# Liquivent®:
# A New Approach to Bronchoalveolar Lavage (BAL)

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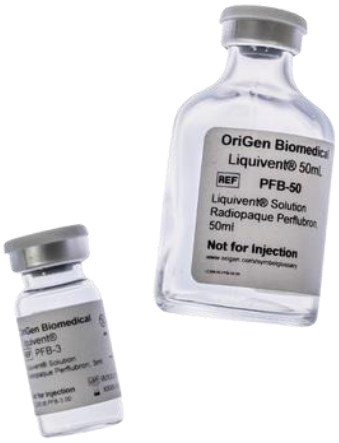


## Abstract

Current therapies for bronchoalveolar lavage (BAL) for foreign matter removal involve the use of Saline or Surfactant to clear out debris. Saline lavage is particularly rough on the patient—it reduces PaO2, removes surfactant, can elicit a cough reflex, and is not very effective in removing debris from the lungs. Liquivent®, a perfluorocarbon (PFC) compound liquid, has notable advantages as a lavage medium that may reduce the risk of these known issues.

**Keywords:** Perfluorocarbon (PFC), Perflubron (PFOB), perfluorooctyl bromide, bronchoalveolar lavage (BAL), lungs, lung lavage, bronchoalveolar lavage fluid (BALF), aspirated foreign matter

## 1. INTRODUCTION

### *1.1 What is a PFC*

Perfluorocarbons (PFCs), molecules consisting wholly of fluorine and carbon, are characterized by high gas solubility, fast release, low surface tension, high volume-quality, average volatility, good histocompatibility, and the absence of absorption and metabolism in vivo[4]. Because of their ability to dissolve large amounts of oxygen and carbon dioxide, PFCs have been used as a liquid breathing medium[5].

The most widely studied perfluorocarbon is Perflubron ($C_8F_{17}Br$ - perfluorooctyl bromide or PFOB)[2]. It is based on a common eight-carbon straight-chain chemical called octane. It has characteristics (Table 1) that make it preferable to saline (Table 2) in providing respiratory care to patients[3]. Perflubron is a radiopaque, inert, colorless fluid that carries a large quantity of oxygen (53 mL of oxygen per deciliter of Perflubron) and carbon dioxide (210 mL of carbon dioxide per deciliter of Perflubron), has the consistency of water, a high specific gravity (density, 1.93 g/mL), low vapor pressure (18 mm Hg at 37 [degrees] C), low viscosity (1.10 centistokes), and low surface tension (18 dyne/cm) [1].

### *1.2 Medical Usage of PFCs*

The potential application of PFCs in medicine was first discovered by Dr. Leland Clark and Dr. Golan in 1966 when they demonstrated that mice spontaneously breathing PFC liquid could maintain adequate gas exchange. The initial preclinical studies with PFCs were focused on breathing in unusual environments such as deep-sea diving, zero gravity, and space travel[33]. With further investigation, PFCs' capacity to carry oxygen was confirmed and later developed as a potential blood substitute called *Oxygent*[7]. Over 250 preclinical studies were performed to understand the safety of *Oxygent* in various animal species before moving on to studies that demonstrated efficacy in humans in the United States and Europe. Toxicology studies showed that the emulsion was well tolerated without severe adverse effects when given at appropriate clinical dosing[29].

 

The first clinical trial of PFC ventilation was performed in neonates with severe respiratory distress in 1989. In the 1990s and 2000s, Perflubron was used in clinical trials studying Liquid Ventilation where it was instilled directly into the lungs of hundreds of neonates, pediatric, and adult patients[30]. The biocompatibility of this compound in direct use in the lungs was well established during these trials, and in patient follow-up years after its use. Patients who received partial liquid ventilation with Perflubron showed decreased progression in respiratory insufficiency to ARDS, but additional clinical trials focusing on liquid ventilation ceased[33].

| Characteristics | Perflubron | Saline |
|---|---|---|
| Respiratory Gas Solubility: | | |
| Oxygen - $O_2$ | 53 ml/100 ml | 2 ml/100 ml |
| Carbon Dioxide - $CO_2$ | 210 ml/100 ml | 70 ml/100 ml |
| Surface Tension | 18 dynes/cm | 75 dynes/cm |
| Spreading Coefficient | 2.7 dynes/cm | |
| Density (25 °C) | 1.92 g/ml | 1 g/ml |
| Vapor Pressure (37 °C) | 11 torr | 47 torr |
| Boiling Point | 140.5°C / 284.9°F | 100°C / 212°F |
| Freezing Point | 5.4°C / 41.72°F | −0.59°C / 30.94°F |
| Viscosity | 1 cSt | 1.02 cSt |
| Molecular Weight | 499 g/mol | 58.44 g/mol |

