination Scientific Symposium

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Rx-360 Glass Symposium 25-May-2011 Meeting Proceedings

I. INTRODUCTION

The Rx-360 Glass Delamination Scientific Symposium was held on 25 May 2011 in Arlington, VA. Over 150 people attended, including pharmaceutical manufacturers, glass manufacturers/suppliers, and representatives from USP, FDA CDER and CBER review divisions, and the FDA Office of Compliance. The program and slides are posted on the Rx-360 web site and can be viewed and downloaded by [clicking here](#). The overview below provides key points from the symposium, and potential opportunities and next steps for the industry. The summary provides some points from the various presentations and details from the panel and audience discussions.

II. OVERVIEW AND OPPORTUNITIES

Key Points

- A “Quality by Design” mind-set and approaches with respect to glass delamination needs to be developed among glass suppliers/manufactures and pharmaceutical manufacturers. This would include developing a better understanding of critical manufacturing/processing parameters that could correlate to delamination events, better understanding of correlations between specific drug product formulation parameters and delamination events; identification of predictive tests; identification of useful test methods specifically geared to glass delamination.
- A glass delamination event, i.e., the detection of actual visible flakes, is the last step in any delamination mechanism/process, and it is a kinetic event that appears to be dependant on manufacture of the glass, treatment of glass after manufacture (e.g., exposure to moisture), and specific formulations (e.g., pH levels and buffer systems). It will be helpful to develop predictive approaches and tests to understanding how and when delamination could occur for your product.
- Improved communication and partnering among glass suppliers and pharmaceutical manufactures is needed. This should include open communication of glass manufacturing processes, aspects of glass formulations, and aspects of pharmaceutical formulations.
- On-going basic research on glass surface chemistry will continue to be helpful in developing knowledge and understanding that could feed into Quality by Design approaches. There appear to be a number of different mechanisms as well as surface layer properties that may lead to delamination, and these need to be better understood.



Opportunities

- Rx-360 could play a role in bringing together suppliers, pharmaceutical manufacturers, academics and regulators in developing
 - Continuing forums for on-going discussion of glass delamination events, case studies, emerging technologies, etc.
 - Collaborating between glass manufacturers, pharmaceutical manufacturers and equipment manufacturers to develop standard glass container shipping package configurations, etc.
 - Points-to-Consider documents on scientific/technical and regulatory issues related to glass delamination.
 - An expanded program for joint testing of glasses from various suppliers under different conditions that would provide information on critical parameters impacting glass delamination, and/or provide models for how companies could evaluate glasses for their products under a Quality by Design paradigm.

III. SUMMARY

Session 1: Background/Context

Robert Swift, Amgen. Amgen Recall Experience

- Delamination seen in broad selection of borosilicate glass vials from a number of different suppliers
- Delamination appears to be from an unstable layer on particular areas of the inside surface of the vial (not from all areas of the inside surface)
- Glass lamellae are generally very thin, about 1 μm thick, and can bend and fold. Numbers within vials ranged from approximately 100-750 particles.
- Delamination did not occur right away (upon formulation/glass surface contact), but rather took several months to occur after filling
- The time lag between filling and the appearance of glass lamellae (visible to the eye) and the rate of incidence varied depending on the source of vial supply
- Higher alkalinity and higher citrate concentrations tended to accelerate delamination and increase the rate of incidence in susceptible vial batches



Michael Eakins, Eakins and Assoc. USP and PDA Considerations

- USP is in the process of updating chapters related to glass containers, specifically <660> Containers/Glass and <1660> Evaluation of Inner Surface Durability of Glass Containers. An extractables studies chapter will be created as well. <1660> will be revised through the Packaging Storage and Distribution Expert Committee and the Physical Analysis Expert Committee, with publication targeted to 4Q 2011.
- USP 660 needs to be revised. Do tests need to be added? If so, what tests? Should the specifications be tightened? Should additional tests/specifications for biotechnology packaging be included?

