Trust but Verify: Importance of Packaging Compendial Testing to Secure the Parenteral Drug Supply Chain

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Trust. We normally think of trust in the context of our personal relationships with other people, but how often do we consider trust with respect to the products we use? Most of the products used on a daily basis we implicitly trust to work as advertised because (a) we assume the company providing the product has done sufficient functionality, safety testing and quality control, (b) that there exists somewhere a governmental/regulatory rule requiring testing of said product for human safety by some approved standard before the product can be sold to the consumer, (c) we usually have experience with the products and expect that any defect will be easily visible by eye, and (d) the potential long-term health impact from a defective product is normally low. But what about those products such as medicines/drugs which we use that bypass our bodies' protective defence mechanisms (skin barrier, stomach acid, mucus membranes, etc.)? For these products (i.e. parenterals) we go one step further with trust but verify, due to the potentially severe impact to patient safety from counterfeit, mis-labelled, mis-packaged, defective or non-compliant products.

Supply Chain and Regional Pharmacopeia for Compendial Testing

While a discussion for verifying the safety of the entire supply chain for a finished drug product is beyond the scope of this article, just assessing the safety (i.e. authenticity and required performance attributes) of the parenteral primary packaging supply chain is a sufficiently demanding task. There are currently an estimated 7.8 billion humans on earth.[1] The worldwide production of borosilicate glass containers (the dominant material used for parenteral products for over 100 years) is approximately 50 billion per year;[2] with significantly increased demand for confrontation of the current global pandemic challenge. This also requires the same amount of closure systems (elastomeric stoppers for vials, plungers/seals/tip caps for syringes or cartridges, not an easy task to procure additional components quickly as the number of major glass tubing manufacturers and elastomer raw material manufacturers is small. Depending on what performance attribute is being assessed, the glass converting process has a much larger impact (i.e. on the hydrolytic resistance of the inner surface) than the processing steps of the primary material by the glass tubing manufacturer. There are tens of different glass compositions and tens of different elastomers available on the international market. Depending on where the finished drug product is sold, different pharmacopeias (i.e. United States Pharmaceopeia – USP, European Pharmacopeia – Ph.Eur., Japanese Pharmacopeia – JP, People's Republic of China Pharmacopeia – ChP) and/or international/national standards (i.e. ICH, ISO, ASTM, DIN, YBB) regulate the testing and release of primary packaging materials. Despite intensive harmonisation efforts between the regulatory/standard bodies, both small and significant testing method differences and requirements remain. This often means for a worldwide drug product release that two or three very similar tests measuring the same performance attribute must be conducted to satisfy the regionally different regulatory requirements.

The process of trust but verify for compendial testing is multi-faceted, with redundant testing built into the system to help minimise mistakes. From a 30,000 foot perspective, this is an iterative process stretching across decades with two possible starting points. The normal procedure is that a raw material or component within the existing design space (i.e. approved materials) is introduced to the market and tested according to existing regulatory/standards, the standards being adjusted over time if required due to increasing product requirements and specifications. As advances are made in materials science, when a new material/component that meets an industry need outside the existing design space is introduced to the market, it requires testing according to existing regulatory/standards as well as additional tests from the manufacturer or end use customer. The additional testing is required because new materials can cause or contribute to new container/drug product interactions to occur that are not found in existing materials, resulting in extensive review and oftentimes update/change/addition to the standards. No matter the starting point, the subsequent use of the raw material or component requires the following testing pathway: (a) testing by supplier to generate a certificate of analysis related to manufacture of material to customer specification and applicable regulatory standards, (b) downstream retesting of the material on a lot-to-lot basis or on a time period basis by the pharmaceutical company/contract filler or by outsourcing to a contract testing laboratory. Downstream testing (i.e. by the pharmaceutical company or their contract filler) of the components is required due to regulatory guidance[3] assigning the final responsibility for finished product safety to the pharmaceutical company.

