LEACHABLES STUDIES

Investigating Leachables in Oral Solid Dosage Forms

By: Chris Connolly and Niculae Miron

INTRODUCTION

Discovering at a late stage of development that a contaminant leached into your drug product is a biopharmaceutical sponsor's nightmare - and can be extremely costly. As drug products become increasingly potent, more-sensitive analytical methods are needed to determine lower acceptable levels of contaminants. The US FDA and European Medicines Agency (EMA) have issued directives to identify and quantify contaminants, such as genotoxic and carcinogenic impurities, at increasingly lower levels, nanogram or lower.

Advanced, highly sensitive testing technologies available today, such as high- performance liquid chromatography (HPLC), can detect extremely low levels of leachables, enabling sponsors or their contract research organizations (CROs) to detect more contaminants in their drug product. For every leachable detected, they must determine whether to conduct extractables and leachables (E&L) studies and the extent of testing necessary to ensure regulatory approval and the safety of their product for patients.

For drug products dispensed from medical devices, sponsors need to know whether any contaminants have leached into the drug from the device components, secondary packaging, or other materials. When leachables are detected, investigators must determine their identity and the level to which they will accumulate in the finished drug product over its shelf-life, as well as the impact of storage conditions, and whether the level of leachables is acceptable. They also need to develop appropriate methods for E&L analyses that are adequately sensitive and specific to the compound. While E&L studies are usually not relevant for solid dosage forms, there are times when these investigations are advisable.

E&L studies can be challenging, and regulatory guidances are not specific. As part of the studies, investigators must develop test methods appropriate to detect, identify, and quantify potential leachables, and if found, assess their toxicity. Consequently, sponsors often outsource these studies to a highly qualified CRO.

In this article, Patheon explains the importance of conducting leachables studies for solid dosage forms in certain situations, and describes its leachables study of an oral solid dosage form delivered in a medical device.

WHAT ARE LEACHABLES & EXTRACTABLES?

Leachables are chemical compounds that migrate into the drug formulation from any product contact material, including elastomeric, plastic, glass, stainless steel, or coating components as a result of direct contact with the drug formulation under normal process conditions or accelerated storage conditions and are found in the final drug product.[1] They can increase the toxicity and impurity levels of the drug product and react with product components. Extractables are chemical compounds that migrate from any product contact material when exposed to an appropriate solvent under exaggerated conditions of time and temperature.[1]

REGULATORY GUIDANCE

The FDA Guidance for Industry, Container Closure System for Packaging Human Drugs and Biologics, provides guidance on principles for submitting information on packaging materials used for human drugs and biologics. For oral tablets and capsules, the degree of concern associated with the route of

and lack of resources begged for Dr. Shetty's David mindset, says Lui.

Many surgeons before him had walked away from the problem, but Dr. Shetty chose to explore a different tact. Maximizing economies of scale to reduce costs, Dr. Shetty now oversees 42 cardiac surgeons who performed 3,174 cardiac bypass surgeries in 2008, more than double than the 1,367 performed by the Cleveland Clinic in the US that year, according to Dr. Liu's blog.

The sheer volume of surgeries performed at Dr. Shetty's hospitals allows each doctor to zero in on a specific area of specialty. Surgeon Colin John, for example, has performed nearly 4,000 Tetralogy of Fallot procedures, a complex procedure that corrects four different heart defects simultaneously. He has almost certainly achieved the 10,000 hours of practice necessary to achieve mastery of a field.

Dr. Shetty's team now performs 12% of all cardiac surgeries in India. That reality gives him tremendous buying power. When a European manufacturer failed to lower the cost of hospital gowns, he convinced a group of Indian entrepreneurs to take up the job, reducing costs by 60%. A new hospital cuts costs by pumping air conditioning only into operating theaters and intensive care units.

Urgency and lack of resources combined to create an environment ripe for a David mindset. Dr. Shetty reduced the cost of surgery to $1600. Compare that to the $106,000 regularly paid for the same surgery in the US. Even accounting for differences in the cost of living (Delhi's cost of living is 54% of Atlanta's), this achievement is staggering.