Kris Evans, Amgen. Audit and Inspection Findings

- The Food Drug and Cosmetic Act defines the container closure systems as part of the “drug,” allowing FDA to inspect these aspects of the product
- FDA has recently issued the process validation guidance, which encourages process validation throughout the product lifecycle. The guideline emphasizes variation as detrimental to quality, and supports approaches to understand the source and impact on the manufacturing process of such variation.
- Process control will also require close collaboration among customer and supplier.
- The industry, both pharmaceutical manufacturers and suppliers, have not yet fully adopted the concept of designing rather than testing quality into a product.
- The European Pharmacopoeia glass tests are often used to determine quality, including delamination susceptibility, but the test results do not correlate with delamination. Industry should consider what are the critical process parameters that can lead to delamination, as well as the critical parameters related to the product that cause delamination susceptibility, and develop a better understanding of product failures and sources of problems through in-process sampling, non-conformance investigations, etc. These approaches are not done in the glass industry.

Panel Discussion

- Mr. Van Trieste provided further context for how serious the glass delamination issue was for patients, healthcare providers, regulators and the company. He explained that in order to address the problem, Amgen recalled every lot of drug product using the glass vials of concern, and did this in an incremental process to ensure that patients had access to quality and safe critical medicines, while the recall was being initiated and replacement product was being produced. The recall included approximately 300 lots, with each lot containing 100,000 vials. The recall was very expensive. Going forward to address the issue, Amgen now puts 800 vials on stability for visual examination of all products during development and includes the first 10 batches of the impacted product using the new vials, and does real time testing just to evaluate glass quality. Further,

Amgen worked with suppliers as well as wholesalers and distributors, and implemented a conservative expiry period for the vials. He noted that regulators are primarily interested in real-time data more than accelerated data. If delamination occurs in marketed product, it is very difficult for patients, healthcare providers and the industry. He noted that FDA worked collaboratively with Amgen to help address the issue for their products.

- A glass supplier noted that often, suppliers do not have staff to support non-conformance investigations and in-process control set-ups, and that the pharmaceutical industry needs to recognize this and provide assistance. Mr. Evans explained that outside expertise could help companies to better understand how quality by design approaches can be effectively implemented.
- What works for one product may not work for another. Whether or not delamination occurs depends on the formulation in contact with the glass surface layer. Some products should not be in glass at all, but they are still packaged in glass, e.g., sodium bicarbonate. Is surface alkalinity a cause or a result of delamination -- data can show both. Industry is still lacking a fundamental understanding of the causes of delamination, but it is also the case that it is product specific. Industry and regulators have not defined what acceptable quality means in this instance and this is why we do not have consistent quality.
- Delamination is not easy to detect and control. From the case studies, it appears that the percentages are 1 in thousands or millions of vials. How do you develop a meaningful specification or acceptance criteria? The challenge we face is how do we manage/control the low rate of occurrence? The event could be triggered by the manufacturing process, how the vial is treated when filling, etc. How far back in the process do we go to be able to find a predisposition for a very small event?
- The pharmacopeia tests should be considered starting points, as each formulation has its own issues. Dr. Eakins asked the participants if they consider 3 tests (powder, arsenic, grains) to be sufficient to control quality of glass containers. About 1/3 of the audience did not think the tests are adequate, but none have told the USP. He noted that the USP wants to hear feedback from industry, and that USP recognizes the need to revise its chapters, and needs to hear from industry what revisions should be made, what tests included, etc. Regarding glass delamination, it is not completely clear what tests would be useful in a meaningful, predictive way. Currently we report what we detect/see.
- The industry should be improving the properties of glass. Current tests in the EP and USP are being used and products meet the standards -- so are the tests telling us the right things? Need to combine what we know now with current discussions on new products, and suppliers need to work with the pharma industry.
- Having better characterization data on the glass as well as the drug product could help companies avoid a delamination event. Further companies will need to develop an understanding of the manufacturing process and how process parameters affect the glass/material being made, and develop a design space for the material. This would need to be done for the drug product as well, linking the glass manufacturing information with the drug product information. It would also help to improve traceability – to be able to track each vial from a particular batch of vials, know when it was made into drug



product (exposed to formulation) and therefore be able to link a delamination event with the original vial batch and understand the timing of the occurrence.