Quality Requirements for Contract Laboratory

One underappreciated, but very important contributor to successful testing, is the qualification and experience level of the testing laboratories. Glass is manufactured normally under ISO quality management systems such as ISO 9001:2015 and ISO 15378:2017[4,5] and tested by the manufacturer under GMP or GLP quality management systems (good manufacturing practice; good laboratory practice). Testing by pharmaceutical/contract fillers is normally conducted under these quality management systems. However, while contract laboratories may operate under GMP/GLP systems, it is increasingly common for contract laboratories to be accredited under a standard quality management system such as ISO 17025:2017.[6] While GMP/GLP/ISO 17025 share many of the same principles, the certification process is significantly different because ISO 17025 requires external, independent, non-customer based assessment via on-site auditing to receive accreditation. ISO 17025 accreditation in addition requires verification that the testing procedures have been validated and traceable back to standards. Of course, customers also audit the testing laboratory, usually based on a combination of ISO 17025 standard and relevant aspects of company-specific

GMP/GLP. There is tremendous variability in the quality of compendial testing that can be directly traced by auditors on the qualification and training of the employees, method validation, equipment selection, qualification of instruments, etc. of the testing laboratory.

Example of Compendial Testing Required for Glass Vials for a Worldwide Product Launch

Let's use for an example of the trust but verify process a pharmaceutical company ready to launch a new drug product worldwide in an ISO 10R tubular glass vial[7] and go through the testing required of the glass container component. We will focus only on the testing required to fulfil compendial regulations for commercial production. A supply agreement has been negotiated with glass vial suppliers on the technical basis of a glass vial specification document to provide a suitable container meeting essential parameters/tolerances. This is part of the risk mitigation process to ensure supply of containers, which also could include supply from multiple production sites, supply from multiple suppliers, warehouse/delivery management, etc. The glass vial suppliers first have to obtain the appropriate glass tubing which comes with a certificate of analysis giving the results of testing for hydrolytic resistance (e.g. ISO 719[8], ISO 720[9]), light protection (e.g. USP <660> [10], Ph.Eur. 3.2.1.[11]), and heavy metals (article 11 of 94/62/EC[12]). The glass tubing supplier ensures tubing passing these tests by regular (daily, weekly, monthly) testing of running tubing production by additional testing of chemical composition, transmission, coefficient of thermal expansion (CTE), density, viscosity, glass stress sealant, transformation temperature (Tg), working point, and other parameters. Glass tubing suppliers also conduct dimensional and cosmetic inspections.[13] The combined testing assures the glass container manufacturer that the glass tubing (i.e. raw material) is of sufficient quality to meet the required pharmacopeia specifications for containers.

By agreeing to produce a 10R tubular vial according to ISO 8362-1,[7] the vial manufacturer commits to producing the container within the dimensional specifications (Figure 1, from[7]) for the selected container and fulfilling the requirement for European blowback/ American blowback / no blowback (Figure 2) along with testing for hydrolytic resistance of the inner surface according to <USP> 660; Ph.Eur. 3.2.1 or ISO 4802-1,[14] residual stress, and cosmetic limits according to ISO 8362-1.[7] This is the bare minimum requirement. If a higher glass cosmetic quality level is part of the glass supply agreement, then additional testing by various tools/systems of each vial will be conducted with agreed-upon acceptable quality limits (AQL) such as for SCHOTT TopLine vials.[15] The classification and identification of non-conformities is conducted either according to industry standards such as the defect evaluation list[16], PDA TR43,[17] or company-specific defect catalogues such as the SCHOTT Vial Defect Manual.[18] The supply agreement will also define the secondary packaging material of the glass container (shrink-wrap, polyethylene tray, tub and nest), number of vials per container, number of units per level of pallet, and number of levels per pallet, configuration of units on each level, pallet protective packaging, and method of transportation. For each lot of vials produced a certificate of conformity or certificate of analysis will be issued to the pharmaceutical client/contract filler showing compliance according to the major pharmacopeia regulations (USP <660>, Ph.Eur. 3.2.1., JP 7.01[19]) and international standards (ISO).

Once the vials are shipped out by the manufacturer, the trust but verify process starts in earnest. Depending on the pharmaceutical company/contract filler and experience with the glass vial manufacturer, vials may be accepted directly into the vial filling process ("accepted by certificate") or undergo incoming inspection. Typical incoming inspection involves a sampling plan based on lot size and AQL-level based on ISO 2859[20] for checking the dimensional and cosmetic attributes of the vials, done directly by the glass manufacturer (i.e. tail gate samples) and accepted on certificate or by the pharmaceutical company in-house staff or outsourced by the pharmaceutical company to third-party laboratories. Per regulatory agency guidance such as the US FDA[3] a regular testing interval check of manufacturer's data has to be conducted. Pharmaceutical companies require this checking for each lot of components for critical attributes like dimension and visual non-conformities where sampling frequency, amount of samples, and skip lot procedure is defined,[20] but for less critical attributes on a reduced frequency basis. This step is the heart of the trust but verify process, in essence a double-checking / double verification of the materials before release and use in the packaging of the intended drug formulation to ensure that the correct packaging is used.

