



Life Sciences

Validation Guide

USTR 2521

Guide to Extractables in Effluents from Pall Ultipor® N66 and Posidyne® Filter Cartridges



Contents

1. Introduction	3
2. Design and Manufacture of Pall N66 Pharmaceutical-rated (P-rated) Filters	3
3. Principles of Extraction and the Non-Volatile Residue Test	3
3.1 Factors Limiting Extraction	3
3.2 Defining Solvent Strength	4
3.3 Materials of Construction of Ultipor N66 and Posidyne Filter Cartridges	5
3.4 Extractable Substances in Polymers Used in Pall Ultipor N66 and Posidyne Filter Cartridges	5
4. Total Non-volatile Residues Extracted from Ultipor N66 and Posidyne Filters	6
4.1 Introduction	6
4.2 Summary of Method	6
4.3 Results	6
4.4 Conclusions	6
5. Identification of Non-Volatile Residues from Water and Alcohol Extracts of Ultipor N66 General Purpose and Posidyne Elements	7
5.1 Introduction	7
5.2 Summary of Method	8
5.3 Results	8
5.4 Conclusions	8
6. Identification of Non-Volatile Residues from Ultipor N66 General Purpose Elements in Other Solvents	8
6.1 Introduction	8
6.2 Summary of Method	9
6.3 Results	9
6.4 Conclusions	9
7. Identification of Non-Volatile Residues from Ultipor N66 Special Purpose Elements	9
7.1 Introduction	9
7.2 Summary of Method	9
7.3 Results	9
7.4 Conclusions	10
8. Compatibility	10
8.1 Introduction	10
8.2 Summary of Method	10
9. Summary	10
10. General References Cited	12
11. Appendix 1	13

1. Introduction

The purpose of this guide is to provide comprehensive information regarding extractables associated with Pall Ultipor N66 and Posidyne nylon membrane filters. Whether performed as part of a quality control program in production, or by Pall's Scientific and Laboratory Services Department, the tests described in the relevant Validation Guides are part of the Pall filter user's assurance of quality. This Guide to Extractables provides data regarding the identity of Ultipor N66 and Posidyne filter extractables. The data presented here can be summarized as follows:

1. Extractables in water and in ethanol are composed of oligomers of nylon 6,6 and PET polyester, with no other components evident. These polymers and all other materials used in the construction of Ultipor N66 and Posidyne filter cartridges are listed as permissible for food contact applications in Title 21 of the U.S. Code of Federal Regulations.
2. The substances extracted from the filter into water, ethanol and a variety of solvents described herein are identical, and composed primarily of oligomers related to the polymers found in the filter.
3. Amounts of extractables are minimal and pass United States Pharmacopoeia (USP) Class VI-121°C Plastics Tests for Biological Reactivity, *In Vivo* (Chapter <88>).
4. Ultipor N66 and Posidyne filter extractables in pharmaceutical fluids that are composed largely of water or another solvent listed in the Pall Ultipor N66 and Posidyne Filter Cartridge Validation Guides can be modeled using the non-volatile residue (NVR) data provided in these Guides.

2. Design and Manufacture of Pall N66 Pharmaceutical-rated (P-rated) Filters

The critical requirements for sterilizing grade filters sought by the pharmaceutical industry include a fluid pathway exhibiting extremely low levels of extractables, a high degree of particulate cleanliness, adequate safety margins in meeting current USP requirements regarding oxidizable substances and pyrogens, and a broad range of compatibility. These requirements are satisfied by Pall N66 filter cartridges through careful design, verified manufacturing control and thorough quality control testing.

Pall's focus on the needs of the pharmaceutical industry is also represented by the product specifications of filter cartridges produced with a Pharmaceutical "P" Rating. The specifications of Pall P-rated cartridges include all aspects of production: sanitary design, selection of qualified materials, manufacture in a controlled environment and stringent quality control to demonstrate that the finished product meets requirements appropriate to intended use in pharmaceutical applications.

Following manufacture under controlled conditions, each filter lot undergoes a series of quality control tests. A Certificate of Test (P-Certificate) is packaged with each P-rated Filter. The P-certificate for sterilizing grade filters documents that each filter lot meets the criteria developed by Pall for P-rated filters, including:

- Fabrication Integrity
- Bacterial Retention
- Materials of Construction
- Effluent Quality

3. Principles of Extraction and the Non-Volatile Residue Test

3.1 Factors Limiting Extraction

Three factors can affect the amount and composition of material that can be extracted from a given polymer into a fixed volume of given solvent: the total amount of each extractable substance present in the polymer, the rate of transfer of the extractable substances to the solvent (generally governed by the relationship of the extraction time to the diffusion constant of

each extractable component within the polymer), and the solubility of each extractable substance in the solvent (Arthur D. Little, 1983). For a method involving extraction in a limited volume of solvent to be extrapolated to a large-scale process, it is necessary to understand which of these three factors is limiting.

Where only the total available quantity of an extractable substance is limiting (Case 1), all of the substance has been extracted, and no more can be transferred to the solvent. In this case, the test result represents the total quantity of the extractable substance that can be extracted from the polymer under any conditions.

When the rate of transfer of an extractable substance to the solvent is limiting (Case 2), the total amount of the extractable substance in the solvent will continue to increase with time (generally gradually after the rapid initial extraction from the polymer surface, see A. D. Little, 1983), so that the test conditions must be carefully chosen so as to represent the actual process. However, unless the solvent can plasticize or swell the polymer so as to increase diffusion rates, depletion of the extractables at the surface of the polymer will occur during the test period, and Case 2 becomes equivalent to Case 1.

If the solubility of an extractable substance in the solvent is the only factor limiting its extraction (Case 3), then its concentration will reach a constant value (with respect to time) even though more material may be available within the polymer for extraction. In this case, the extent of extraction will be influenced by the solvent strength. Where an extractable substance is present in only small quantities, its concentration in the polymer will be depleted before its solubility limit is reached, and Case 3 also becomes equivalent to Case 1.

Thus, except where amounts of extractables are large or the volume of solvent is very small, Case 1 usually applies, and the NVR method (described below) utilized by Pall provides a result directly related to the total extractables expected in the process system. In some cases, a simple additional test (a second extraction of the filter cartridge in the same solvent) has been conducted to confirm that Case 1 applies.

