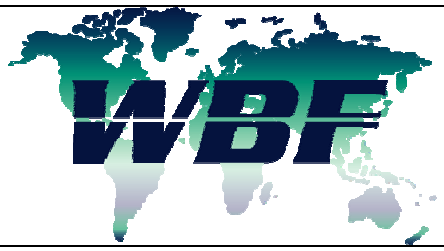
Presented at the **WBF** **North American Conference** **Atlanta, GA** **March 5-8, 2006**		**195 Wekiva Springs Road, Suite 200** **Longwood, FL 32779-2552** **+1.407.774.5764** **Fax: +1.407.774.6751** **E-mail: info@wbf.org** **www.wbf.org**

Fast and efficient configuration & integration of automation solutions in a global perspective – A practical approach

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ABSTRACT

Fast and efficient configuration & integration of automation solutions is a prime requirement in the pharmaceutical industry. The key to success is to use standardized modules, which can be pre-configured and pre-qualified before implementation on site, possibly by suppliers in low cost regions. This will save time and money for both implementation and validation and ensures flexibility for future adaptations. In order to ensure full exploitation of this principle it is necessary to set up an efficient execution framework which supports all project phases with the necessary standards & guidelines.

This paper describes how you can adopt modular engineering and set up the overall framework for fast and efficient configuration & integration of automation solutions world wide. It comprises tools for analysis and specification of requirements based on S88 & S95 models, functional specification using computer based modeling tools, configurable library modules for various platforms and computer based tools/methods for test according the GAMP guideline. These are all tied together in an overall Automation Project Activity Model (A-PAM) for handling of the necessary documents. An illustrative example covering the implementation of a new API plant shows how it works in practice.

The Market Challenge

Fast launch of products is very important in the pharmaceutical industry. Upon many years of heavy investments in research and development it is vital to get fast to the market when the approval of a new drug is in place. As outlined in figure 1 it is normal to start up the design and construction of new production facilities for a new drug already upon successful completion of Clinical Trial Phase II. However due to uncertainty of the Clinical Trial Phase III and uncertainty about the real market potentials for the new drug it would be preferable to postpone the investment in new production facilities as late as possible. Most pharmaceutical companies therefore ask for late start and very fast execution of new plant projects. For engineering companies this requirement has become the prime challenge.

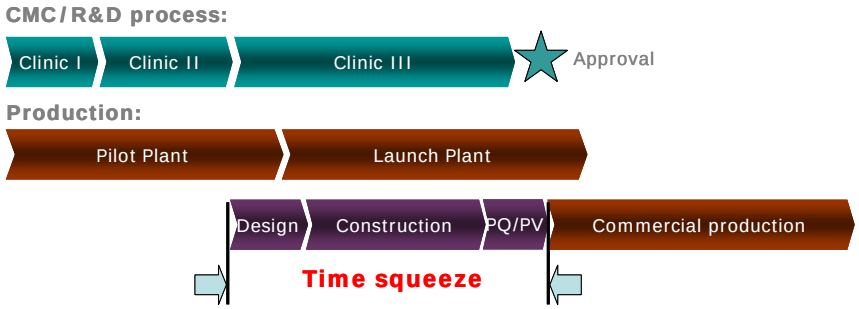

Fig. 1 Fast launching of products is vital in the pharmaceutical industry

The Modular Approach

The modular approach is the most obvious response to requirement for fast implementation. If the process equipment can be designed as large standard Lego-bricks it is possible to make a customized solution very fast. Fig. 2 illustrated how this approach can be applied in all phases from conceptual design to handover and support of the solutions. Each step in the overall project implementation model is briefly described below.

