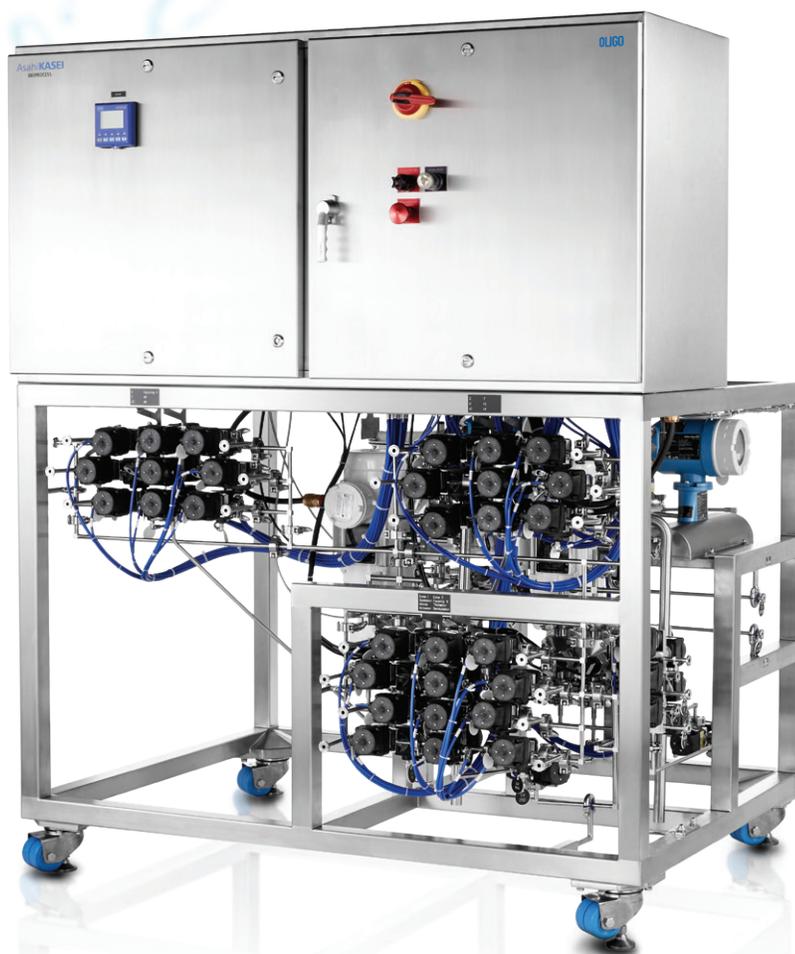


Asahi Oligosynthesizer™

From millimole- to mole-scale solid phase oligonucleotide synthesis



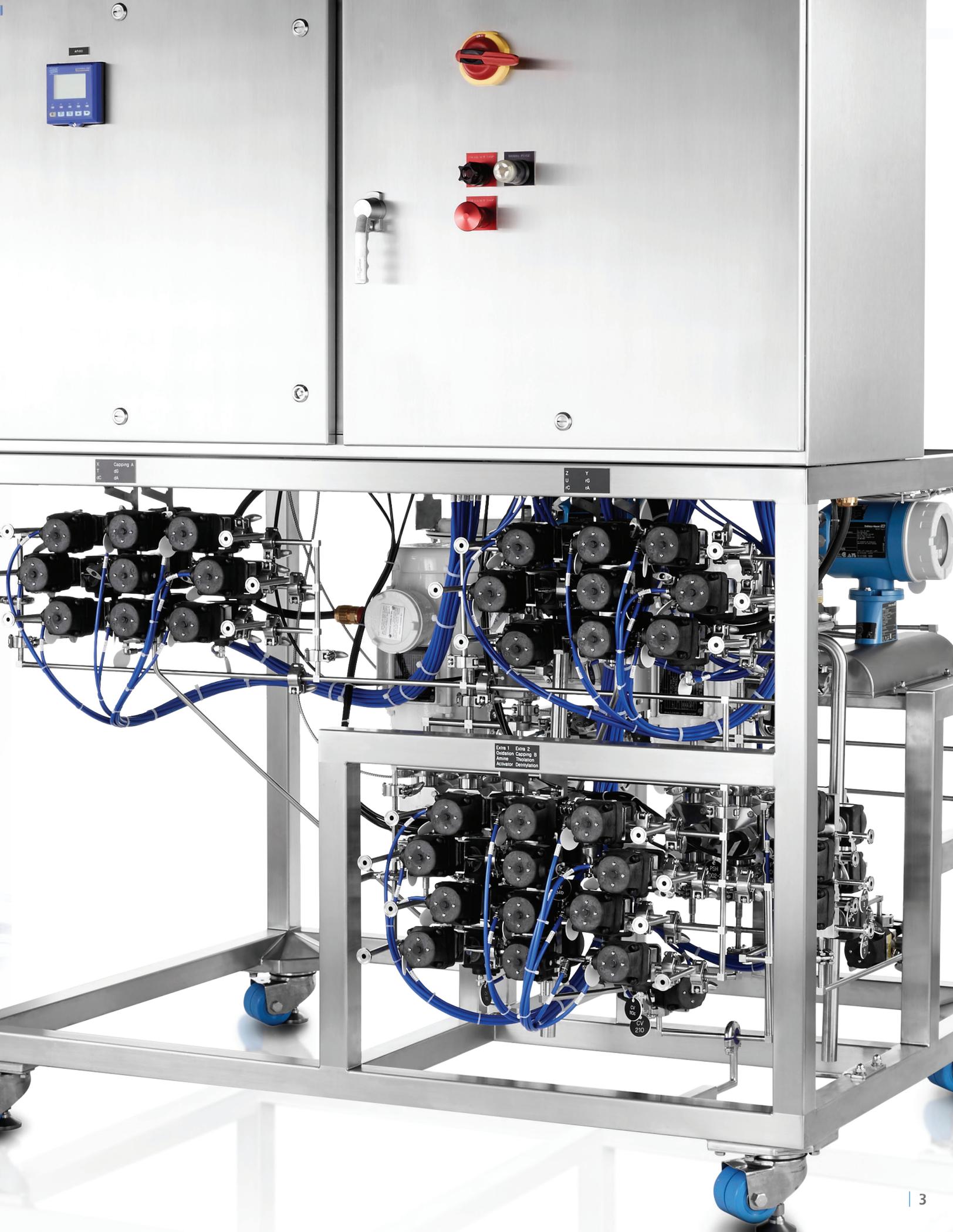
Built For You.

At Asahi Kasei Bioprocess, we bring over a decade of experience to every oligosynthesizer project that we undertake, continually improving our platform as we gain valuable feedback from sponsors and contract manufacturers alike.

This wealth of knowledge allows us to understand that oligonucleotides are a rather unique breed of therapeutic – chemically synthesized, yet much larger in size than classic small molecules. Hence, our engineers employ a hybrid approach when designing manufacturing-scale equipment for oligonucleotides, blending the best of antibody equipment and small molecule equipment design principles together to generate the ideal solution specifically for your oligonucleotide.



The Asahi Oligosynthesizer™ was awarded Patent number EP1714695 by the European Patent Office.



X Clamping A
T d1
C GA

Z Y
U rG
C rA

Exit 1 Exit 2
Oxidation Clamping B
Amine Thiolation
Acetator Demethylation

CV
210

Proven for Mid-Scale and Large-Scale Oligosynthesis