Key Attributes	10R
Brimful Capacity (mL)	13.5 ± 1
D1 Body Width (mm)	24 ± 0.2
D4 Inner Neck Diameter (mm)	12.6
H1 Overall Height (mm)	45 ± 0.5
R1 Shoulder Wall Thickness (mm)	4 ± 2
S1 Body Wall Thickness (mm)	1 ± 0.4

Figure 1: Selected key dimensional attributes of 10R vial from ISO 8362[7]

The pharmacopeia mandated tests for glass containers for parenteral products are given e.g. in USP <660>, Ph.Eur. 3.2.1., and JP 7.01. For example, USP <660> requires determination of the hydrolytic resistance by glass surface and glass grains extraction and subsequent titration tests to assign the glass to one of three types: Type I, II, III (Figure 3). As an alternative to the glass grains testing, surface etching testing can be used to confirm Type I (borosilicate

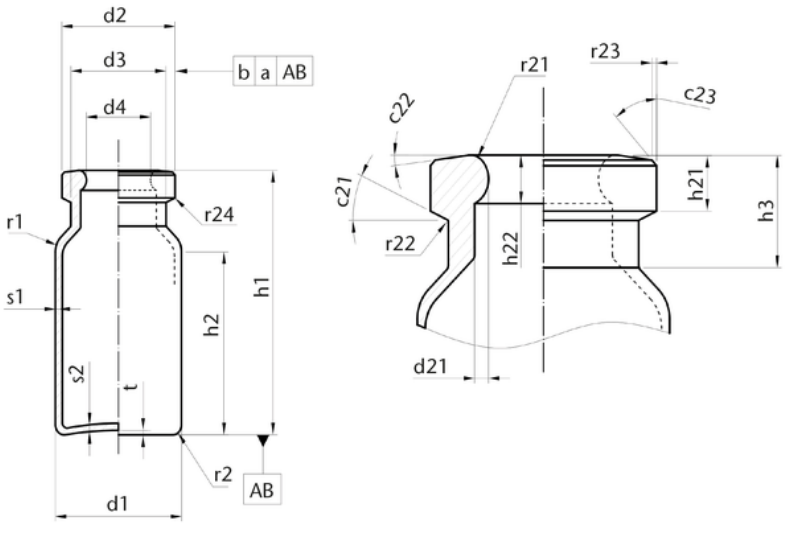

Figure 2: Exemplary SCHOTT 10R European blowback tubular injection vial drawing

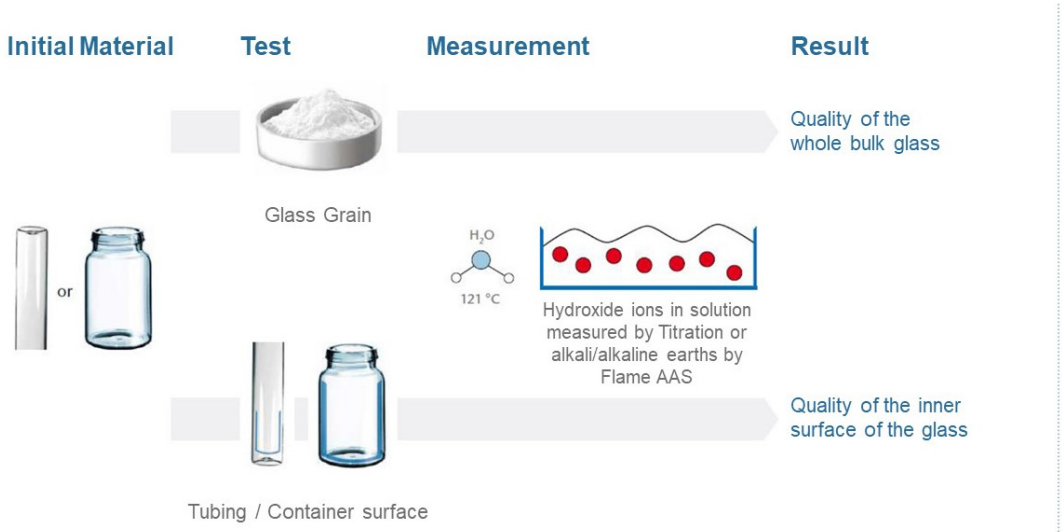

Figure 3: Glass hydrolytic resistance testing methods to distinguish between Type I, II, III glasses and to check quality of the raw glass and finished glass containers

