



ADVENT
ENGINEERING
SERVICES, INC.

**Bio-Process & Pharmaceutical
Engineering Services**

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ADVENT Engineering Services, Inc. is a consulting firm providing design level and quality systems engineering services to the biotechnology and pharmaceutical manufacturing community. ADVENT provides a wide array of services supporting various phases of the product lifecycle – from development to clinical scale through large scale commercial manufacturing. Our innovative consulting services cover for process development, scale up, technology transfer capabilities through to equipment design, integrated commissioning-qualification, and process validation. In addition, ADVENT provides engineering for compliance consulting including design review, facility inspection readiness, quality systems remediation, internal audit support and reverse engineering services.

ADVENT SERVICE OFFERINGS:

- Process Development Consulting
- Process Optimization
- Equipment Design & Sizing
- Risk Assessment/Management
- Process/Automation Engineering
- Start-up/Commissioning - Integrated Commissioning & Qualification
- Process Validation
- Analytical Validation
- Technical Writing
- Project Management
- Technical Training
- Compliance Consulting

FACILITIES

- | | |
|---|---------------------------------------|
| • Large Scale Biotechnology Bulk Product Manufacturing | • Vaccine Manufacturing |
| • Pharmaceutical Oral Dosage | • Small-Molecule API |
| • Clinical Manufacturing | • R&D Product Development |
| • Blister Packaging | • Potent Product Manufacturing |
| • Multi-Product Biologics Contract Manufacturing | • Aseptic Fill-Finish |

ENGINEERING

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|---------------------------------------|--|
| • Process Design, Optimization | • Scale-Up/Tech. Transfer |
| • Process Engineering | • Automation Engineering (PLC/DCS/BAS/PC Systems) |
| • Utilities Design | • Specification Development (Requirements and Design) |
| • Start Up/Commissioning | • Project Management |
| • FMEA, Risk Assessment | • Risk Based ICQ |

VALIDATION (CQV)

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|--|---|
| • Analytical Methods Validation | • Controls System Validation |
| • Cleaning Validation | • Regulatory Compliance/Audits |
| • Equipment Qualification | • Risk Assessment |
| • Clean Utilities Qualification | • Pre-Approval Inspection Support |
| • Process Validation | • Project Management/Master Planning |

PROCESS

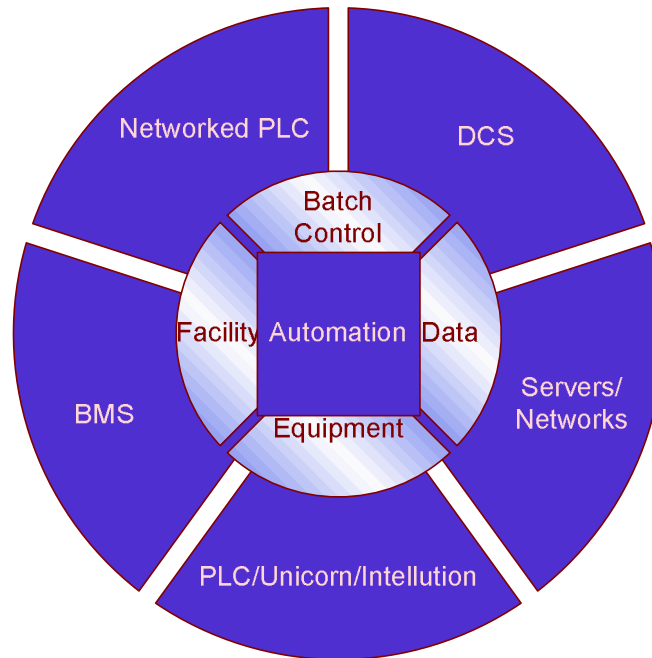
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|--------------------------------------|--|
| • Chromatography/UF-DF | • Lyophilization |
| • Fermentation/Cell Culture | • Mabs, Recombinant Proteins, Vaccines, Factor VIII, Inhalation Solutions, Controlled Release, Oral Dosage, Injectables |
| • CIP/SIP (Cycle Development) | • Fill-Finish Equipment |
| • Washers | • Autoclaves |
| • Aseptic Processes | • Centrifugation/Seperation |