THE IMPORTANCE OF GOLIATH

Innovation involves taking risks and breaking rules. This is something individuals do. Companies do the opposite. The larger the company, the more the rules. Gigantic cash flows can smother the incentive to find better ways of doing things. Institutional memory can inhibit new ideas at their source. Lipinski's Rules, hERG liabilities, and other rules of drug selection do more to stifle development than to facilitate it.

Goliath shouldn't try to be David. And yet, we very much need our Goliaths in this industry. So too did the armies in the time of David. In fact, as Gladwell points out, every army had their massive foot soldiers, clad like Goliath with swords and armor, leading the army into battle. But they also had infantry - those sling-bearing soldiers like David, in the rear. Together they formed a powerful combination.

We have thousands of Davids out there slogging away at their science in pursuit of a spark. Most of them are in biotech. But biotech needs big pharma to takes those ideas that work to the next level. Only big pharma can bankroll a trial of hundreds of rare patients across 15 nations.

Drug development is an industry uniquely replete with Davids. They provide the spark that drives development. David and Goliath, working for the same common cause, form a potent army in the war against disease. This is the model for our generation. ◆

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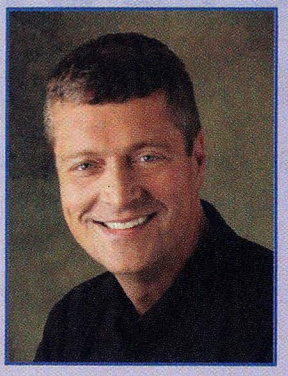
BIOGRAPHY



Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2006, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

administration is low, as is the risk of interaction between packaging components and a solid oral dosage form. For tablets, appropriate reference to the indirect food additive regulation for each material of packaging construction can be submitted.

For medical devices, extractables and leachables testing is required by the Center for Devices and Radiological Health (CDRH) of the FDA. The CDRH requires a 501(k) premarket submission: an assessment of the stability and compatibility of each drug or biologic intended to be used with the medical device, and a safety evaluation of any leachables, extractables, impurities, and degradants from the medical device into the drug product.

Various ISO guidelines address the issue of impurities. The following are four key guidances for the biological evaluation of medical devices:

- ISO 10993-13: Identification and quantification of degradation products from polymeric medical devices.
- ISO 10993-15: Identification and quantification of degradation products from metals and alloys.
- ISO 10993-17: Establishment of allowable levels for leachable substances.
- ISO 10993-18: Chemical characterization of materials.

Development, validation, and testing of components must be carried out under International Conference on Harmonization (ICH) and US Pharmacopeia guidelines.

The ICH Tripartite Q6A guideline Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances indicates that an extractables study is only recommended for oral liquid and parenteral drug product, but not for tablets or hard capsules.

In addition to various ICH guidances on impurities, the FDA Guidance for Genotoxic and Carcinogenic Impurities in Drug Substances and Products recommends approaches to characterize and reduce the risk of patient exposure to these impurities. The guidance references the threshold of toxicological concern (TTC) as 1.5 micrograms per day.

STUDY OF TABLETS DISPENSED FROM A MEDICAL DEVICE

Patheon conducted a study to determine the source of the leachables discovered in a low-strength tablet (label claim: 10 micrograms/tablet and 15 micrograms/tablet) packaged in a medical device, and whether the drug product met the acceptable level of contaminants for the particular compound.