Demand for cGMP oligonucleotides continues to increase as RNA and DNA therapeutics advance through clinical trials. Driven by a desire to reduce manufacturing costs and increase product yields, Asahi Kasei Bioprocess offers a suite of proven solid-phase flow-through Asahi Oligosynthesizer options in the millimole (mmol) to mole (mol) range. Our synthesis technology has produced multiple compounds at various scales, including validation batches. The Asahi Oligosynthesizer™ is ideally paired with our Asahi SCS Column™ or Asahi ACS Column™ and is engineered so that processes can be seamlessly transferred from other oligosynthesizers.

Scalable Oligosynthesis

At Asahi Kasei Bioprocess we take pride in applying good engineering practices when designing your Asahi Oligosynthesizer. After confirming your target linear velocity and column diameter range, we will deliver an Asahi Oligosynthesizer that meets your unique process requirements and ensures seamless scale-up and consistent full-length purity of your oligonucleotide. Figures 1 and 2 show conductivity and UV trends, respectively, from a 40 mmol cGMP batch of RNA synthesis.

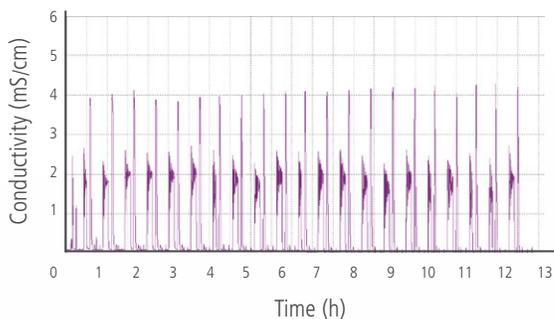


Figure 1. Conductivity through 40 mmol cGMP batch of 21-mer RNA compound.