glass) vs Type II (treated soda lime glass) to assign if the hydrolytic resistance performance measured by the glass surface test is accomplished by the inherent glass chemistry (i.e. borosilicate) or by treatment (i.e. ammonium sulfate inner surface treatment of soda lime glass). Determination of the amount of arsenic is required by testing according to e.g. USP <211>[21] or Ph.Eur. 3.2.1. If the glass containers are coloured (i.e. amber glass) to provide light protection of the drug product then the containers must be assessed spectrophotometrically via UV-VIS spectroscopy to meet transmission limits based on the size of the container. Ph.Eur. 3.2.1. allows for an alternative method for surface hydrolytic resistance testing via flame spectrometry, which is comparable to ISO 4802-2 testing.[22] JP 7.01 adds additional testing requirements for visual conformity and soluble iron. Careful reading of these pharmacopeia tests reveals small differences in the methods. Taking the example of hydrolytic resistance testing, method variations include type of acid used for hydrolytic resistance testing (hydrochloric vs. sulfuric), acid concentration (0.02 M vs 0.01 M), pH indicator (methyl red vs bromocresol green), heating temperature (121°C vs 100°C), heating time (30 minutes vs 120 minutes), etc. For some tests, totally different analytical techniques for detection are described. Regarding arsenic release testing, Ph.Eur. 3.2.1. needs an instrument-based detection method (hydride generation atomic absorption spectrometry) whereas USP <211> uses colorimetry.

Example of Compendial Testing Required for Rubber and Polymer Components

The pharmacopeia mandated tests for

Sample Type	Test method	Standard	Technique
Container (glass)	Hydrolytic resistance of the inner surface	ISO 4802-1 / ISO 4802-2	Titration / FAAS
	Glass surface	Ph.Eur. 3.2.1. / USP <660>	Titration
	Glass surface etching	Ph.Eur. 3.2.1. / USP <660>	Titration
	Glass grain / glass powder	DIN EN ISO 719 / ISO 720 Ph.Eur. 3.2.1. / USP <660>	Titration
	Arsenic	Ph.Eur. 3.2.1. / USP <660>/<211>	FAAS / Colorimetric
	Light transmission	Ph.Eur. / USP / JP	UV-VIS
	Visual conformity	JP 7.01, test 1	Visual Inspection
	Soluble alkali	JP 7.01, test 3 method 1	Titration
	Soluble iron	JP 7.01, test 5	Colorimetric
	Heavy metals	EUR-Lex Article 11 94/62/EC	ICP-OES
	Boron oxide	ChP 4009 / YBB 00232003-2015	Titration
	Inner surface 121 °C	ChP 4006 / YBB 00242003-2015	Titration
	Glass grains 121 °C	ChP 4001 / YBB 00252003-2015	Titration
	Glass grains 98 °C	YBB 00362004-2015	Titration
	Acid resistance	YBB 00342004-2015	Gravimetry
	Alkali restistance	YBB 00352004-2015	Gravimetry
	Heavy metals	YBB 00372004-2015	Colorimetric (ICP-MS)
Syringe (glass)	Needle diameter and composition	DIN EN ISO 9626 and ISO 5350	SEM-EDS / VGA
	Tungsten	In-house	ICP-MS
	Silicone oil	In-house	GF-AAS
	Flange strength	In-house	Pressure testing
	Needle pull-out force	In-house	Tensile testing
Rubber component	UV	DIN EN ISO 8871-1	UV
	Ash	DIN EN ISO 8871-2 / ISO 247	Gravimetry
	Density	DIN EN ISO 8871-2 / ISO 2781	Balance
	Particle count	DIN EN ISO 8871-3	Microscopy
	Solution S tests	Ph.Eur. 3.2.9. / USP <381>	Colorimetric / UV-VIS / AAS / Balance / Titration
	Bromobutyl rubber plungers	YBB00082004-2015	Colorimetric / UV-VIS / AAS / Balance / Titration
	Polyisoprene rubber caps	YBB00102004-2015	Colorimetric / UV-VIS / AAS / Balance / Titration

