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Lipid-induced environmental stress cracking (ESC) in medical device components

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Abstract

Polycarbonate materials are used in a wide range of medical devices, including components used in catheters, such as luers and syringes. Nonpolar, lipid-based solutions are often used for dissolving non-water soluble pharmaceuticals, for the delivery of agents across the cell membrane and the blood-brain barrier, and in the intravenous administration of cancer and antiviral therapeutics, as well as in cardiac arrest [1, 2, 3]. As lipophilic solutions may seriously compromise the integrity of polycarbonate in medical devices, we provide an effective testing methodology to demonstrate when the use of polycarbonate should be approached with caution, and also explore strategies for luer selection.

1 Introduction

With medical plastics accounting for an estimated 21% use for fluid parts and 16% for medical parts, polycarbonate (PC) resins have been broadly used as a replacement for glass and metal in medical devices since their commercial availability in the 1960s, as they provide transparency, high strength and impact resistance, low water absorption, and feasible cost [4]. PC also satisfies plastic biocompatibility requirements found in both the FDA-modified ISO 10993, Part 1 "Biological Evaluation of Medical Devices" requirements for 30-day indirect blood contact, and the American standard US Pharmacopeia, Class VI. To prevent patient contamination for use in medical devices, PC has also desirable sterilization properties: is compatible with steam, ethylene oxide, and irradiation, is found in formulations that survive with minimal yellowing, and is also provided in formulations that provide a color indicator [5]. There may even be options to help minimize contamination with biofilm through a coating of selenium nanoparticles [6]. PC is amenable to processing using standard injection molding equipment, can be blow-molded into hollow containers, extruded into film, sheet, and a wide range of tubing thicknesses, and also can be configured as rods and slabs that are readily machined for prototypes.

2 Case study: Design criteria for catheter luer

To select candidate materials for a luer, which will be bonded to PEBAX®, in a catheter possibly used in the administration of nonpolar contrast and lipophilic agents (*e.g.* chemotherapeutics), the following design characteristics were considered:

1. *Mechanical requirements:* Strength to withstand flow rate of >1.5 mL/min at 160 psi, stiffness, resilience, and resistance to wear.

2. *Physical requirements:* Dimensional stability.

3. *Chemical requirements:* Resistant to both lipophilic (nonpolar) and polar solvents, as well as chemotherapeutic agents, resistant to radiation sterilization, and biocompatible. *Specific focus on Ethiodol® (Guerbet LLC, France) as a contrast agent that will likely be used with the device.*

4. *Appearance:* Clear with wings, smooth finish, easy grip.

5. *Manufacturing properties:* Methods of manufacturing and assembly, effects of processing on material properties and behavior over a period of time, compatibility with other components in the door, and cost of materials and manufacturing.

2.1 Nonpolar solutions + Hoop stress = PC component failure

Testing was performed with the PC luer bonded to PEBAX® tubing in an assembly subjected to the designated pressure range and flow rate, initially using saline and later with a polar contrast agent (Omnipaque® 300) with no observable component failures. The next phase of device testing focused on use with a nonpolar contrast agent, Ethiodol®. Sold as a replacement for Ethiodol®, Lipiodol® Ultra-Fluide (Guerbet LLC, France) is very similar in composition to Ethiodol®. Lipiodol is 48% iodine w/v (480 mg iodine/mL) while Ethiodol® is 37% iodine w/w (475 mg iodine/mL); both are provided in 1% of poppy seed oil (ethyl esters of iodized fatty acids of poppy seed oil). Based on their similarity in composition, both Lipiodol® and Ethiodol® are interchangeable for not only the purposes of this document, but in clinical use as well. There are currently strict limitations on supply of ethiodol/lipiodol as contrast agents due to severe manufacturing shortages, and because the current supply was restricted for the use of life-saving procedures, a simulated contrast agent formulation was sought and obtained (mixture of 1%(w/w) poppy seed oil in ethyl stearate at 37 °C). We found during testing that the PC luers and 1-way stopcocks withstood the desired 200 psi hydrostatic pressure. Though they remained intact after exposure to lipophilic agents, jets of saline were observed shooting out from cracks in a subset of lipid exposed luers and stopcocks. An investigation ensued for the root cause of the joint failure, and three candidates were identified for further evaluation: the cyano adhesive, the PEBAX® tubing, and the PC-make materials.