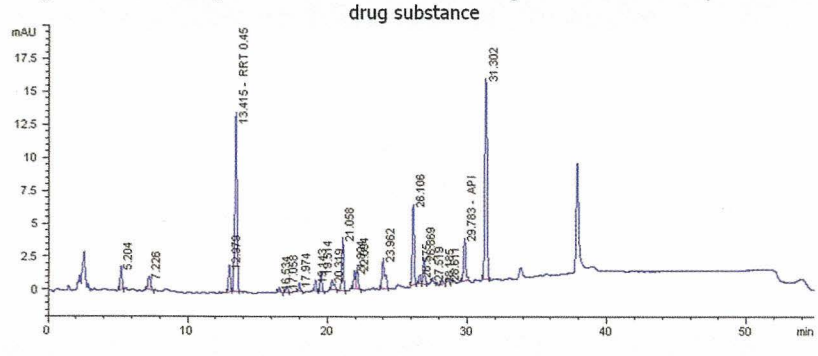
During Phase II studies to test the chemical and physical stability of the product, two unknown impurities were detected in products packaged in a polycarbonate cartridge in a foil pouch with oxygen-scavenging sachet. One of the key chemical attributes tested was changes to the profile of related substances (impurities), which indicate degradation of the active pharmaceutical ingredient (API). The related substances method was developed to detect and quantitate impurities down to the ICH reporting threshold for the lowest tablet strength.

The investigators conducted a study to determine the source of two unknown impurities detected at relative retention times (RRT) of 0.45 and 0.76 RRT and tested under accelerated and long-term storage conditions. RRT is an analytical parameter used in chromatographic procedures to control impurities in a drug product, correcting variation in peak retention time related to HPLC system variance. The RRT relates each impurity peak retention time to that of the reference standard of the API.

When testing the impact of storage conditions on drug product stability, the investigators found that the relative magnitudes of these peaks were higher in samples stored at 40°C/75% Relative Humidity (RH) compared with those at 25°C/60% RH, and increased with storage

FIGURE 1

Figure 1. A chromatogram of extract solution of the Original Foil Pouch in the presence of drug substance



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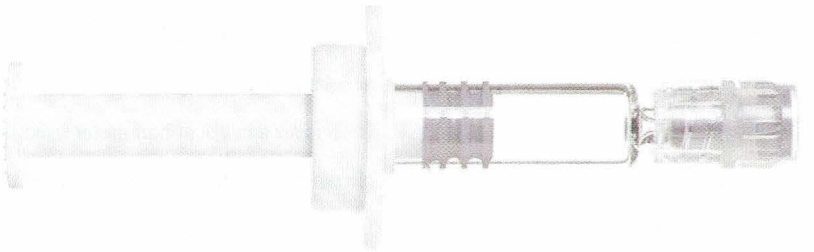

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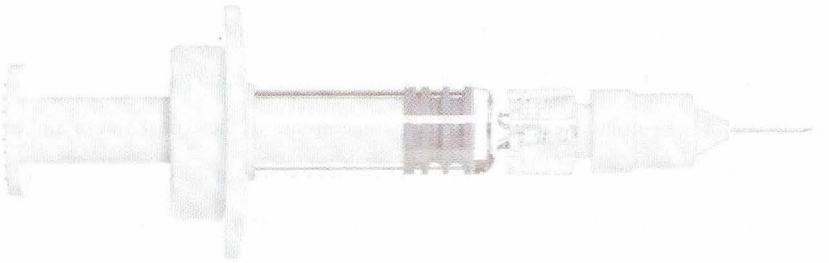

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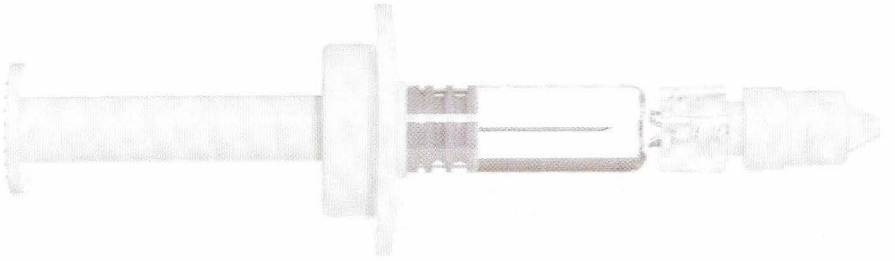

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time for products packaged in cartridges. When testing the product in different secondary containers, they found that neither of the impurities was detected in the product packaged in plastic HDPE bottles. Because the impurities were not detected in the bottle configuration, the investigators suspected they might originate from the cartridge components or pouch material.

