

**ThermoFisher**  
S C I E N T I F I C

## POROS™ Solvent Reduction

J. Cincotta 25Apr18

# A Mission We are Proud of



We enable our customers to make the world healthier, cleaner and safer.

*life*  
technologies

# POROS™ Chromatography Resin Product Attributes

- **Polystyrene-Divinylbenzene Backbone**

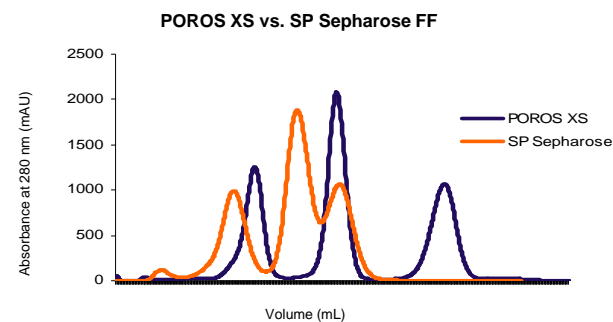
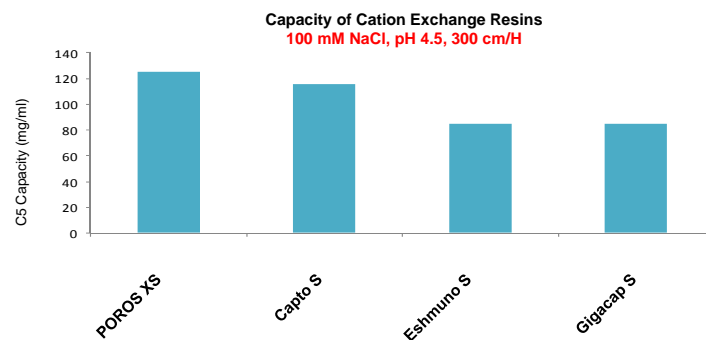
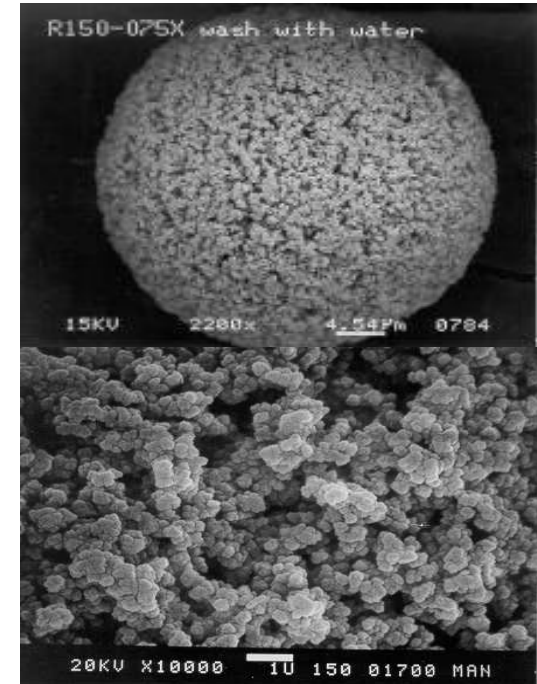
- Rigid, incompressible base bead
- Robust physical and chemical stability