HVAC

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| • Class 100, 10000, 100000 Rooms | • Aseptic Fill-Finish |
| • Design Review | • AHU Controls (CV & VAV-VFD) |
| • Isolator-Barrier Technology | • BMS |

CLEAN UTILITIES

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| • Purified Water Systems (Pre-Treatment-RO-CDI w/ Heat/Ozonation or HotPW) | • Water for Injection Systems (Multi-Effect Stills) |
| • Clean Gases (Compressed Air, Nitrogen, CO₂) | • Pure Steam Systems (Generation & Distribution Systems) |
| • Chilled Water/Glycol for PW/WFI, HVAC-Cooling Coils | • Plant Steam for PW/WFI/Pure Steam, HVAC-Reheat |
| • Start Up/Commissioning | • Project Management |
| • IQ/OQ/PQ | • Standards Development – SOP/PM |



AUTOMATION SYSTEMS

- | | |
|---|---|
| <ul style="list-style-type: none"> • Unicorn Systems | <ul style="list-style-type: none"> • PLC-PC (Wonderware, Intellution) |
| <ul style="list-style-type: none"> • DCS (MOD-300, Delta V) for Batch Control (S88) | <ul style="list-style-type: none"> • BMS (Siemens, Johnson Controls, Andover, ThermoSys.) |
| <ul style="list-style-type: none"> • PLCs (Networked & Stand-Alone) | <ul style="list-style-type: none"> • SCADA |

AUTOMATION CAPABILITIES

- | | |
|--|---|
| <ul style="list-style-type: none"> • Structured Risk Assessment (E-Records & E-Signatures) | <ul style="list-style-type: none"> • Specification Development (URS/FS, SDS, HDS) |
| <ul style="list-style-type: none"> • Traceability Matrices | <ul style="list-style-type: none"> • Start up/Commissioning |
| <ul style="list-style-type: none"> • Design Testing/Engineering Check-Out | <ul style="list-style-type: none"> • Computer/Automation Qualification |
| <ul style="list-style-type: none"> • Programming (PLC/Taylor Control Logic) | <ul style="list-style-type: none"> • Instrumentation (Loop Testing) |

BUSINESS HIGHLIGHTS

- | | |
|--|---|
| <ul style="list-style-type: none">• Corporation (CA State) | <ul style="list-style-type: none">• Focus: Nuclear Energy & Bio-Pharma Regulated Industries |
| <ul style="list-style-type: none">• Providing Engineering Services for > 20 Years (Incepted in 1988) | <ul style="list-style-type: none">• Operations/Projects in USA, Canada, Ireland, Europe, Japan, Singapore, India |
| <ul style="list-style-type: none">• 45 Staff Engineers | <ul style="list-style-type: none">• Licensed Engineers |

ADVENT's professional staff is primarily comprised of Engineers from various disciplines (Civil, Mechanical, Chemical, and Electrical). Most of our engineers are Process Engineers, many of whom possess professional licenses or advanced degrees. Our engineering base allows for a competent staff with the ability to add value to any project; whether it involves process development, engineering, qualification, or regulatory compliance. ADVENT personnel have published/presented over 30 technical papers in journals and industry-wide forums including:

Presentations & Publications

- ACS National Meetings
- AIChE Annual Meetings
- CASSS Annual Meeting
- Biotechnology Progress
- Chemical Engineering Journal
- Chemical Engineering Science
- Electrophoresis Expression
- Protein and Purification
- ASCE Engineering Mechanics Specialty Conference
- ASME Pressure Vessel and Piping Conference
- International Journal for Numerical and Analytical Methods in Geomechanics
- International Journal of Heat and Mass Transfer
- Proceedings of the International Conference on Computational Engineering Science

Novel Approaches in Engineering, Commissioning, & Validation for Biotechnology

- Integrating Risk Assessment into Validation Planning
- Practical Risk Assessment Techniques for API Processes
- System Suitability in the Quality Assessment of Cell-Based Bioassay
- Approach to Equipment Validation for Clinical Manufacturing
- Reverse Engineering: A First-to-Market Means to Compliance
- Application of Risk Assessment to Minimizing Qualification Costs for Temperature controlled Chambers
- Cleaning Validation in Contract cGMP API Manufacturing: Analytical Optimization
- Statistical analyses in Pharmaceuticals and Biotechnology
- Thermocouples: Fundamentals and validation issues
- Chromatography Column Packing studies
- Antibody Purification: Affinity Chromatography and other techniques
- Overview of Analytical methods for Biotechnological and Pharmaceutical industries.