Related substances of the low-strength solid dosage form were determined using an HPLC method with a diode array detector (DAD) and quantitation at 235 nm (limit of quantitation ~ 0.05 micrograms/mL). To identify the source of the two impurities, pouch materials and each of the cartridge components were separately extracted in an aqueous buffer solution at 50°C for 72 hours and in an organic medium at room temperature for 24 hours. Extracted solutions were analyzed with the product-related substances test method. Both the RRT of the peaks and UV spectra collected from the DAD were used for peak identification.

Based on the RRT and UV spectra analysis, the RRT 0.45 was found to be a leachable from a pouch material, while RRT 0.76 was a leachable from two of the cartridge components and identified as Bis-Phenol A (BPA).

TABLE 1

Table 1: Peak Area Count of Impurity RRT 0.45 detected in pouch material extracts

Extraction Condition	pH 2.2 Buffer 50°C 72 hours	pH 2.2 Buffer 50°C 72 hours With Drug Substance	ACN/Water 2 hours Sonication	ACN/Water 2 hours Sonication With Drug Substance	ACN/Water 24 hours 50 °C	ACN/Water 24 hours 50 °C With Drug Substance
Original Pouch	450.2	562.5	109.63	140.0	1059.5	1821.1
Alternate Pouch	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

FIGURE 2

Figure 2. A chromatogram of the drug product with the impurity at RRT 0.45

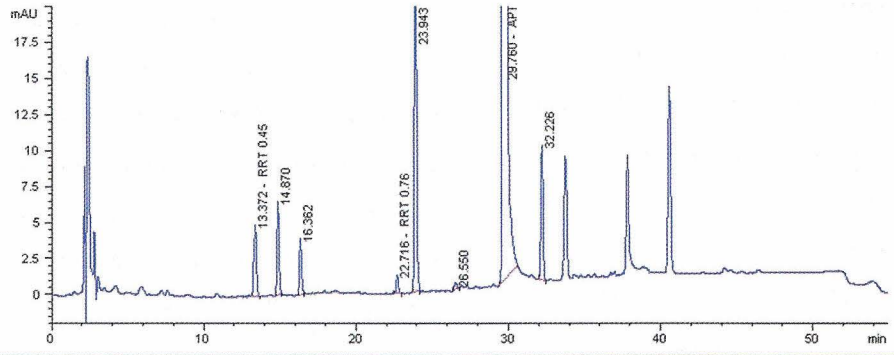
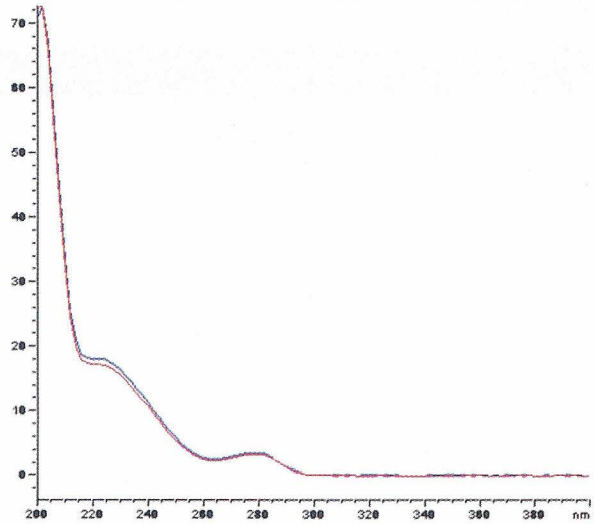


FIGURE 3

Figure 3. UV spectra collected from the peak of RRT 0.45 of original foil pouch extraction (Red) and a drug product sample (Blue)



RESULTS

Leachable Study for Impurity Peak at RRT 0.45

In chromatograms of the extracts of a pouch material in both aqueous buffer and organic medium, a peak was observed at RRT 0.45 (Figure 1). As a comparison, a typical chromatogram of a drug product sample with the impurity at RRT 0.45 is shown in Figure 2. UV spectra of these peaks also matched that of the RRT 0.45 impurity in the drug product (Figure 3). This peak was not observed in the chromatograms of extracts from the cartridge components. Therefore, the impurity was determined to be a leachable that migrated from the pouch material into the dosage form during drug product stability storage.

