

New Plastics for Old Vials

Michael N. Eakins

Although it may appear that plastic reigns supreme for primary packaging of pharmaceuticals, it has thus far failed to make much headway in the area of parenteral vials, bottles, or prefilled syringes. In the past this could be explained by a general lack of availability of clear plastics with an overall combination of suitable physical characteristics including the ability to withstand terminal steam sterilization, together with the fact that few plastic vials or plastic prefilled syringes were available from the medical component manufacturers. So it would have to be a pressing need indeed for a pharmaceutical company to undertake the design and to commission the manufacture of plastic vials or syringes for a particular project. The situation has changed in the past couple years, with several medical component companies launching clear plastic vials and prefilled syringes



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using “new” plastics called cyclic olefins.

That’s the good news. The disappointing news is that when one approaches pharmaceutical and biotechnology companies to try to persuade them to try these new plastics, the response from many is generally similar to the one given by Benjamin Braddock in the movie *The Graduate* to a suggested career in “Plastics”: polite disinterest.

This article reviews the properties of cyclic olefins and their use for vials and prefilled syringes and addresses some concerns put forward by pharmaceutical development departments and manufacturing operations about their use to replace glass. Because one major area of concern is the regulation of plastic containers in Europe and the United States, I provide an overview of the regulations and guidelines covering plastic containers.

CYCLIC OLEFINS

The first thing to say about cyclic olefins is that they are not new

compositions of matter, having been discovered 50 years ago (1), about the same time as polycarbonate. So when cyclic olefins are called “new,” it refers to their use in the pharmaceutical industry as packaging components rather than their existence as a plastic material. They can be prepared by the addition polymerization of monocyclic olefins (for example cyclobutane or cyclopentane or bicyclic olefins such as norbornene). *Addition polymerization* simply describes the chemical reaction by which monomers are added to one another to form long-chain molecules (polymers) without by-products. The resulting materials have very attractive physical and chemical properties combining a glass-like transparency with excellent chemical resistance and water vapor transmission barrier properties. However, the early manufacturing processes were difficult to control and produced only small quantities of very expensive materials, making cyclic olefins of academic interest but not a commercial proposition.

PRODUCT FOCUS: PARENTERAL FORMULATIONS

PROCESS FOCUS: FILL AND FINISH, PACKAGING, DRUG DELIVERY

WHO SHOULD READ: FORMULATION DEVELOPMENT, PACKAGING DEVELOPMENT, PHARMACEUTICAL DEVELOPMENT, MANUFACTURING, REGULATORY AFFAIRS AND QA/QC PERSONNEL

KEYWORDS: CYCLIC OLEFINS, PLASTIC CONTAINERS, PREFILLED SYRINGES, VIALS, DRUG MASTER FILES, PHARMACOPEIAL STANDARDS

LEVEL: BASIC, INTRODUCTORY

The road to commercialization was through the invention and use of new, single-site catalysts. Work cited by VEB Luena in 1974 used a multi-sited Ziegler-Natta type catalyst to copolymerize ethylene and 2-norbornene (2). Mitsui Petrochemical Industries produced copolymers of ethylene and other cyclic olefins using soluble vanadium-based Ziegler-Natta catalyst in 1986 (3) that eventually led to the commercialization of the Apel amorphous polyolefins. In the late 1980s and the early 1990s, both Mitsui (4) and Hoechst (5) began using single-sited metallocene catalysis in the polymerization of cyclic olefins that led to the development of the cyclic olefin copolymer (COC) Topas by Ticona. In this process, 2-norbornene is reacted with ethylene in the presence of a metallocene catalyst to produce a series of copolymers whose properties can be modified by varying the norbornene percentage in the material. Use of metallocene catalysts allows the manufacture of sharply defined products with a narrow molecular weight distribution combined with a minimum of byproducts and impurities.

Another commercially viable route is through a two-step process based on the ring-opening metathesis polymerization (ROMP) of dicyclopentadiene followed by complete hydrogenation of the double bonds to form cyclic olefin polymers (COP). Using this process, the Zeon Corporation developed the Zeonex and Zeonor line of COPs. An earlier process resulted in another clear plastic called Crystal Zenith (CZ) that is available only as finished containers.