- **Perfusion Chromatography**

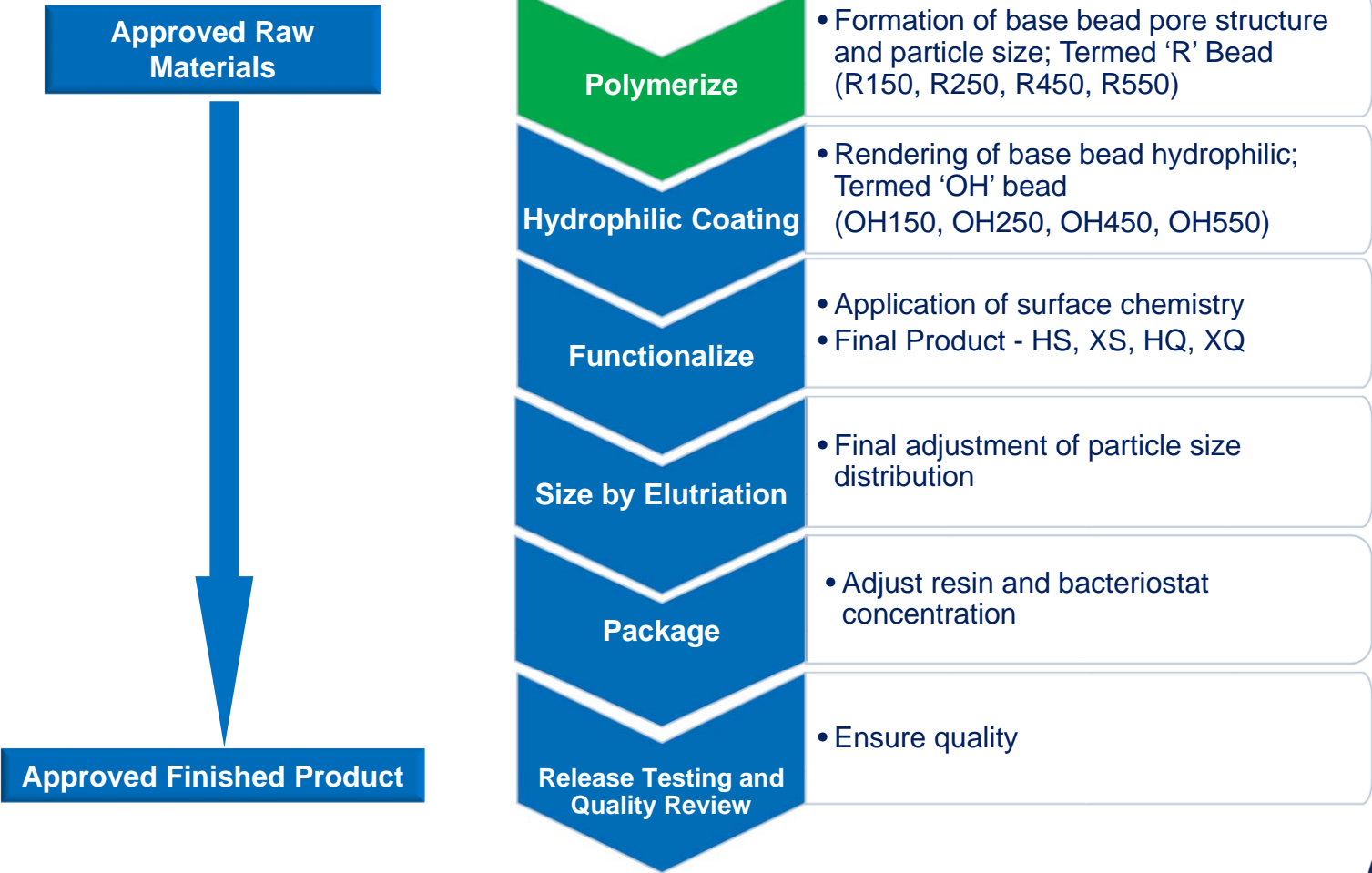
- Pore Structure with Large Throughpores suitable for purification of large biomolecules
- Increased convective flow, reduced diffusional limitations
- Improved mass transfer, more efficient purification

- **50 Micron Particle Size**

- Superior resolution
- Excellent pressure-flow properties



# POROS Manufacturing Process Flow Diagram



# The Opportunity: Solvent Usage in R Product Recovery

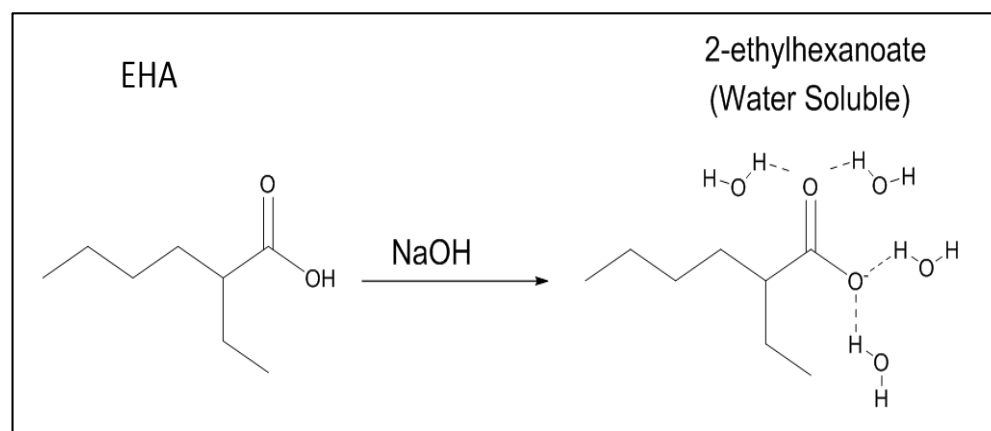
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- Over 2,000L of organic solvent used to wash each batch of our R base beads including acetone, methanol and Tetrahydrofuran (THF)
- Over 150 batches of R manufactured per year
- Total solvent used, and waste produced, is over **300,000L (530,000 pounds)** annually
- Ethylhexanoic Acid (EHA) is the most difficult to remove from the beads