Cyano adhesive as candidate for root cause Though the chemical resistance data lists that polycarbonate (PC) may be vulnerable to cyanoacrylate, cyanoacrylate adhesive was considered but eliminated as a possibility for the independent and primary cause of failure because the joint design incorporates the adhesive in a thickness that in past experience and verification testing did not compromise the PC. In addition, the primary mode of failure was cracking in the luer where the adhesive was not applied (proximal, rather than distal, end of the luer).

PEBAX® material as candidate At this point in the investigation, the PEBAX®-based device component (branch tubing) was suspected to be chemically susceptible. According to Arkema, PEBAX® material chemical resistance improves with increasing durometer (*e.g.* 63D is more chemically resistant than 55D). Arkema's recommendation was to evaluate the PEBAX® materials directly with Lipiodol® and chemotherapeutics (with the device cross-sectioned) in order to conclude whether the crosstalk could result from lack of chemical resistance. We investigated two devices that were retested for air leak (pressurized to 200 psi). Saline and lipiodol were infused and the devices were incubated at 37 °C for $\sim$ 2.5 hours. It is noted that all three branches were filled with lipiodol (infusion, balloon, and guide wire). Both samples, including the lipiodol exposed device (with the reworked lipid resistant luers), did not show evidence of leak or crosstalk, and we were unable to find that PEBAX® 6333 (related to PEBAX® 63D) was chemically susceptible to the

lipophilic contrast agent.

PC-make components Polycarbonate has been demonstrated in published literature to be susceptible to lipiodol and other lipophilic solutions [7, 8]. From the chemical resistance data provided by Dow Chemical®, it appears that polycarbonate is susceptible to aromatic hydrocarbons including those found in the mixture of lipiodol and chemotherapeutics (which include aromatic, phenolic, amine-based, and basic functional groups). The resin for the female luer lock was found to originate from CALIBRE® polycarbonate. Improper molding of the luer components was also eliminated as a possible root cause. From a back-of-the-envelope calculation for mechanical stresses on a thin-walled hoop, the PC luer sustains 3.7 MPa of hoop stress (=535.7 psi, assuming 200 psi on a 0.0805" inner radius luer with wall thickness of 0.030"), where

$$\text{hoop stress} = \frac{\text{pressure} \times \text{inner radius}}{\text{wall thickness}} \tag{1}$$

or

$$\sigma_\theta = \frac{p \times r_i}{t} \tag{2}$$

This hoop stress is amplified multifold by hand tightening of the stopcock to the luer.

The luer exposed to only polar agents did not show evidence of crazing under applied hoop stress. Nor did we find crazing on exposed female luer lock joints merely after the PC luer was exposed to the lipophilic or simulated contrast agent. Also, luers merely soaked in lipiodol that were not tightened in a luer-lock connection showed no evidence of crazing. However, crazing was seen when these same exposed luers were then stressed by joining and tightening with a 1-way stopcock in multiple samples (Figure 1). Both the simulated lipiodol solution (1% poppy seed oil in ethyl stearate at 37 °C overnight, n=5) or lipiodol (n=1) induced the same susceptibility to stress-induced crazing, and indicate that the results from the simulated solution (only missing the iodo groups found in ethyl (mono- and di-) iodostearate found in both lipiodol and ethiodol) are consistent with results of testing in lipiodol. The crazing worsened into cracking when luers were loosened and retightened (all torquing by hand) multiple times.