PROPERTIES OF CYCLIC OLEFINS

Cyclic olefin polymers and copolymers possess many excellent properties beginning with a glass-like transparency (see the "Cyclic Olefin Properties" box) (6). Excellent optical properties enable cyclic olefins to substitute for glass in precision optical components such as lenses for copiers, printers, and CD drives. Their low dielectric loss means they can replace

polypropylene in thin-film and high-temperature capacitors as examples of electrical applications. However, it is the combination of their clear optical properties and low moisture permeability, high purity, and biocompatibility that contribute to their attraction for primary pharmaceutical packaging. On the negative side, cyclic olefins are moderately permeable to gases and should not be used with high concentrations of fats or oils or with nonpolar or halogenated solvents.

The ability to provide a range of formulations with varying glass transition temperatures (T_g) is an advantage because different packaging applications require different heat resistance. Thus, film incorporating cyclic olefins for tablet blister packaging will not need to undergo terminal steam sterilization and so can have a T_g of below 121 °C. Cyclic olefin formulations for vials and syringes that may undergo terminal sterilization need higher T_g of greater than 130 °C. For Topas, this is achieved by increasing the level of norbornene in the formulation to increase stiffness, strength, glass transition, and heat deflection temperatures (HDT). In this way, Topas is currently available in five formulations ranging in T_g from 80 °C to 180 °C (Table 1). Zeon Corporation offers three formulations with T_g s ranging from 70 °C to 136 °C under two different trade names, Zeonor and Zeonex (Table 1).

CYCLIC OLEFINS IN MEDICAL PACKAGING

Until recently, the only available vials and prefillable syringes made from clear plastic were those manufactured from CZ by Daikyo in Japan and supplied through West Pharmaceutical Services. The range of choices has expanded rapidly in the past couple of years with prefillable syringes now available from Baxter, Becton Dickinson, and Schott in clear plastic, and vials available or under development at Alcan, MedInstill Aseptic Technology, Owens-Illinois, and Schott (Table 2). Although the prefillable syringes from Becton Dickinson, Schott, and West are

CYCLIC OLEFIN PROPERTIES

Cyclic olefins offer the following properties:

- Glass-like transparency
- High purity (low potential extractables)
- Very low water absorption and permeability
- Biocompatibility
- Formulations available as "Medical Grade" (complies with USP Plastic Class VI)
- Low density
- Broad range of glass transition temperatures (T_g)
- High heat deflection temperature (HDT)
- Good resistance to acids and bases
- Excellent insulator (low dielectric loss)
- Good molding characteristics including low shrinkage
- High dimensional stability
- Coextrude with other plastics as film

available to be filled at a purchaser's site of choice, Clearshot syringes from Baxter are manufactured in-line and filled only at Baxter's manufacturing facility. The vials produced by Aseptic Technologies represent a new approach to vial handling and filling. The vials and stoppers are molded and assembled immediately under clean conditions and gamma sterilized. Filling is achieved by piercing the closure and then immediately resealing the puncture with a laser. The system is unsuitable for terminal steam sterilization because of the thermoplastic nature of the closure.

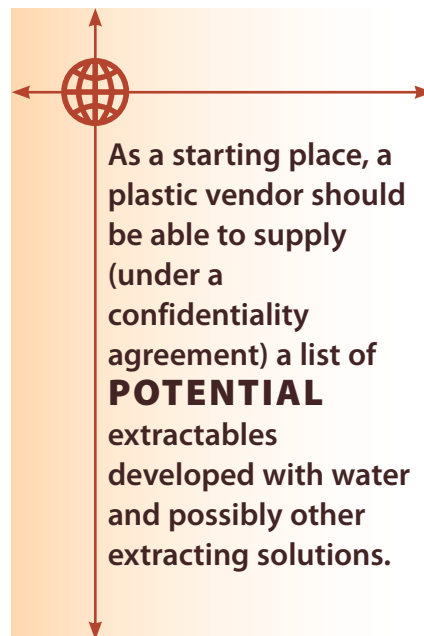
PHARMACEUTICAL DEVELOPMENT CONCERNS

Several reasons explain why companies are reluctant to try plastic prefilled syringes or plastic vials. A major concern is a fear of project failure due to lack of knowledge of plastic packaging. Increased development

expense and time is also cited as a key factor.