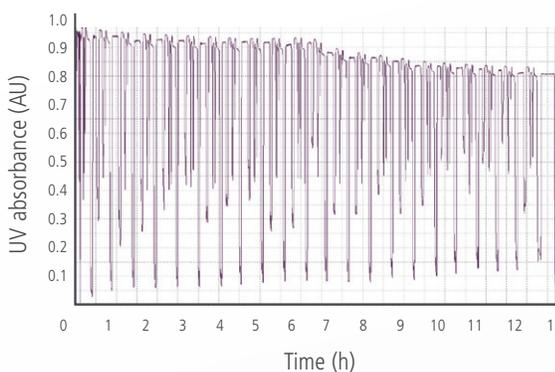


Figure 2. UV absorbance through 40 mmol cGMP batch of 21-mer RNA compound.

Pumps with Hygienic Design, Reliable Metering

The Asahi Oligosynthesizer delivers the monomer and reagent onto the synthesis column via hygienic triple-head diaphragm pumps. These pumps are both mechanically polished and electropolished for enhanced cleanability, further preventing any hold-up of your high value raw materials. The mechanically actuated design with a double diaphragm inherently protects the process solution from contamination because no hydraulic oil is used in the pump, and finally, the triple-head configuration minimizes pulsations seen by the column to improve reaction chemistry.

The standard Asahi Oligosynthesizer has two pumps as shown in Figure 3. One pump is sized for monomer and Capping A delivery, while the second, larger pump is intended for activator, reagent and Capping B delivery. We also custom design oligosynthesizers that include a third pump or even different pump technologies for more flexible large-scale operation.



Hygienic triple-head pump

Engineered Systems with Patented Valve Design

At the core of the Asahi Oligosynthesizer are our patented zero-static (ZS) inlet valve manifolds. Multiple ZS inlet valve manifolds are utilized to congregate the monomer and reagent to the pumps on the Asahi Oligosynthesizer. Developed through computational fluid dynamics modeling, ZS inlet valve manifolds are multiport valves with minimized hold up volume. Carryover of amidite and reagents is reduced, and the manifold is fully cleanable. Thus, you can expect improved full-length purity and reduced wash volume requirements.