2.2 Alternate component material selection for lipid resistance

Based on the failures observed in contact with lipiodol, we recommended that the PC-make components in the device (1-way and 3-way stopcocks, 1 cc syringe, and possibly even the hemostasis valve (RHV) in the existing design) be replaced by resistant materials (replacements summarized in Table 3). We were limited to testing of other materials using off-the-shelf luers due to the tight timeframe for the investigation. No luers with the desired dimension and configuration to replace the PC part were found in HDPE. Luer options tested included copolyester (COPE), polypropylene (PP), and nylon. We were also limited to investigating materials that could be bonded with only the currently specified adhesives, Loctite® 4013 (cyanoacrylate) and Dymax® 1187-M (UV).

Both PC and COPE were found to not be lipid resistant (as indicated by the crazing in Figures 1 and 2). Loctite advised use of a primer to help with difficult to bond materials such as PP and nylon. Because Loctite 7701 primer was already used in the bonding of another component in the device, use of this same primer would be ideal for use in bonding the branch tubing to the luer if a change requiring the primer for bonding of the component is implemented.

We were able to find two candidates as replacement off-the-shelf luers suitable for use with lipiodol/ethiodol: (1) a radiation stable, biocompatible DEHP-free PVC luer and (2) a machine-modifiable PP barb luer that also allows for adequate slip fit and bonding. Luers were reworked onto both subassemblies and also final test assemblies, and found to withstand >27.5N of tensile force as described in ISO 594-1 for luer fittings and >35N in ISO 594-2 for luer lock fittings (Table 2). As the 1 cc syringe was also

confirmed by Becton-Dickinson to be of PC-make, a PP 1 cc luer lock replacement was also recommended.

There was no crazing or cracking with $\sim$ 24 hour exposure to the simulated lipiodol mimic, and the PVC luer bonded to PEBAX® 6333 branch tubing sustained hydrostatic pressures of 200 psi after exposure to the simulated lipiodol. This makes the PVC luer with wings (radiation stable grade of PVC) attractive for an interim replacement for polycarbonate (non-lipid resistant) luers.

PVC is a primary material used in disposable medical devices, ranging from intravenous fluid containers and blood bags to medical tubing (including Tygon® tubing). As noted in the Baxa® bulletin "Non-DEHP Materials and Lipids," PVC is not inherently hazardous to patients, but its most commonly used plasticizer may be. As stated in the Lowell Center for Sustainable Production Report commissioned by the Health Care Without Harm Campaign, di(2-ethylhexyl) phthalate (DEHP) is a phthalate ester widely used as a plasticizer to make vinyl or PVC medical products soft and flexible.

While plasticizers may be required for flexible tubing, the use of PVC (DEHP-free) is attractive from the standpoints of chemical resistance, mechanical strength, rigidity, ease of bonding (same adhesives may be used as polycarbonate without need to introduce primer), and chemical resistance to lipiodol. And as noted in the package insert for Taxol and other chemotherapeutics, we find that the main source of concern in the use of PVC is the potential interaction between DEHP and chemotherapeutics (and other lipophilic compounds). DEHP is known to introduce developmental and reproductive toxicity in animal studies.

The PVC used in the luer replacement candidate (Qosina® p/n 71351, AlphaGary® PVC 2212RHT/1-118) has no phthalates, no DEHP, or plasticizers (website and statement from Manager of Regulatory Compliance, AlphaGary®). PVC in the absence of DEHP or plasticizers is a lipid resistant material suitable for use in a rigid luer, particularly catheter devices. We also have evidence that the particular grade of PVC used in this part is biocompatible (Toxikon® Biocompatibility Report for AlphaGary® 2212RHT-1-118). This is satisfactory per the FDA Public Health Notification (PVC Devices Containing the Plasticizer DEHP, July 2002), where it is recommended that the use of alternatives to DEHP-containing products, formulation of products to decrease/eliminate DEHP exposures, and labeling of DEHP-containing products. With this particular grade of PVC luer, we are assured that our product will remain DEHP-free.

