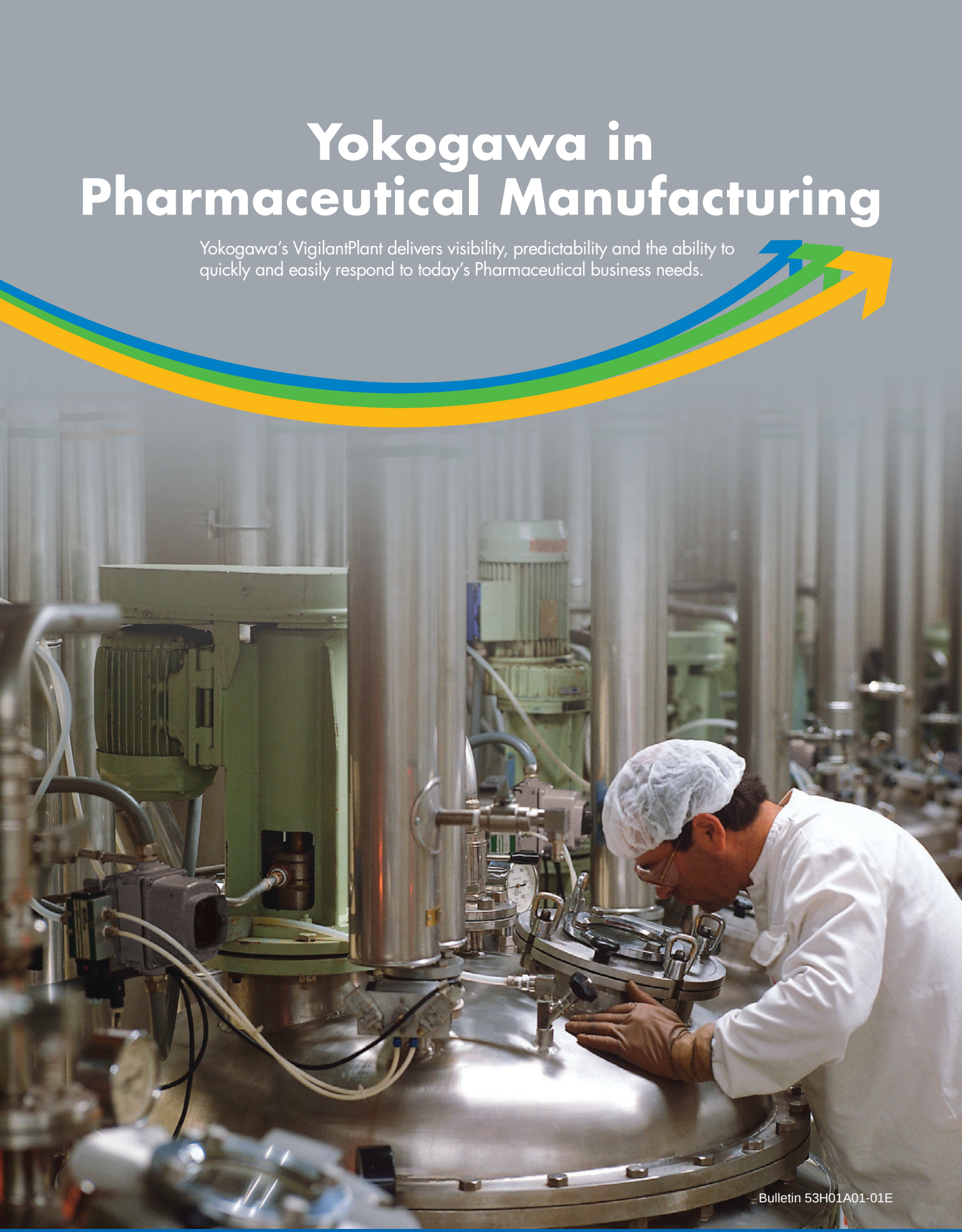
Yokogawa in Pharmaceutical Manufacturing

Yokogawa's VigilantPlant delivers visibility, predictability and the ability to quickly and easily respond to today's Pharmaceutical business needs.



Bulletin 53H01A01-01E

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The clear path to operational excellence

YOKOGAWA

vigilantplant.®

The clear path to operational excellence

Envision a plant where people are watchful and attentive while your business responds to change quickly and efficiently. Now picture an operation that delivers consistent production, real-time information and accurately controlled and safe processes that comply to the regulatory and demanding requirements of the pharmaceutical industry.