**Table 1.** *Characteristics of Perflubron and Saline[3, 31]*

| Property | Perflubron | Saline |
|---|---|---|
| Lavage Action | buoyancy | mixing and dilution |
| Elicits Cough Reflex | no | yes |
| Biological Reactivity | inert | biocompatible |
| Biocompatible with Lung Tissues | yes | yes |
| Clear Liquid | yes | yes |
| Blocks Oxygen Transfer During Lavage | no | yes |
| Removes Surfactant | no | yes |
| Sterilization Method | sterile fill | autoclave |

**Table 2.** *Comparison of Substantial Equivalence*

Lavage with PFCs has been shown to be safe for the treatment of persistent and difficult-to-treat lung atelectasis[34]. Bronchoalveolar lavage utilizing Perflubron was performed without incident in infants with severe alveolar proteinosis during conventional mechanical ventilation without requiring the additional support of extracorporeal membrane oxygenation. Furthermore, recent studies have reported safe imaging studies in bronchopulmonary patients[35].

It is also noteworthy that Perflubron is the only medical grade perfluorochemical approved by the FDA for emergency medical use[33].

### *1.3 Perflubron vs Saline*

Saline has been used as a respiratory medium for lung lavage since 1920[31], but has its limitations. Compared to air, saline's oxygen solubility is low and its viscosity and density are high. Because of this, in addition to the fact that saline can wash out surfactant and impair lung function[32], the use of saline in supporting pulmonary gas exchange has been limited to hyperbaric applications[7]. Saline has a number of drawbacks when used as a lavage agent, and some of these disadvantages are serious enough that medical professionals have recommended that saline no longer be used as a lavage agent[10].

Perflubron can dissolve approximately 17 times more $O_2$ and almost 4 times more carbon dioxide than saline solution[2]. The density of the Perflubron is great enough to displace water as it moves into the dependent, consolidated areas of the lungs. This quality allows it to float toxic, damaging exudates and infectious material, to the top of the PFC, where it can be removed using suction[3]. PFCs have proven themselves to be excellent lavage agents as they do not obscure the view through a bronchoscope or block oxygen transfer[9].

## 2. CHARACTERISTICS OF PERFLUBRON

### *2.1 Safety*

The effects of perfluorocarbons on the lungs have been the subject of many studies over the years. Relevant data on safety information in use in the human lungs is presented below.

*2.1.1 Cough Reflex.* Currently, saline lung lavage is the standard of care for removing debris from the lungs. However, saline is a moderate irritant to the bronchial mucosa and elicits a coughing reflex in the patient. If patients are not anesthetized, coughing can be dangerous and can disrupt other treatments which may be in process. During lavage, the patient is proned on one side while the lower lung is flushed with 0.9% sodium chloride solution until the returns run clear. Meanwhile, the patient is ventilated through the upper lung. Lavage attempts to remove debris, aspirated liquids, solids, and accumulations of alveolar lipoproteins through a mechanism of dilution and rinsing. Liquid ventilation trials with PFCs were sometimes done on patients who were fully awake because Perfluorocarbon compounds do not elicit a cough reflex.

*2.1.2 $PaO_2$.* Saline is currently the most commonly used agent for lung lavage; however, it effectively eliminates the gas interface within the lung. In doing so, it reduces the effectiveness of Oxygen transfer during lavage. It was found that the use of saline lavage on ventilated patients reduced $PaO_2$ from 100 to 78 mm Hg following administration of sodium chloride solutions and the decline in $PaO_2$ persisted for 30 minutes following lavage[11]. It was also found that instilling saline prior to suctioning in bronchial lavage has an adverse effect on oxygen saturation[12], and it was recommended that the practice of instilling saline prior to suctioning should be abandoned as a routine lavage procedure. In another study on the side effects of saline lavage during bronchoscopy on cardiopulmonary function[10], it was noted that there was a decline in arterial oxygen tension of 15 mm Hg, a decrease deemed 'significant' by the researchers. Tests indicated that bronchial lavage with saline was responsible for a decline in arterial oxygen tension seen during lavage with a bronchoscope.