3.2 Defining Solvent Strength

When an insoluble solid containing a solute (such as some extractable substance in a polymer) and a liquid solvent are at equilibrium, the amount of the solute that will partition from the solid phase into the liquid phase can be predicted. The relative abilities of various solvents to extract a given solute (termed "solvent strength") depend on solubility parameters, which have been extensively studied and successfully modeled. For ionic species and other very polar solutes, dielectric constant is an accepted measure of solvent strength, and water is the strongest solvent. For very hydrophobic solutes (e.g. n-alkanes), where solubility depends only on van der Waal's interactions, solvent strength ("Hildebrand Parameter") is a function of boiling point (more correctly, of free energy of vaporization, see E. Grulke, in Bandrup and Immergut, 1989). For polar organic solutes (including most materials extractable from polymers), solubilities of three model compounds have been used to define solvent strengths and selectivities (Snyder, 1974; 1978).

The solvent strength of a mixture can be predicted from the solvent strengths of the individual components and their volume fractions (see Figure 18-8 in Fritz and Schenk, 1974). Solvent strength of a mixture with respect to extraction processes varies as a linear combination of the solvent strengths of its component solvents. That is, the solvent strength P of a mixture of i components each with solvent strength P_i and comprising a volume fraction x_i of the total, is given by (Snyder, 1974): $P = \sum P_i x_i$

The ability of a component added to a fluid, to change the solvent strength of that fluid, is both predictable and limited by the volume fraction and solvent strength of the added component.

Extraction of polymers has been extensively studied, and the behavior of many polymer-solvent systems can be assigned to Case 1, 2 or 3 (or a combination thereof) on the basis of such studies. This is particularly true for polymers listed for food contact in parts 170 – 200 of

Title 21, Code of Federal Regulations. This is because the food contact listings consist of a set of specifications limiting both types and amounts of additives that a given base polymer may contain, and the maximum amounts of extractables in defined solvents.

3.3 Materials of Construction of Ultipor N66 and Posidyne Filter Cartridges

Ultipor N66 (General Purpose) Filter cartridges contain only nylon 6,6 (found in the membrane), poly[ethylene terephthalate] polyester (in the endcaps, O-ring adaptor, and “bomb fin” locating tab), poly[ethylene terephthalate/isophthalate] copolymer (in nonwoven fabric drainage layers and internal support within the membrane), and polypropylene (in the core and outer protective cage). Posidyne Filter cartridges use the same polymers in their hardware and drainage layers as Ultipor N66 General Purpose Filter cartridges, and contain a membrane formed using the same nylon 6,6 resin found in Ultipor N66 cartridges, manufactured with quaternary ammonium groups bound covalently throughout the resin.

Ultipor N66 Special Purpose (“S”-series) elements are constructed solely of nylon 6,6 (membrane) and polypropylene (nonwoven fabric drainage layers, internal membrane support where present, and all other hardware), and have been pre-extracted with methylene chloride to further reduce total extractables in most solvents. Neither PET polyester nor copolymers with isophthalate are used in Ultipor N66 Special Purpose filter cartridges.

Pall Ultipor N66 and Posidyne Filter cartridges contain only the polymers listed above. They are manufactured by welding of the polymer components, without any adhesives, and contain no wetting agents or surfactants. All materials of construction of these cartridges are listed for food contact applications in Title 21 of the Code of Federal Regulations, parts 170 – 200. A review of the types of materials that may be extracted from each of the food-contact grades of polymers used in construction of Pall Ultipor N66 and Posidyne Filter cartridges is presented below.

3.4 Extractable Substances in Polymers Used in Pall Ultipor N66 and Posidyne Filter Cartridges

The food contact listings in Title 21 of the Code of Federal Regulations (CFR) parts 170 – 200, constitute a set of specifications, established by the FDA for the listed materials, which include limits of extractables in model solvents measured as gravimetric non-volatile residue (NVR). Nylon 6,6, or poly[hexamethylene adipamide] is one of a number of nylon resins permitted for food contact applications as defined in 21 CFR, part 177.1500. No permissible additives are listed for nylon 6,6 in this section, and the levels of extractables in water, ethanol, ethyl acetate, and benzene are strictly defined. Poly[ethylene terephthalate] (or PET polyester) as listed for food contact applications may not contain certain low molecular weight plasticizers (such as bis[ethylhexyl] phthalate). Also, any copolymer with isophthalate must be made up of at least 98% ethylene terephthalate units by weight, and other additives are strictly defined (21 CFR 177.1630). PET polyester always contains approximately 1% by weight of residual cyclic trimer from polymerization (Wick & Zeitler, 1983), but is highly crystalline so that only the extractables at the surface of the polymer are available in most solvents after even very long extraction times.

Polypropylene will often contain additives to improve molding and extrusion characteristics (slip and mold release agents) which are usually stearate salts or ethoxylated stearate esters. Polypropylene also often contains antioxidants, such as butylated hydroxytoluene (BHT) and related compounds, and may contain a secondary antioxidant (Crompton, 1979). Permissible limits of extractables in xylene and hexane for polypropylene to be used in food contact applications are defined in 21 CFR, 177.1520, “Olefin Polymers”.

Permissible antioxidants and/or stabilizers for polymers intended for food contact applications are listed in 21 CFR 178.2010.

4. Total Non-volatile Residues Extracted from Ultipor N66 and Posidyne Filters

4.1 Introduction

The quantities of extractables obtained under worst-case conditions in a wide variety of solvents is too low to detect effectively in the presence of active ingredients and other non-volatile components of pharmaceutical fluids. For this reason, Pall provides Non-Volatile Residue (NVR) data in a wide range of pure, volatile solvents (including water), and recommends that users select a model for their process fluid from among these reference solvents to provide a worst-case estimate of filter extractables. The NVR test method and modeling approach utilized by Pall is adapted from methods referenced in Title 21 CFR, parts 176 and 177, which include specifications for extractables limits in model solvents for materials intended for food contact.

4.2 Summary of Method

Pall Publication USTR1029, "Validation Guide for Pall 0.2 µm Ultipor® N66 and Posidyne Filter Cartridges," describes the non-volatile residue (NVR) test method used to quantify extractables from Pall P-rated cartridges, and lists the results obtained in a wide variety of volatile solvents. Briefly, the test involves reciprocating a filter for four hours in 1500 cc of solvent at room temperature. The solvent is then evaporated and the remaining non-volatile material is collected for gravimetric analysis. This sequence is illustrated in Figure 1.

