

CUNO Application Brief

A Review of the Practices of Using Carbon in the Production of Fine Chemicals

Introduction:

Carbon has been used in the pharmaceutical industry for many years to remove impurities in production processes. These impurities are typically derived from chemical reactions producing colored byproducts. Carbon is used to remove chemical impurities as it has many structural characteristics that are suitable.

This CUNO Application Brief describes a traditional process using bulk carbon compared to the same process using the ZetaCarbon® cartridge system where the carbon is immobilized in an easy-to-use cartridge form. The ZetaCarbon cartridge system addresses the following issues of using bulk carbon:



Aspect Of Production Concern	Concern
Operator Exposure	Carbon dust
Quality	Cleanliness, Carbon breakthrough, Reproducibility
Cost	Rework of failed batches, Rework of solvents, Efficiency

Theory of Carbon

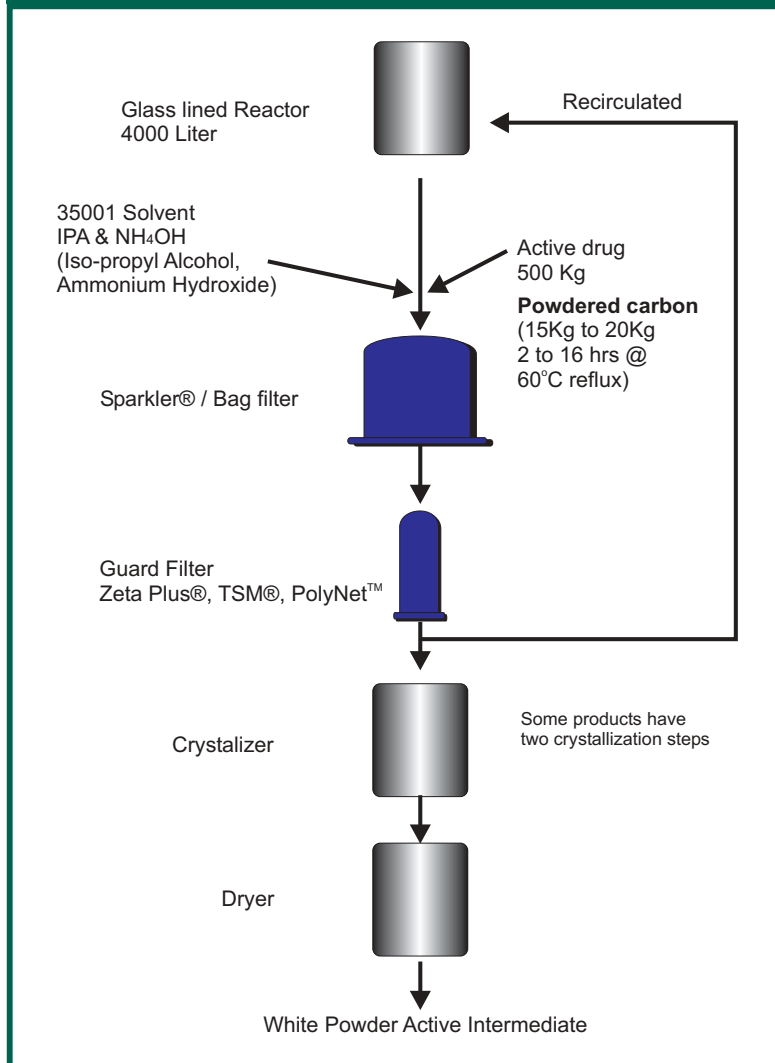
To provide an understanding of the ZetaCarbon cartridge system it is important to understand carbon. Carbon is made from many source materials such as wood, bone, peat and coconut shell. Due to concerns of BSE (Bovine Spongiform Encephalopathy), viruses and prions, carbon derived from bone is not recommended and carbon from vegetation is usually used. The source material is first activated by one of two methods, steam or chemical. The activation process produces different carbon characteristics. Steam activation leads to a greater number of micropores (less than 100nm) and mesopores (100nm to 1µm) compared to chemical, while chemical treatment produces more open macropore (>1µm) structures. The activated carbon is then used in powdered, extruded and granular formats. Activated carbons have very large surface areas (>500m²g⁻¹) and remove contaminants by adsorption. Adsorption is caused by London Dispersion Forces, a type of Van der Waals Force. The type of molecules adsorbed are predominantly organic compounds and larger molecular weight inorganic compounds. The adsorption efficiency of carbon is affected by the number of active sites on the carbon, and process parameters such as contact time, temperature, and concentration of contaminant.