ADVENT's client list includes the industry's leading companies, both on the east and west coast of the US. The following is a list of the clients to which ADVENT has provided long lasting, cost-effective engineering and validation services.

CLIENTS	
 Abgenix Fremont, CA	 DURECT Cupertino, CA
 ADVANCIS PHARMACEUTICAL CORP™ Puerto Rico, Ireland	FIBROGEN South San Francisco, CA
 AMGEN Dramatically Improving People's Lives Longmont, CO	Genentech In Business for Life SSF, Vacaville, Hillsboro, Singapore, Oceanside
 ARADIGM ADVANCING DRUG DELIVERY Hayward, CA	MiddleBrook PHARMACEUTICALS™ Ireland
 barr Laboratories, Inc. Making medicines work for everyone™ OH, VA, NJ	 NC STATE UNIVERSITY Raleigh, NC

 <p>Bayer</p> <p>Berkley, CA and RTP, NC</p>	 <p>NOVARTIS</p> <p>Holly Springs, NC</p>
 <p>Baxter</p> <p>Glendale, CA Hayward, CA</p>	 <p>PLIVA <i>A member of the Barr Group</i></p> <p>Zagreb, Croatia</p>
 <p>BIOMARIN PHARMACEUTICAL</p> <p>Novato CA</p>	 <p>sanofi pasteur <i>The vaccines business of sanofi-aventis Group</i></p> <p>Swiftwater, PA & Toronto, Canada</p>
 <p>CHIRON</p> <p>Emeryville, CA</p>	 <p>Talecris BIOTHERAPEUTICS</p> <p>RTP, NC</p>
 <p>COVANCE THE DEVELOPMENT SERVICES COMPANY</p> <p>RTP, NC</p>	 <p>Teikoku Pharma USA, Inc.</p> <p>San Jose, CA</p>
 <p>DIOSYNTH Active Pharmaceutical Ingredients</p> <p>RTP, NC</p>	 <p>Wyeth</p> <p>Sanford, NC</p>

ADVENT measures its success on the basis of customer satisfaction. Our core values place our clients' interest at the center of focus. How our clients perceive our performance is the only true indication of our value to them. Here are some of their comments:

A senior validation manager at Diosynth, RTP reported:

You not only provided Diosynth with technical, professional, and compliance leadership, but also provided lessons on what the expectations are in the Industry. Your patience, perseverance, and knowledge, has put the project where it needs to be today. Your impact for me and the company was not only a "validation job", but a valuable learning experience!

A senior director of quality at Genentech said of Advent staff:

Our process operational testing for process equipment pioneered by *ADVENT Staff* is now a key element of our innovative validation program for multi-use equipment.

A vice-president and senior director at Bayer said in a recommendation of one of Advent's staff:

Performed excellent under extreme time constraints.

A senior scientist at Abgenix said:

ADVENT staff demonstrated expertise in the different aspects of large scale manufacturing systems. They developed advanced systems that provide high-quality, rapid and cost-effective approaches to analytical characterization, process capability demonstration, and equipment cleaning methodologies for commercial antibody production.