4.3 Results

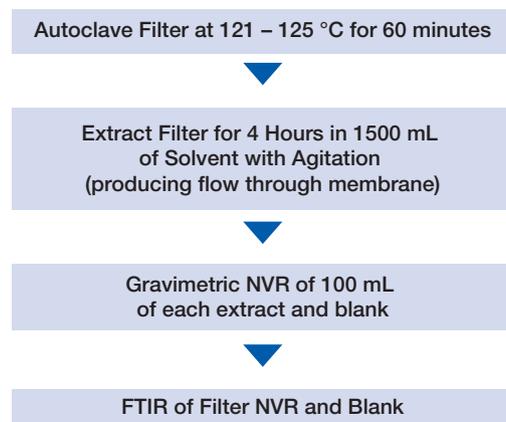
NVR levels for Ultipor N66 general purpose AB1NRP (0.2 micron) and pre-extracted special purpose AB1NRPS cartridges extracted in several solvents that might be encountered in pharmaceutical process streams appear in Table 1. Additional tests of Pall Posidyne cartridges (including AB1NFZP 0.2 micron, AB1NTZP 0.1 micron, and AB1NNXZP 0.45 micron rated cartridges) in water and ethanol, produced NVR levels comparable to Ultipor N66 General Purpose cartridges.

4.4 Conclusions

NVR values for Ultipor N66 AB1NRP (0.2 micron) filter cartridges in the aqueous and water-miscible organic solvents listed in Table 1 fall in a range of roughly 20 – 400 mg. These values were determined with filters that have been autoclaved but not flushed prior to testing, and thus represent worst-case conditions. Neither longer exposure, nor repeating extraction with fresh solvent, will increase these NVR values appreciably. These NVR values approximate the total material that can be extracted from the cartridge into each solvent regardless of volume of solvent or contact time.

Figure 1

Extraction Protocol Results



Because the amount of filter extractables from a 10-inch cartridge is extremely low, this analysis cannot be accurately performed in the presence of pharmaceutical products which themselves

contain non-volatile substances. However, aqueous solutions are adequately modeled by water as a volatile extraction solvent. Testing has shown that low percentages of a variety of other volatile components (such as benzyl alcohol, chlorobutanol, and chlorocresol) do not increase levels of Pall filter extractables measured as NVR. The list of solvents for which NVR data have been obtained spans a wide variety of physical and chemical characteristics. Pall's Scientific and Laboratory Services Department can provide advice on selecting a volatile solvent or solvent system to model a given process stream.

5. Identification of Non-Volatile Residues from Water and Alcohol Extracts of Ultipor N66 General Purpose and Posidyne Elements

5.1 Introduction

Infrared spectral analyses of NVR residues extracted from Ultipor N66 General Purpose and Posidyne filter elements in 95% ethanol USP and in water have been used to identify the substances present. The results were spectra consistent with the presence of oligomers of nylon 6,6 and oligomers of PET polyester, with no other major components. No new components were detected in ethanol relative to water.

Table 1

*Non-Volatile Residues Extracted from Autoclaved Ultipor N66 General Purpose (AB1NRP) and Special Purpose (AB1NRPS) Cartridges**

Fluid (mg)	General Purpose NVR (mg)	Special Purpose NVR
Acetic acid (70%)	48**	62
Acetone	270***	28
Acetonitrile	240***	10
Ammonium hydroxide 28%	58	41
Benzyl alcohol	290	97
N-butanol	52	47
N-butyl acetate	84	37
Dimethyl formamide	263***	36**
Ethanol, 3A	51	26
Ethanol, absolute	44	ND
Ethanol, 50%	69	21
Ethanolamine	264	106
Ethyl acetate	220	24
Ether (diethyl)	35	64
N-heptane	22	44
Hydrochloric acid 10%	410	245
Isopropyl alcohol	35	52
Methanol	41	63
Methyl isobutyl ketone	180	25
Propylene glycol	155	30
Pyridine	310***	35
Water	22	19
Xylene	230	42

* 4 Hour Reciprocating Soak in 1.5 Liters of the Indicated Solvent at Room Temperature. These conditions yield approximately the same results as flowing for 4 hours. No haze upon dilution with water for water-miscible solvents, unless otherwise noted. All NVR values are nominal.

** Slight haze on dilution with water.

*** Haze or precipitate on dilution with water.

ND = Not determined.

5.2 Summary of Method

Each NVR obtained as described above was subjected to analysis by Fourier Transform Infrared Spectroscopy (FTIR) either by transmission or by reflectance. Because the entire sample was not analyzed, the transmittance scale is not a quantitative measure of the amount of sample and is, therefore, presented without units.

5.3 Results

Infrared spectroscopy of NVR obtained after extraction in water of Ultipor N66 General Purpose 10-inch cartridge filters produces a characteristic spectrum (Figure 2). This spectrum is essentially a superposition of the spectra of nylon 6,6 (Figure 3) and of PET polyester (poly[ethylene terephthalate] Figure 4). Spectra of extracts from 0.1 and 0.2 micron-rated double layer Ultipor N66 General Purpose cartridges have been examined with essentially identical results.

The NVR obtained from Ultipor N66 General Purpose cartridges by extraction in 95% ethanol USP has also been examined by infrared spectroscopy. A typical spectrum is shown in Figure 5. This spectrum is also a superposition of nylon and polyester spectra, except that the absorbance peaks characteristic of PET (arrows in Figures 2 and 5) are more prominent than in spectra of NVR from water extracts. Extraction of a Posidyne element (AB1NNXZP, 1.2/0.45 micron double-layer cartridge) in water produced NVR with the spectrum shown in Figure 6. An ethanol extract of a Posidyne element (AB1NNXZP) produced the spectrum shown in Figure 7. These spectra are not significantly different from the spectra of the corresponding NVR obtained from Ultipor N66 General Purpose cartridges. In particular, no additional signals are apparent in the spectra of the Posidyne NVR samples. Similar results were obtained with 0.1 micron sterilizing grade (NTZP) Posidyne cartridges.