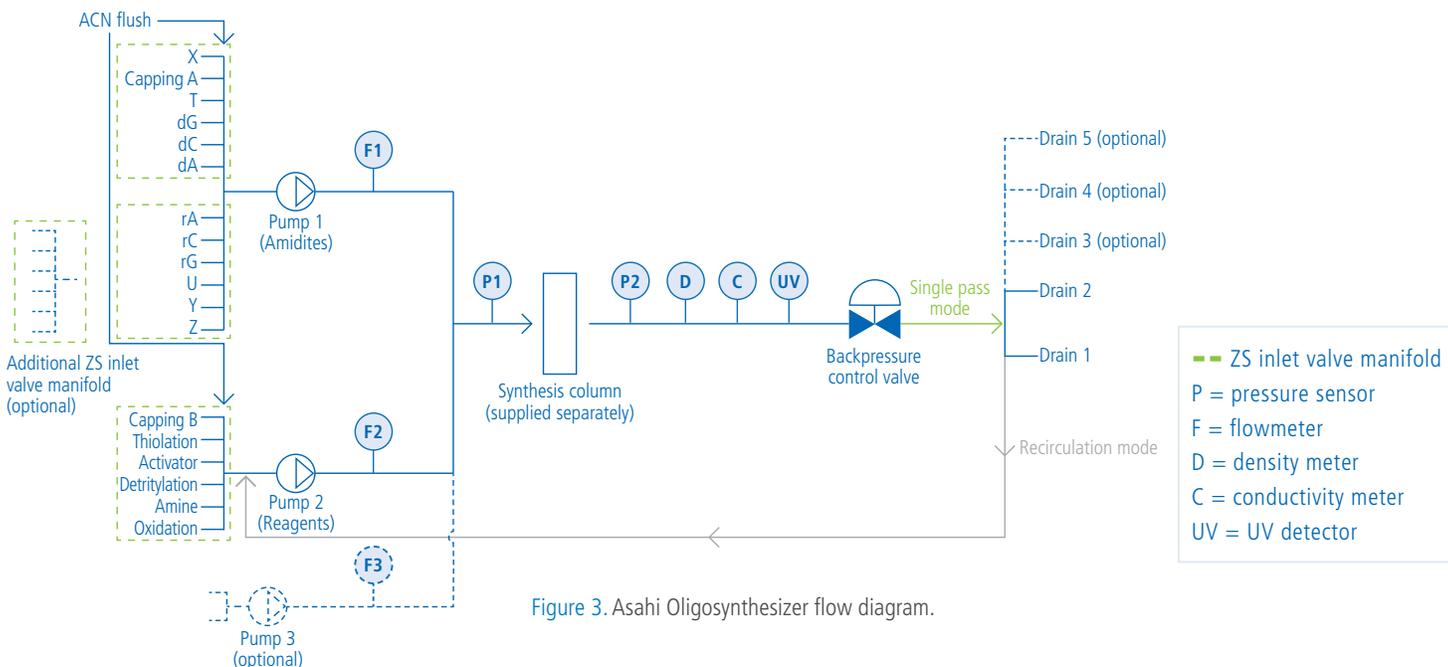


Figure 3. Asahi Oligosynthesizer flow diagram.

Amidites and reagents are supplied to the Asahi Oligosynthesizer inlet ports from vessels (supplied separately) that are typically pressurized to 0.5 to 1 barg pressure. A sterile access valve block is located upstream of each ZS inlet valve. This block contains two valves, labeled a and c in Figure 4. Valve a acts as an isolation valve and as redundant protection to prevent pressurized amidite or reagent from weeping into the ZS manifold when the inlet port is not in use. Only in the extremely unlikely event that both valve a and adjacent valve b fail, could unexpected chemical reach the synthesis column. Valve c routes acetonitrile (ACN) to the ZS inlet port after the amidite/reagent addition to “push” the remaining chemical onto the synthesis column. The ACN push also serves to clear the ZS inlet valve manifold in preparation for the next addition in the oligosynthesis sequence. Inlet valve status is shown in Table 1.

The standard Asahi Oligosynthesizer has two ZS inlet valve manifolds with twelve total amidite inlets and one ZS inlet valve manifold with six reagent inlets. As an option, a fourth ZS inlet valve manifold can be added for a total of twenty-four inlets.

Table 1. Inlet valve status for the Asahi Oligosynthesizer.

Process Step	Valve Status		
	Amidite/reagent valve a	ZS inlet valve b	ACN inlet valve c
Amidite/reagent addition step	open	open	closed
ACN push step	closed	open	open

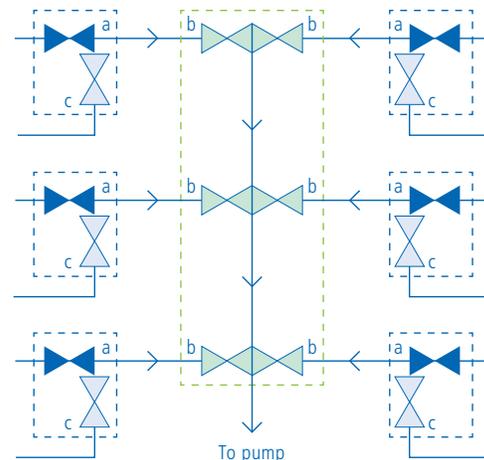


Figure 4. Flow through the sterile access valve block and ZS inlet valve manifold.



Advanced Process Controls



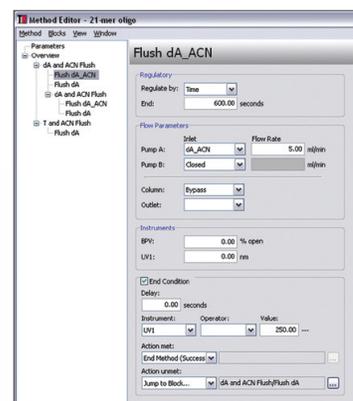
Coriolis mass flowmeter

In order to ensure the highest level of control over the synthesis process, Asahi Oligosynthesizer has various in-process controls. Each pump is monitored and controlled by an independent coriolis mass flowmeter, the most accurate and precise inline flow measurement device available, to ensure that both the flow rate and the total monomer and reagent volume delivery is consistent with programmed set points. Column backpressure can also be controlled through an automated backpressure control valve in order to optimize your synthesis performance. Three different post-column monitors are available. Conductivity monitors are standard on every Asahi Oligosynthesizer, while our advanced Asahi UV detector, capable of monitoring between 190 and 740 nm, is available with a modern ethernet output. Optionally, density measurement is available.

