

Parenteral Products: Pharmacopeial Control of Containers, Storage and Distribution

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National pharmacopeias, for example the U.S. Pharmacopeial Convention (USP), The Japanese Pharmacopoeia (JP), and The European Pharmacopoeia of the Council of Europe (EP), set quality standards for active pharmaceutical ingredients, drug products, excipients, packaging materials, labeling and storage conditions. The USP also has General Information chapters numbered above <1000> that contain no standards, tests, assays or other mandatory specifications with respect to Pharmacopeial articles, but provide information and guidance on a large variety of topics including packaging, storage and distribution practices. This article will concentrate on the quality control of container materials used for packaging parenteral products (glass, plastic and elastomers), good storage and shipping practices as well as providing an overview of new topics that the USP is developing relevant to parenteral products within the Packaging, Storage and Distribution Expert Committee for the 2010-2015 cycle.

Container Materials for Parenteral Products

While plastic dominates primary and secondary packaging materials for most types of pharmaceutical dosage forms, glass remains the primary packaging material of choice for parenteral products at this time. Glass vials and bottles are manufactured by molding while ampules, cartridges, pre-fillable syringe barrels and vials are manufactured from tubing glass. Both manufacturing methods use borosilicate glass (Type I) which has a high resistance to hydrolytic attack. The limits for tests on the hydrolytic resistance of glass containers in the EP and USP determine compliance of Type I borosilicate glass and Types II and III for soda-lime glass [1,2]. The methods for glass grains (EP) and the powdered glass (USP) test are similar in that they both determine by titration the amount of alkali released after autoclaving glass containers containing purified water. However there are differences in the details as to exactly how the methods are performed [1,2]. The EP also uses the surface glass test to determine compliance of Types I, II and III glass while the USP has a similar test called water attack at 121°C used for determining compliance of Type II glass. The surface glass test is present in the USP chapter but does not determine glass Type (Table 1). A proposed revision to USP <660> Containers-Glass has just been published in the Pharmacopeial Forum [3]. This revision proposes to adopt the EP's methodology for the glass grains test, to incorporate the surface glass test to determine glass Types and to delete the water attack at 121°C test. In addition, it is proposed to extend testing for arsenic impurities to Type II glass. If adopted, these changes will bring the USP chapter into close alignment with the EP chapter. The JP does have the glass grains and surface glass tests but does not use the classification of glass Types I, II and III [4].

The Pharmacopeial Forum (PF) is the bimonthly online journal through which USP develops and revises standards by a process of public review and comment. As of January 2011, the PF is now a free, online publication

that may be accessed at www.usp.org/USPNF/pf. New issues are posted online every two months and the comment period is 90 days.

Table 1. Determination of Glass Types in European and United States Pharmacopeias

Container Type	General Description	EP Tests	USP Tests Current	USP Tests Proposed
Type I	Borosilicate glass	<ul style="list-style-type: none"> • Glass grains • Surface glass • Surface etching 	<ul style="list-style-type: none"> • Powdered glass * [Surface glass] 	<ul style="list-style-type: none"> • Glass grains • Surface glass • Surface etching
Type II	Treated soda-lime glass	<ul style="list-style-type: none"> • Glass grains • Surface glass • Surface etching 	<ul style="list-style-type: none"> • Water attack at 121°C * [Surface glass] 	<ul style="list-style-type: none"> • Glass grains • Surface glass • Surface etching
Type III	Soda-lime glass	<ul style="list-style-type: none"> • Glass grains • Surface glass 	<ul style="list-style-type: none"> • Powdered glass * [Surface glass] 	<ul style="list-style-type: none"> • Glass grains • Surface glass

* [Surface glass] Test is present but does not define glass Type

Plastic is beginning to make inroads into glass' domination as the material of choice for primary packaging of parenteral products. Plastic bags have been used for quite some time for large volume parenterals. Several vendors now provide an alternate choice to glass pre-fillable syringes with pre-fillable syringe barrels manufactured from clear cyclic olefin polymer or cyclic olefin copolymer [5-7]. A range of clear plastic vials is also available [7]. There are striking differences between the control of plastic materials in the EP versus the JP and USP. The EP has a series of chapters on individual plastic materials for packaging pharmaceuticals and a separate chapter on plastic containers [8-18] while the JP and USP each have a chapter on plastic containers covering several plastic materials [19,20]. The plastic materials covered in the three pharmacopeias are shown in Table 2.