The Process

There are many chemical processes that use bulk carbon to produce active pharmaceutical intermediate compounds. These processes can be in use 24 hours a day using a three-shift operation due to the expense of keeping the equipment idle. Figure 1 shows a typical process step where bulk carbon is used. The chemical reaction in the glass lined vessel causes contaminants that are colored. The contaminants need to be removed as these will cause an off white final product and the product will fail Quality Control. In order to remove the colored contaminants, bulk carbon powder is poured into the reaction vessel. The operator has to wear a protective suit and breathing apparatus due to the carbon dust and the hot fumes of the reactor. The optimum amount of carbon is not used due to the inconvenience of handling left over carbon.

Many product licenses do not specify the type or quantity of carbon to be used. For this reason, additional quantities of activated carbon are used for the convenience of the operator. Weighing precise amounts of carbon into a reactor is difficult and disposing of small quantities left in the 25Kg bags is time consuming. Figure 1 shows the filters that are in contact with the product, but there are additional filters (e.g. 1.0 μm rated CUNO PolyNet[®] filters) that are used on solvent lines leading to the reactors. Due to the capital equipment involved in the plant, it typically costs over \$6000 (7,000 Euro's) per hour to leave the plant idle. Therefore the plant is used efficiently and the rate limiting steps are continuously being reduced. Production plants are used 24hrs a day with minimal downtime during the year. The solvent is added to the reactor and heated to the desired temperature. The active drug is added to the solvent and stirred. Once the reaction is complete the carbon is added and in some cases kieselguhr / diatomaceous earth is added to aid filtration when the carbon is removed. The solution is re-circulated for the appropriate time. Samples are taken to determine the remaining color by spectroscopy or light absorbency / transmission methods. Once the quality has been reached the product is then committed to the crystallizer. A final quality step that includes the level of impurities and color is performed before the release of the product.

Figure 1. - A typical Production Process To Decolourise An Active Pharmaceutical Intermediate with Powdered Carbon



Sparkler[®] is a registered trademark of Sparkler Manufacturing Company.

Issues Related to the Use of Bulk Carbon

Many Fine Chemical Manufacturers have concerns with powdered carbon. These concerns center around three primary areas related to the use of carbon, namely operator exposure, the quality of the process, and the operating costs associated with the process.

Once the carbon is in the reactor, adsorption of the byproducts and impurities occurs. This can be inefficient as the powdered carbon randomly moves through the reactor and relies on chance. Once the quality criteria are reached, the carbon needs to be removed. This again means that the carbon is not contained. The operator has to be exposed to the carbon, solvent, product and contaminants.

Operator Exposure:

- **Exposure to Carbon Dust:** Carbon is usually supplied in bags that an operator must open and pour into the reactor. Operator exposure to carbon dust can cause lung damage. To avoid this, operators must wear protective equipment that may include airlines (Code of Federal Regulations – Title 29, Subpart Z, par.1910.1000, Table Z-3 the use of dust masks). Also, carbon dust is considered a fire hazard (activated carbon is classified by the UK Fire Research Station as group (b) dusts in the explosibility test). Furthermore, when carbon becomes wet, it depletes oxygen from the surrounding environment. Lastly, all environments need to be thoroughly cleaned before protection is removed. All of this means that the simple step of adding carbon to a reaction vessel is in reality complex, and that the process is not contained in the reactor.
- **Exposure to Reactor Fumes:** As the reactor contains hazardous chemicals at elevated temperatures the operator must wear breathing suits to avoid breathing chemical fumes and carbon dust. Since at this stage the reactor is opened to the environment, there is also the possibility for product contamination as well.

Quality:

- **Cleaning:** To prevent batch to batch contamination, thorough cleaning of all equipment is essential. Removing all carbon fines from the vessel, valves and pipe-work is time consuming, and validation of this operation is a major expense.
- **Carbon Particle Contamination:** Carbon break through is often experienced leading to black particles in the final product. In addition carbon may be seen in the solvent recovery plant causing further problems.
- **Reproducibility:** The random nature of contact and adsorption by powdered carbon in the reactor leads to variability of contaminant removal from product batches. This can lead to costly re-work of out-of-specification batches.