For predicate medical device use, PVC is still used in luers (Smiths Medical® OEM), in IV Sets and Accessories in the Care Fusion® system, for IV hospital bags storing lipophilic emulsions such as Intralipid® (Baxter® and Fresenius Kabi® AB), for cardiovascular tubing (Natvar™), and cartridge blood set/hemodialysis blood lines (Gambro®). Further examples are provided in "Alternatives to PVC and DEHP Medical Devices" compiled by Health Care Without Harm.

3 Important considerations and lessons learned for plastic joints

Joint strength depends on a material compatibility, surface preparation, and joint design, where contaminants adversely affect adhesive bonding [10]. In addition to the use of USP Class VI plastics for medical applications, materials should be tested by the manufacturer in relation with the extent and duration of patient contact in mind, as additives (*e.g.* plasticizers, crosslinking agents, heat stabilizers), fillers and reinforcements (*e.g.* barium sulfate), impact modifiers (*e.g.* ABS for PC), colorants (*e.g.* organic and inorganic pigments), and various combinations with adhesives could affect the biocompatibility and bonding of the material [11, 15].

For general part failure, mechanical challenges to overcome include ductile fracture, which takes place

Table 1. Physical properties of ethiodol and simulated ethiodol.

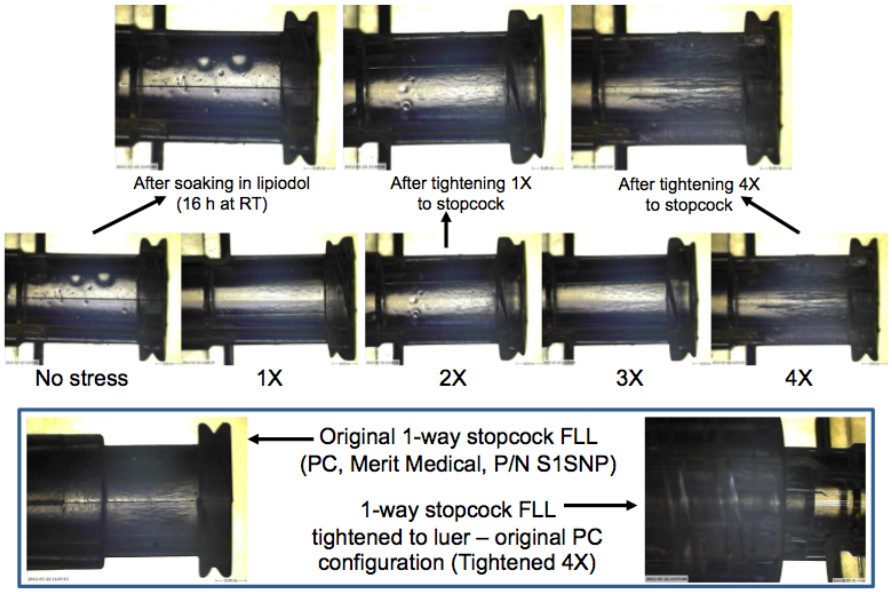
	Actual	Simulated	
Property	Lipiodol	Ethyl stearate	Poppy seed oil
Physical state	oily liquid	white solid	liquid
Density	1.290 g/cm^3	0.8973 g/cm^3	0.902 g/cm^3
Melting point	–	34 – 38 °C (93 – 100 °F)	-5 °C
Boiling point	125 °C	213–215 °C (415–419 °F) at 2 kPa (15 mmHg)	229.5 °C
Flash point	177 °C†	113 °C (235 °F) closed cup	110 °C
Solubility in water	insoluble	insoluble	insoluble

†Closed container, iodine vapors released >173 °C.

