PACKAGING DIAGNOSTIC REAGENTS WITH CONFIDENCE

As a seemingly inconsequential part of the shipping and storage process, the material used for packaging diagnostic reagents can have a significant impact upon quality. As a commonly used material, glass can pose a significant hazard because it cracks and shatters easily. Plastic has, therefore, been introduced as a viable and safe alternative. When selecting a plastic, it is essential to realize the differences between resin types and the impact that these can have on the purity of the contained reagent. Here, we discuss these different properties and the potential implications that these could have on resulting downstream data.

Diagnostic companies are facing ever-increasing pressures to deliver new products safely and efficiently. With diagnostic reagents as the basis of any experimental protocol, it is essential that they remain highly pure and that the potential for any contamination is minimized. Reagent packaging has commonly taken the form of glass bottles and containers, which have a well-known mode of failure: they break and shatter. This poses a significant hazard in terms of spilled reagents and exposed sharp edges. More recently, plastic has been introduced as a safer packaging material — it's resistant to breakage, and plastic bottles are lighter and more durable, making them an ideal alternative to glass.

Plastic Properties

The properties of any plastic used for packaging will affect the type of reagent that can be stored safely. There is a wide range of commercially available plastics and they vary in terms of their chemical composition. The molecular weight of a plastic can range from 40,000 to ≥100,000 kDa. As molecular weight increases, so do the physical (temperature resistance, surface hardness) and chemical resistance properties of the plastic. Manufacturing plastic bottles and containers from high molecular weight materials, however, is more challenging. In addition, intramolecular forces can also affect the resulting plastic properties:

- Strong intramolecular forces tend to form more crystalline materials, where there is a higher level of order and structure, producing an opaque plastic with good temperature and chemical resistance.
- Weaker intramolecular bonds produce more amorphous materials with less molecular order. These tend to have better clarity, but lower temperature and chemical resistance.

Selecting the Best Plastic

Different plastic resins have varying physical and chemical properties and it is, therefore, important that the correct plastic packaging is used to maintain purity. Diagnostic reagent packaging is commonly made from three different polymers:

- **Polyethylene terephthalate (PET)** has thin walls, providing a flexible material with an effective O_2 and CO_2 barrier. It has a relatively poor water barrier and poor chemical resistance to most solvents and virtually all aromatic solvents. Strong bases will also depolymerize it.
- **Polyethylene terephthalate glycol modified (PETG)** is noncytotoxic and makes excellent radiation

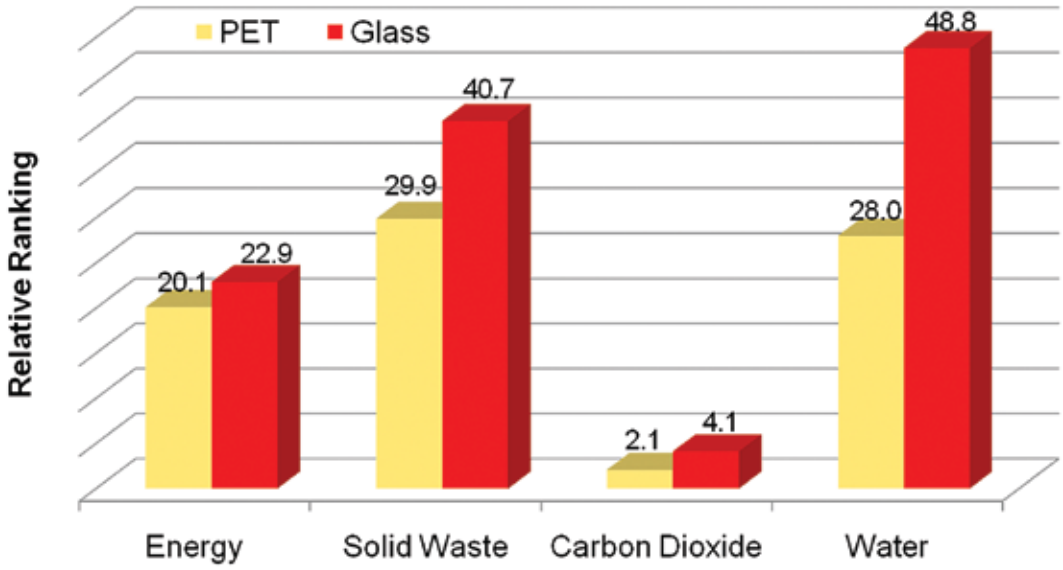

Figure1: The life cycle inventory of PET in comparison to glass.