# The Potential Solution:

- Introduce a dilute Sodium Hydroxide wash
- EHA is converted to ethylhexanoate, which is water soluble



- Now the EHA can be removed with water washes instead of organic solvent washes

# Feasibility/Proof of Concept:

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- Lab scale batches produced to test new washing protocol
- Experimentation showed excellent results and suggested a 40% reduction in solvent usage was possible



# Barrier # 1 – Customer Requirements

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- How do we test and implement?
- What are the validation requirements?
- Is customer notification required?
- What additional testing is required to prove no negative impact to the base bead and customer application?





# Overcoming Barrier # 1 – Customer Requirements

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- Cross functional team gathered to determine customer requirements and appropriate validation criteria
  - QA, R&D, MFG, QC, EHS, PdMgmt and Engineering
- Extensive lab and analytical testing to be performed
  - Lab scale control created using old product recovery method
  - Final product functional testing
  - Two extractables tests
- Additional testing allowed us to justify the process improvement and prove no impact to final product quality

# Barrier # 2 – Manufacturing Schedule

- Currently, manufacturing is operating close to full capacity
- Limited time available to schedule validation batches
- Batches must be held to perform additional validation testing, therefore they are unavailable for manufacturing use

2-Apr-18		POROS Suite								
		V-2470 - Hastelloy		V-2460 - Hastelloy		V-2440 - Hastelloy		V-2570 - Hastelloy		
		To	RC	To	RC	To	RC	To	RC	
		Activity	MC	Activity	MC	Activity	MC	Activity	MC	
		at	lbs	at	lbs	at	lbs	at	lbs	
		Assigned		Assigned		Assigned		Assigned		
Monday	10pm	RS-184 - Water Wash	0.5	HS250-432 - Water	0.5	R250-1503 - Filter	0.25	HS250-433 - Water	0.5	
	11pm	RS-184 - Water Wash	0.5	HS250-432 -	1	R250-1503 - Filter	0.25	HS250-433 - Water	0.5	
	12am	RS-184 - Prep	1	HS250-432 -	0.5	R250-1503 - Mat	0.25	HS250-433 - Water	0.5	
	1am	RS-184 -	0.5	HS250-432 -		R250-1503 - Mat	0.25	HS250-433 -	1	
	2am	RS-184 -		HS250-432 -		R250-1503 - Filter		HS250-433 -	0.5	
	3am	RS-184 -		HS250-432 -		R250-1503 - MEQH	0.33	HS250-433 -		
	4am	RS-184 -		HS250-432 -		R250-1503 - Acetone	0.33	HS250-433 -		
	5am	RS-184 -		HS250-432 -		R250-1503 - Filter		HS250-433 -		
	6am	Crosslink		Crosslink				Crosslink		
	7am	RS-184 -		HS250-432 -	0.33	R250-1503 - Filter		HS250-433 -		
	8am	RS-184 -		HS250-432 -	0.33	R250-1503 - THF Wash	0.33	HS250-433 -		
	9am	RS-184 -		HS250-432 - Water	0.25	R250-1503 - THF Wash	0.33	HS250-433 -	0.33	
	10am	RS-184 -		HS250-432 - MEQH	0.75	4206	R250-1503 - MEQH	0.75	4206	4206
	11am	RS-184 -		HS250-432 - MEQH	0.75	4206	R250-1503 - Acetone	0.33	4206	4206
