USP ‹381› Compliant Polyisoprene Compounds

Elastomeric Closures for Medical Devices

New Synthetic Elastomers Meet Stringent Type I Requirements

Parker offers a new generation of synthetic polyisoprene compounds that meet or exceed the current stringent USP ‹381› Type I requirements for elastomeric closures.

In addition, the new polyisoprene elastomers demonstrate exceptional self-sealing capabilities, even with needles as large as 16-gauge. Closures have survived 20 pierce/vacuum test cycles with no trace of leaks.

These new elastomers require minimal force for piercing, improving both septum performance and user safety, while offering the strength and other physical/mechanical properties of traditional polyisoprenes.

Contact Information:

Parker Hannifin Corporation
Medical Systems Division
3191 E. La Palma Avenue
Anaheim, CA 92806 USA

phone 714-632-7710
fax 714-632-5647
Techsales@parker.com

www.parker.com

Product Features:

- Meets USP ‹381›, ISO 8871, JP 7.03 and EP 3.2.9. guidelines
- Very low UV absorbance (0.1 to 0.2)
- More than two times higher resistance to reducing substances than traditional polyisoprene compounds, such as Parker RJ614-40 and RJ649-40
- Easy needle penetration: just 3.5% of force limit set by USP ‹381›
- Excellent self-sealing, even with needles as large as 16-gauge
- Tested to withstand 20 piercing/vacuum test cycles without leakage — ideal for multiple-dose or multiple-sample containers
- No visible fragmentation after penetration, greatly reducing the risk of contamination and leakage

Medical Device Applications

- Pierceable Septa
- Closure Seals for Diagnostic Sampling
- Duckbill Valve Seals
- Catheter Port Seals

ENGINEERING YOUR SUCCESS.

Traditional Polyisoprene Compounds Cannot Meet Rigorous New Industry Standards

Natural polyisoprene, or natural rubber (NR), with repeating unit cis-1,4 polyisoprene was used for decades for elastomeric closures for medical devices, e.g. septa. Unfortunately, natural rubber has a strong odor as well as natural impurities and proteins that can elicit severe allergic reactions.

To avoid NR's limitations, synthetic polyisoprene with Ziegler-Natta catalysts (IR) has been widely used in the medical industry for years.

Traditional IR Compounds: Attributes

- Low odor, no risk of protein allergy, cleaner compared to NR
- Superior mechanical properties compared to other synthetic elastomers
- Biocompatibility issues, high UV absorbance, high sulfides, and undesired extractables.

Goals and Challenges Posed by USP ‹381›

USP General Chapter "‹381› Elastomeric Closures For Injections" (May 2009 Revision) was developed to address a number of medical and pharmaceutical concerns, including:

- **Difficult-To-Pierce Closures:** Too much required piercing force can result in needle slippage and subsequent needle pricks.

- **Inferior Septa Self-Sealing:** Leading to leakage during fluid transfer (creating a hazardous work area, as well as waste) while compromising the preservation of the preparation via evaporation, non-sterility and pharmaceutical spoilage.
- **Fragmentation:** Fragments generated after needle penetration of the septum can contaminate contents and/or create a leak path.
- **Biocompatibility:** Per *in vitro* and *in vivo* testing (USP ‹87› and ‹88›, respectively), to ensure no undesired biological effects.

USP ‹381› also harmonized its guidelines with the guidelines of the European Pharmacopoeia (Ph. Eur.), Chapter 3.2.9 Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders.

The FDA states, in "Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics," that USP ‹381› requirements *are typically a baseline* for demonstrating the safety of such components.

A New Generation of Synthetic Polyisoprene Septa

With its extensive experience in elastomer formulation and processing, the Engineered Materials Group of Parker Hannifin (a global leader in motion and fluid control technologies) carefully examined the challenges posed by USP ‹381›.

To meet these challenges, Parker has developed and thoroughly tested a new generation of synthetic polyisoprene compounds, which were formulated for optimal performance as elastomeric closures for medical devices. These new elastomers meet USP ‹381› guidelines for Type I enclosures, which are significantly more stringent than those for Type II closures.

Physical and Mechanical Testing

Table 1 compares the physical and mechanical properties of RJ651-30 with two traditional polyisoprene compounds that have historically been used in septum applications.

The hardness of the three compounds is typical for such materials, ranging from 31 to 35 Shore A durometer. RJ614-30 and RJ651-30 both exhibit excellent tensile strength, high elongation and very good tear strength. *All three compounds demonstrate comparable mechanical and physical properties* and perform especially well in compression set resistance tests at 70°C; see Table 1.