Audience Questions

- Companies need to know that glass surface quality is good from the beginning – so do I need to test the internal surface to know what my starting point is? Do we need to cut open all the vials? Have vendors look at this?
 - Delamination is a kinetic event, so a glass may look fine incoming, but may delaminate at 2 months, and if an event occurs, the product formulation is also a factor. Unfortunately there are often no original vials to examine after the event because of the length of time it takes for the event to occur. There may be no tell-tale signs at the start that the glass may delaminate, although there could be some indicators that glass quality could deteriorate.
 - It is not clear what tests would be helpful. USP tests are titration tests on individual vials and will provide an average of the inside surface of the vial. But delamination occurs only on specific a portion of the surface of the vials. How do we better understand the root causes? Industry transitioned from certain vials to EP vials. However, flaking appears to be random. No correlation between EP and flaking. Hydrolytic test
 - There are good manufacturing processes and bad manufacturing processes. Good processes will provide a higher probability that no delamination will occur. But an aggressive drug may still cause delamination. Within the glass industry there are tests to determine if delamination is probable, and you can address this with process control. EP33 has been made through establishing careful process controls, but these approaches appear to have been forgotten or lost over time. One supplier is doing a delamination study with a university – all of the glass industry should do this type of study.
- In the case study, the flake was several microns wide, and about 1 micron thick. To conduct EDS the sample has to be on a substrate. With a flake that thin, how do you know that you are not analyzing the substrate rather than the flake?
 - For the EDS testing, the lamellae were analyzed on polycarbonate filters.
- Glass delamination is unpredictable, so how do you set expiry date – delamination may occur at 18 or 6 months?
 - In the Amgen case, the company talked with FDA about approaches to setting the dates as well as providing products to patients. The company needed to share a great deal of data with FDA in order to establish an agreeable timeframe for expiry. The company looked at all products using the vials. Although there is never 100% certainty that the dates will prevent delamination, the dates are conservative. These dates were also implemented along with extensive in-process controls at glass manufacturing, controls of incoming materials, and during product manufacture. The company also put thousands of vials on stability. The company will eventually switch out to different vials, and will use real time data to do this.

- We should differentiate between marketed product and products in development. If you see preliminary signs of potential delamination in development then you can do stability studies to see what might happen and use this information to make a corporate risk/benefit decision.
- Has FDA asked companies to consider plastic as an alternative?
 - Companies are looking at many options. But for some products the formulation or the API, especially biologics, may be very sensitive to new extractables and leachables related to container changes and produce unanticipated safety or efficacy results.

Session 2: Mechanisms of Glass Delamination

Carlo Pantano, Pennsylvania State University. Science of Glass Corrosion

- The rate of delamination can depend on the uniformity of the glass surface. When exposed to water, the glass surface will become less dense, the composition will change, with the introduction of oxygen and hydrogen to the surface atoms. The flakes that we detect are actually bits of this modified glass layer, not the original glass (i.e., the chemical composition will be different from the bulk glass).
- It is possible that the modified surface is like a gel layer, and it is this gel layer that becomes lamellae. Because they contain water, they will shrink when dehydrated.
- pH of the formulation/environment as well as composition of the glass will have large effects on the thickness of the surface layer.
- Generally, the flakes seen from delamination mechanisms are larger and more flexible than what you might see for other types of glass particles

Emmanuel Guadagnino, Stevanato Group. Product Contact and Glass Interactions

- The first stage of a delamination process, both for soda-lime and borosilicate glasses, is the formation of an altered silica enriched layer. Re-hydration of the layer can result in surface swelling and flaking
- pH 9 with small glass containers can give dissolution, not just delamination (precipitation of silicate products as well as delamination). Neutral solutions do not tend to dissolve the silica layer, but can give leaching and hydration.
- EP titration values are not reliable indicators of delamination risk, particularly at higher pH values (8 or higher). Citric acid is three time more aggressive than glutaric and cause extensive delamination at pH 8.
- Accelerated tests with KCl and the increase of dissolved silica by ICP can be used as reliable indicator of glass corrosion and delamination propensity.