Continuation of Supply: The amount of plastic material consumed by the pharmaceutical industry is negligible compared with the amounts used in the automotive, electrical, and optical industries. This means that a plastic vendor can replace a particular formulation with another one to satisfy its main (nonmedical) client for financial reasons. Swapping a particular plastic formulation that is under development for primary parenteral packaging is not an option that can be done quickly or cheaply because new stability studies would most likely have to be performed. Withdrawal of a particular formulation is more likely to occur for generic formulations — polypropylene is one example that I have experienced. The two major suppliers of cyclic olefins have made major investments in production of the particular formulations that have medical grade status, so continuation of supply should be less of a concern.

Knowledge Base: For a company with no history of using plastic as a primary packaging material for parenteral products, the first project using plastic is a voyage into the unknown. Major concerns are the product–plastic interaction, identification of potential extractables and leachables, determination of which potential extractables and leachables should be studied as stability parameters, and regulation of plastic containers in Europe and the United States. The first place to start is with the manufacturer of the resin and the supplier of the empty plastic components to gather as much information as possible. Such companies may also have internal pharmaceuticals experts to guide development or can recommend consultants who are experts in developing drugs with a particular plastic. This approach can save both time and direct expense by reducing unnecessary work done in gaining experience with the plastic and on selecting potential extractables and leachables to study.



As a starting place, a plastic vendor should be able to supply (under a confidentiality agreement) a list of **POTENTIAL extractables developed with water and possibly other extracting solutions.**

However, it is quite clear that the number of potential compounds that may be an extractable or leachable is higher for plastic than for glass because the number of components in the formulation will be higher. These compounds are organic, whereas glass potential extractables are inorganic. As a starting place, a plastic vendor should be able to supply (under a confidentiality agreement) a list of potential extractables developed with water and possibly other extracting solutions. This list will be fairly limited for the cyclic olefins and will be smaller than the list for plastic containers made up of multilayers of different plastics, e.g., plastic bags that can have between three and five plastic layers along with a different multi-layered plastic for the port tubing.

Table 1: T_g and HDT values for medical-grade cyclic olefins

Medical Grade	Glass Transition Temperature (T_g)	Heat Deflection Temperature (HDT)
Crystal Zenith	140 °C	123 °C
Topas		
8007	80 °C	75 °C
5013	140 °C	130 °C
6013	140 °C	130 °C
6015	160 °C	150 °C
6017	180 °C	170 °C
Zeonex 690R	136 °C	136 °C
Zeonor		
750R	70 °C	68 °C
1020R	105 °C	101 °C

Table 2: Vials and prefillable syringes available in clear plastic

Company	Component Available	Clear Plastic	Size Range (mL)
Alcan	Vials	Topas	2 and 5
Baxter	Prefillable syringes*	Clear copolymer	1, 3, 5, and 10
Becton Dickinson	Prefillable syringes	Crystal clear polymer	5 to 50
MedInstill	Vials**	COC	2 to 100
Owens-Illinois	Vials	Multi-layer including COC or COP	10 to 250
Schott	Prefillable syringes Vials	Topas Topas	0.5 to 50 2 to 50
West Pharmaceutical Services	Prefillable syringes Vials	CZ CZ	1 to 100 1 to 100