A study of therapeutic lung lavage using PFCs showed no reduction in oxygenation in animals with meconium aspiration[16]. Saline lavage for meconium aspiration causes impaired lung function, but lavage with PFCs facilitates meconium removal and reduces lung barotrauma[17]. Lavage with exogenous surfactant in combination with Perflubron improved pulmonary gas exchange after a meconium aspiration[14]. In an animal study of induced respiratory distress[14], sheep insufflated with cotton smoke were randomized to receive lavage with either saline or perfluorocarbons. That study found that perfluorocarbons reduced transient hypoxemia associated with saline bronchoscopic lavage and further noted PFC lavage can be considered safe for patients with acute lung injury. It was found that installation of Perflubron into the lungs diminishes oxidative damage to injury-prone tissues[13].

Gas exchange during lung lavage was studied[27] in an animal model with Oleic acid infusion and saline whole lung wash, and it was concluded that Perfluorocarbon lavage removed pulmonary edema fluids and improved gas exchange after severe lung injury. Bronchioalveolar lavage with PFCs can be performed safely during conventional mechanical ventilation[15]. Robust long-term data on the effects of Perflubron lavage does not exist, though existing case reports of patients evaluated 9–12 years following treatment make no mention of any detrimental impact.[6]

*2.1.3 Surfactant.* Although the irritating action of saline in the lungs may assist in removing pulmonary debris, it has also been shown to remove pulmonary surfactant[20]. In a study of PFCs instilled directly in the lungs, it was determined that PFC did not affect spontaneous surfactant secretion[21]. The same conclusion was reached in an experimental model of meconium aspiration in adult guinea pigs[19].

In a study of liquid absorption during Perflubron installation into the lungs[13], it was found that Perflubron did not remove natural surfactant, which was beneficial in reducing pulmonary edema. In a direct study of the effects of PFCs on phospholipid production in the lung[18], it was concluded that Perflubron in the alveolar space does not have a negative impact on endogenous surfactant production. In conclusion, lung lavage with perfluorocarbons is at least as safe as lavage with saline.

## *2.2 Efficacy*

As mentioned above, Perflubron has many advantages as a lavage medium. It has excellent oxygen and carbon dioxide carrying capacity compared to saline and allows for homogeneous ventilation and improved recruitment of injured lungs. It is insoluble in all biologically known media and does not wash out surfactant in the process of ventilation[28]. Perflubron's surface tension and spreading coefficient make it favorable to restore the lining of the alveoli for stable inflation. The density, viscosity, and surface tension of Perflubron allow it to descend into the dependent, consolidated areas of the lungs, allowing toxic, damaging exudates, as well as infectious material, to float the top of the Perflubron, where it can be removed via suctioning[3]. With saline lavage, aspirated liquids are even more problematic. Saline can only dilute aspirated liquids, not displace them, and repeated flushing is used to attempt dilution and removal.

Activated charcoal is frequently used in absorbing ingested toxins, and is sometimes accidentally aspirated by patients. Activated charcoal is extremely difficult to remove with saline lavage, and when allowed to remain in the lungs, can develop into chronic lung disease [23, 24]. Charcoal aspiration remains a life-threatening problem in managing pediatric patients [23, 24]. However, the density of Perflubron (2.0 g/ml) is much greater than the density of charcoal (0.2 g/ml) or even some soils (1.6 g/ml). These substances will float on top of the Perflubron meniscus, making them easy to suction off.

Unlike exogenous surfactant, PFCs exposed to plasma proteins in the lungs do not lose their surface tension-reducing abilities[18], making their function as a lavage agent more uniform.

## *2.3 Biocompatibility*

As a class, PFCs are inert both chemically and biochemically. Their non-reactivity in biological systems precludes the potential for direct cytotoxicity, antigenicity, or genotoxicity, all of which promote high biocompatibility. The long-term effects of Perflubron in humans have been the subject of many detailed follow-up studies over the last 20 years [14, 18] and have demonstrated no negative effects[33]. In addition to those results from use in the lungs, the use of perfluorocarbons in the circulatory and digestive systems further underscores its biocompatibility.

*2.3.1 Blood Studies.* Perflubron has been carefully studied in clinical trials in the circulatory and respiratory systems for more than 20 years. There have been no long-term ill effects reported in any of the clinical studies of its use in the respiratory or circulatory systems[26]. In an extensive study of the effect of perfluorocarbons directly infused into the blood[22], Perflubron emulsions did not affect coagulation function in healthy volunteers.

*2.3.2 Clearance from the Body.* In the lungs, PFC liquids are absorbed minimally by the respiratory epithelium and eliminated by evaporation through the lungs[25] at an initial rate of 13.6 +/- 4.5 mL/h.[1] Radiographic evidence of Perflubron elimination appeared to plateau at approximately 48 h following administration of the last dose[1]. A similar evaluation of radiographs reports that two-thirds of the Perflubron is eliminated by 7 days after administration of the last dose of Perflubron and minimal Perflubron remains after 21 days. However, an exact quantification of residual Perflubron would be difficult to obtain[1]. There is demonstrated evidence of residual Perflubron in the lung, thorax, mediastinum, and retroperitoneum[33].