Imagine no further. This is the vision and promise behind VigilantPlant, the clear path to right the first time operational excellence.

20,000L Bioreactor at Lonza Biologics Inc., Portsmouth, NH (USA)

Making critical plant information fully visible is just the beginning of the vigilant cycle.

Seeing clearly gives you the knowledge necessary to anticipate changes required to understand the variability in your process. Knowing in advance brings you the speed and flexibility to optimize your plant in real-time. And by acting with agility, you are able to adapt to the variability of the process to enable your business to benefit from improved consistency and product quality.

VigilantPlant excels at bringing out the best in your plant and your people – keeping them fully aware, well informed, and ready to face the next challenge.

ACT WITH AGILITY

Free of bottlenecks

Reduce delays, lost opportunities, knowledge silos

SEE CLEARLY

Less blind spots

Avoid guesswork, instability, sub-optimization

Minimize reactive measures, unexpected downtime, quality variations

Fewer surprises

KNOW IN ADVANCE

Be secure in the knowledge that your control system meets all regulatory requirements

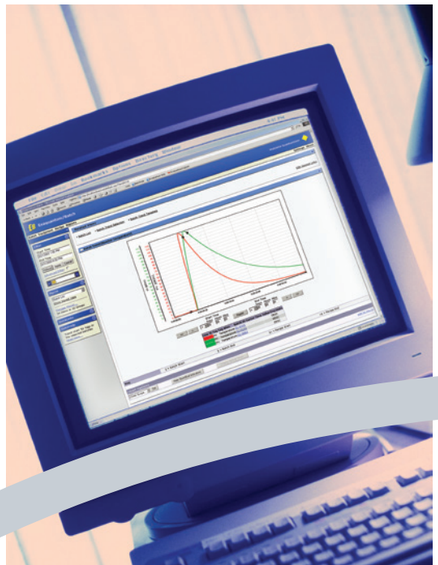
The plant's alert approach to operation, maintenance and information is obvious. Operators are calm and in control. Managers are well informed, but never overwhelmed with data. All facilities are validated and under control, ready for internal audits and inspections by regulatory authorities. At the same time potential problems are anticipated before they happen. All this in a day in the life of operating a VigilantPlant.

Batch operations run to order, are clearly visible and are totally reliable

At 07:00 the plant operators are ready to start the first batch of the shift. The previous shift's completed batches are ready for release and the currently executing batches are handed over without a hitch.

The control and safety systems automate the whole process so as to maximize throughput in the most efficient and safest manner possible.

The plant's information system is used to enable on-line data analysis and to compare current and previous batches. This information is paramount in enabling operators and other plant personnel to subsequently increase plant utilization, improve product quality and manufacturing efficiency.



Batches are run to optimize the use of resources on all levels

A fault on one of the reactor vessels has meant that batches need to run in a different order.

A previously validated and approved recipe is loaded from the control system's recipe manager and the system is ready to continue processing the next batch.

The complex plant is controlled via Yokogawa's highly developed batch software that is based upon the ISA-88 (IEC 61512) Batch standard.

An on-line Near-Infrared (NIR) Analyzer is used to measure the composition of the product to ensure consistent product quality in line with the FDA's Process Analytical Technology (PAT) initiative.

A dynamic alarm monitoring system sets alarm values depending upon the recipe being run and present plant status.
All plant information is gathered for audit purposes to help users comply with the FDA's 21 CFR Part 11 regulations on Electronic Records and Electronic Signatures.

Maximize your assets and be sure your plant is safe

In today's world, predictive maintenance and the ability to foresee problems in advance saves on plant down-time and protects your investment.

Quietly in the background the system is monitoring your assets. The smart instrumentation is connected via a digital network, providing data that is used to create predictive diagnostic information as well as the connected process with all plant systems. Through the unified architecture, asset information for the whole plant is gathered and made available for operations and maintenance personnel.

Maintenance staff are thereby informed of upcoming failures and can take the necessary preventative action. Changes to instrumentation can be made remotely, with changes recorded for audit trail purposes.

In the control room operators receive rich diagnostic information from the intelligent digital devices.

Continuous improvement is a reality not a dream

While dispensary personnel are accessing the recipe inventory lists, the plant manager accesses data from his PC, all of which are provided through the plant's thoroughly integrated and secure management information system.