AAS: Atomic Absorption Spectroscopy; FAAS: Flame Atomic Absorption Spectroscopy; GF-AAS: Graphite Furnace - Atomic Absorption Spectroscopy; ICP-MS: Inductively Coupled Plasma - Mass Spectrometry; ICP-OES: Inductively Coupled Plasma - Optical Emission Spectroscopy; SEM-EDS: Scanning Electron Microscopy - Energy Dispersive X-ray Spectroscopy; UV: Ultra-Violet; UV-VIS: Ultra-Violet - Visible; VGA: Vapour Gas Analysis

Table 1: SCHOTT pharma services compendial and standard testing methods

elastomeric closures (i.e. stoppers, tip caps, etc.) of glass containers for parenteral products are given in e.g. USP <381>[23] and Ph.Eur. 3.2.9.[24] For example USP <381> requires biological reactivity (according to USP <87> or <88>), physicochemical, and functionality testing to confirm suitability for usage and classification of the elastomer as a Type I or Type II closure. USP <381> physicochemical testing requires preparation of extraction solution from the elastomer and testing for appearance (turbidity/opalescence), colour, acidity or alkalinity, absorbance, reducing substances, volatile sulfides, and ammonium. Ph.Eur 3.2.9. physicochemical testing in addition requires testing for extractable zinc, extractable heavy metals, residue on evaporation. These physicochemical testing requirements are also found in ISO 8871-1.[25] USP <381> functional testing assesses penetrability, fragmentation, and self-sealing capability. Type I closures have the highest requirements and are preferred for all injectable applications whereas Type II closures have improved mechanical attributes for specific device functional needs (e.g. multiple piercing) but do not meet the Type I specifications for appearance, absorbance, and reducing substances.

Other ISO and USP Standards

Other international industry standards give guidance for additional testing on filled finished pharmaceutical products. Taking as an example a filled glass syringe, ISO 11040-8:2016[26] details the testing via the following performance characteristics: Break loose and gliding forces, burst pressure resistance, flange strength resistance, closure system removal force/torque, connectivity/leakage testing, residual volume, needle penetration force, and needle pull-out force. These tests are designed to ensure that the delivery device for the injection functions performs as intended and is within established specification ranges for patient safety and patient comfort attributes of the injection device.

Besides glass, plastic packaging systems are more and more used as primary packaging materials for pharmaceutical use; e.g. for prefillable syringes, cartridges, vials, among others. These plastic packaging systems demand a high stability of the materials used during the manufacturing process and while stored with drug formulation or cosmetic preparation for which these are intended. The requirement and specification of testing depends on the type of end material used. In this case, the pharmacopeia mandated testing for plastic materials of construction and plastic packaging systems for pharmaceutical use are given in USP <661>,[29] which will be replaced by USP <661.1>[27] and USP <661.2>.[28] The packaging components or systems need to be constructed from well-characterised materials for its envisaged application. Examples of these polymeric materials are made out of cyclic olefin copolymer (COC), cyclic olefin polymer (COP), polypropylene (PP), polyvinylchloride (PVC), among others. Their physicochemical properties and chemical suitability for intended use have been well established by suitable testing and defined acceptance criteria.

Overview of Compendial Tests Supported by SCHOTT Pharma Services

Different test procedures inside the various pharmacopeias as well as the different national and international guidelines

occupy a significant amount of technical and human resources to fulfil the requirements for drug product distribution. Providing and maintaining these resources and always staying updated with regulations and guidelines is often not economical for the pharmaceutical company. SCHOTT pharma services provides compendial and standard testing under DIN EN ISO/IEC 17025 accreditation for glass containers, elastomeric closures, and needles as per Table 1 below. In-house methods have been validated and standard compendial test methods based on regulatory standards have been verified according to DIN EN ISO 17025 requirements.

Summary

Because human health matters, it is very important to secure the supply chain for parenteral drugs by compendial testing of the applied primary packaging components. A verification of compliance of received components by the drug manufacturer is required in addition to test properties and certificates provided by the component supplier. A broad knowledge base about regionally different pharmacopeia regulatory standards and a very high quality level for the supporting contract laboratory is fundamental to support the pharmaceutical industry for compendial testing of glass, elastomer and polymer packaging components.

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Laboratories of SCHOTT pharma services are DIN EN ISO/IEC 17025 accredited (DAkkS) and FDA registered. SCHOTT pharma services can access more than 40 years' experience in analytical testing of pharmaceutical packaging containers. All quality relevant documents are electronically available, ensuring a smooth audit process.

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