Suppliers of pharmaceutical packaging components and delivery devices have been working closely with the industry in an effort to provide solutions for mitigating the risk associated with extractables and leachables. This effort includes managing both the technical and regulatory aspects of the subject. The following example illustrates the challenges faced by the industry.

A company that produces and fills an injectable drug product wanted to move from a glass vial with a bromobutyl stopper to a pre-filled syringe delivery system. With a prefilled syringe system, there is direct contact between the elastomeric plunger and the drug product in the syringe system. The same bromobutyl elastomer used for the vial stopper was also used for the syringe plunger.

The Chemistry, Manufacturing and Controls (CMC) reviewers at the FDA are asking for similar information from other companies as a part of their drug applications. Initially these requests were inconsistent. The topic of extractables and leachables had been initiated with inhalation and nasal drug dosage forms, and so these CMC reviewers more familiar with these types of drug products began to bridge these requests into injectable drugs. These same reviewers were also responsible for the initial internal education of the FDA on this issue. Since there was no written guidance on this subject, the industry was confused about a path forward. One point of confusion was the belief that compendial testing was an acceptable way to address the extractable issue.

A major extractable ingredient in the elastomeric formulation was zinc ions from zinc oxide, which was used as part of the cure system. The drug company completed stability studies of the prefilled syringe format and supplemented their work with leachable testing for Zn+2. However, the US FDA rejected their application because it lacked sufficient extractables and leachables testing.

The drug company had assumed that since the elastomeric formulation was the same for both the vial stopper and the syringe plunger, the limited leachables work they had completed would be acceptable. As they found out, this was not the case.

The US Pharmacopeia (USP) is the major compendium of standard testing requirements for the pharmaceutical industry in the US. USP Section 381 defines physicochemical testing associated with elastomeric closures used for injectable drug products. Although judging the correct approach to addressing extractables and leachables testing in the development of prefilled syringe products can prove to be a challenge, and getting it wrong can cause major set-backs in product commercialisation when it comes to the regulatory process. Here, Fran DeGrazio, Vice-President of Marketing and Strategic Business Development at West gives examples of how and why confusion can arise, and suggests strategies for making sure the right decisions are made.

“THE MAJOR DRIVER FOR CONDUCTING EXTRACTABLES/LEACHABLES TESTING IS DUE DILIGENCE IN ASSURING APPROPRIATE SUITABILITY FOR INTENDED USE OF THE PACKAGING COMPONENTS OR DELIVERY DEVICES”
this compendium is currently going through a major update that will bring it much closer in requirements to the European Pharmacopeia, the test series that has been in place does not even have specifications defined for the physicochemical series. Additionally, the series of tests are antiquated, wet-chemical methods that are nothing more than a gross type of chemical testing. This testing bears no relationship to true extractables testing.

From an industry standpoint, one major hurdle was defining how to test for extractables. Once this was understood, the next question was how to test and what to test for leachables. The questions then became, “How do we quantify?” and, “What do we quantitate?”

The industry came to realise that the FDA did not consider leachables in the same category as a drug degradation product. As a result, the ICH guidance, “Q3B Impurities in New Drug Products” was not applicable to leachables. This guidance had at one time been thought of as an answer to quantification limits.

The first written guidance the industry received on the subject was the FDA’s “Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics”, published in 1999.

The guidance defined *Suitability for Intended Use* as consisting of:
- Protection
- Safety
- Compatibility
- Performance

In recent years, there has been a tremendous amount of progress made by the industry in an effort to standardise the definitions and the approach to the extractables and leachables issue.

Understanding this issue is critical because the risk of delaying a drug application approval can have a dramatic negative effect on a pharmaceutical or biotechnology company.

For this reason, extractables and leachables should be addressed before the pharma/biotech company submits a drug application to the regulatory agency. In addition, an understanding of the reasons why the regulatory agencies are requesting these studies is also important.

So, why are the FDA and other regulatory agencies around the globe concerned with extractables and leachables?

Although the most obvious reason is patient safety, the major driver for conducting extractables/leachables testing is due diligence in assuring appropriate *Suitability for Intended Use* of the packaging components or delivery devices. Due diligence helps assure that there is a basic understanding of the extractables species that could leach into and are present in a drug or biologic product over its shelf life.

**THERMOSET COMPONENTS INJECTABLE DRUG PRODUCTS**

Thermoset elastomers used for the pharmaceutical industry consist of the same raw materials that are commonly used for products such as tyres and in electronics. There are no “pharmaceutical grade” elastomeric raw materials. Suppliers to the pharmaceutical industry must understand the raw material production process and conduct a thorough analytical evaluation of the raw materials used in these components.