Each synthesis route is configured in our acclaimed Method Editor software, allowing users to easily build “blocks” for each step in the sequence. Blocks are organized in a parent-child format, allowing the user to keep various steps grouped together. Blocks can be copied and pasted, and even imported into and exported out of the Method Editor in XML format, simplifying method creation with less chance of human error.

Each monomer addition can be independently programmed to be applied either as a single-pass addition to the column or in recirculation mode for a given duration or volume, in order to enhance the reaction chemistry.

Different end conditions can also be programmed into the Method Editor. A block may be set to monitor the UV, conductivity or pressure of the product stream and compare it to a user-defined value. If the condition is met, the block will perform the programmed “Action Met” function (for example, proceed to the next block). If the condition is not satisfied within the block time or volume, an “Action Unmet” function will be executed (for example, pause the system).



Method Editor software

Automation Features

- » Manual or automated control
- » Flexible programming of blocks
- » Step regulation by time, volume or column volume
- » Sophisticated end condition monitoring
- » 21CFR Part 11 capability with electronic signature and audit trail
- » Data export
- » OLE (Object linking and embedding) process control (OPC) compatibility
- » Customizable batch reports
- » Optional GAMP-5 lifecycle documentation

Enjoy the Freedom of Customization

The standard Asahi Oligosynthesizer, suitable for typical applications, is available with short lead times. However, we recognize that your unique synthesis processes or multi-product applications may require an instrument that is different than the standard offering. In keeping with our focus on artisanal fluid management, Asahi Kasei Bioprocess has an experienced staff of engineers and designers who will craft you a customized solution based on our standard Asahi Oligosynthesizer platform. Customizable options include the following:

- » Number of inlet ports or outlet ports
- » Third pump for high flow reagent delivery
- » Heat exchangers
- » Software customization
- » Hazardous area ratings (NFPA and ATEX)
- » Modified footprints to fit into tight spaces and within fume hoods

Artisanal Fluid Management



The Equipment Division of Asahi Kasei Bioprocess combines its extensive knowledge of fluid management technology with a passion for oligonucleotide synthesis and dedication to craftsmanship. Our commitment to quality is rooted in the following tenet: expectations of our customers and the expectations of our society shape the quality that we aim to create.

Pair your Asahi Oligosynthesizer with one of our industry-leading Asahi SCS or Asahi ACS columns for a proven, turnkey solution. With Asahi Oligosynthesizer and synthesis column pairings installed across the US, Europe, Korea and China, we invite you to join our growing list of satisfied customers who enjoy the benefits of Artisanal Fluid Management.

Ordering Information

Catalog No.	Product Specification	Pressure Rating	Typical Asahi ACS or SCS Column Pairing
Synth30	3 – 30 mmol*	10 bar	10 – 15 cm i.d. **
Synth100	10 – 100 mmol*	10 bar	10 – 30 cm i.d. **
Synth300	30 – 300 mmol*	10 bar	15 – 50 cm i.d. **
Synth1000	0.1 – 1 mol*	6 bar	30 – 90 cm i.d. **
Synth1500	0.15 – 1.5 mol*	5 bar	30 – 100 cm i.d. **
Synth2500	0.25 – 2.5 mol*	5 bar	30 – 100 cm i.d. **

*Actual synthesis scale is dependent on solid support loading and packed bed height.

**Column pairing is dependent on loading of solid support.

Contact Information

North and South America

Glenview, IL, USA

Tel: +1-847-556-9700

Fax: +1-847-556-9701

Email: info.us@ak-bio.com

Europe

Cologne, Germany

Tel: +49-221-995007-59

Fax: +49-221-9950077-59

Email: info.eu@ak-bio.com

India and Southeast Asia

Mumbai, India

Tel: +91-22-6710-3962

Fax: +91-22-6710-3979

Email: info.jp@ak-bio.com

East Asia and Oceania

Glenview, IL, USA

Tel: +1-847-556-9700

Fax: +1-847-556-9701

Email: info.jp@ak-bio.com

Technical Support and Warranty Information

A reliable technical support network is available throughout the United States, Europe and Asia.

We offer an extendable 1-year warranty, service contracts and a personalized level of service for peace of mind and timely support when you need it.

For more information, please visit:

www.ak-bio.com

Asahi Oligosynthesizer is a trademark of Asahi Kasei Bioprocess America, Inc.

Asahi SCS Column is a trademark of Asahi Kasei Bioprocess America, Inc.

Asahi ACS Column is a trademark of Asahi Kasei Bioprocess America, Inc.

© 2016 Asahi Kasei Bioprocess America, Inc. All rights reserved.

UME91001-2.0