A new alternate foil pouch material was extracted under the same conditions, and the impurity was not detected under any tested

TABLE 2

Table 2: Peak Area Count of Impurity RRT 0.76 detected in extract solution from cartridge component and pouch material (ND: Not detected)

Extraction Condition	pH 2.2 Buffer 50°C 72 hours	pH 2.2 Buffer 50°C 72 hours With Drug Substance	ACN/Water 2 hours Sonication	ACN/Water 2 hours Sonication With Drug Substance	ACN/Water 2 hours sonication and 24hours 50 °C	ACN/Water 2 hours sonication and 24h hours 50 °C With Drug Substance
Base	ND	ND	28.3	30.7	410.3	401.2
Shuttle	2.3	2.8	ND	ND	ND	ND
Shipping Tablets	1.9	2.1	ND	ND	ND	ND
Cover	ND	ND	35.9	24.7	1680	283.4
Spring	ND	ND	ND	ND	ND	ND
Shuttle Catch	0.9	1.4	ND	ND	1.8	2.1
Recon Dome	1.7	2.2	ND	ND	ND	ND
Dowel Release	ND	ND	ND	ND	2.0	3.1
Original Pouch	ND	ND	ND	ND	ND	ND
Alternate Pouch	ND	ND	ND	ND	ND	ND

conditions (Table 1). Therefore, in the absence of any other consideration between the two pouch materials, the original pouch was replaced by the alternate pouch for future packaging.

Leachable Study for Impurity Peak at RRT 0.76

Two of the cartridge components contributed to a peak at RRT 0.76, which was identified as BPA, a plasticizer known to be present in the polycarbonate cartridge components. Table 2 summarizes results of the RRT 0.76 impurity extracted from cartridge components and foil pouch material in an aqueous medium and organic solvents. Aqueous extracts of cartridge components showed a small peak at RRT 0.76, whereas the foil pouch material extracts did not show any peak. Organic extracts of most of the components did not show any significant peak at RRT 0.76. However, the cartridge base and cover extracts in organic solvent had the RRT 0.76 peak in large amounts. A typical chromatogram of extract solution from a cartridge component is depicted in Figure 4.

Because a significant amount of RRT 0.76 impurity was extracted from the cartridge base and cover made from polycarbonate, BPA, a plasticizer for polycarbonate manufacturing, was analyzed using the liquid chromatography (LC) method (Figure 5). The investigators observed that the retention time of BPA was very close to the RRT 0.76 impurity extracted from cartridge base and cover in organic solvent. The UV spectra of BPA, the impurity of RRT 0.76 from cartridge base extraction, and the impurity of RRT 0.76 in the drug product are displayed in Figure 6.

UV spectra collected from the three sources have identical UV absorption profiles. We concluded that the impurity of RRT 0.76 in the drug product sample is BPA, a leachable from the cartridge base and cover.

Recently, BPA has been the subject of health concerns. During product development, the highest BPA amount detected was 0.34% for a 15-microgram strength product, which equates to 0.001 mg intake per day. According to the EPA's Integrated Risk Information System, the reference dose for chronic oral exposure (RfD) of BPA is 5 x10-2 mg/kg-day. For a 50-kg adult patient, BPA intake from the drug product is 2500 times less than the threshold at which a health concern will be raised. Therefore, there is low risk in the cartridge/pouch system for the dosing device.

Because the BPA levels in the packaged product were several orders of magnitude lower than the EPA's acceptable limit, no changes were determined to be necessary for the cartridge materials.