Ronald Iacocca, Eli Lilly. Glass Delamination in Pharmaceuticals

- Complexity of the glass and the formulation, surface layers, the way the glass is manufactured (e.g., flame polishing, annealing) or treated after manufacture (e.g., washing, depyrogenation) all can effect the propensity for delamination.
- The basis for delamination is exposure to water/moisture. It is known that moisture has a great effect on glass, e.g., antique glasses in museums are kept in humidity controlled environments, stained glasses cannot be washed under risk of color changes). The effect on the surface layer corresponds to the depth of water integration. For a lyophilized product that is in liquid form for only a short time, then delamination may not be an issue.
- Compendia tests are incomplete in the sense that other tests can be done that could be predictive – you want to be able to understand and build knowledge early in the development process regarding the propensity for delamination, rather than waiting to see visible flakes. Formation of flakes is the final step in the delamination process. It would be helpful to be able to link test results with the occurrence of flakes. Understanding potential mechanisms of delamination for your product, what parameters will impact the delamination process (e.g., changes in pH, changes to the chemical nature of the glass). There is a need for more predictive testing that you can use to link observations of the glass to actual delamination, and data that would allow you to understand the glass delamination design space for your product – “quality by design” information. This will need to include working with your supplier to understand manufacturing process, potentially compositional information, etc.
- The appearance of flakes, the rate and extent of delamination, and the root cause, will be product specific, although it is usually not the API but the buffers/solvent that will encourage the delamination process.

Matthew Hall, Alfred University. Design of Experiments to Understand Glass Delamination

- The DoE looked at manufacturing processes such as forming operations, different sized vials, and used dynamic light scattering to examine delamination mechanisms prior to actual visible flaking.
- Location of the delamination will be specific. Different areas of the vials will be susceptible, and this seems to be based on how the vials are physically manufactured (e.g., ring of susceptibility near bottom of vial where bottom has been attached to the glass tube). Also molded versus tubing vials will have different susceptibility. Heterogeneity of the glass will have an effect on susceptibility.

Panel Discussion

- It would be helpful if a larger experiment and DoE was done that included a large number of glass suppliers (not just one glass supplier). Is this something that the pharmaceutical industry should fund and expand to include more variables? It wouldn't make sense to do these types of studies in isolation – one study on one glass manufacturer's processes and a separate one on another. A larger study would provide consolidated data on a variety of glass products.
- Would it be better to perform depyrogenation at low humidity? We need guidance from the glass industry on this. Also does it make sense to store vials at low humidity? You would also need to know the levels of moisture in the vials going into depyrogenation. Perhaps this is something that should be discussed with the depyrogenation instrument industry and develop some points to consider?
- Controlling atmosphere is not always the key. Flat glass with thin film coatings also has same problems.
- Stress points in the glass are thought to accelerate the delamination process, and within the glass industry these stress points are known. Should this be monitored by glass manufacturers so that the contribution to glass delamination is better understood?

Audience Questions

- There are several mechanisms and possibly combinations of mechanisms that may cause delamination. We have seen phenomenon where when glass is heated and boron and silicates are boiled off, they redeposit forming a skin held in place by sodium, which is different from gel layers. Water can cause the skin to peel off. What about possibility of other significant mechanisms?
 - Leaching can be a root cause of flaking. Also the formation of these skin layers can be localized. Agree there are many mechanisms for initiation and action of the delamination process. These mechanisms will be affected by the formulation, glass processing, glass composition, among other things.
- One other mechanism is phase separation of glasses, forming a liquid-liquid metastable phase. Borosilicate glass will undergo phase separation. In Pyrex 33 the sodium borate phase will separate as a droplet within a silica-rich matrix. In 51 borosilicate glass, the phase separation occurs so that sodium borate is the matrix with silica-rich droplets.
- Conducting more extensive studies using products from different suppliers is an interesting idea, but for practical reasons, as a glass manufacturer, it is difficult to know whether we would support this. We would see benefit in exchanging information to understand better what a low delamination glass might look like or have a new test in the EP or USP. Suppliers also have a common goal of patient safety.
 - Some papers on delamination studies do exist in the literature. One study discusses several glasses used in the industry and addresses some studies on how materials are behaving in different environments.