Table 1: Physical & Mechanical Testing of Polyisoprene Compounds

Property	Test Method	Traditional RJ614-30	Traditional RJ649-40	New Parker RJ651-30
Hardness, Shore A	ASTM D2240	31	35	**32**
Tensile Strength (MPa)	ASTM D 412	13	10	**14**
Elongation at Break (%)		890	440	**770**
Modulus at 100% Elongation (MPa)		0.85	1.2	**1.3**
Tear Strength (KN/m)	ASTM D 624, Die C	14.0	11.4	**12.5**
Compression Set (%), 25% Deflection after 22 hours @ 70°C	ASTM D 395, Method B	10.5	6.9 to 11.4	**7.8 to 14.2**

In Physiochemical Tests, RJ651-30 Outperforms Traditional Polyisoprene Compounds

Table 2 shows the results of the USP ‹381› tests for UV absorbance and reducing substances. While the traditional compounds satisfy Type II guidelines for UV absorbance, they fail to meet Type I absorbance guidelines.

In contrast, the Parker RJ651-30 compound meets Type I absorbance guidelines, with UV absorbance of 0.1 to 0.2. In addition, the new elastomer's resistance to reducing substances is two to three times that of the traditional compounds.

Table 2: Test Results — UV Absorbance & Reducing Substances

Test	Parker Compound	USP ‹381› Type I Limit	USP ‹381› Type II Limit	Result
Absorbance (UV)	RJ614-30	<0.2	<4.0	1.5 AU
	RJ649-40			0.3 AU
	RJ651-30			0.1 to 0.2 AU
Reducing Substances	RJ614-30	Difference between titration volumes for test and blank solutions <3.0 mL	Difference between titration volumes for test and blank solutions <7.0 mL	(-) 1.67 mL
	RJ649-40			(-) 2.3 mL
	RJ651-30			(-) 0.74 to 1.1 mL

The complete physiochemical requirements of USP ‹381› are presented in Table 3. All requirements were readily met by the new RJ651-30 polyisoprene.

Table 3: USP ‹381› Physiochemical Testing

Tests	Limits	New Parker RJ651-30
Turbidity (Opalescence)	≤ 6 NTU (Type I) or 18 NTU (Type II)	≤ 6 NTU
Color	≤ color standard intensity	Met
Acidity or Alkalinity	≤ 0.3 mL of 0.01N Sodium Hydroxide produces blue color (Type I), or ≤ 0.8 mL of 0.01N hydrochloric acid produces yellow color (Type II)	≤ 0.3 mL of 0.01N NaOH
Absorbance (UV)	≤ 0.2 (Type I) or ≤ 4.0 (Type II)	0.1 to 0.2 AU
Reducing Substances	≤ 3.0 mL (Type I) or ≤ 7.0 mL (Type II)	(-) 0.74 to 1.1 mL
Extractable Heavy Metals	≤ 2 ppm	2 ppm
Extractable Zinc	≤ 5 ppm	0.626 ppm
Ammonium	≤ 2 ppm	2 ppm
Volatile Sulfides	≤ control solution intensity	Met
Residue on Evaporation	≤ 2.0 mg	0.4 mg

Meets All USP ‹381› Biocompatibility Tests

USP ‹381› lists two stages of biological tests. The first stage is *Biological Reactivity Tests, In Vitro,* USP ‹87›. Materials that do not pass the *in vitro* tests must proceed to the *in vivo* tests: *Systemic Injection Test and Intracutaneous Test* per the general test chapter *Biological Reactivity Tests, In Vivo,* USP ‹88›.

Even though the new RJ651-30 compound passed the *in vitro* ‹87› tests, Parker scientists also subjected the elastomer to the *in vivo* ‹88› tests. The new polyisoprene passed all biological tests, as shown in Table 4.

Table 4: Biological Testing

USP General Chapter	Tests	New Parker RJ651-30 Polyisoprene
In vitro testing per USP ‹87›	USP Elution Cytotoxicity Study	Met USP requirements
In vivo testing per USP ‹88›	USP Systemic Toxicity Study in Mice	Met USP requirements
	USP Intracutaneous Study in Rabbits	Met USP requirements
	USP Muscle Implantation Study in Rabbits - 7 Day	Met USP requirements

Closure Performance That Exceeds USP ‹381›

Table 5 shows that the RJ651-30 closures perform exceptionally well per functionally testing guidelines of USP ‹381›.