Table 2. Physicochemical and Biological Tests on Plastic Materials in European, Japanese and United States

EP	JP	USP
Physicochemical Tests – Plastics Materials for Containers for Parenteral Preparations <ul style="list-style-type: none"> • Polyolefins • Polyethylene • Polypropylene • Polyethylene Terephthalate • Polyethylene Vinyl Acetate • Poly(vinyl chloride) 	Physicochemical Tests – Plastics Containers for Aqueous Injections <ul style="list-style-type: none"> • Polyethylene • Polypropylene • Polyethylene Vinyl Acetate • Other Plastics 	Physicochemical Tests – Plastic Containers for Non-Defined Use <ul style="list-style-type: none"> • All Plastics
Physicochemical Tests – Plastic Containers for Parenteral Preparations <ul style="list-style-type: none"> • All Plastics 	Physicochemical Tests – Plastic Containers for Dry Solid or Liquid Oral Dosage Forms <ul style="list-style-type: none"> • Polyethylene • Polypropylene • Polyethylene Terephthalate • Polyethylene Terephthalate G 	Physicochemical Tests – Plastic Containers for Dry Solid or Liquid Oral Dosage Forms <ul style="list-style-type: none"> • Polyethylene • Polypropylene • Polyethylene Terephthalate • Polyethylene Terephthalate G
	Biological Tests – All Plastics <ul style="list-style-type: none"> • Cytotoxicity 	Biological Tests – All Plastics <ul style="list-style-type: none"> • Biological Activity, In Vitro • Biological Activity, In Vivo

Not only does the EP cover more plastic materials, the number of physicochemical tests conducted on extracts is far greater. Taking Polyolefins as an example of an EP chapter [9], there are ten tests on extracts including four for metals (Al, Ti, Zn, heavy metals) and an additional four tests on extracts in the chapter on plastic containers [18]. The USP chapter <661> Containers-Plastics has four physicochemical tests including a test for heavy metals [20]. The situation is reversed when it comes to biological testing. Here the EP chapters have no biological test requirements while the USP has both in vitro and in vivo requirements [21,22].

Elastomers are widely used in primary parenteral packaging as stoppers for vials, plungers and tip caps for pre-fillable syringes, plungers and seals for cartridges and ports for plastic bags. Here the EP and the USP are already closely aligned in their tests and specifications following the revision of the USP chapter <381> in 2008 [23,24]. There are considerable differences between the EP and USP chapters on elastomers and the test for rubber closures in the JP [25].

A final word on packaging components, although this is in reference to solid dosage forms. A new chapter entitled <670> Auxiliary Packaging Components was added to the USP in the second Supplement of USP 33 NF 28 in 2010. This chapter covers cotton, rayon and polyester pharmaceutical coil which is added to containers to prevent breakage of tablets and capsules during shipment [26,27]. There are no equivalent chapters in either the EP or JP on pharmaceutical coil.

Extractables from Container Materials

Extractables are chemicals that are removed from a material under exaggerated conditions such as time and temperature in the presence of an appropriate solvent. The pharmacopeial chapters on glass, plastic and rubber all have methods and specifications for extractables such as alkali ions from glass and metals and organic molecules from plastics and rubber. The question to be considered is whether the current requirements in the pharmacopeias are sufficient. To address this issue, the USP has recently announced that it is preparing a new overarching guidance chapter on extractables that will be followed by updating USP's chapters on glass, plastics and elastomers [28]. This initiative also dovetails with the USP's previously announced plan to revise the methodology for elemental impurities [29-31] and will affect the test for arsenic in glass and the test for heavy metals (as lead) in both plastics and elastomers. Moving away from the old colorimetric assays to modern analytical technologies will not only provide for greater accuracy but allow the quantification of specific elements. The USP <231> Heavy Metals test [32] is for elements that react with sulfide ions, with the resulting color being measured against a lead standard. Elements that typically respond to this test are antimony, arsenic, bismuth, cadmium, copper, lead, mercury, molybdenum, silver and tin. Thus a replacement test would either need to sum these elements or set limits on individual elements.

Storage and Distribution

The USP currently defines product storage conditions such as container and temperature definitions in General Notices and Requirements [33]. A proposal has been published in the PF to move these definitions to a new general chapter <659> Packaging and Storage Requirements and to add a number of new definitions and topics [34]. Pharmaceutical product storage, distribution and shipping practices are covered in general information chapter <1079> [35]. A proposed revision has been drafted that reflects the move from a regional supply chain to a global one for drug products and the increased importance of cold chain storage due to the development of biotechnology-derived drugs requiring refrigerated storage. The revised chapter was published in the PF [36] and

has received a large number of comments. The USP Packaging, Storage and Distribution Expert Committee have reviewed the comments and a revised draft chapter will be published in the PF by mid-year of 2011 [37].

Supply Chain Integrity

The importance of maintaining the integrity of the supply chain beginning with the source of active pharmaceutical ingredients and excipients, the safe international and national distribution of drug products, combating the rise in theft of high value pharmaceutical cargoes and the insertion of counterfeit drugs into the supply chain has lead the Packaging, Storage and Distribution Expert Committee to be begin work to develop a guidance chapter covering these subjects [28,37]. It is hoped to have the draft chapter published in the PF for public comment in 2011.

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