µg/cm² at 22 °C	Human fibrinogen			BSA, unfractionated			Human IgG		
Material	pH 7.4	pH 5.8	pH 5.0	pH 7.4	pH 4.9	pH 4.0	pH 8.5	pH 7.4	pH 5.0
Borosilicate glass	0.50	0.35	1.05	0.02	0.09	0.44	0.06	0.06	0.13
Nalgene HDPE	0.48	0.60	1.05	0.07	0.20	0.29	0.21	0.23	0.33
Brand 1 HDPE	0.50	0.58	1.05	0.06	0.20	0.44	0.22	0.16	0.33
Nalgene PETG	0.60	0.58	1.05	0.06	0.15	0.44	0.17	0.33	0.35

Table 1: Hydrophobic proteins will be more likely to bind to HDPE than PET/PETG, but can adhere to most surfaces in the absence of surfactants.

sterilizable containers. It is clear with thick walls, moderately flexible, and provides an effective CO_2 and O_2 barrier. It has greater temperature resistance than PET, but still has relatively poor chemical resistance to most solvents and virtually all aromatic solvents.

- **High density polyethylene (HDPE)** is translucent with an excellent water barrier and is usable across a broad temperature range. It has a relatively poor O_2 and CO_2 barrier, but very good chemical resistance. Solvents can cause permeation and softening, which is reversible, but oxidizers (nitric acid, perchloric acid, sodium peroxide) will result in degradation of the polymer following extending exposure.

Reduced Environmental Impact

With an increasing concern to maintain a 'green' laboratory, more and more users are taking into account the environmental impact of their purchasing decisions. A 2009 study demonstrates the environmentally friendly aspects of plastic through a representation of the life cycle inventory, from raw material procurement to delivery of the container to the filling line.[1] It includes the amount of energy needed to produce, ship and dispose of the materials, as well as the impact in terms of CO_2 generated, water consumed and weight/volume of waste generated at the end of the packaging's usable lifespan. In this comparison of PET and glass, plastic requires less energy in the production process than glass, because of the lower temperatures required to process the raw materials (Figure 1). Plastic is also significantly lighter to ship and, therefore, saves on vehicle emissions to provide a more cost-effective and environmentally friendly method of delivery. The methods used in this study are consistent with those for Life Cycle Inventory as described in the ISO 14040 and 14044 standards.[2]

The Importance of Purity

When packaged for shipping or storage, it is essential that the composition of the reagents remains unchanged and highly pure. Any decrease in purity can have a detrimental effect on resulting downstream data, potentially rendering results unusable. Once packaged, the reagents are in constant close contact with the surrounding material and the most common factors to decrease purity are, therefore, leachables and extractables. Because all plastic packaging essentially looks the same, it can be easy to overlook their differing chemical composition. Factors such as ash and metal content, and protein binding can also have a detrimental impact on the resulting purity of the contained liquid.

Extractables and Leachables

Extractables are released from the plastic into stored liquids following exposure to high temperatures or strong solvents, which can alter its chemical composition and, therefore, represent a "worst case." Leachables are those chemicals being released under the normal use conditions of the plastic. Furthermore, to help prevent degradation of the plastic from heat, oxygen or radiation, for example, resin manufacturers can use additives. Bottle grades of HDPE typically include antioxidants and heat stabilizers, whereas PET and PETG contain few, if any. All three resins have an innate resistance to radiation.

Ash Content

Ash represents a mixture of inorganic materials trapped in the polymer matrix. To define the ash content of a variety of plastics, the polymer is burned away under controlled conditions, leaving behind any inorganic residue. Metals can be present in the plastic from a number of different sources as a result of catalyst residue in the resin, such as tin and silicon, slip agents (zinc, calcium or magnesium stearate) or the molding and molding machine, which use aluminium, nickel, iron, cobalt or chromium.

Protein Binding

Diagnostic reagents commonly contain proteins; it is essential, therefore, to understand the interactions between the stored reagent proteins and the packaging materials. Numerous factors affect protein binding, including pH and protein isoelectric point; temperature; salts; surfactants; and other proteins, and hydrophobicity/hydrophilicity of those proteins. Protein binding may be greater in solutions of higher

ionic strength or with pH levels below the isoelectric point of the protein. Hydrophobic proteins, such as integral membrane proteins or lipoproteins, will be more likely to bind to HDPE than PET/PETG, but can adhere to most surfaces in the absence of surfactants (Table I).