FIGURE 4

Figure 4. A chromatogram of extract solution of the Cartridge Base in the presence of drug substance

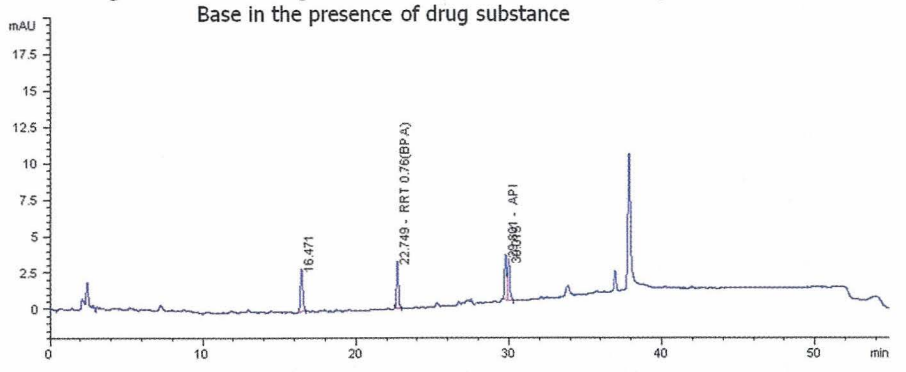


FIGURE 5

Figure 5. A chromatogram of Bis-Phenol A (BPA)

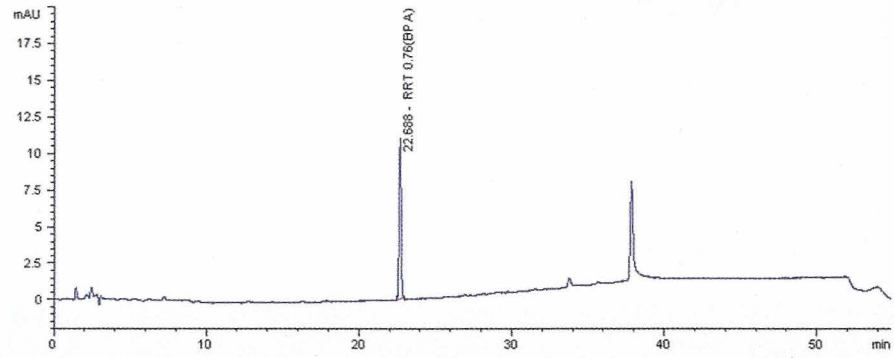
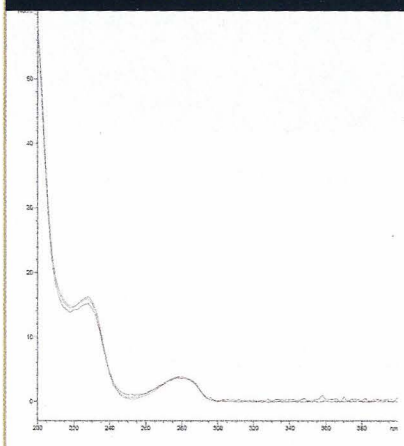


FIGURE 6



UV spectra collected from peak RRT 0.76 of cartridge base extract (Red), BPA (Green), and a drug product sample (Blue).

Study With Modified Packaging Configuration

An experimental lot of drug product was packaged in a polycarbonate cartridge sealed in the alternate foil pouch (the pouch that did not display the RRT 0.45 impurity in the leachable study) and stored at accelerated conditions (50°C/75% RH). At the 3.5-month time point, a review of chromatographic traces of this sample did not show any impurity peak at RRT 0.45, and the amount of the RRT 0.76 impurity was 0.053%.