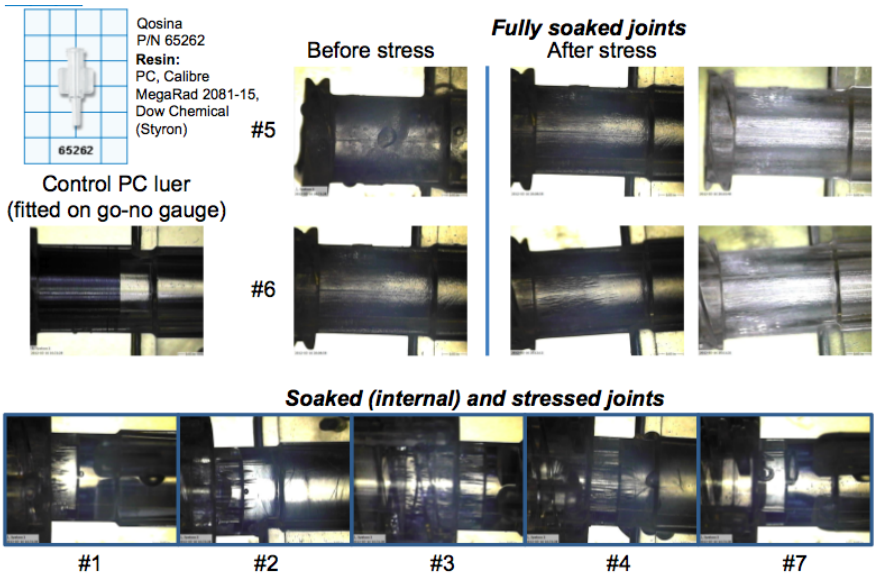
Table 2. Tensile testing at 10 in/min for luers to PEBAX® 6333 tubing: (a) Groups A, D, and E were units bonded with Loctite® 7701 primer and Loctite® 4013; (b) Groups B and C were units bonded with Dymax® 1187M.

	Peak force, N				
Sample number	Group A PP	Group B PVC	Group C COPE	Group D Nylon	Group E PC
1	50.9	79.1	58.3	20.7	48.2
2	51.4	78.6	61.4	32.0	45.2
3	47.4	74.7	61.3	37.1	52.7
4	49.2	75.4	-	55.9	54.6
5	55.3	75.5	-	-	49.9
	50.8 ± 2.9	76.7 ± 2.0	60.3 ± 1.8	36.4 ± 14.7	50.1 ± 3.7

along planes where shear stress is a maximum; brittle fracture takes place along the crystallographic plane (cleavage pane) where the normal tensile stress is a maximum; and creep is the permanent elongation of components under a static load maintained for a period of time, and the specimen fails eventually by rupture (necking and fracturing) [10]. Fatigue can also occur under cyclic stresses much lower than the ultimate tensile stress [12]. These mechanical issues, combined with physiochemical reasons, such as leaching of low modeling weight compounds leading to embrittlement, as well as dissolution, leading to disintegration, and worse than FDA recalls, can lead to catastrophic failures in medical devices [12, 13]. When cooled, most thermoplastics form amorphous glassy structures that could be likened to lengthy strands of spaghetti or entanglements that temporarily act as cross-links depending on random chain-based molecular motion and sliding due to elastic properties (at temperatures closer to glass transition temperature, as opposed to crazing by chain scission), that over time could be susceptible to chemical attack [16, 17]. Crazing involves ellipsoidal heterogeneities ranging from 10 μm to 10 mm for the major axis, and < 10 μm for the minor axis, and can be seen using transmission electron microscopy (TEM) to reveal microvoids and fibrils tracing the path of the tensile forces; cracks can initiate from defects such as microvoids that lead in turn to stress concentration; crazing also are formed under tension (never under compression) [17]. Chemically induced stress cracking can cause craze formulation at much lower stress and strains necessary for their intitation in air [17]. An obvious route to circumvent these issues could be to specify that the device not be used in contact with the compromising solutions that induce failure; however, as noted in the classic *The Design of Everyday Things*, it might be the best design to assume the



(a) Original nonpolar contrast agent.



(b) Simulated nonpolar contrast agent.