From here, plant engineers can easily compare previous and current batches can be easily compared against each other via Gantt charts and other graphical means to showing incredibly detailed batch information.

From this vital information the plant manager is able to identify bottlenecks in the system and thus understand how to improve recipes and sequences of operation for plant optimization leading to continuous operational improvement and the ultimate 'Golden Batch'.

This is the way all plants should run - allowing you to See Clearly, Know in Advance, and Act with Agility. It should run like a VigilantPlant.

Real Stories in the Pharmaceutical Industry

EVONIK INDUSTRIES

Project reference

Germany

Evonik Technochemie is a custom synthesis specialist in Dossenheim, Germany, where it operates a plant that produces pharmaceutical intermediates and active ingredients. In line with Evonik's focus on the pharmaceutical business, and due also to the reason that this plant was operating at capacity limits, the company decided in 2008 to build a second active ingredient plant in Dossenheim. Key technical requirements for the new facility included the need to comply with Good Automated Manufacturing Practice (GAMP) and to have greater flexibility in active ingredient production, which is mainly sequentially controlled.

To control production operations at this new facility, Evonik selected Yokogawa's CENTUM VP production control system and the CENTUM VP Batch recipe management package. Although it has been used as a single-purpose facility, the Dossenheim plant was originally intended to be a multi-purpose facility and has space available for future expansion. The CENTUM VP production control system

Evonik
Control System

- CENTUM VP
- 3 Operator Stations
- 2 Field Control Stations
- 800 I/O
- VP Batch

has all the capabilities for handling multi-purpose operations. To accommodate the very tight production schedules of these processes, the CENTUM VP Batch recipe management package gives operators the flexibility to control the recipes for all basic module functions such as filling, heating, and cooling.

GAMP compliance is essential in the pharmaceutical industry. Besides, the electronic record and electronic signature capabilities specified in the EU GxP Guide Annex 11 is required for any systems project. The system software that has been developed to automate all process functions is typically validated and qualified by engineers and operators using predefined test procedures. Yokogawa's engineering practice complies with these requirements based on GAMP 5.

MSD

Project Reference

Singapore

Reflecting Yokogawa's leadership in industry, MSD International GmbH, Singapore Branch (formerly Schering-Plough Ltd, Singapore Branch) chose Yokogawa's Distributed Control System (DCS) – CENTUM CS 3000 for their project at Tuas, a multi-product plant in Singapore.
The plant utilizes state of the art equipment for Active Pharmaceutical Ingredient (API) manufacture and offered Yokogawa the prestige of being associated with the major drug, ZETIA® (ezetimibe) used for cholesterol management.

Two projects were undertaken. In addition to the DCS, Yokogawa also supplied 80% of the instrumentation used for both projects. During these projects Yokogawa embraced the GAMP guidelines methodology for the execution of the project and also provided installation and operational qualifications (IQ/OQ), calibration and validation services with all Yokogawa personnel involved with the project

MSD International
(formerly Schering-Plough)
Control System

- CENTUM CS 3000 R3
- 50 Operator Stations
- 18 Field Control Stations
- 12,000 I/O

receiving the appropriate cGMP, GDP and GAMP training.

The project was a beneficial experience for both Yokogawa and Schering-Plough as it was executed according to a Joint Management Agreement, the major drive being to improve efficiency of project execution and enhance the quality of the system delivered.

"We are very happy to work with Yokogawa, and have continued to rely on Yokogawa to help us design and develop control systems for our new and very important expansion projects." Dr. Patrick Yeung, retired Executive Director of Project, Schering–Plough, Singapore.

Takeda

Project Reference

Ireland

Yokogawa executed a project for Takeda Pharma Ireland Ltd (a subsidiary of Takeda Pharmaceutical Company Ltd) at their API plant located in Dublin, Ireland. This was Takeda's first API facility which constructed outside Japan.
The plant utilized Yokogawa's CENTUM CS 3000 R3 control system for process control.

The plant is used to develop and produce APIs used in clinical trials through to launch and full commercialization. In addition Takeda also planned to produce APIs in order to continue to supply existing world markets with products such as their diabetes blockbuster drug Pioglitazone (brand name Actos).
To meet the above challenges the system was specifically designed to be multipurpose allowing a large number of products to be manufactured utilizing Yokogawa's CENTUM CS 3000 batch control system which is based on the ISA-88.01 batch

Takeda Pharma
Control System

- CENTUM CS 3000 R3
- 8 Operator Stations
- 1 Audit Trail Server
- 5 Field Control Stations
- 4,500 I/O
- Profibus Communications to Packaged Equipment
- On-line Batch and Process Reports

standard.
The system helped Takeda comply with the current FDA requirements for the use of Electronic Records and Electronic Signatures (i.e. FDA's 21 CFR Part 11) an issue of vital importance when supplying control and information systems to the pharmaceuticals industry.