CONCLUSION

With increasingly potent drug products and lower acceptable levels of contaminants today, more-sensitive analytical methods must be used to detect and analyze leachables and determine drug product safety. Although the risk of interaction between packaging components and a solid oral dosage form is small, E&L studies may be necessary for low-dose products when the related substance profile is monitored with a very sensitive method. For drug products in medical devices, investigators must understand E&L testing methods and make sure the devices are unadulterated to the drug products they deliver. A highly experienced E&L partner can help you conduct these sensitive and specific analyses, mitigating risk at this late stage in product development. . ◆

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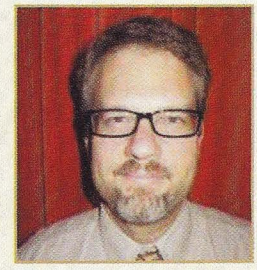
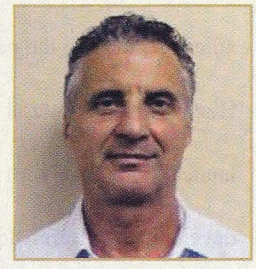
REFERENCES

1. Bioprocess Systems Alliance.

BIOGRAPHIES



Chris Connolly earned his BSc in Biochemistry and has worked in the biotechnology and pharmaceutical industries for 19 years, starting as an analytical chemist, and rising to be manager of analytical chemistry and of operations excellence. He joined Patheon in 1999, and is Manager of Analytical Development for Pharmaceutical Development Services. He has worked on dozens of early-to-late clinical-stage development projects for solid and semi-solid dosage forms, leading activities including development and validation of analytical methods, formulation evaluation, development of product specifications, clinical batch release, stability studies, and CMC reviews.



Niculae Miron earned his BSc in Chemical Engineering from the University of Ploiesti, Romania. He has worked as an analytical chemist for more than 15 years with various Canadian pharmaceutical companies. He has been working as a Senior Chemist since 2008 with Patheon Inc., within the Analytical Development Laboratory of Pharmaceutical Development Services.

PARENTERAL CONTAINERS

A Novel Approach to Mitigating Oxygen Permeation in Prefilled Syringes

By: Peter Sagona, MS, Rómulo Romero, MS, and Adam Breeland

SiO_2 Medical Products (SiO) is a vertically integrated manufacturer of primary containers. Using advanced materials science, SiO has developed a line of parenteral drug containers that offer improved performance and consistency over existing containers. SiO's containers are precision-molded from medical-grade plastics, and the interior surface has a thin, transparent, silicon-oxide based coating system. Our containers combine the durability of plastic with the high-purity and barrier properties of glass, while eliminating the shortcomings of existing glass and plastic containers.

INTRODUCTION

Parenteral drug containers are multicomponent systems designed to safely store a drug until it is ready for administration to the patient. Historically, parenteral drugs are first launched in vials, with subsequent development of prefilled delivery options. Recent trends in the industry, however, show an increase in the use of prefilled syringes as the primary container of choice.[1] There are several factors to consider when selecting the components for a drug delivery system, such as the nature of the active pharmaceutical ingredient (API) (eg, molecule size and complexity), oxygen sensitivity, formulation pH, cytotoxicity, and stability, among others. In this article, we will focus on oxygen permeation into a sealed syringe and detail how the individual system components (syringe, needle shield, and plunger) contribute to the overall Oxygen Transmission Rate (OTR). Whole article testing refers to an experimental design in which the OTR of a fully assembled syringe is measured, mimicking the environment that a drug product would be subject to in a prefilled, ready-to-use syringe. Glass has historically been the material of choice for the syringe, and while glass provides an excellent oxygen barrier, other factors should also be taken into account when selecting components for a prefilled syringe system. More complex formulations reaching the market today, such as proteins, monoclonal antibodies (mAbs), and other biologics can have compatibility issues with the silicone oil that must be used to provide lubricity for glass. Oxygen ingress is not limited to the syringe wall; the other components of the prefilled syringe (the plunger and needle shield) also contribute. SiO offers an alternative to traditional glass primary packaging, namely cyclic olefin polymer (COP) parenteral containers with an internal coating of pure silicon oxide providing glass-like oxygen barrier properties.[2] As part of a Quality-by-Design (QbD)-driven development process, SiO has developed a means for quantitatively