* Clearshot prefillable syringes offered for custom filling at Baxter

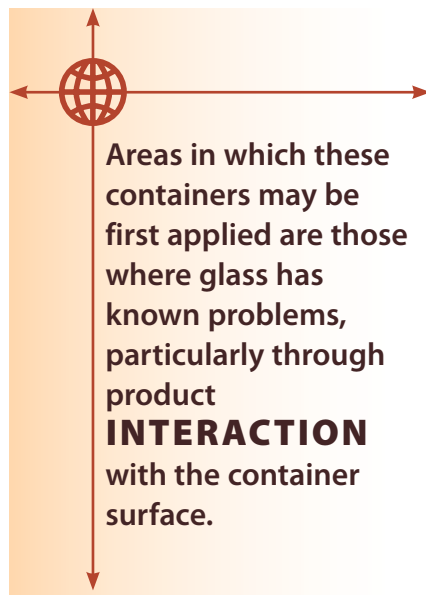
**In development

MANUFACTURING OPERATIONS

The introduction of plastic vials or plastic prefillable syringes also has implications for manufacturing operations. Whereas glass prefillable syringes are already being filled from a “ready-to-fill” configuration in tubs, a switch to plastic prefillable syringes in the tub format can be achieved using the same filling machines. If plastic prefillable syringes are supplied only in a clean, bulk format, then they will require washing before filling, which could entail purchase of a new syringe washing/filling line. Glass vials are washed and then depyrogenated and sterilized by heat on site before filling. Plastic containers pose a problem because high temperatures cannot be used to depyrogenate and sterilize them, and all handling operations must be designed to avoid scratching their outer surfaces. They can be depyrogenated by repeated washing with water for injection and sterilized using radiation (gamma or e-beam) or ethylene oxide. These issues are addressed in the FDA’S 2004 *Guideline to Aseptic Filling* (7). The speed of the filling line may have to be adjusted to accommodate lighter plastic vials.

REGULATION OF PLASTIC CONTAINERS

Although both European and US regulatory authorities require detailed information on the manufacture and composition of the plastic, the procedure to supply this key information is totally different in Europe from the United States. Europe, Canada, and the United States have a Drug Master File (DMF) system in which companies provide confidential information on the constituents and manufacturing process for their products. Information on packaging materials can be supplied in a Type II DMF in Canada and Type III in the United States (8), but not in Europe. There, the DMF system is limited to providing information on drug substances and has recently been renamed to *Guideline on Active Substance Master File Procedure* (9). Therefore, the only approach in Europe is for a drug company itself to provide the required information on the packaging materials in the product application



having first obtained it from the vendor of the plastic itself or the plastic components. In the case of the cyclic olefins, Ticona has filed a Type III DMF #12132 for all its cyclic olefin copolymers (COC) Topas, and Zeon has filed DMF #14084, #14932 and #13885 respectively, for its Zeonor and Zeonex cyclic olefin polymers.

Guidelines on what information is required for plastic containers can be found in the newly revised *Guideline on Plastic Primary Packaging Materials* (10) for Europe, whereas the document entitled *Container Closure Systems for Packaging Human Drugs and Biologics* provides guidance from the FDA (11). Both the *European Pharmacopoeia* (EP) and the *United States Pharmacopoeia* (USP) have chapters relevant to the control of plastic material and plastic packaging, but their approaches differ. Section 3.1 of the EP on *Materials Used for Manufacture of Containers* (12) has very detailed individual chapters on six different plastics including “Polyolefins” (13) (directly relevant to cyclic olefins) as well as chapters on the control of plastic containers in 3.2. (14–16). By contrast, the USP combines the control of plastic containers and plastic materials in Chapter <661> (17). Sections here deal specifically with only polyethylene, polyethylene terephthalate, and polypropylene and not in as much detail as in the EP.

In relation to biological testing, the USP has chapters on both in vitro (18) and in vivo testing (19). The classification of plastics from Class I

to Class VI, in which Class VI has the most strict requirements, is found in Chapter <88>. The USP recently added Chapter <1031> on the biocompatibility of materials used in drug containers (20). This chapter is clearly modeled after the ISO document 10993, entitled *Biological Evaluation of Medical Devices* (21), which already has Parts 1 to 17 published. USP <1031> notes that seven of the toxicology procedures are “to come,” whereas they are published in detail in the ISO 10993 series (Parts 3, 4, 10, 11). The EP is silent on toxicology testing of plastics for containers.

The greater complexity of plastic materials and requirements of the regulatory guidelines also appear to contribute to a reluctance to switch to plastic, and especially to a new plastic. As with issues with extractables, assistance in regulatory matters may be obtained by asking the vendors for either in-house expertise or a recommendation of external consultants.

VIABLE ALTERNATIVES

The past two years have seen a sustained effort to provide viable plastic alternatives to glass for vials and prefillable syringes. Areas in which these containers may be first applied are those where glass has known problems, particularly through product interaction with the container surface. Packaging of diluents in glass, particularly water for injection or 0.9% saline, have resulted in difficulties in controlling the solution pH because of leaching of alkali ions. Another example is a high solution pH of >8.5, from which glass is quite susceptible to attack. In biotech, product–surface interaction is an issue both from the point of view of protein absorption and aggregation and from stability issues such as unfolding. Plastic containers can play a role here (22).