Delivering to your needs

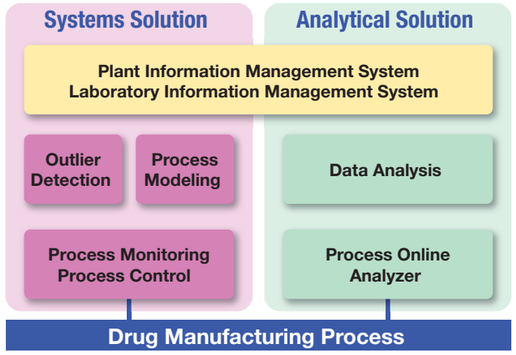
Committed to the Pharmaceutical Industry

As one of the world's leading Industrial Automation suppliers Yokogawa is committed to delivering the best possible measurement and control systems for your plant. All analytical equipment is calibrated to pharmacopoeia standards and validation standards and can be readily supplied with the relevant supporting documentation. Yokogawa's DAQSTATION DXAdvanced R4 paperless recorders, CENTUM VP DCS and Exaquantum/Batch Plant Information Management Systems (PIMS) can be validated to comply with 21 CFR Part 11 and offer extensive documentation supporting facilities.

Software development within Yokogawa is subject to stringent QA protocols that describe and monitor each step of a system's development, from user requirements specifications to product release and life cycle management.

Process Analytical Technology

Yokogawa is committed to support the FDA's Process Analytical Technology (PAT) initiative. In fact we see the FDA's reasoning behind the PAT initiative as being very much in keeping with our own VigilantPlant initiative – **See Clearly** - Measure the process as accurately as possible, **Know in Advance** – Understand the process in order to be able to control the process most effectively, **Act with Agility** – Optimize the operation of the plant based on the information received and on the knowledge of the process and how it is best controlled. Our approach to the PAT solutions relies on real-time monitoring of critical quality attributes (CQA) and the use of process modeling technology to monitor process health.



PAT leads to quality assurance within the manufacturing process

FDA Compliant Systems

Yokogawa is committed to supplying all of our systems according to the relevant regulatory requirements and appropriate industry standards. For example our DAQSTATION DXAdvanced R4 paperless recorders include two versions with support for 21 CFR Part 11 while both our CENTUM VP control system and our Exaquantum/Batch Plant Information Management Systems comply with the FDA's regulations. We supply safety systems compliant with IEC 61508 and IEC 61511 and batch control systems based on the ISA-88 (IEC 61512) standards and information systems according to ISA-95.01 standards.

Life Cycle Approach to Computer System Validation

Yokogawa is committed to the life cycle approach to computer system validation as per the GAMP 5 guidelines. The life cycle approach sets out a clear path for how the system is to be developed, manufactured and installed. GAMP 5 guidelines are also tried and tested and are widely accepted by most of the major pharmaceutical companies as an acceptable method of establishing the necessary documentary evidence required for the validation of their systems. Although the concept is very simple it provides many advantages such as a rigorous project execution where each stage of the project cycle must be assured before progressing to the next stage.
Such a way of working instills heightened confidence and visibility in ensuring that a project is delivered according to requirements the first time.

Long Term Customer Relationships and Support

Yokogawa is committed to establishing long term customer relationships. Such long term relationships benefit you the customer in a number of ways, not least in enabling Yokogawa to understand your business demands and therefore being able to best provide for your needs.

With Yokogawa our interest and support does not end on completion of the commissioning phase of the project. We understand that customers require long term support and continued assistance to ensure the smooth running and longevity of their investment.

For these reasons Yokogawa provides a comprehensive upgrade path for any existing system. With this in mind existing software can commonly be re-used as part of a system upgrade.

In addition to the above we are also committed to providing you with the best possible after sales services such as maintenance and support contracts and other services including calibration and system validation.