Thermoset elastomers, which are commonly used for sterile, injectable drug applications, are typically composed of six to ten raw materials. Under the heat and pressure of component manufacturing, breakdown products and reaction products of the raw materials are formed. Additionally, each raw material has its own combination of additives or process aids that could lead to a leachable in a drug product.
An example is the polymer used as the base of an elastomeric formulation. Table 1 shows a list of potential extractables from a general raw polymer used for a typical pharmaceutical application.

Other common sources of extractables from the finished elastomeric formulation are the cross-linking system, which is composed of a series of curatives, accelerators and activators, along with plasticisers, process aids and reaction products of these materials.

Among the reasons the FDA is asking for extractables data on components are qualification and quality control of the components.

Pharmaceutical component suppliers have continued to adjust to the market and to the regulatory environment. Initially, suppliers developed potential extractables lists on every formulation. The lists were created from a theoretical standpoint, not an experimental standpoint. All raw materials were considered, along with any process aids or other materials relating to the raw materials, as possible reactions or by-products from the manufacturing process.

As time went on, suppliers provided more support for pharmaceutical companies. The pharmaceutical/biotech industry’s core knowledge is around drug development, not packaging materials and their extractables and related leachables. In an effort to expand the level of support for their customers, some component suppliers developed laboratory services to provide both extractables and drug leachables testing.

An experienced component supplier such as West can advise and consult with customers on leachables testing to initiate. A formal testing program should provide scientifically sound data to support what leachables are tested in a drug product.

Component suppliers have also introduced products that can help pharmaceutical and biopharmaceutical companies meet current quality requirements for finished pharmaceuticals. For example, West’s NovaPure® components can provide a ready-to-use solution that is certified on a lot-to-lot basis for extractables, and includes an extractables profile and extractables specifications.

Certification helps assure pharmaceutical companies that the composition of the closures, and the closure manufacturing processes, are uniform from laboratory-scale studies until commercialisation. NovaPure® components can minimise the risk of extractables in the drug solution because they are manufactured with a barrier film. In addition, the closures are vision inspected to minimise defects and subvisible particle specifications are applied to assure consistency as an input to the finished drug product fill/finish process.

Table 1: Potential extractables from a general raw polymer used for a typical pharmaceutical application.

<table>
<thead>
<tr>
<th>Component Suppliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oligomers</td>
</tr>
<tr>
<td>• Calcium stearate</td>
</tr>
<tr>
<td>• Antioxidant (BHT, etc.)</td>
</tr>
<tr>
<td>• Epoxidised soybean oil</td>
</tr>
<tr>
<td>• Halide ions</td>
</tr>
</tbody>
</table>

**CASE STUDY**

The following case study illustrates the impact of extractables and leachables on drug products delivered in prefilled syringe systems. In 2003, a safety issue led to a market recall of Eprex, a recombinant human erythropoetin (EPO), by Ortho Biotech (a division of Johnson & Johnson).

A news report from Reuters, London, summarises the incident:

“August 12, 2003 – Johnson & Johnson said on Tuesday it was recalling certain batches of its anaemia drug, Eprex, in most countries outside the US after discovering they were tainted by chemical reactions with stoppers. Details of the recall emerged after Britain’s Medicine and Healthcare Products Regulatory Agency issued an alert on its website saying the company had found low levels of ‘extractables’ in the product.”

The drug was packaged in a pre-filled syringe format with an uncoated plunger. A change was made to the drug product by incorporating Polysorbate 80 to replace Human Serum Albumin in the drug product. This changed the migration potential of extractables in the elastomeric formulation, leading to a higher level of leachables. Interaction between the extractables from the elastomeric syringe plunger and the drug product formulation caused the adverse event of pure red cell aplasia in certain patients.

The resolution for this issue was a move to a barrier-coated plunger to minimise migration of extractables into the drug product.

**MINIMISING RISK**

To support the pharmaceutical and biotech industries effectively, suppliers must stay on the leading edge of the evolving requirements in the area of extractables and leachables. Although tremendous progress has been made over the last decade, this issue continues to evolve.

To minimize the potential of extractables and leachables, suppliers must stay on the leading edge of the evolving requirements in the area of extractables and leachables. Although tremendous progress has been made over the last decade, this issue continues to evolve.

Direct suppliers to the industry play an important role in transforming raw materials into components that are critical to the delivery of life-saving pharmaceutical and biotechnology products. By working closely with their component suppliers, pharmaceutical and biopharmaceutical companies can mitigate regulatory and product-related risk related to extractables and leachables.

NovaPure® is a registered trademark of West Pharmaceutical Services, Inc, in the US and other jurisdictions.