Costs :

- **Re-work of Failed Batches :** Carbon fines found in the final product usually results in re-processing the batch. The cost is dependent on the value and quantity of product involved.
- **Re-work of Solvents :** Carbon fines found in the recovered solvents results in reprocessing of the solvents and therefore further costs.
- **Efficiency :** The production costs are high due to the special protective precautions required when using bulk carbon and the potential reworking of contaminated batches of product and solvents.

The CUNO Solution

CUNO has a full range of carbons to meet the industry's requirements. The problems associated with the use of bulk carbon can be alleviated by employing the ZetaCarbon cartridge system. The ZetaCarbon system consists of lenticular style cartridges that contain carbon within the structure of the medium. The carbon is held within a matrix of refined cellulose fibers and a proprietary binding resin. The cartridges are then installed in a totally enclosed, sanitary design cartridge housing. This system resolves many of the problems associated with bulk carbon. Figure 2 shows the microscopic structure of the ZetaCarbon medium, while Figure 3 depicts the cartridge construction.

Figure 2. - ZetaCarbon Medium Magnified

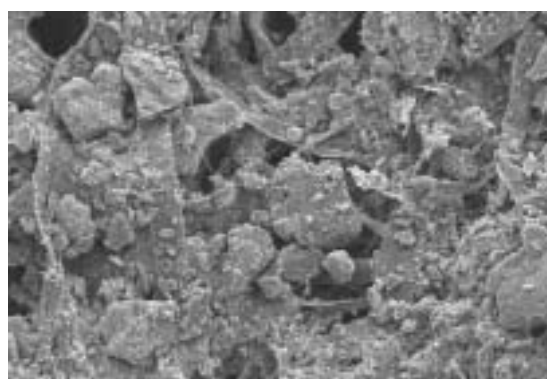
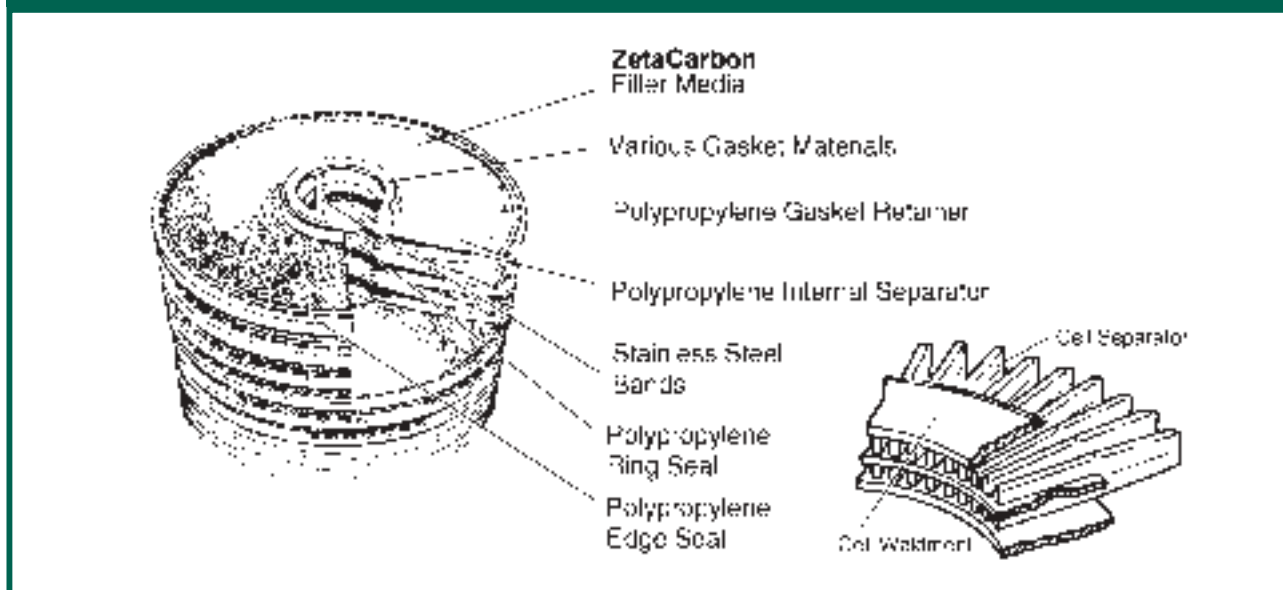


Figure 3. - ZetaCarbon Cartridge Construction



The list that follows highlights some of the benefits of the ZetaCarbon cartridge system:

Operator Exposure:

- **Exposure to Carbon Dust:** Since the carbon is fixed in the ZetaCarbon cartridge media, safety is greatly improved for the operator as contact with large quantities of dust, exposure to product and solvent is eliminated. ZetaCarbon cartridges are easy to use. They can be installed and removed from cartridge housings in fifteen minutes. The elimination of dust by ZetaCarbon cartridges also results in a cleaner process and virtually eliminates equipment and solvent contamination with carbon dust. In addition, all of the product is forced through the ZetaCarbon cartridges and therefore comes in contact with the carbon-activated sites, a much more efficient process than adding bulk carbon to a reaction vessel. This again reduces processing time and enhances the de-colorization reaction.
- **Exposure to Reactor Fumes:** ZetaCarbon cartridges are installed in a housing. The housing is blown dry before installation and removal of the cartridges. This eliminates direct contact and exposure of the operator with the solvents and product and increases yields.

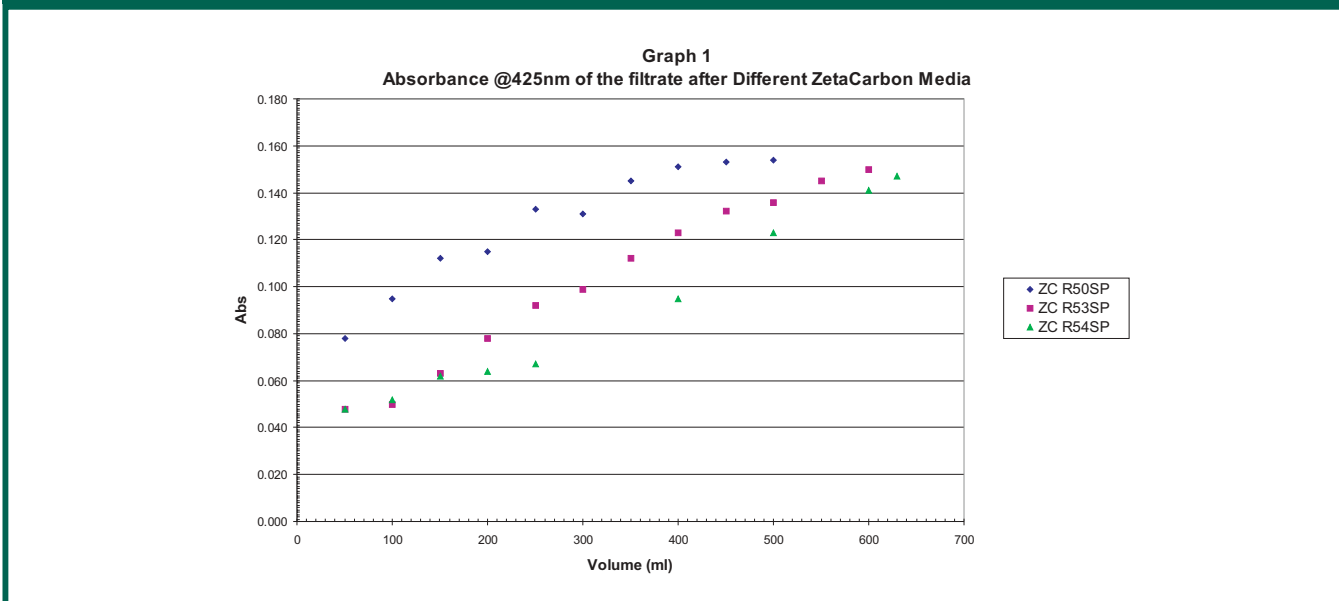
Quality :

- **Cleaning:** The ZetaCarbon cartridge system minimizes the amount of cleaning required for the vessel, condensers, piping and the surrounding area. Condensers are used on top of the chemical reactors so that the solvent fumes from the reactor are trapped. Condensers are practically impossible to clean. It has been noted by several pharmaceutical chemical processors that powdered carbon has been found in products when carbon has not been used in the chemical reactor for up to three months. It is believed that powdered carbon contaminated the condenser in previous batches and subsequently fell into the reactor at a later date.
- **Elimination of Carbon Particle Contamination:** ZetaCarbon cartridges replace the carbon trap filter and can replace the guard filter. This removes a process step simplifying the process and providing greater efficiencies. This also has the advantage of less errors, training and documentation.
- **Reproducibility:** Laboratory optimization studies conducted by CUNO SASS (Scientific Application Support Services) ensures that quality is maintained or is improved. The laboratory studies can then be linearly scaled.