Yokogawa is also able to provide consultancy services include process analytical technology consultancy, control and safety systems consultancy and products and systems validation consultancy.

vigilantplant.®

> Visualizing the right information ensures product quality

SEE
CLEARLY

Analytical Technology

Yokogawa provides a wide range of analytical instruments including pH, conductivity, dissolved oxygen and gas analyzers. Our pH and conductivity instruments are world renowned and are used by more than 4,000 companies world wide. All loops can be supplied with validation protocols documenting the wetted parts of the sensors, pharmacopoeia compliance and configuration of the transmitter. SOPs are provided for Good Calibration Management.

FLXA 21

Process Fourier Transform NIR

NIR is one of the most informative analytical techniques where chemical and physical process characteristics are concerned.

Yokogawa's NR800 Fourier Transform NIR takes process analytical information to a new level with unrivalled stability, wavelength and precision.

Direct transfer of a calibration model from laboratory to the process, or among processes, is also possible, this together with the ease of operation and user friendly software are key design concepts for the NR800.

NR800

Flow, Pressure and Temperature

Accurate and reliable measurement of your process is essential if you are to capitalize on your investment. Yokogawa provides a wide range of flow, pressure and temperature transmitters to suit a number of applications.

All instruments are calibrated to NIST traceable standards. Our Ultrasonic flow meter which stays outside the process is used widely for external verification of installed flow meters.

Yokogawa's range of flow meters comprise four different types of technologies i.e. Vortex, Differential Pressure, Magnetic and Coriolis Mass flow.

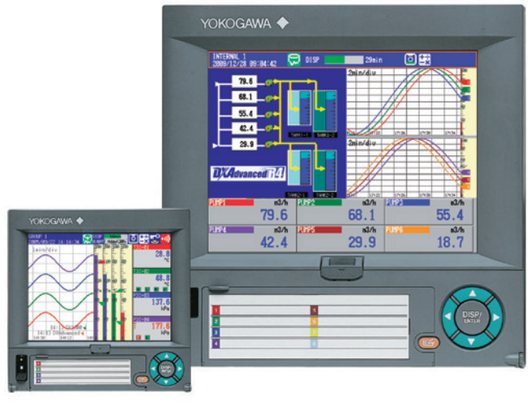
DPharp EJX

ADMAG AXR

ROTAMASS

Data Acquisition

Yokogawa's recorder portfolio includes both the more conventional chart recorders and paperless recorders. The DAQSTATION DXAdvanced R4 DX1000/DX2000 paperless recorders expanded security function provide electronic record keeping functions that comply with the requirements of FDA regulation 21 CFR Part 11. The DX1000/DX2000 display measured data in real-time on a high resolution color TFT liquid crystal display. Electronic signatures can be added to the saved data records at the DXAdvanced R4 DX1000/DX2000 itself or using the included PC software package. In addition to the above DX recorders can also be networked to a PC server and accessed via Microsoft Internet Explorer. Yokogawa can even provide as a package all the necessary validation protocols required to complete Installation and Operational Qualification of these recorders.



DX1000/DX2000

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> Predicting plant behavior enables effective planning & management

KNOW
IN ADVANCE

Distributed Information at Your Fingertips

CENTUM VP is a full featured DCS that enables users to see clearly and know in advance of any situations that may contribute to the quality or safety related aspects of the process.
The system includes a variety of methods by which information can be quickly and clearly displayed as standard such as an explorer style navigation utility. Historical trends and events can all be displayed using powerful search and view facilities.

True to the VigilantPlant philosophy, alarm information is only highlighted when an abnormal event occurs. CENTUM VP can also be provided with the Yokogawa Alarm Administration suit that enables dynamic alarm values to be set by the system depending upon the plant conditions.

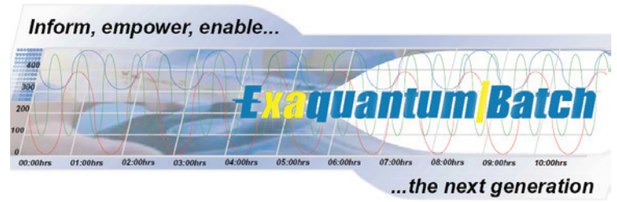
Real-Time Device Maintenance

Yokogawa's Plant Resource Manager (PRM) is a real-time device maintenance and management tool that provides access to instrument data which can be viewed in a control room or office environment.

Managing device records through the PRM database together with Plug and Play device registration enables an efficient and cost effective method by which to maintain plant instrumentation.