Although glass and plastic surfaces exhibit a similar level of protein binding, there are a number of important differences in the binding mechanism. Protein binding to the borosilicate glass is highly unstable, making it inconsistent and difficult to predict the resulting purity of the reagent. As the protein molecules adsorb and detach from the surface, denaturation of the proteins can occur. Protein binding to the plastic surfaces is more stable, reducing the cycle of adsorption and detachment and thus minimizing the occurrence of protein denaturation.

Conclusion

As demonstrated in this article, plastics are a viable and effective alternative to glass for the packaging of in vitro diagnostic reagents. When selecting a plastic, it is essential to realize the differences between resin types and the impact that these can have on the purity of the contained reagent. Although no plastic will be 100% free from leachables, products from different bottle manufacturers can have dramatically different levels present and it is key that users are aware of which extractables and leachables will be the most problematic to their application. One should only purchase plastics from a reputable source; look for products tested for biological toxicity or made from ISO 10993-6/10993-11 or USP <88> Class VI compliant resins; and look for suppliers who use pharmaceutical/medical- and food-grade resins containing minimal additives. **Pharma**

References

1. www.container-recycling.org/assets/pdfs/LCA-SodaContainers2009.pdf
2. www.iso.org/iso/catalogue_detail?csnumber=38498

For more information

Dan Dwyer
Product Development
Technical Manager
Thermo Fisher Scientific
www.thermoscientific.com

DISPOSABLES IN PHARMACEUTICAL FILLING AND PACKAGING APPLICATIONS

Disposable systems are playing an increasingly important role in aseptic pharmaceutical production, and this trend extends to liquid product filling and packaging. There are a number of reasons why this is the case. Biopharmaceuticals have ushered in a number of changes to the filling and packaging process. Batch sizes are often very small, but the financial value can be very significant. Many of the products are highly toxic, creating the need for maximum operator protection. Any risk of cross-contamination must be eliminated.

In response to the revolutionary developments in the industry, most systems must be designed to handle a certain variety of products. Cleaning and subsequent system validation can take up to several days. A disproportionate amount of time is spent on cleaning at the expense of system utilization. Single-use items provide a way of reducing the amount of time and effort spent on cleaning.

On filling systems, disposables are normally used in combination with peristaltic pumps. Disposable tubes are routed through the peristaltic pumps to the filling nozzles, which can also be made of single-use materials. With this solution, the pumps do not contact the product and do not require time-consuming cleaning. Elimination of clean-in-place (CIP) and steam-in-place (SIP) systems also reduces capital investment costs.

In deciding on whether or not to use disposables, system designers assess the trade off between greater flexibility and the long-term cost of disposables, which can be a significant factor if large quantities are used. Moreover, the filling accuracy of today's peristaltic pumps cannot match that of time/pressure systems. This may be a significant factor in the cost/benefit equation depending on the value of the product being handled.

Peristaltic pumps have a reputation for being very gentle on the product. This is a welcome feature for many delicate, large-molecule biopharmaceuticals. The effectiveness of APIs remains unaltered following dosing with peristaltic pumps. As well as greater system flexibility, this can be a major factor in the decision to take the disposable option. Disposable systems normally have interfaces that are bridged with plug-in connectors. The interfaces must be carefully configured to eliminate potential sources of impurity and contamination.

Disposable technologies are also used in filling and packaging systems to introduce materials via sterile transfer into isolator-protected areas. The items involved can include syringe plungers transferred in bulk or pharmaceuticals in powder form. The sterile path is created with foil liners and bags that contain the sterile material and are welded together for transfer using a special welding process (Stericon). A welding unit can be a worthwhile investment even in applications where transfer frequency is in the low to medium range, because the familiar Alpha/Beta systems are substantially more expensive than the bag/liner solution. When environmental considerations play a role in the decision, waste accumulation and disposal versus cleaning agent consumption and CIP/SIP energy costs are factors to consider.

In conclusion, even on biopharmaceutical filling and packaging projects, the parameters to consider are too specific to make a general statement about the use of disposables. There can be no doubt, however, that single-use solutions extend the range of options available for providing solutions that are tailored to the varied needs of the industry. **Pharma**

For more information

Jürgen Schäfer
Managing Director
Optima Group Pharma GmbH
www.optima-packaging-group.de