Table 5: Closure Performance/Functionality Tests per USP ‹381›

Closure Tests	USP ‹381›	Parker RJ651-30 Elastomer
Penetrability	<10 N	0.35 N ± 0.22 (pass)
Fragmentation	<5 fragments (visible to the naked eye)	No visible fragments detected (pass)
Self-Sealing Capacity	No trace of blue dye in any vial	No trace of dye in any vial (pass)

Because RJ651-30's self-sealing capacity performance exceeded the level required in USP ‹381›, this test was extended to further examine the new polyisoprene's limits. First, the compound's self-sealing capacity was tested using larger needles, including 16-gauge needles (that have four times the cross-sectional area of the 21-gauge needles specified in USP ‹381›); see Table 6.

Table 6: Self-Sealing Capacity with Larger Needles

Needle Size for Dye Test	21g	20g	19g	18g	16g
Parker RJ651-30 Elastomer Closure	No Trace	No Trace	No Trace	No Trace	No Trace

Septa Survive 20 Piercing/Vacuum Test Cycles

Next, the self-sealing capacity was tested using a more rigorous procedure: With 20-gauge needles, vials were pierced, vacuum tested, pierced, vacuum tested and so on, until a leak was detected. The closures survived with no trace of dye in any vial before testing ceased at 20 cycles, indicating the compound's potential to be utilized in septa for multiple-dose medicines or multiple-sample containers.

Available Now For Your Closure Applications

Parker's RJ651-30 compound is now commercially available for your product development needs. Potential septum applications include:

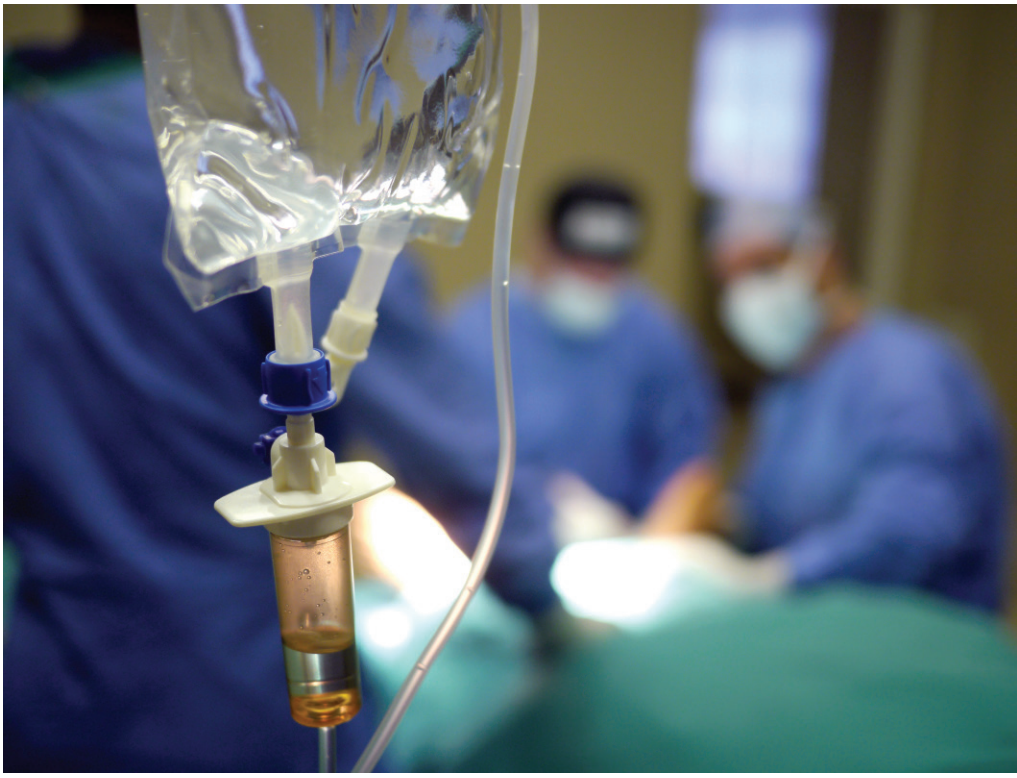
- Pharmaceutical Packaging
- Medical Devices
- Chromatography
- Diagnostics
- Research Laboratories

Custom Septum Design and Manufacturing

- Material is available now in tan/natural color
- Traditional compression or transfer molding options
- Suitable for flash-free transfer molding
- Design assistance at every stage of your closure and device development, supported by Parker's advanced non-linear FEA capability

ISO-13485 Certified

Parker's Medical Systems Division facilities are ISO-13485 certified for the development and manufacture of custom-molded elastomer products and devices for the life science market.



BUL MSD TB6801 02-15

ENGINEERING YOUR SUCCESS.