	12pm	RS-184 -		HS250-432 - Water	0.5		R250-1503 - Acetone	0.33	4206	4206
	1pm	RS-184 -		HS250-432 -	0.25		R250-1503 - Filter	0.33	4206	4206
	2pm	RS-184 -		HS250-432 - V-2330	0.5		R250-1503 - Filter	0.33	4206	4206
	3pm	RS-184 -		HS250-432 - W	1		R250-1503 -	1	4206	4206
4pm	RS-184 -		HS250-432 -	0.5		R250-1504 - Transfer	1	4206	4206	
5pm	RS-184 -		HS250-432 -			R250-1504 -		4206	4206	
6pm	RS-184 -		HS250-432 -	0.75		R250-1504 -		4206	4206	
7pm	RS-184 -		HS250-432 -	0.75		R250-1504 -		4206	4206	
8pm	RS-184 - Plug	0.5	HS250-432 -	0.33		R250-1504 -		4206	4206	
9pm	RS-184 - Plug		HS250-432 -			R250-1504 -		4206	4206	
10pm	RS-184 - Plug	0.5	HS250-432 -	0.33		R250-1504 -		4206	4206	
11pm	RS-184 - Water Wash	0.33	HS250-432 -	0.33		R250-1504 -		4206	4206	
12am	RS-184 - Acetone	0.5	2706	HS250-432 - Sulfuric	0.33	R250-1504 -		4206	4206	
1am	RS-184 - Acetone	0.5	2706	HS250-432 - Sulfuric	0.33	R250-1504 - Plug	0.5	4206	4206	
2am	RS-184 - Water Plug	0.33		HS250-432 - Sulfuric	0.33	R250-1504 - Transfer	1	4206	4206	
3am	RS-184 - Water	0.33		HS250-432 - Sulfuric	0.33	R250-1504 -		4206	4206	
4am	RS-184 - Filtration	0.25		HS250-432 - Sulfuric	0.33	R250-1504 -		4206	4206	
5am	RS-184 - X	0.75		HS250-432 - Water	0.33	R250-1504 -		4206	4206	
6am	RS-184 - X	0.75		HS250-432 - Water	0.33	R250-1504 -		4206	4206	
7am	RS-184 - X	0.75		HS250-432 - Sulfuric	0.33	R250-1504 -		4206	4206	
8am	RS-184 - X	0.75		HS250-432 - Plug	0.5	R250-1504 -		4206	4206	
9am	RS-184 -	0.5		HS250-432 - Water	0.33	R250-1504 -		4206	4206	
10am	RS-184 - Washout	1.5		HS250-432 -	1	R250-1504 -		4206	4206	
11am	RS-184 - Nitrogen	1		HS250-432 - Clean	1	R250-1504 -	0.5	4206	4206	
12pm	RS-184 - Ampsa	1		HS250-432 - Clean	1	R250-1504 - Plug	0.5	4206	4206	
1pm	RS-184 - Ampsa	0.33		HS250-432 - Clean	1	R250-1504 - Mat	1	4206	4206	
2pm	RS-184 - Ampsa			HS250-432 - Clean	1	R250-1504 - Mat	0.25	4206	4206	
3pm	RS-184 - Ampsa			HS250-432 - Clean	1	Water Wash		4206	4206	
4pm	RS-184 - Ampsa			OH150-175 - LCR	1.5	R250-1504 - Filter	0.25	4206	4206	
5pm	RS-184 - Ampsa			OH150-175 - OH	0.75	R250-1504 - Mat	0.25	4206	4206	
6pm	RS-184 - Ampsa			OH150-175 - OH	0.75	R250-1504 - Mat	0.25	4206	4206	
7pm	RS-184 - Ampsa			OH150-175 -	1	R250-1504 - Filter		4206	4206	
8pm	RS-184 - Ampsa			OH150-175 - OH	0.5	R250-1504 - MEQH	0.33	4206	4206	
9pm	RS-184 - Ampsa			OH150-175 - OH	0.5	R250-1504 - Acetone	0.33	4206	4206	
10pm	RS-184 - Ampsa			OH150-175 -	0.75	R250-1504 - Filter	0.33	4206	4206	
11pm	RS-184 - Ampsa			OH150-175 -	0.5	R250-1504 - Filter		4206	4206	
12am	RS-184 - Ampsa			OH150-175 -	0.5	R250-1504 - THF Wash	0.33	4206	4206	
1am	RS-184 - Ampsa			OH150-175 -	0.5	R250-1504 - THF Wash	0.33	4206	4206	
2am	RS-184 - Ampsa			OH150-175 -	0.5	R250-1504 - Water	0.33	4206	4206	
3am	RS-184 - Ampsa			OH150-175 -	0.5	R250-1504 - Acetone	0.33	4206	4206	
4am	RS-184 - Ampsa			OH150-175 -	1	R250-1504 - Acetone	0.33	4206	4206	