5.4 Conclusions

Based on the results of FTIR analysis, the NVR extracted from a variety of Ultipor N66 General Purpose filters in water is composed of small oligomers of nylon 6,6, with small and variable amounts of oligomers of PET polyester, the polymer which is used in the support and drainage materials and in filter hardware. Water extracts of Ultipor N66 and Posidyne cartridges are essentially identical. The compositions of NVR obtained from ethanol extracts of these filter cartridges differ from those of the water extracts only in the relative amounts of the two major component substances present (i.e. oligomers of nylon and oligomers of polyester). No new substances could be identified by infrared spectroscopy in NVR from alcohol extracts relative to NVR from water extracts. In addition, lack of significant differences between spectra of extracts from Ultipor N66 and Posidyne cartridges confirms that the moiety conferring positive charge to the Posidyne membrane is covalently bonded and cannot be extracted.

These results also show that neither the very small amounts nor the identities of extractables change significantly with filter pore size (a mechanical property of the membrane, rather than a chemical property), so that these data can be applied to any of the Ultipor N66 General Purpose and Posidyne cartridges. More importantly, no differences have been observed in the identities of extracted materials found in water and alcohol extracts.

6. Identification of Non-Volatile Residues from Ultipor N66 General Purpose Elements in Other Solvents

6.1 Introduction

The same NVR and infrared spectral methods applied to extracts prepared in ethanol and in water were also applied to extracts prepared in propylene glycol and in mixtures containing small amounts of volatile solutes. The results are consistent with known solvent properties, and can be generalized to allow selection of a single volatile solvent to serve as a worst-case model for virtually any compatible fluid.

6.2 Summary of Method

NVR obtained as described above was subjected to analysis by Fourier Transform Infrared Spectroscopy (FTIR) as described for NVR prepared from water and ethanol extracts. Because the transmittance scale does not reflect the amount of sample, it is presented without units.

6.3 Results

Infrared spectroscopy of NVR obtained after extraction of a Ultipor N66 General Purpose 10 in. cartridge filter (AB1NRP) in propylene glycol produces a spectrum (Figure 8) which is similar to the spectrum (Figure 5) of NVR prepared from an ethanol extract, except that the signals attributable to nylon oligomers are weaker. Addition of benzyl alcohol (7.5%) to the extracting solvent did not result in any new infrared signals. Similarly, addition of 3% n-butanol produced no change in the extractables in water. These volatile solutes may be regarded as reasonable models for active ingredients.

6.4 Conclusions

NVR from propylene glycol has a composition virtually identical to that of NVR from ethanol, namely low molecular weight oligomers of nylon and polyester, with ethylene terephthalate (PET polyester) oligomers predominating. Low concentrations of a variety of organic compounds (such as benzyl alcohol) in the extracting solvent have no effect on the composition of the NVR as determined by infrared spectroscopy. These observations confirm that NVR identity does not change over a substantial range of compatible aqueous and aqueous/organic solvent mixtures. Since active ingredients and other nonvolatile components in process fluids are typically present in low concentrations, these results justify the use of appropriate volatile model solvent systems for pharmaceutical process streams. A precedent for this approach may be found in the model solvents specified in Title 21, Code of Federal Regulations, parts 170 – 200, defining NVR limits for materials intended for food contact.

7. Identification of Non-Volatile Residues from Ultipor N66 Special Purpose Elements

7.1 Introduction

The same NVR and Infrared spectral methods described above were applied to extracts prepared from Ultipor N66 Special Purpose (pre-extracted) elements in 1:1 methanol:water and in 1:1 methylene chloride:hexane. These filters differ from Ultipor N66 General Purpose filter cartridges in that they contain only nylon 6,6 and polypropylene.

7.2 Summary of Method

NVR obtained as described above was subjected to analysis by Fourier Transform Infrared Spectroscopy (FTIR) exactly as described above. Because the transmittance scale does not reflect the amount of sample, it is presented without units.

7.3 Results

Infrared spectroscopy of NVR obtained after extraction of a Ultipor N66 10 in. special purpose (NRPS) cartridge filter in methanol:water (1:1) produced a spectrum (Figure 9), which is essentially identical to the spectrum (Figure 3) of nylon 6,6. This differs from the spectrum of NVR prepared from a general purpose element extracted in water (Figure 2) only in that, consistent with the complete absence of polyester from the elements of special purpose cartridge construction, no signals from PET polyester are present. NVR obtained after extraction of an Ultipor N66 10 in. special purpose (NRPS) cartridge filter in methylene chloride:hexane (1:1) produced the infrared spectrum shown in Figure 10. The spectrum is similar to that of atactic polypropylene (Figure 11). The signals at 1720 – 1740 cm^{-1} can be assigned to salts or esters of carboxylic acids. A signal at 3600 – 3700 cm^{-1} indicates the presence of hindered phenolic antioxidants related to BHT.

7.4 Conclusions

The spectrum of NVR prepared from an extract in a methanol/water mixture matches that of nylon. NVR from Pall Ultipor N66 special purpose (NRPS) cartridges in alcohol/water mixtures consists primarily of oligomers of nylon 6,6. In more hydrophobic solvents, signals attributable to components of the polypropylene hardware appear. An extract in a methylene chloride/hexane mixture produces signals attributable to low molecular weight oligomers of polypropylene, stearate salts or esters, and phenolic compounds. Both stearates and phenolic antioxidants related to BHT are substances frequently present in polypropylene, and their extraction into this solvent mixture is expected both on the basis of the hydrophobic nature of the solvent and the ability of methylene chloride to swell and plasticize polypropylene.

These observations show that NVR from special purpose elements, which are manufactured with polypropylene hardware and drainage materials, may contain extractables attributable to substances found in polypropylene as well as extractables from the nylon membrane.

Aqueous solutions generally extract only nylon oligomers from the membrane and do not produce detectable quantities of extractables from the polypropylene hardware.

Organic solvents, particularly those capable of swelling or plasticizing polypropylene, may extract components from the polypropylene hardware preferentially.

Extracts of Ultipor N66 special purpose (NRPS) cartridges produced at elevated temperatures (121°C) in both aqueous and nonaqueous solvents produced negative results in the tests for biological reactivity *in vivo* (Class VI-121°C) specified in the United States Pharmacopoeia (USP), <88>, as reported in Pall publication USTR1029: "Validation Guide for Pall 0.2 µm Ultipor® N66 and Posidyne Filter Cartridges".

8. Compatibility

8.1 Introduction

This document addresses the amounts and identities of extractables obtained in a wide variety of solvents. Quantitative determination of NVR is valid only in a fluid which is compatible with the filter. In this sense, "compatible" means that the fluid does not affect the filter's ability to perform its intended function.