Plant Information Management Systems

Exaquantum/Batch provides Management Information that enables you to capitalize on your investment. The system utilizes Client/Server technology and supports fault tolerant systems for added reliability.
Exaquantum/Batch requires minimal configuration (and therefore minimal validation effort) and provides users with a simple and intuitive graphical interface based on Microsoft Internet Explorer.



Exaquantum/Batch enables information to be displayed in a variety of ways including web, Gantt chart, histogram and trend display formats, all of which are standard and require no configuration.
Exaquantum/Batch also provides a facility whereby Key Performance Indicators (KPIs) can be associated with batches.

This process can therefore be used to indicate 'Golden Batch' quality attributes and to provide Six Sigma quality type monitoring and process optimization information.

When connected to Yokogawa's CENTUM VP, Exaquantum/Batch utilizes automatic equalization whereby the CENTUM VP database and recipe information is automatically read by the system. Such functionality enables the system to be easily validated due to the fact that only standard software is being used.

vigilantplant.®

> Robust control and integrated safety assures speed and flexibility of business

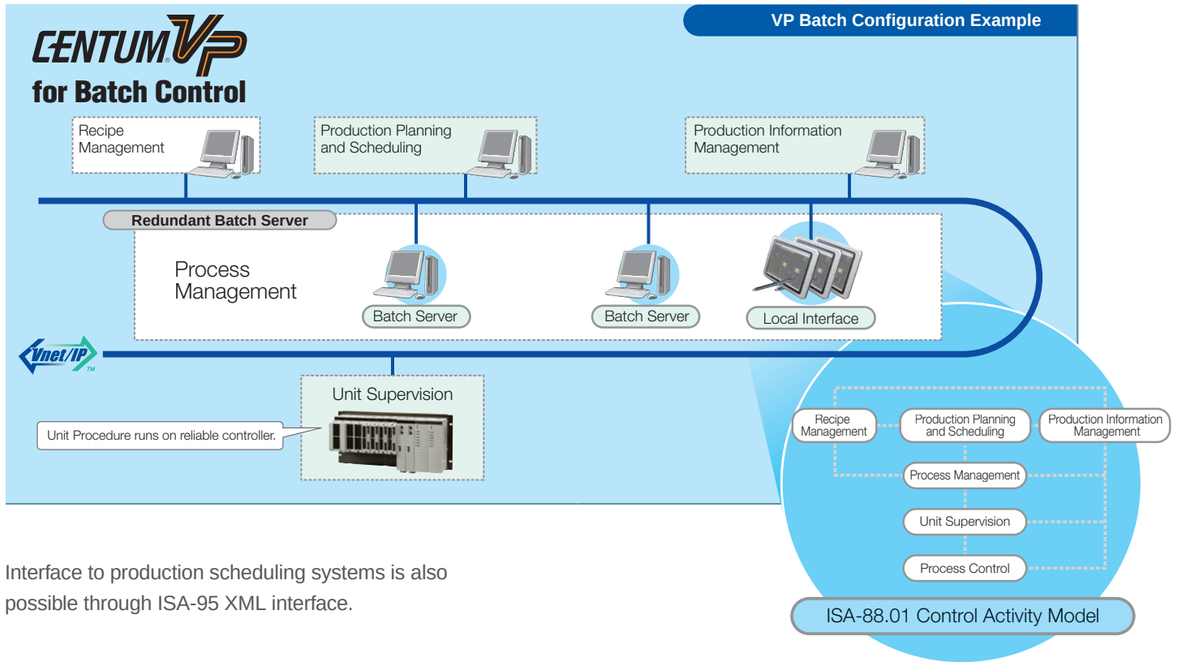
ACT
WITH AGILITY

DCS Control for Batch

CENTUM VP is a truly scalable, modern, DCS that runs on Windows OS platforms.

The system is built to provide the ultimate in reliability as all components can be supplied in a dual redundant format for all components (e.g. processor cards, communications and powers supplies). Continuous control is provided via the standard CENTUM VP operating environment whereas batch control is provided via the VP Batch Recipe and Batch management system thus enabling batch systems to be implemented according to the ISA-88.01 batch standard.