Pharmaceuticals are already in development with these plastics, so if you start now, you can feel safe that you will not be the first to file your dossier with these new plastics with the regulatory bodies. So come on, “Benjamin Biotech” — take another look: Perhaps the future really is in “Plastics.”

REFERENCES

- 1 Anderson AW, Merckling NG. *Polymeric Bicyclo-(2,2,1)-2-Heptane*. US Patent 2,721,189; 1955.
- 2 Koinzer J-P, Langbein U, Taeger E. *Verfahren zur Herstellung Alterungsbeständiger Norbonen-Äthylen-Copolymerer*. German Democratic Republic Patent 109,224; 1974.
- 3 Kajiura H, Oda H, Minami S. *Random Copolymer*. US Patent 4,614,778; 1986.
- 4 Ishimaru N, et al. *Cyclo-Olefinic Random Copolymer, Olefinic Random Copolymer, and Process for Producing Cyclo-Olefinic Random Copolymers*. US Patent 5,003,019; 1991.
- 5 Breker M-J, et al. *Process for the Preparation of Cycloolefin Polymers*. US Patent 5,087,677; 1992.
- 6 Lamonte RR, McNally D. Uses and Processing of Cyclic Olefin Copolymers (COC). *Plastic Engineering* 56, November 2000: 51–59.
- 7 US Food and Drug Administration *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*. September 2004; www.fda.gov/cder/guidance/5882fnl.pdf.
- 8 US Food and Drug Administration *Guideline for Drug Master Files*. September 1989; www.fda.gov/cder/guidance/dmf.htm.
- 9 Committee for Proprietary Medicinal Products. *Guideline on Active Substance Master File Procedure*. CPMP/QWP/227/02; 11 February 2004; www.emea.int/pdfs/human/qwp/022702.pdf.
- 10 Committee for Proprietary Medicinal Products. *Guideline on Plastic Primary Packaging Materials CPMP/QWP/4359/03-Consultation*; 25 February 2004; www.emea.int/pdfs/human/qwp/435903en.pdf.
- 11 US Food and Drug Administration. *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics — Chemistry, Manufacturing, and Controls Documentation*. May 1999; www.fda.gov/cder/guidance/1714fnl.pdf.
- 12 Chapter 3.1. Materials Used for the Manufacture of Containers. *European Pharmacopoeia* 5.0, 2005.
- 13 Chapter 3.1.3. Polyolefins. *European Pharmacopoeia* 5.0, 2005.
- 14 Chapter 3.2. Containers. *European Pharmacopoeia* 5.0, 2005.
- 15 Chapter 3.2.2. Plastic Containers and Closures for Pharmaceutical Use. *European Pharmacopoeia* 5.0, 2005.
- 16 Chapter 3.2.2. Plastic Containers for Aqueous Solutions for Parenteral Infusion. *European Pharmacopoeia* 5.0, 2005.
- 17 Chapter <661> Containers. *United States Pharmacopoeia 27–National Formulary* 23, 2004.
- 18 Chapter <87> Biological Reactivity Tests In Vitro. *United States Pharmacopoeia 27–National Formulary* 23, 2004.
- 19 Chapter <88> Biological Reactivity Tests In Vivo. *United States Pharmacopoeia 27–National Formulary* 23, 2004.
- 20 Chapter <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants. *United States Pharmacopoeia 27–National Formulary* 23, 2004.
- 21 ISO 10993, Parts 1 to 17. *Biological Evaluation of Medical Devices*. International Organization for Standardization, 1992–2003.
- 22 Quadry SS, et al. Evaluation of CZ-Resin Vials for Packaging Protein-Based Parenteral Formulations. *Int. J. Pharm.* 252, 2003: 207–212. 🌐

Michael N. Eakins is principal consultant at Eakins & Associates, East Windsor, New Jersey (1-609-448-3411), mneakins@comcast.net, specializing in the pharmaceutical packaging for parenteral products and anti-counterfeiting strategies. Before becoming a consultant, he spent over 20 years in the pharmaceutical industry at Bristol-Myers Squibb and Bracco SpA, most recently as head of Bracco's International Packaging Center.