In a comprehensive double-blind study of clearance of perfluorocarbon from the circulatory system[22], it was concluded that Perflubron compounds were not associated with any systemic inflammatory response. There were no differences in cell-mediated immune responses, hematology complement levels, or cytokine levels between groups receiving Perflubron and saline. They further noted that the clearance of Perflubron from the circulation appeared to consist of two phases: the rapid first phase where clearance is dominated by

the mononuclear phagocyte system, and the slow second phase consisting of expiration from the lungs. There has been no evidence of any adverse events associated with a subsequent slower phase of Perflubron clearance from the circulation.

## 3. ABOUT ORIGEN BIOMEDICAL

### *3.1 Liquivent*

OriGen Biomedical supplies a pharmaceutical-grade Perflubron, which is radiopaque (opaque on x-ray) and meant for single use only. The filling of the solution into vials is done aseptically in a validated process and the final product is tested for sterility. Vials are Type 1 borosilicate assembled with butyl stoppers and crimped aluminum caps. Each lavage solution is accompanied by product labeling indicating the device should be used by or under the direction of a licensed and qualified healthcare professional.

The Liquivent product line has been tested for stability and sterilization to meet its shelf-life requirements as a raw material and final product. Liquivent solution has been evaluated at 3 years with no chemical alteration. There is no chemical alteration that occurs in the OriGen process and the containers and packaging have been fully evaluated. Sterilization is performed via sterilizing filtration and filling into a sterile final product container by aseptic processing per ISO 13408. All materials in the fluid path after the sterilizing filter are sterilized before use. End-of-lot sterility testing is performed on every lot. Liquivent is tested at batch release for endotoxin and sterility per USP <85> and sterility per USP <71>. All raw materials, in the fluid path and after the sterilizing filter, undergo regular monitoring for their pyrogen and bioburden levels.

Liquivent is CE marked and available for research use only in the USA.

### *3.2 Company Information & History*

OriGen Biomedical, Inc. is a leading producer of cryopreservation, cell culture, and intensive respiratory care products. OriGen has a range of products that support the treatment of cancer, genetic conditions, and other life-threatening diseases. Founded in 1997, our first product was a dual lumen ECMO catheter. It was originally made of polyurethane in pediatric sizes and OriGen was the only supplier of ECMO catheters in the United States for many years. Insertion techniques for cutdown and percutaneous placement were developed. A wire-wrapped reinforced catheter for use in pediatric through adult sizes was introduced in 2008.

In 2005, OriGen began investigating the use of Perflubron for removing meconium in ECMO patients. Research continued into the adult population, and CE-mark approval was granted in 2007 for use in lung lavage procedures. Our products are designed with the patient and user in mind. We strive to maintain excellent customer service to ensure that patient care is our priority. Quality is the foundation of all product designs at OriGen, and each product is produced with the intention that it will improve patient health. Founded in 1997 and headquartered in Austin, Texas, OriGen is certified annually to ISO 13485 standards and regularly inspected by the FDA, MDSAP, ISO certification organizations, and our customers. To learn more, please visit www.origen.com.

## 4. CONCLUSION

Based on review of the literature, Perflubron is safe and effective to use for lung lavage. Data suggests that it is bioinert and therefore biocompatible with successful use in human lungs for over 30 years. Long-term data on the effects of perfluorocarbon lavage do not currently exist, but case reports of patients evaluated 9-12 years following treatment make no mention of any harmful effects[6]. Studies have shown that it does not interrupt oxygen transfer during lavage, does not remove surfactant, and does not elicit a cough reflex. Perflubron is a dense, clear liquid with a low viscosity that can be instilled into the lungs and can more easily achieve debris removal through buoyancy than saline. After treatment, it can be removed from the lung through suctioning or allowed to evaporate. These features suggest that Perflubron could provide an improved standard of care for lung lavage than saline.

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## OriGen Biomedical, Inc.

**Richard Martin** is the Founder and Chairman of the Board at OriGen Biomedical. He has extensive knowledge of medical devices, especially in the respiratory realm, from his years of experience in the ECMO community and OriGen’s ECMO catheters. **Kirsten Krupps** is the Product Marketing Manager at OriGen Biomedical. Liquivent® is a registered trademark of OriGen Biomedical, Inc.

Mission Statement: *We create innovative medical products that improve people’s lives.*

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