8.2 Summary of Method

For Pall sterilizing grade cartridges, a fluid is determined to be compatible with the filter if the filter maintains integrity after exposure to the fluid under the conditions of intended use.

Integrity is determined by the Forward Flow test. For purposes of characterizing filter extractables in a given fluid, a model solvent approach is employed. Table 2 illustrates the effect on model solvent selection by the degree of compatibility of Ultipor N66 and Posidyne filter cartridges with a wide range of fluid classes. Because compatibility is a function of process conditions as well as of solvent composition, this table should be considered illustrative only.

For information on compatibility in a given application, please contact Pall.

9. Summary

Pall's design and manufacturing controls, combined with extensive testing of P-rated cartridges, provide assurance of effluent cleanliness with respect to both particles and extractables.

The results of quality control testing applied to P-rated cartridges are documented on the P-Certificate accompanying the filters and further information is provided in the respective filter Validation Guides.

Quantities of NVR extracted from autoclaved Ultipor N66 and Posidyne filter cartridges in a wide variety of solvents have been determined, and these data are provided as part of the filter Validation Guides.

NVR of extracts from autoclaved Ultipor N66 General Purpose and Posidyne filter cartridges in water, ethanol, and propylene glycol have been shown to be composed of oligomers of nylon 6,6 and PET polyester. The same substances were found in propylene glycol and ethanol extracts as in water extracts, namely low molecular weight oligomers of nylon and polyester. Composition of NVR is not

changed by low concentrations of a variety of other solutes, demonstrating the absence of synergistic effects. For special purpose elements, which are manufactured with polypropylene hardware and drainage layers, composition of NVR prepared after extraction in more aggressive solvents may also contain substances extracted from the polypropylene components of the cartridge, due to their increased solubility in the solvent or the ability of the solvent to plasticize polypropylene. These filters have been subjected to the same stringent Class VI-121°C *in vivo* biological reactivity tests as the general purpose elements. These results show that filter extractables in pharmaceutical fluids with an organic solvent base can be modeled using the NVR data published in Pall Validation Guides.

The materials used in the construction of Ultipor N66 and Posidyne filter cartridges are resistant to a wide range of chemical substances and process conditions, and are compatible with the vast majority of fluids found in pharmaceutical process streams.

All materials of construction of Ultipor N66 and Posidyne filters are listed for food contact applications in Title 21 of the Code of Federal Regulations. Biological safety of the materials of construction of Pall nylon membrane filter cartridges has been demonstrated using the *in vivo* biological reactivity tests specified for Class VI-121°C Plastics in the USP.

Table 2

Applicability of Model Solvent Approach for Ultipor N66 and Posidyne Filters at Ambient Temperature

Chemical Class	Examples	Applicability
Alcohols (esc. phenolics)	Ethanol, isopropanol	A
Aldehydes and Ketones	Acetone, formaldehyde, MEK	A
Amides	Dimethylformamide	A
Amines	Ethanolamine, TEA	A
Aqueous (neutral pH)	Water, Buffers, Saline Solutions, Sugar Solutions	A
Aromatics	Benzene, toluene, xylenes	A-L (S)
Caustics (concentrated)	Sodium, potassium hydroxide, 30%	X
Caustics (dilute)	Sodium, potassium hydroxide, 5%	L
Cellosolves, Cellosolve esters	Methyl Cellosolve	A
Chlorinated hydrocarbons	Methylene chloride, trichloroethane	A-L (S)
Ethers	Diethyl ether, THF, dioxane	A
Ethylene oxide	Ethylene oxide 12% in freon	A
Freons	Freons 12	A
Hydrocarbons	Heptane, pet ether, mineral spirits	A
Hypochlorites, chlorine	Sodium hypochlorite	X
Mineral Acids	Nitric, hydrochloric, phosphoric acid	X
Mineral Acids (dilute)		L-X
Organic Acids	Acetic acid, propionic acid	X
Organic Acids (dilute)		L-X
Organic esters	Ethyl acetate	A
Peroxides	Hydrogen peroxide 30%	X
Peroxides (dilute)	Hydrogen peroxide 3%	A
Peroxy acids (concentrated)	Peracetic acid	X
Peroxy acids (dilute)	Peracetic acid	L

^A (Applicable) indicates that extractables from Ultipor N66 and Posidyne filters into most fluids composed of substances in this chemical class can be determined using a Model Solvent approach for most process conditions.

^L (Limited) indicates that fluids containing substances in this chemical class may have an effect on the filter. Compatibility issues should be taken into account before using a Model Solvent approach.

^X (Not Compatible) indicates many fluids containing substances in this chemical class will have a severe effect on the filter after even short-term exposure. Extractables in such incompatible fluids should not be estimated using a Model Solvent approach.

^(S) Indicates special purpose cartridges.

In all cases, Pall recommends testing of filters in individual solvents and chemicals for compatibility under specific process conditions, using the safety precautions provided in the Material Safety Data Sheet for each chemical or solvent.

10. General References Cited

Solvent Strength, Extraction, Partition Coefficients:

"Quantitative Analytical Chemistry", J. S. Fritz and G. H. Schenk (Allyn and Bacon, Boston 1974) pp 355-382.

"Classification of the Solvent Properties of Common Liquids," L.R. Snyder (1974) *Journal of Chromatography* 92, 223-230.

"Classification of the Solvent Properties of Common Liquids," L.R. Snyder (1978) *Journal of Chromatographic Science* 16, 223-234.

Extractables in Foods and Simulating Liquids: Typical Materials, Time-dependence, Modeling.

"Additive Migration from Plastics into Food", T. R. Crompton (Pergamon, Oxford 1979) pp 1-19.

"A Study of Indirect Food Additive Migration" (Arthur D. Little, Inc. 1983) Final Summary Report, FDA Contract Number 223-77-2360.

General Information on Polymers: Polymerization, Properties, Additives, Uses.

"Polymer Handbook" 3rd Edition, J. Bandrup and E. H. Immergut, Eds. (Wiley and Sons, New York, 1989).

"Encyclopedia of Polymer Science and Engineering" Second Edition, H. F. Mark *et al.* Eds. (John Wiley and Sons, New York 1985).

Residual Oligomers and Other Materials in Polymers: Weight Fractions, Analytical Methods.

"HPLC Analysis of Cyclo-oligoamides 6 and 66," C. Guaita (1984) *Makromol. Chem.* 185, 459-465.