Costs :

- **Reduced Failed Batches:** The number of batches that are reprocessed depends on the production process but have been reported to be as high as twelve batches a year. The ZetaCarbon cartridge system minimizes the number of re-processing of batches, greatly reducing potential re-processing costs that can range from \$10,000 to \$500,000 per batch.
- **Reduced Solvent Contamination:** Solvent recovery and reprocessing plants can experience carbon fine contamination in their plants. This causes batch rejects due to the solvent quality and further costs and delays in releasing the solvent are incurred. ZetaCarbon minimizes the risk of carbon fines being transferred to the solvent recovery plant.
- **Improved Efficiency:** Carbon is immobilized in the ZetaCarbon cartridge, improving containment, increasing the contact time of the impurities with the carbon active sites and thus improving the decolorization efficiency when compared to bulk carbon. The production operation time is significantly reduced. Production can double the number of batches processed in a given period if a single passage through a ZetaCarbon cartridge system is implemented, since a second chemical reactor is not required as a holding tank before the crystallizer. Therefore processing costs are reduced and production yields are improved with the use of ZetaCarbon cartridges.

Graph 1. - Test Results Using Different ZetaCarbon Grades

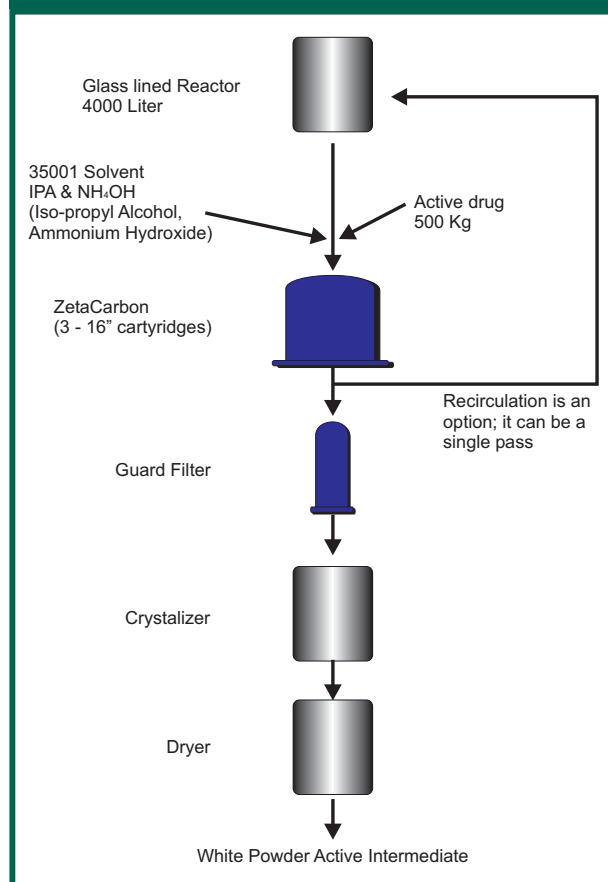


Implementation

Before optimization studies are performed there must be a review of the current process. A full understanding of the drug license is required with respect to the type of carbon and quantity. In addition to this, information on the quality procedures should be understood. These factors will determine whether the ZetaCarbon cartridge standard range of carbons are used or that the existing production carbon is incorporated into a ZetaCarbon cartridge. Laboratory studies mimic the full-scale process taking into account of flow rates, volumes and process times. The different types of ZetaCarbon media are tested to evaluate the optimum type. Graph 1 shows the results from a laboratory study selecting the optimum ZetaCarbon grade using 47mm discs under similar conditions at an example flow rate $2.9 \text{ cm}^3\text{min}^{-1}$. The graph indicates that the ZetaCarbon R54SP medium is more effective at removing the color in this product.

The results from the laboratory studies are then used to provide larger pilot plant studies and then finally, linearly scaled to full-scale production. Figure 4 shows a typical process with employing ZetaCarbon cartridges. ZetaCarbon cartridges can be used in a re-circulation mode or by a single pass to the crystallizer. Full training is given to the operators in the handling of the ZetaCarbon cartridge system including installation and removal. A total filtration package can also be given covering certificates of conformity and Regulatory Support Files to support validation.