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
Analytical Equipment	<ul style="list-style-type: none"> • TOC Analyzers • Spectrophotometers - UV-Vis, FT-IR, mass spectrophotometers • BIACore 3000 bimolecular interaction analyzers • Flex Stations • Capillary Electrophoresis
Analytical Method Validation	<ul style="list-style-type: none"> • pH & osmolality • Protein concentration A280 • TOC Method determination – LOQ determination • Binding Assays for Pro A using ELISA
Analytical Method Qualification	<ul style="list-style-type: none"> • Chemical Assays – SDS Page • Binding Assays – ELISA • Chromatographic Assays – CEX, SEC
Autoclave	<ul style="list-style-type: none"> • Fedegari (IOQ, PQ, RQ) • Finn Aqua/Steris (IOQ, PQ, RQ) • Dry Heat Oven (Bayer)
Bioreactors	<ul style="list-style-type: none"> • 1500 & 5000 L Commissioning & Qualification • 100, 500 & 2000 L Design Specifications

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
<p>Centrifuges, Chromatography, TFF & UF/DF</p>	<ul style="list-style-type: none"> • Control System Software OQ (Pharmacia-Unicorn, AKTA & DCS) • IQ/OQ/PQ (Millipore-Prostak, Pellicon) • IQ/OQ/PQ (Pharmacia AKTA) • Cleaning Validation • 0.5”-1.5” TFF Systems • Filter Validation
<p>Controlled Temperature Environment</p>	<ul style="list-style-type: none"> • Cold Rooms • LN2 Freezers (RQ) • CO2 Freezers • Incubator • Rate Controlled Freezer – Cell Banking
<p>Depyrogenation Tunnel</p>	<ul style="list-style-type: none"> • Tunnel Sterilizer (IOQ, RQ) • Dry Heat Oven
<p>Fermentor</p>	<ul style="list-style-type: none"> • Cleaning, SIP • IQ/OQ/PQ • Modifications & Automation
<p>Lyophilizer</p>	<ul style="list-style-type: none"> • Stokes Lyophilizer (Full Upgrade) • BOC Edwards Lyophilizer (IQ/OQ/PQ, Cleaning Validation, RQ) • Stokes Lyophilizer (RQ)

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
Parts Washer	<ul style="list-style-type: none"> • Huebsh Stopper Washer (RQ, PQ) • Stopper Processors ICOS, SMEJA, Huber • Hamo T- 410/T-420/Getinge • Belimed (IOQ)
Pasteurizers, Viral Inactivation	<ul style="list-style-type: none"> • Thermal Mapping and Insulation Verification, IQ, OQ, PQ
HVAC Systems	<ul style="list-style-type: none"> • IQ (Instrumentation, Air Handling Units) • OQ (Air/Water Balance, Pressurization, Control) • PQ (Room, Temperature/RH/DPT)
Purification Suite	<ul style="list-style-type: none"> • IQ, OQ, PQ of chromatography & UF/DF skid, thaw tank, viral inactivation tank, and carts & transfer lines
Sterility Isolators	<ul style="list-style-type: none"> • Laboratory Modification including equipment installation, SAT, IQ, OQ • Skan AG (SAT, IOQ)
Vial Washer	<ul style="list-style-type: none"> • Vial Washer (IOQ, RQ) • Glass Washer (IOQ)

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
Column Packing Skid	<ul style="list-style-type: none"> • Process development studies
Cleaning Cycle Development	<ul style="list-style-type: none"> • 400L NBS Fermentor & associated equipment CIP cycle development • MPC CIP Skid • Open Top Vessels
Building Automation System	<ul style="list-style-type: none"> • Johnson Controls • Andover Controls, • Siemens and Voltec
DCS System	<ul style="list-style-type: none"> • ABB ADVANT 300 IQ/OQ/PQ • ABB MOD 300
CIP System	<ul style="list-style-type: none"> • Cycle Development • User Training • Circuit Qualification • CIP Abort Mitigation • CIP IQ/OQ/PQ (Re-circulation & Once-thru)
Clinical Manufacturing Facility	<ul style="list-style-type: none"> • Fermentor, transfer lines, media exchange IQ,OQ,PQ
Design Review/Failure Analysis	<ul style="list-style-type: none"> • HAZOP/FMEA Study of engineering project • Contamination investigation • Root cause analysis