Figure 1. Testing of PC luer in various forms of lipiodol (original and simulated): (a) Testing of polycarbonate (PC) luers in original nonpolar iodinated contrast (lipiodol) and (b) in simulated lipiodol solution (ethyl stearate with 1% poppy seed oil).

error could reoccur in the field, as "to err is human" [14]. In this white paper, we have also highlighted the possibility that the nonpolarity of solutions used with the device could also have a significant impact on part integrity and increase the chances for stress-cracking, a common mode of failure in plastics [9].

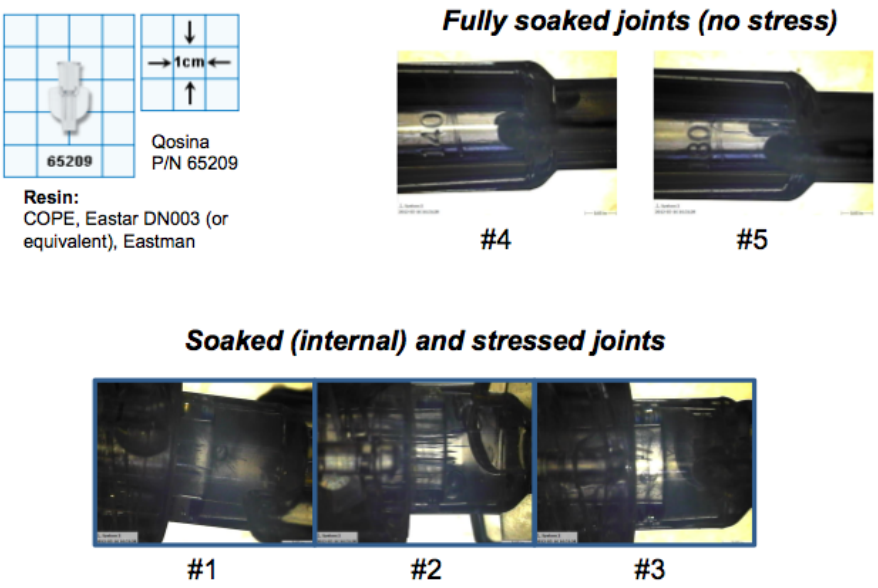


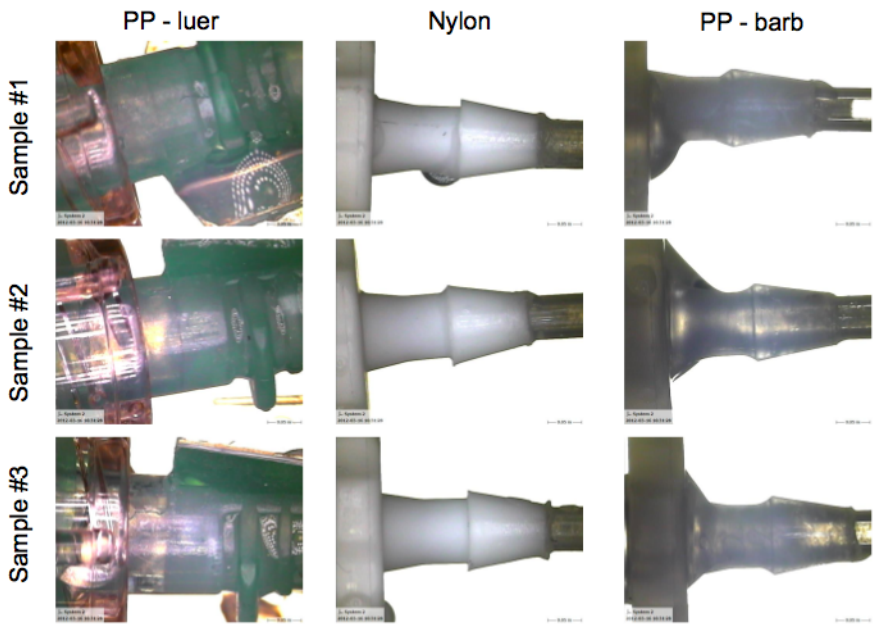
Figure 2. Evaluation of Copolyester (COPE) luers with simulated lipiodol.