- The PDA or Rx-360 can provide forums for industry and other stakeholders to collaborate. Rx-360 has infrastructure to share science and audit data among industry.
- It is important to control the manufacturing processes. As a glass supplier it is good to hear the basics regarding how a process must be controlled and to understand that a container is part of the drug. Comparison among real time and accelerated study data would be helpful.
 - Suppliers will consider the costs of testing and control strategies, but some suppliers are starting to move toward concepts of understanding reproducibility, process understanding, etc.
- We have seen delamination in molded type 1 vials. In tubing vials delamination occurs near the bottom of the vial. Possible solution is to purchase higher quality vials, but this means a higher price. It is not clear if purchasing departments understand this.
 - It is important in these cases to coordinate quality, purchasing and affected groups so that all have the same understanding of what is needed and acceptable.

Session 3: Glass Manufacturing

Juan Cerdan Diaz, Amcor. Glass Manufacturing and Chemical Durability

- Chemistry/Property relationship Methodology (Glass Science and Technology) can be utilized very effectively to improve the chemical durability of both the glass tubing as well as the converted vials.
- Refinements and improvements in glass chemistry alone resulted in superior chemical durability and glass corrosion/delamination resistance.
- The Chemical Durability (EP) of the converted vials was improved for the first time to values consistently below 40% without any changes in the manufacturing process. This significant improvement is purely related to the chemistry refinement.

Don Kraus, Gerresheimer. How to Use the Converting Process to Control Glass Delamination

- Studied manufacture/formation of vials. Noted that stress rings and pitting forms near the bottom and shoulder areas of the vials. These are areas near flame cutting and forming of container bottoms and shoulders, where strain from annealing and cooling would have large impact. These areas show macro-delamination (flakes greater than 100 microns across).
- New machines to produce glass vials are not needed -- existing machinery can be adapted to address issues identified.
- Suppliers/manufacturers of glass need to understand what user applications are.

Carlo Pantano, Pennsylvania State University. How to Control Glass Delamination During Manufacturing

- Non-uniformities can occur throughout the glass surfaces composition, with some areas having high concentration of silicon and others with a mixture of sodium, calcium and carbonate. Delamination activities will take place at the top 10-90 nanometers of surface material. Also, higher alkalinity is seen at the top surface (1-4 nm depth). It is possible that certain elements become concentrated at different regions of the glass surface after many washing cycles – a phase separation. This will not show up until the surface is stressed.

Audience Questions

- FDA noted that there seemed to be mixed messages conveyed, i.e., case studies claim that delamination (visible flakes) typically occurs in only a small number of products. However, other studies seem to show, from the various surface micrographs, that delamination can occur quite frequently.
 - Even though images show patches of unstable layers or some corrosion, this does not mean that actual flaking into a product will occur. All glass has hydrated layers, and it may be the formulation that causes the layer to behave in a certain way, e.g., create visible flakes. It may be that certain formulations do not cause any visible flakes and therefore they are fine.
 - We had product lots with about 2-8% flaking and some with no flaking. The actual occurrence of flaking may be due to multi-factorial issues – the individual history of the vial will have some impact on whether flaking actually occurs. It is possible to have very small flakes that dissolve and other that are preserved; in other cases you may have a disrupted glass surface but no actual flaking occurs. Additional factors such as depyrogenation, washing, physical filling process, etc can affect the tendency for disrupted surfaces and flake formation. To understand your incident rate you will need to look at a number of factors.
 - If there is enough energy for the delamination to occur, then it will occur, or the reaction may simply be “at the edge” of occurring but not occur without surpassing the activation energy. As such the appearance of visible flakes is the final step in the mechanism and is therefore not the best way to test or understand what is happening – you need to start earlier with predictive studies.
- FDA representative asked whether, since humidity and moisture has a significant effect on glass, shouldn't the glass manufacturer look at moisture permeability and the resistance of the container, and put the vials in packaging when the vials are sent to the customer? Wouldn't this at least help to control one parameter in the process, i.e., moisture?
 - Moisture exposure is an on-going process. Before packing, during depyrogenation, and filling, during all these processes, vial is exposed to moisture.