"Cyclische Oligomere in Polyestern aus Diolen und Aromatische Dicarbonsauren," G. Wick, H. Zeitler (1983) *Die Angewandte Makromolekulare Chemie* 112, 59-94.

"Liquid Chromatographic Determination of Residual Reactants and Reaction By-Products in Polyethylene Terephthalate," T. Begley, H. C. Hollifield (1989) *Journal, Association of Official Analytical Chemists* 72, 468-470.

11. Appendix 1

Figure 2

Ultipor N66 Filter NVR From Water

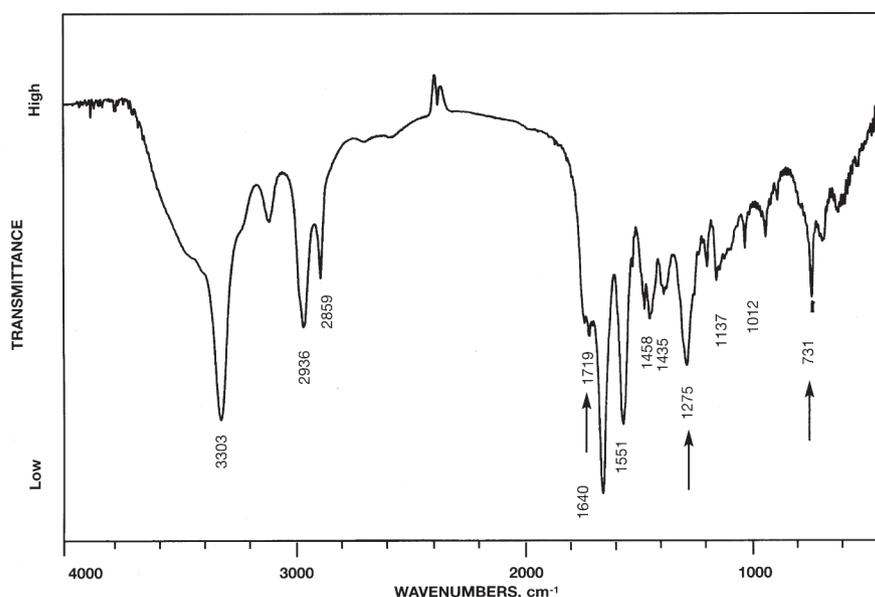


Figure 3
Polyamide 6, 6 Reference Spectrum

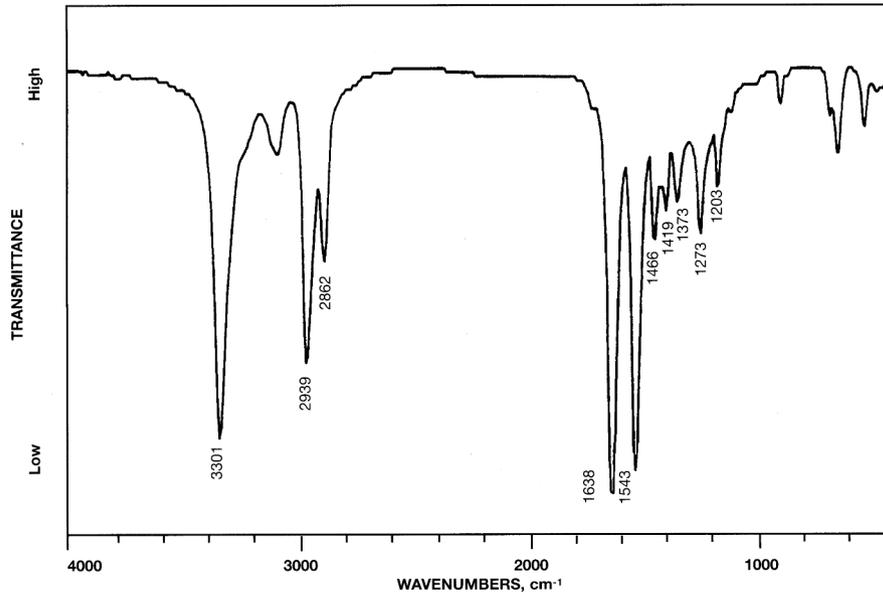


Figure 4
PET reference Spectrum

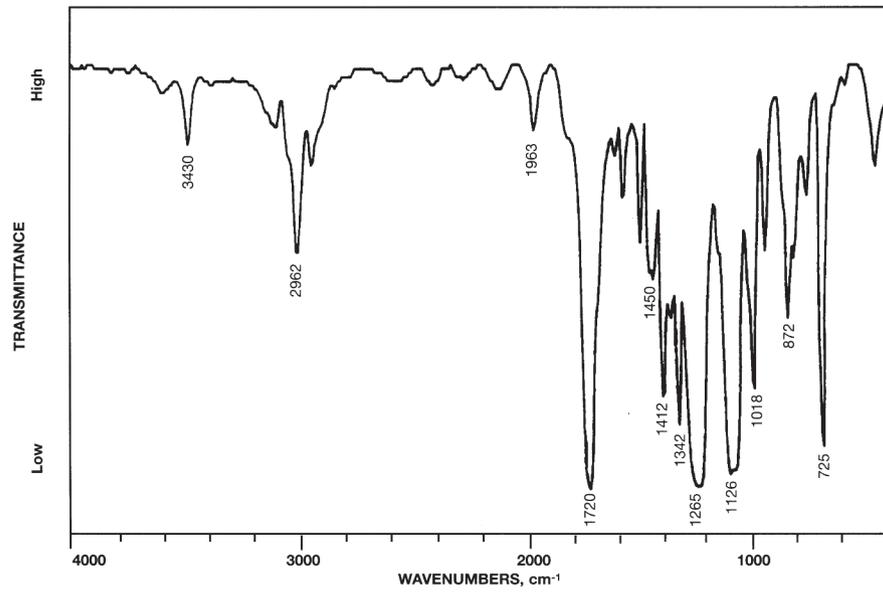


Figure 5
Ultipor N66 Filter NVR From Ethanol