Table 3. Recommended replacement components.

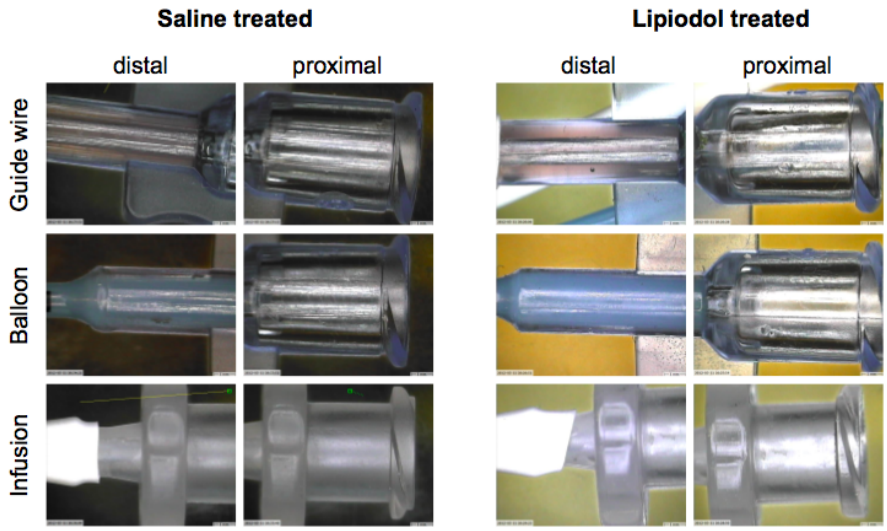
Original components					
	Stopcocks				
Luer	1-way	3-way	Heat shrink	Syringe	Rotating hemostasis valve
PC	PC	PC	N/A	PC	PC
Recommended lipid-resistant replacement components					
	Stopcocks				
Luer	1-way	3-way	Heat shrink	Syringe	Rotating hemostasis valve
PVC	Lipid-resistant PC	Lipid-resistant PC	Polyolefin	PP	PS or PE

4 Conclusions

A material substitution is recommended for all of the components currently formed from polycarbonate, especially if highly lipophilic solutions (*e.g.* lipiodol/ethiodol and embolization agents) will be used with the device. Satisfactory substitute materials include lipid-resistant PC, PVC, PS, PE, and PP. If a suitable lipid-resistant component replacement cannot be found, plasma treatment of the original part is another path for exploration. Testing of the replacement parts has been performed by Hantel, complete with testing to confirm functional equivalence of the new luer and other components (chemical resistance, tensile, and pressure testing, with identification of a rework procedure to incorporate the new materials. The capabilities for needs in design, regulatory, engineering, manufacturing, quality, supply chain, and clinical trials to help bring a medical device idea from concept to patient bedside may be found at Hantel Technologies™ (Figure 4).



(a) Substitute luer material candidates.



(b) Replacement luer candidates.

Figure 3. Testing of substitute candidate luers in simulated lipiodol: (a) Evaluation of nylon and propylene (PP) luers with simulated lipiodol; and (b) reworked branch tubing and luers using PVC and PP substitute luers.

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About Hantel Technologies

Hantel™ was founded in 1999 with a vision of a company that would bring medical devices to market, with all services provided under one roof. Since then, Hantel has become a leader in contract design and manufacturing, having developed hundreds of products for a wide array of applications. Hantel retains a highly qualified and diverse workforce with expertise in all aspects of medical device development and manufacturing. Located near the heart of Silicon Valley, Hantel is convenient and accessible to a wide array of device and biotech firms. Providing fast and flexible service, Hantel was built to meet your needs.