- FDA representative wondered if sterilization and depyrogenation processes needed to be done – could clean and “ready to use”/sterile glass be obtained/used?
 - Depyrogenation is expected when using glass – it is done because the industry has always done it. On the other hand, about half of, e.g., oral and IV drugs are delivered/stored in plastic and depyrogenation processes are not needed for those types of containers.
 - It would be helpful to understand what steps have greater damaging effects on the glass, e.g., forming and melting, annealing, depyrogenation, etc., or are all of these factors additive?
 - Some reduction in depyrogenation could happen in industry but it will take a huge mental change for industry and regulators not to conduct depyrogenation.
- FDA representative asked if there had been any long term studies leaching of aluminum from glass.
 - A presenter noted that his lab was conducting extractions on the glass. The aluminum could be coming off the corroded glass from the surface layer, and it is not clear if actual leaching would occur from the glass bulk.
- Wouldn't depyrogenation dehydrate the glass, and if glass is then put in a humidity controlled environment afterwards, then the resulting level of moisture may be low, and a good starting point. It is also possible that you will have a dehydrated, but altered surface layer.

Session 4: Analytical Techniques

Dan Haines, Schott Pharma Services. Analytical Techniques to Predict Glass Delamination

- It is possible to produce vials that will not undergo delamination under specific conditions, but you will need to understand the technology, the science, the critical parameters and attributes that will impact the glass
- Currently there are test methods that can be used to consider if the vial will have a tendency to delaminate. One can use an analysis bundle consisting of scanning electron microscopy, secondary ion mass spectrometry, and ICP to identify root cause of delamination, and in conjunction with accelerated testing be used as a screening method to determine if drug product/container interaction leads to delamination. Have found that after processing there are higher levels of silicon at the bottom of the vial but lower concentrations of silicon elsewhere in the vial. Silicon rich areas appear to be more stable than those where there is less silicon.
- It is possible to identify risk factors, e.g., by studying the behavior of a number of different glasses exposed to different pH conditions, different temperatures, etc., and use these risk factors to understand what key parameters or influences should be avoided, controlled, etc in certain circumstances.



- The drug formulation presents about 70% of the problem as it chemically attacks the glass surface.
- Suppliers (and their glass products) would very much benefit from knowing more about the formulations that their customers intend to use with the glass vials

Joseph Phillips, Amgen. New Analytical Techniques to Predict Glass Delamination

- Using MFI techniques to examine size and quantity of lamellae. MFI can be used for routine quality control testing
- Also have used differential interference contrast microscopy, which may have some utility in a QC environment.
- Have seen a positive relationship between alkalinity and appearance of lamellae, for the company's specific product.
- Have seen a great deal of variability among measurements from labs using European Pharmacopoeia tests. The titration endpoints are not standardized.

Audience Questions

- FDA/CBER representative noted that the surface alkalinity test does not seem to be a predictive method for understanding the propensity for delamination, e.g., is it possible make a correlation between say, 60% alkalinity and a delamination event? Are better test methods needed? Are there better detection methods that could accurately quantify the numbers of lamellae, such as differentiating between 10 and 100 lamellae? And isn't the visual appearance test (via eye) rather limited?
 - Currently the European Pharmacopoeia tests are the ones that we have, although the test may not be appropriate or applicable for delamination issues. Approaches using ICP/MS, or MFI could present advances.
 - MFI is capable of providing a quantitative range of sub-visible to visible particles.