

# Custom Resins



## Overview

Occasionally commercially available chromatographic resins from Tosoh Bioscience and other manufacturers do not work efficiently for a given process step. This may delay the production of materials for clinical trials or lead to an inefficient or expensive manufacturing process. Many of our customers have asked for optimization of our existing resins or the development of custom products. Of course, these details are confidential. This section explains in general terms Tosoh's custom resin development procedure.

## Tosoh manufacturing capacity

Tosoh's manufacturing capacity for bulk chromatographic resins is 50,000L per year. If demand for custom resin products continues to grow, Tosoh is prepared to increase production capacity so that there is no impact on its ability to supply all commercial Toyopearl and TSK-GEL bulk resin products.

## Tosoh's Resin Innovation Program (TRIP)

Tosoh Corporation of Japan has introduced a new resin innovation program. Ideal candidates for the TRIP program are drug targets that have been selected for clinical trials which, if successful in the clinic, will be commercially manufactured. This program is not available for early stage laboratory research or the isolation of small amounts of new therapeutic proteins.

## When TRIP is needed

The following circumstances create the need for custom chromatographic and specialty resins:

1. Resin screening for GMP pilot plant production fails to identify an adequate chromatographic product.
2. If the initial resin selection is successful, later expression system optimizations change the impurity profile of the feedstock necessitating resin re-screening with resultant failure to find an adequate chromatographic product.
3. Post approval process reengineering studies point to a new resin to improve process economics.
4. A customer desires for reasons of process economics a custom affinity resin for one step purification.
5. Novel resins are needed for use in bioreactors, synthesis, and other areas, for non-chromatographic applications.

## New project approval for TRIP

Not every customer request receives a "Go" status for TRIP. During the preliminary discussions, prior to the generation of scouting samples, an assessment is made of whether the project fits into Tosoh's core competencies. If a fit is established, the projected liter volume for the new resin is reviewed. Because decisions are based on the quantity projected for use after therapeutic approval and launch, liter volume is normally not a cause for a "No Go" decision at this point in time. For high value added resins, projected commercial liter volumes of less than 100 liters have been approved.

## New resin development time line

Tosoh Bioscience and Tosoh Corporation of Japan have the resources to develop custom resin products parallel with the production of already commercial resins. The custom resin optimization timeline closely mirrors a customer's need to produce products for clinical trials. In most cases, if resin development is delayed, it is because of the inability of a customer to provide sample evaluation data back to Tosoh in a timely manner. Not having this data means that sample chemistry optimizations cannot be made or manufacturing lot release criteria established, thus delaying the actual resin manufacturing at large scale.

## Resin optimization (semi-custom commercial resins)

In many cases the optimization of an already commercial resin can be accomplished by a more judicious selection of particle size, pore size, and currently available ligands (Table I). See the various combinations of these physical parameters in the Toyopearl SEC section of this catalog. When these products are combined with the comparable polymer chemistry TSK-GEL PW-type products (Table II), there are 56 different combinations (Table III) to act as a scaffold for an improved resin product.

Table I

Traditional Chromatographic Ligands	
Anion Exchangers	Diethylaminoethyl (DEAE) Quaternary Anion Exchanger (QAE)
Cation Exchangers	Sulfopropyl (SP) Carboxymethyl (CM) Sulfonic Acid (S)
Hydrophobic Interaction	Hexyl Butyl Phenyl Polypropylene glycol (PPG) Ether

Table II

Tosoh Methacrylic Base Beads used for SEC							
Pore size(Å)	50	125	400-500	750	1000	>1000	>1700
Product name							
Toyopearl HW-Type:	40	50	55	60	65	75	80
TSK-GEL PW-Type:	G1000	G2000	G4000	G5000		G6000	

← Increasing pore surface area

Table III

Available particle and pore size combinations								
Pore Diameter (angstroms)	Particle Size (microns)							
	200	100	75	65	35	30	20	15
>1700		★						
>1200	★	★						
1000		★		★	★	★	★	★
750		★	★	★				
400-500	★	★		★	★	★	★	★
125				★	★			
50	★	★		★	★			
	★ commercial	★ experimental						

**7 x 8 = 56 possible combinations**

### Custom resins

In more difficult situations custom resins can be developed for a customer. Ligand screening, selection, density, length of spacer arm degree of crosslinking and degree of grafting all add to the fundamental engineering of the semi-custom resins. *Table IV* shows the manufacturing parameters available for semi-custom, custom, and one step affinity resin development.

The objective in designing a certain resin is to develop a bead that has maximum accessible surface area with an optimized ligand density using an appropriate spacer arm which fits the conformational attachment requirements of the target. These parameters can have a dramatic effect on the resin's chromatographic and economic performance.

The goal is to create a bead that is optimized for the molecular size of a given therapeutic target.

Table IV

Resin optimization parameters	
Semi-Custom Resins	Polymer Structures Particle Engineering Pore Size Engineering Standard Ligand
Custom Resins	Ligand Selection Ligand Density Spacer Arm Degree of Crosslinking
One Step Affinity Resins	Commercial Ligand Available

### One step affinity resins

For semi-custom and custom resins, most customer resin requests involve the optimization of the more traditional chromatographic modes such as ion exchange and hydrophobic interaction.

In some cases, however, a customer may have identified a commercially available ligand that acts in a very selective (affinity)

mechanism with his target. If this ligand were properly immobilized on a resin bead only the active therapeutic target with perhaps some minor impurities would be captured from the customer's feedstock. This one step process would have significant economic advantages over a multi-step purification.

As described in the affinity section of this catalog Tosoh offers many activated and reactive phases (*Table V*) for the immobilization of molecules from small peptide mimetics to large proteins. When attaching affinity ligands to a support it is important that the ligand be immobilized without destroying its binding sites, with the ligand spaced the optimum distance from the bead itself, and in the correct conformation to access the binding domain of the targeted therapeutic. The breadth of coupling chemistries available from Tosoh give a high probability for the successful creation of a new custom affinity support for a customer.

Table V

Resin chemistries for custom ligand immobilization	
Chemistry	Linkage Type
Carboxy	peptide bond
Amino	peptide bond or secondary amine
Formyl	secondary amine
Epoxy	secondary amine or sulfide
Tresyl	secondary amine or sulfide

### Getting started

To initiate the TRIP program contact your local Business Development Manager.

A period of due diligence will be started where the appropriate information can be exchanged in confidence. Detailed communications on these topics requires an in-effect two way Confidential Information Disclosure Agreement between Tosoh Bioscience LLC and the customer.

If the project looks promising to both parties laboratory samples will be prepared and sent to the customer site for evaluation.

The scouting samples will determine whether simple fine tuning is needed for the custom resin or if additional optimization is required. It is our experience that the rate determining step for the development timeline is the customer's sample evaluation and data feedback.

### Commercialization

Once a "Go" decision is made, the performance specifications are determined from the optimized scouting samples, the custom resin enters into Tosoh's "ISO 9001:2000" product commercialization process. Several small manufacturing batches are then made establish set lot release criteria. Regulatory support studies are initiated at this time.

Many custom and semi-custom resins are based on the polymerization chemistry of the Toyopearl SEC base bead materials and the functionalization chemistries used to make them commercial IEX and HIC products. Regulatory support information on these chemistries has existed since 1990.







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