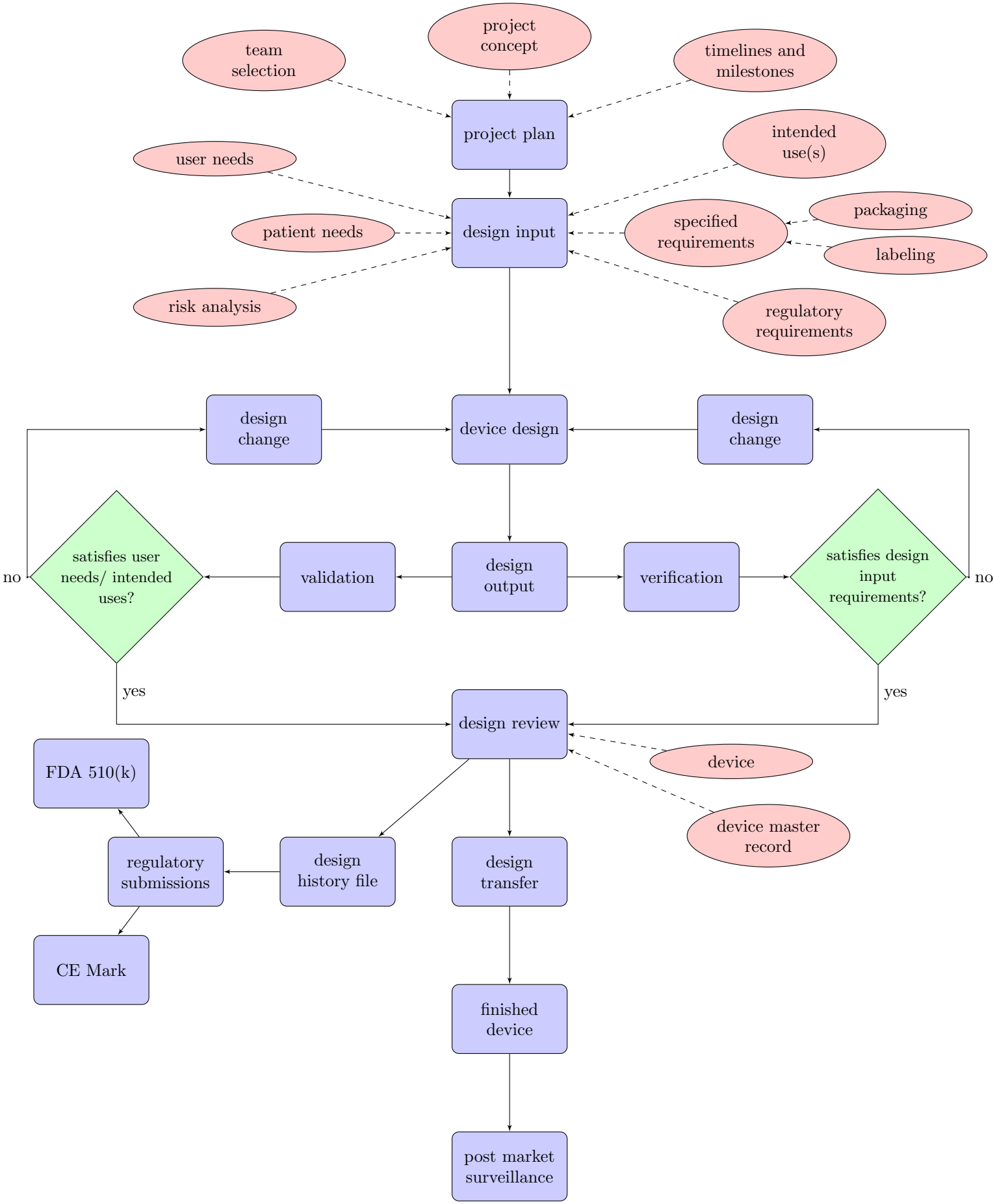

Figure 4. Flow chart of engineering capabilities available at Hantel Technologies.

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