The system is completely scalable – ranging from one operator station, one Field Control Station and a few I/O to systems with multiple operator stations, multiple controllers and tens of thousands of I/O. Engineering is modular and efficient due to the use of the large number of standard function blocks supplied with the system. Reusability of common functions is maximized by the use of generic parameter variable naming. Compliance with the FDA's 21 CFR Part 11 ruling on the use of Electronic Records and Electronic Signatures can also be achieved including license options for audit trails for operations and engineering.
The system interfaces to other sub-systems via a large number of industry standard protocols such as Modbus RTU and TCP, Profibus, FOUNDATION Fieldbus, DeviceNet, OPC and XML.
CENTUM VP automatically links to Exaquantum/Batch to provide Electronic Batch Records and enhanced information displays.



Interface to production scheduling systems is also possible through ISA-95 XML interface.

Network Based Control Systems

STARDOM is an IEC 61131-3 Network Based Control compliant system. As such it can be programmed in Ladder, Sequential Function Chart, Structured Text, Instruction List and Function Blocks.

STARDOM includes a Web Server allowing your process data to be displayed and analyzed using a simple web browser such as Microsoft's Internet Explorer.

The system is completely scalable and can be supplied in dual redundant format. Connection to the outside world can be via Ethernet, Fieldbus or Serial communications. OPC communications makes it easy to connect to a host of other systems including commonly available SCADA systems including Yokogawa's FAST/TOOLS.

STARDOM

Safety Systems

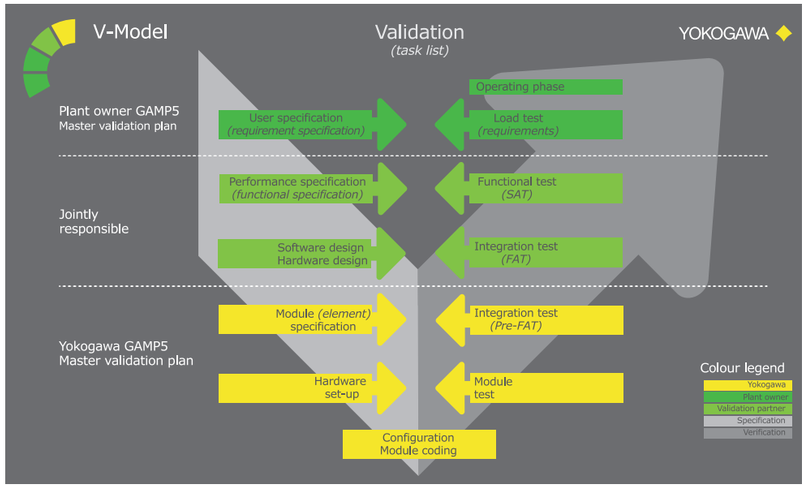
For systems requiring Safety Integrity levels up to SIL3, ProSafe-RS offers PLC type technology but with the reliability and dual redundant operation expected of a Safety system. Both the ProSafe-RS and the Yokogawa organization have been certified by TÜV to be in compliance with IEC 61508 and IEC 61511.
ProSafe-RS is certified as SIL3 in a single module configuration with redundancy for high availability. No gateway or interface hardware is required for data exchange between DCS and SIS functions. For systems requiring SIL levels up to SIL4 then ProSafe SLS offers a solid state dual redundant solution.

ProSafe-RS

Project Execution and Life Cycle Services

Project Execution

The ability to deliver projects on time and per customer requirements is as essential as the products and systems themselves.
Over the years, Yokogawa has successfully realized numerous projects complying with GAMP. We prepare a Project Validation Plan (PVP) for this purpose and proceed according to the "V model" described in GAMP 5: functional specifications, design specifications, implementation, factory testing and site acceptance test. The verification and test results, including IQ/OQ serve as objective indicators for determining whether or not the project requirements have been met.



Project execution conformed to GAMP 5 V-Model

Life Cycle Services Support

Maintenance

Yokogawa provides maintenance and support for all our products and systems.
Yokogawa is able to provide local support from over 80 offices around the world. Maintenance contracts are provided to suit your exact requirements.
Typical contracts include guaranteed call out and response times, bonded spares and periodic site maintenance visits to keep your system running smoothly and reliably.

Training

Yokogawa provides both standard and custom training courses.
Training courses are available for all of our products and systems and are commonly run either at our customer's own premises or at our local Yokogawa office.
Custom courses are especially useful where specific training is required (e.g. operator training for a particular application). In this regard Yokogawa is able to tailor courses to suit your exact needs.