Figure 4. - A Typical Production Process To De-colorize An Active Pharmaceutical Intermediate with ZetaCarbon Cartridges



Conclusion and Summary

The traditional way to de-colorize solutions is still being used as it has been tried and tested for many years demonstrating carbon is a robust method. However, the traditional method of using bulk carbon has limitations, especially in relation to operator safety, product quality, and operating costs. Good Manufacturing Practice is a requirement for many regulatory authorities. To meet these guidelines many companies have moved to the CUNO ZetaCarbon cartridge system as the carbon is trapped within the filter matrix, reducing many of the concerns of bulk carbon. CUNO can assist in the change from bulk carbon to ZetaCarbon cartridges. CUNO Scientific Application Support Services (SASS) provide full support from laboratory optimization studies through pilot and into full production. CUNO training of operators assists in the smooth transition to the ZetaCarbon cartridge system.

Scientific Applications Support Services

The cornerstone of CUNO's philosophy is service to customers, not only in product quality and prompt service, but also in problem solving, application support and in the sharing of scientific information. CUNO's **Scientific Applications Support Services (SASS)** group is a market-oriented group of scientists and engineers who work closely with customers to solve difficult separation problems and aid in the selection of the most effective and economical filtration systems. CUNO offers specialized support to the pharmaceutical and biotechnology industry through our **Validation Support Services Program**. SASS routinely provides end-users with:

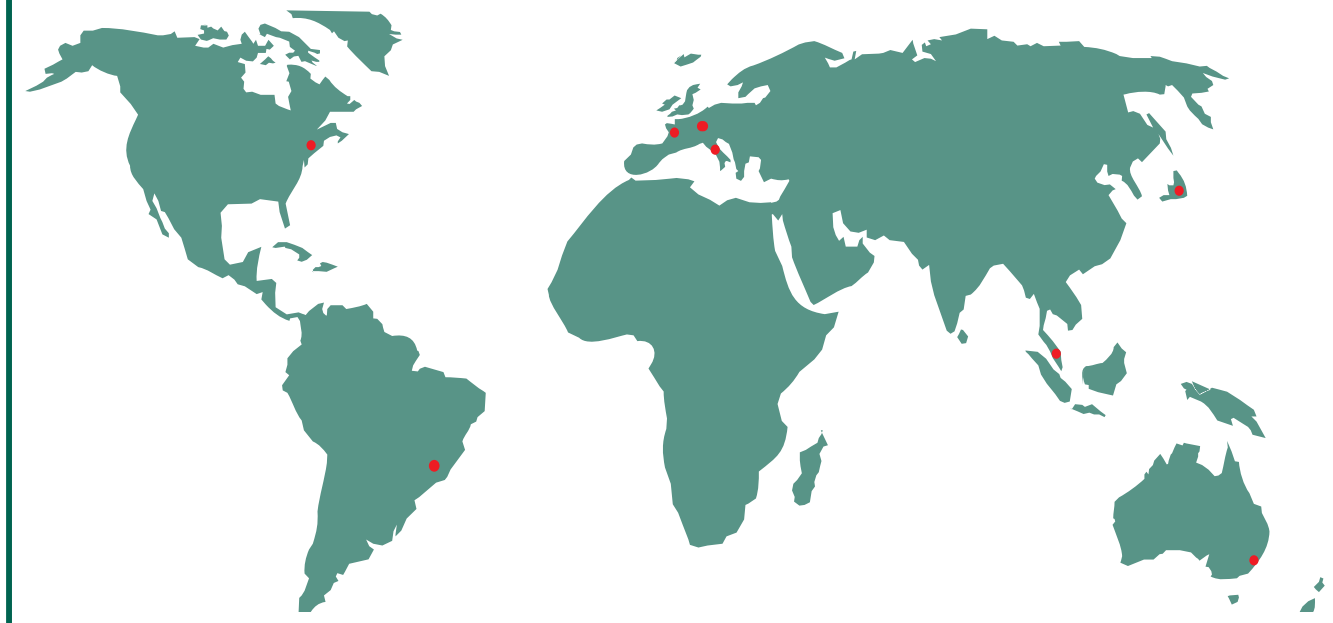


- Validation And Regulatory Support
- Extractable And Compatibility Analysis
- Filter System Optimization Studies
- CUNOCheck[®] 2 Integrity Tester Validation.

For more information regarding CUNO's Validation Support Services, please contact CUNO Technical Services or your local CUNO Distributor.

CUNO ... A World Leader in Fluid Purification

CUNO's manufacturing sites have ISO 9001 registered quality systems. Global manufacturing together with trained stocking distributors and state-of-the-art laboratory support bring quality solutions to existing and challenging filtration applications.



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