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
Hold Studies	<ul style="list-style-type: none"> • Buffer Hold Studies • Intermediate Process Hold Studies • Clean & Dirty Hold Methodology & Studies
Clean Utilities	<ul style="list-style-type: none"> • HWFI CWFI Capacity Studies • PW/WFI System Design & Validation • Clean/Pure Steam (Steris, Pyropure) • US Filter Reverse Osmosis IQ, OQ PQ • Finn Aqua Multi Effect Still IQ, OQ, PQ • Water hammer mitigation, minimum flow return criteria, automatic valve prioritization • Clean Gases
Training	<ul style="list-style-type: none"> • CIP System • Lyophilizer Operation
Automation	<ul style="list-style-type: none"> • PLCs • Microprocessor Controllers • Taylor Control Logic (TCLs) • BAS/DCS Systems • CFR Part 11 (Computer Validation Master Plans/ Gap Analysis) • Custom spreadsheets/databases • Servers/Networks/Data-highways/RIOs/Virtual IOs • PC Workstations/OS/Support Utility Software • Custom Of The Shelf (COTS) Software • Patented PLC Security Module Technology • Computer Compliance and Remediation • Risk Assessment Implementation and Training • Aegis Translational Analysis - Selection

EQUIPMENT/PROCESS /FACILITY	EXPERIENCE
Aseptic Filling	<ul style="list-style-type: none">• Vial and Pre-Filled Syringe Line Qualification• Isolator Technology Selection & Design Review• Process Engineering Management for New Green Field Fill/Finish Facility• Validation Master Planning & Risk Assessment for Aseptic Fill/Finish Facility• Design Qualification for Vial & Pre-Filled Syringe Expansion Facility• VHP Sterilization• Clean Room to Isolator Technology Transition
Packaging	<ul style="list-style-type: none">• Labelers• Handle, Tablet, Bottle Feeders• Ultrasonic Welders• Assembly Robots• Check-weighers• Cartoners• Vision Systems and Monitoring• Printers

CLIENT	PROJECTS
ABGENIX	<ul style="list-style-type: none">• Analytical Method Qualification & Validation• Analytical Equipment Validation• Process Validation• Cleaning Validation – cell culture, media prep/hold, purification and clean/dirty hold equipment• Project Management
ADVANCIS PHARMACEUTICAL	<ul style="list-style-type: none">• MG Futura Encapsulator Qualification• Sustained Release Antibiotic Manufacturing Expansion Facility Commissioning & Qualification
AMGEN	<ul style="list-style-type: none">• Cleaning Validation, Process Equipment
ARADIGM	<ul style="list-style-type: none">• Facility and Equipment Validation for Drug Delivery Products
BARR LABS	<ul style="list-style-type: none">• Vaccine Facility PM & Validation• Equipment Validation (Tableting, Glass Washer)• Utility Validation (Clean Steam, CDA, WPU)• Blister Packaging Equipment Validation• Building Automation Systems Integration & Validation• Computer and Part 11 Remediation & Validation• Validation Department Management• Site Master File Development
BAXTER	<ul style="list-style-type: none">• Fractionation Facility As-built P&ID Development• As-built PFD Development• Utilities and Cold Room Validation

CLIENT	PROJECTS
<p>BAYER</p>	<ul style="list-style-type: none"> • Lyophilizer Validation IQ/OQ/PD/PQ • Facility Reverse Engineering and As-found IQ/OQ • CIP Control System Validation • Process Equipment Commissioning and Validation • Requalification Program 2000, 2001, 2003 • Perfusion Fermentor System Commissioning • Licensing Support for Purification Process • UF/DF Cleaning Validation • Chromatography Skid Validation • Assessment of UNICORN computer systems for 21 CFR part 11 compliance • Development of User Requirement Specifications, AKTA Chromatography Skids • Development of Functional Requirement and Design Specifications, AKTA Chromatography Skids • Development, execution and closure of multiple IQ, OQ and PQ Protocols, AKTA Chromatography Skids. • Buffer stability studies • Process Intermediate Hold Studies • Preventive Maintenance SOP Development • Purified Water System Design • Purification Area HAZOP
<p>BIOMARIN PHARMACEUTICALS</p>	<ul style="list-style-type: none"> • Process Equipment Validation, Aldurazyme Project
<p>CHIRON, INC.</p>	<ul style="list-style-type: none"> • Column Packing Studies, Millipore Chromaflow Column