MFG schedule completely booked



# Overcoming Barrier # 2 – MFG Schedule

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- Showed MFG the potential value of the project to their workcenter –
  - Productivity Savings
  - Cycle Time Reduction
  - No investment required
- Concurrent validation approach approved – release validation batches to MFG as they meet validation criteria
- Scheduled 1<sup>st</sup> validation batch several weeks in advance



## Barrier # 3 – Scale Up and Product Quality

Extractable	R150-946 Conc (ppm)	Validation Specification (ppm)	Pass/Fail
1-Pentanol	229	≤300	Pass
Styrene	169	≤150	Fail
m-EVB	48	≤170	Pass
p-EVB	36		
m-DVB	6		
p-DVB	6		
EHA	1350	≤3000	Pass

- Lab testing showed successful results, however, scale up was not linear
- Organic extractables levels for Styrene failed validation criteria in 1<sup>st</sup> validation batch

# Overcoming Barrier # 3 – Product Quality

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- Re-processing of validation batch 1 was required
- Cross-functional team gathered to determine path forward
- Decision made to add an extra acetone wash to help reduce organic phase extractables
- All validation batches passed extractables and all additional validation criteria thereafter

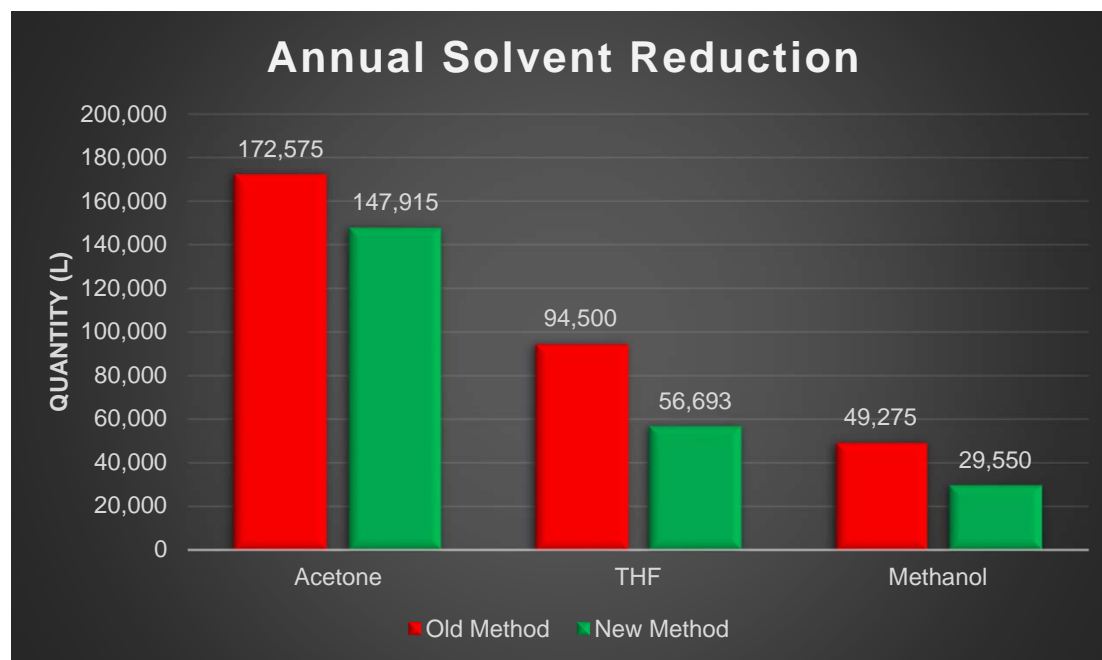
# Overcoming Barriers

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- The keys for us to overcome our barriers were:
  - Develop robust validation plan
  - Present business case
  - Show potential value to stakeholders
  - Plan ahead
  - Work as a team
  - Persevere



# Final Outcome



- Represents a 28% reduction for these processes
- Over 80,000L of organic solvent used and organic waste produced saved per year
- \$218,000 total savings estimated annually
  - \$195,000 in raw material savings
  - \$23,000 in organic waste removal savings





**THANK YOU FOR  
LISTENING**

**DO YOU HAVE ANY  
QUESTIONS?**