Calibration

Calibration of Yokogawa instrumentation can be conducted either on site or at many of our local offices.
Periodic calibration of your instrumentation is commonly a manufacturing requirement to ensure that the process is operating correctly. As part of our calibration service Yokogawa provides calibration test certification according to nationally recognized and industry based standards.

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VigilantPlant = *The clear path to operational excellence*

Plant-wide integration

ERP

Optimize

Production Management

Plant Information Management,
Advanced Process Control

Asset Management and Operational Efficiency

Plant Resource Management,
Operational Efficiency Improvement

Control

Production Control and Safety Management

Continuous and Batch Production Control,
Safety Management, SCADA and Network-based Control

Data Acquisition and Logic Control

Recorders, Data Acquisition, IT Machine
Control, Single Loop Control

Measure

Analysis and Quality Control

Process Gas, Process Liquid, Stack Gas,
City Water, Waste Water Analysis

Sensing and Actuation

Pressure, Temperature, Flow, Level Measurement,
Final Control Elements,
Primary Elements and Auxiliaries

Revamp and Expansion

Online Expansion,
Hot Cutover

Maintenance and Upgrade

Asset Optimization,
Online Upgrade,
Lifecycle Solution Support

Operation and Optimization

Optimization Consulting,
24/7 Operation Support,
Online Diagnosis Support

Computer System Validation

Process Analytical Technology
Consultancy and Validation
Consultancy Services

Design and Engineering

Front-End Engineering & Design
(FEED), Main Instrumentation
Vendor (MIV) Services

Installation and Commissioning

Site Engineering, Integration
Tests, Turn-Key Services

Life cycle optimization

Making critical plant information fully visible is just the beginning of the vigilant cycle

Seeing clearly gives you the knowledge necessary to anticipate the changes required in your process.
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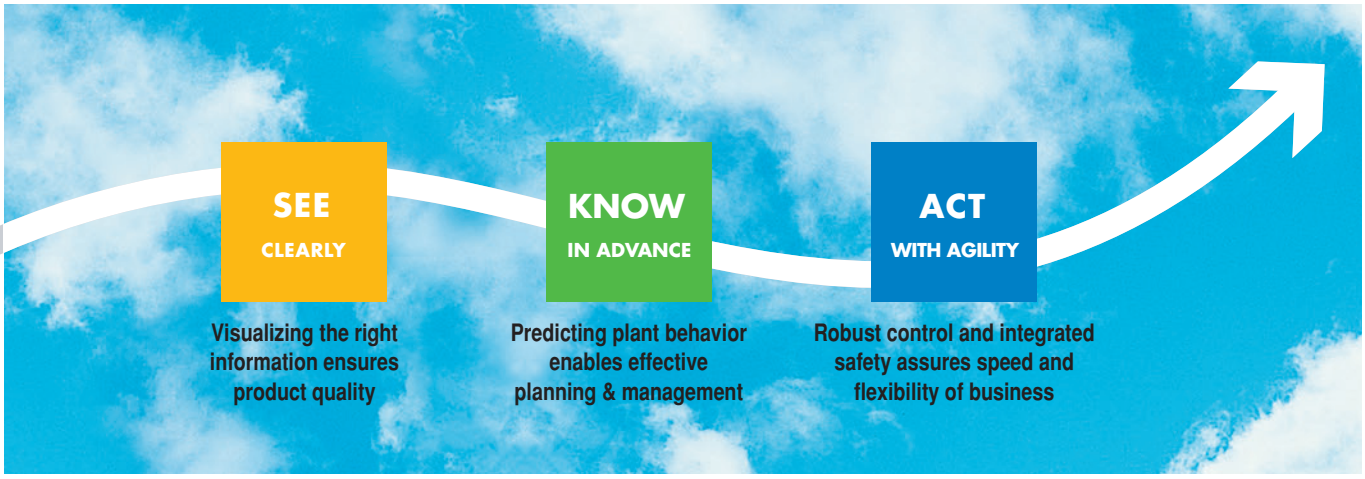

VigilantPlant excels at bringing out the best in your plant and your people - keeping them fully aware, well informed, and ready to face the next challenge.

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vigilantplant.®
The clear path to operational excellence

SEE CLEARLY | KNOW IN ADVANCE | ACT WITH AGILITY

VigilantPlant is Yokogawa's automation concept for safe, reliable, and profitable plant operations. VigilantPlant aims to enable an ongoing state of Operational Excellence where plant personnel are watchful and attentive, well-informed, and ready to take actions that optimize plant and business performance.

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