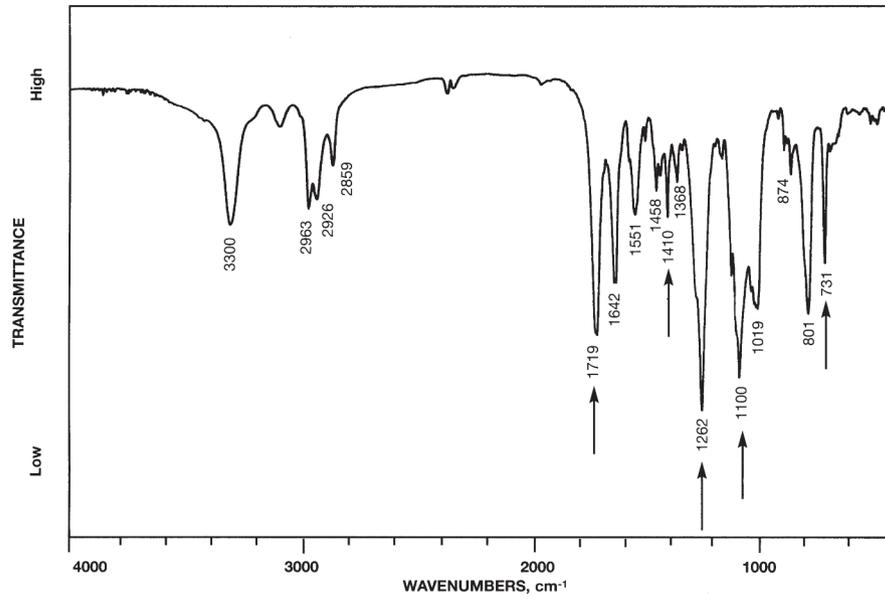


Figure 6
Posidyne Filter NVR From Water

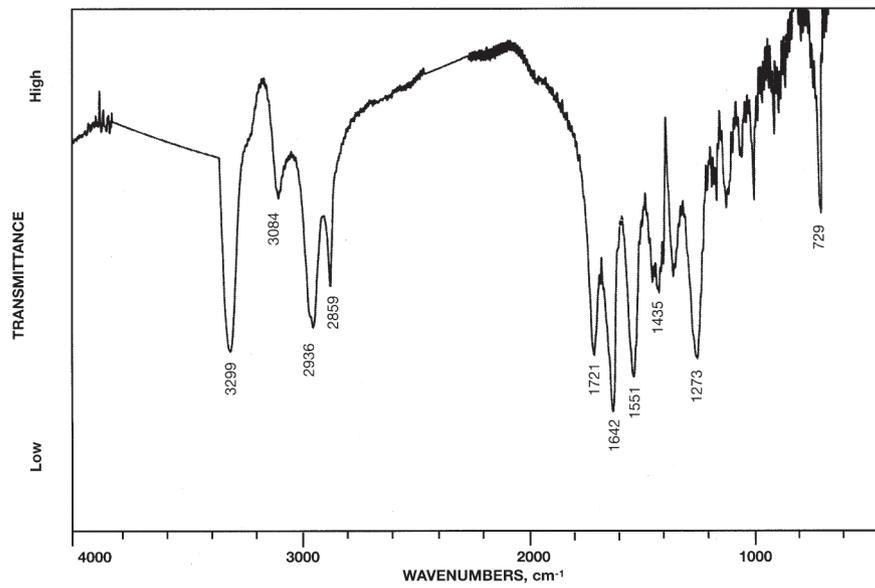


Figure 7
Posidyne Filter NVR From Ethanol

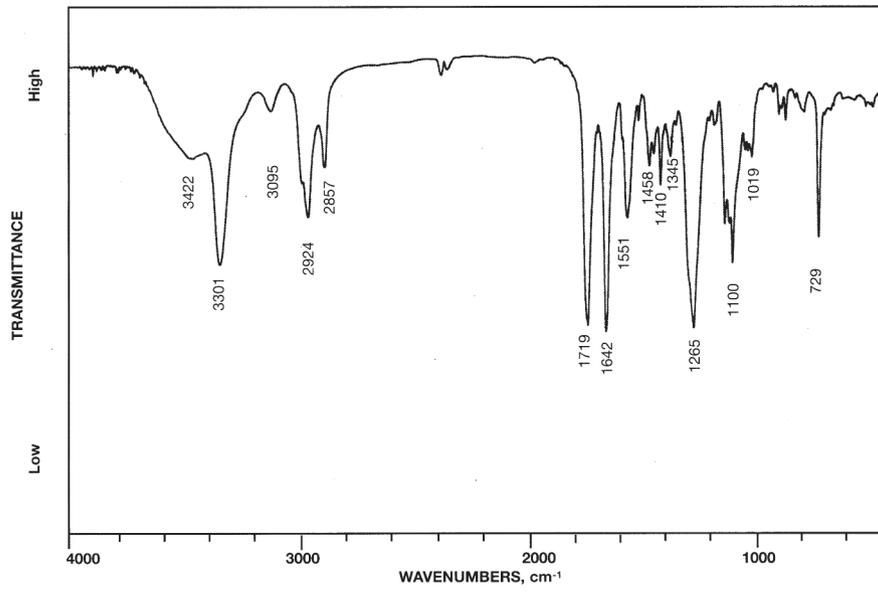


Figure 8
Ultipor N66 From Polypropylene Glycol/Benzyl Alcohol

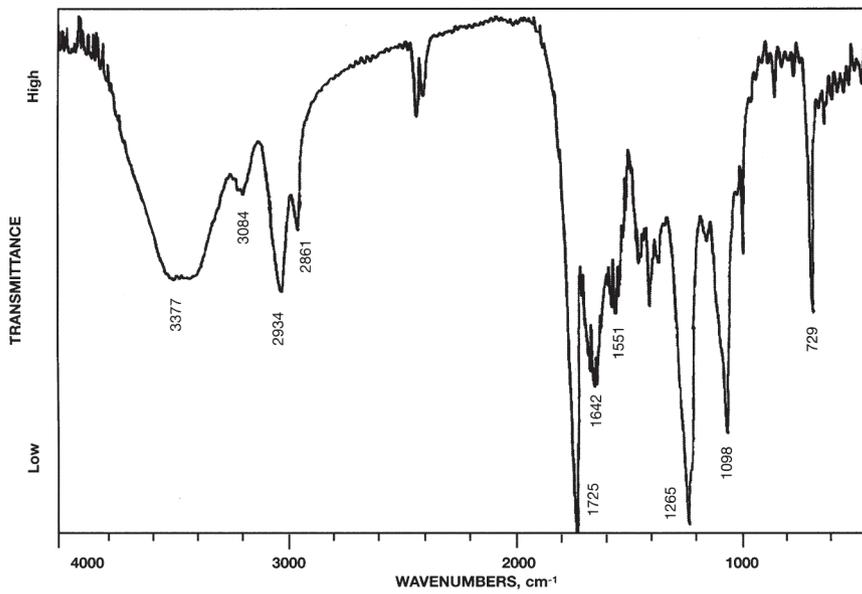


Figure 9

Ultipor N66 Special Purpose Filter NVR From Methanol/Water

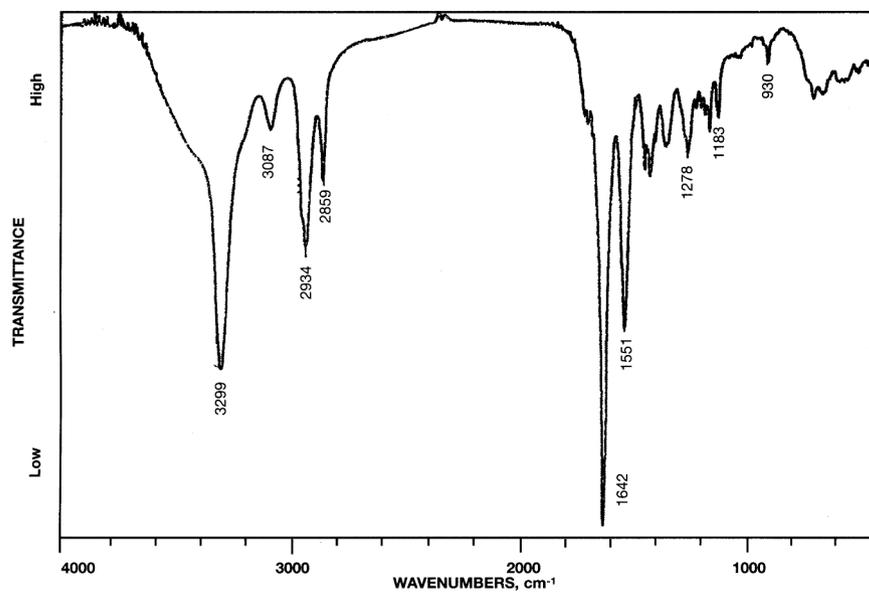


Figure 10

Ultipor N66 Special Purpose Filter NVR From CH₂Cl₂/Hexane

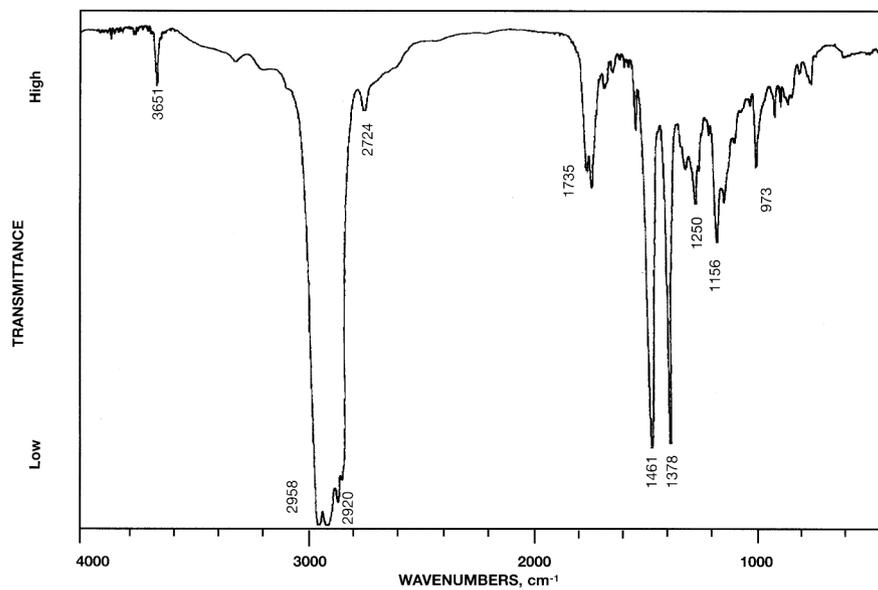
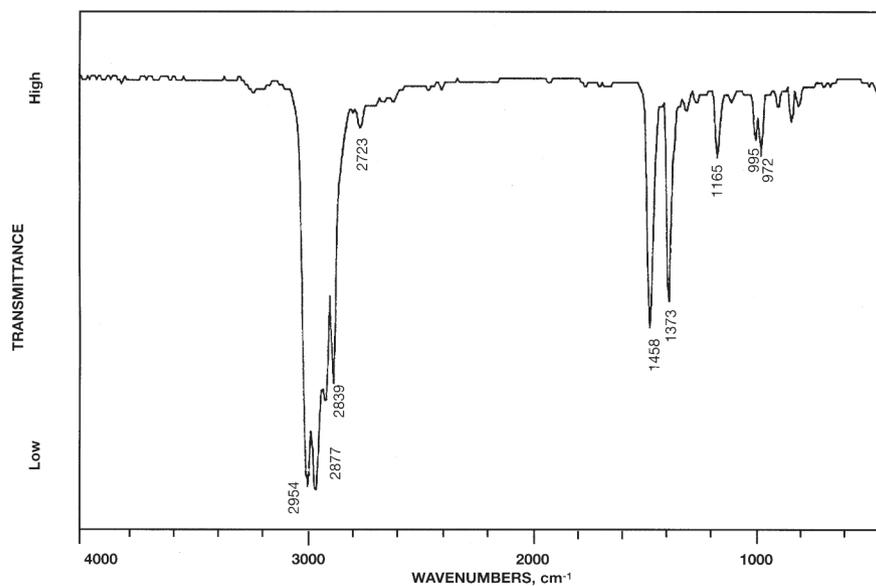


Figure 11
Polypropylene Reference Spectrum



New York – United States

800.717.7255 toll free (USA)
516.484.5400 phone
516.801.9548 fax
biotech@pall.com e-mail

Portsmouth – Europe

+44 (0)23 9230 3303 phone
+44 (0)23 9230 2506 fax
BioPharmUK@europe.pall.com e-mail

**Visit us on the Web at www.pall.com/biopharm
E-mail us at biotech@pall.com**

International Offices

Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States, and Venezuela. Distributors in all major industrial areas of the world.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

© 2009, Pall Corporation. Pall, , Ultipor and Posidyne are trademarks of Pall Corporation. ® indicates a trademark registered in the USA. Filtration. Separation. Solution. is a service mark of Pall Corporation.