CLIENT	PROJECTS
COVANCE BIOTECHNOLOGY	<ul style="list-style-type: none">• Specification Documentation and Process Equipment Validation• Design Specification Documentation for CIP Systems• CIP Cycle Development
DIOSYNTH	<ul style="list-style-type: none">• ABB DCS TCL Automation Validation• ABB 800xA DCS Validation• Buffer Hold & CIP Commissioning & Qualification• Validation of Laboratory Analytical Equipment• Validation of Various Bio-pharmaceutical Purification Systems• Purification Suite Equipment & Controls IQ/OQ/PQ• Process Validation for CIP and SIP systems• DCS Controls Qualification• Validation of a new Water for Injection (WFI) System• New Purified Water System Process Engineering• Raw Data Server Design & Validation• Project Management• Internal Audit Preparation & Gap Closure• Facility Shutdown – Commissioning & Qualification
DURECT	<ul style="list-style-type: none">• Facility and Equipment Validation Master Plan for Drug Delivery System
FIBROGEN	<ul style="list-style-type: none">• Fermentor CIP & SIP Cycle Development

CLIENT	PROJECTS
GENENTECH	<ul style="list-style-type: none">• Revalidation Program (Lyophilizer, Vial Washer, Autoclaves, Cold Rooms, Freezers, Dry heat Oven)• Clinical Manufacturing Facility (CMF) Validation• Rituxan, C2B8, TKN, HER2, NGF, Enbrel, Process Equipment Validation• Legacy Systems Freezer Validation (Risk Based)• Shipping Validation• Control System Software Support• CIP Chemical Change-Over Study (GPMF)• GPMF Freeze Thaw Skid Validation• CD11A Filling Process Qualification• Stopper Silicone Uniformity Study in Stopper Processors (Fedegari and ICOS)• Fill/Finish Facility Equipment Validation• Fill/Finish Facility Engineering & Commissioning Management
MIDDLEBROOK PHARMACEUTICALS	<ul style="list-style-type: none">• Ackley Variable Ramp Printer Qualification
NC STATE UNIVERSITY	<ul style="list-style-type: none">• CIP System Design Review and Retrofit Design
NOVARTIS V&D	<ul style="list-style-type: none">• New Vaccine Campus Expansion – C&Q Lead• Bulk Manufacturing Process Systems – C&Q• Chemical Process – C&Q• Technology Development & Transfer

CLIENT	PROJECTS
PLIVA	<ul style="list-style-type: none">• New Multi-Product Biotechnology API Manufacturing Facility Design Review and Qualification• New Vial and Syringe Filling Facility Design Review and Qualification• New Sterile Chemical Synthesis API Manufacturing Design Review and Qualification
SANOPI PASTEUR	<ul style="list-style-type: none">• Vaccine Expansion – Downstream Process Lead• Vaccine Facility Expansion - Commissioning• New Fermentation Train and CIP Construction & Commissioning Project• New Tank Purchase - Engineering Support• Centrifuge Operation - Ethanol Waste Assessment• Startup and Commissioning Support for a Fermentation Facility Retrofit• Stationary Tank - Evaluation to Global Engineering Guidelines
TALECRIS BIOTHERAPEUTICS	<ul style="list-style-type: none">• Unicorn Software and ÄKTA Explorer Chromatography Systems Commissioning & Qualification
TEIKOKU	<ul style="list-style-type: none">• Process Review - Pilot Plant (Sterile Manufacturing)• Sterilization Process Review• Aseptic Process Change - Cost Analysis

CLIENT	PROJECTS
WYETH VACCINES	<ul style="list-style-type: none">• Fermentor, CIP & DCS Modifications• CIP Cycle Development• Cleaning Validation (MPC CIP skid with portable process vessels and process hoses)• Washer Cleaning Validation, Hamo T-420 and Getinge• Fedegari Autoclave Validation• COP of Open Top Vessels• Lyophilizer Qualification & Cleaning Validation• Getinge Washer FAT• UF Filter Validation• Ultra Filtration Skids Equipment Qualification• Disinfectant Validation