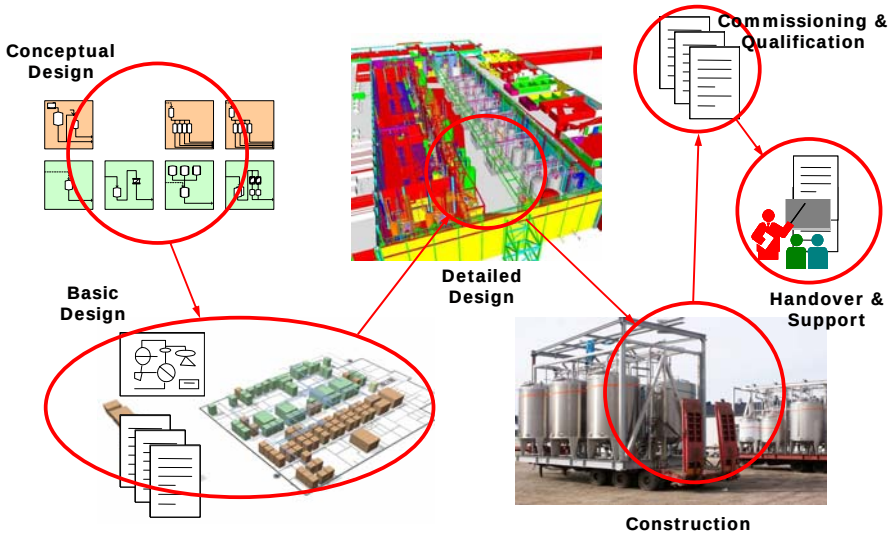

Fig. 2 Modular Engineering from Conceptual Design to Handover & Support

Conceptual Design comprises the definition of the modular structure by use of simple and clear module diagrams. It is important that the project scope is unambiguous – and still defined at a sufficient high level to allow fast changes and evaluations of alternatives. Since space allocations, building structure, utility requirements and investment costs are all derived from the modular structure changes can quickly be propagated.

Basic Design includes more detailed specification of the requirements for each module. In this phase it is possible to apply systematic reuse of module specifications – within and across projects. Reference or standard modules can be modified to meet the specific demands of the client. Besides being cost-efficient the reuse provides a more exact cost-estimate – and excellent benchmarking possibilities.

Detailed Design includes detailed specifications and models for implementation of each module.: The modular structure confirmed during basic design must be retained all through the project – both in the cost structure, in the contracting and in the project organization – giving everybody clear objectives that match a resulting process or building function. All aspects of the facility must be designed according to the modular structure. Due to the strict interface management it is still feasible to add or substitute modules – as long as the physical production/delivery time allows it. The modules may be designed by different vendors as the capabilities of the vendors allows.

Construction based on modular engineering allows for the simultaneous off-site construction of each single process module and building part on different locations depending on competences and cost. The units are then transported to the site and lowered into the plant, where the final IQ, OQ, and PQ are performed.

Qualification can be performed fast and efficient since a major part of the equipment is commissioned and qualified in parallel and potentially off site, without dependencies to adjacent upstream and downstream equipment. Modular Engineering even allows for qualification activities, such as IQ, to take place off-site.

A new plant based on Modular Engineering has many advantages for the end user:

- it is inherently flexible and expandable.
- the structure of the process equipment is easy and repetitive.
- the automation system follows the same structure.
- the interdependencies in operation (e.g. CIP) are minimized.
- the validation documentation is clearly structured.

Because Modular Engineering is founded on the re-use of well-known solutions it increases the odds for a fast approval process and ensures reliable production from the day the facility is handed over.

The definition of Standard Modules

The definition of standard modules may be based on recognized engineering standards like ISA S88 and S95. As outlined in fig 3 a complex plant may be decomposed into a number of predefined process modules (e.g. fermentation lines), each process module into a number of predefined units (e.g. tanks), each unit into a number of pre-defined equipment modules (e.g. tank filling systems) and each equipment module into a number of pre-defined control modules (e.g. valves). Each level in the decomposition of the equipment part has its equivalent for the automation part and in this area it is possible to re-use predefined configurable software modules kept in a library for each of the most used platforms.

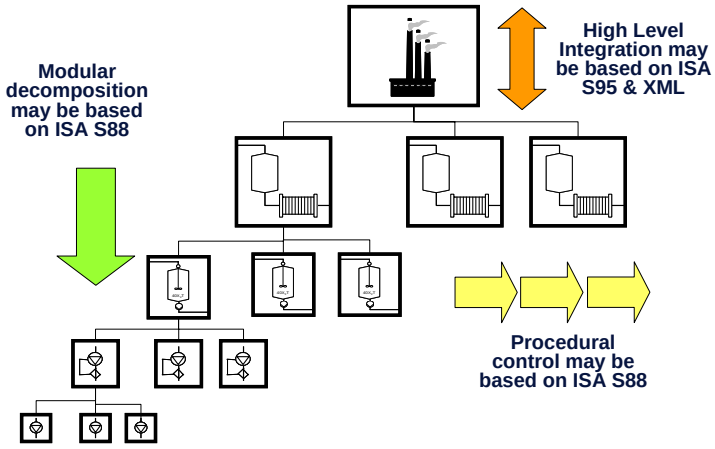

Fig. 3 Decomposing of complex plant into simple modules based on recognized engineering standards like ISA S88 & S95

Among the modular building blocks the process module is especially interesting for fast configuration of new customized solutions. A process module may be defined as an independent module which can handle execution of the batch between several units including CIP of units in between process batches and parallel with production. Several batches may be executed simultaneously in a process module (this definition corresponds to a process cell in S88 terms). A process module must be defined by a cross disciplinary effort in order to cover building, mechanical and automation aspects. Very important is the definition of interfaces covering the necessary flow of material, energy and information. The success of modular engineering is fully dependent on well defined interfaces. For the automation part of a process module it covers batch control functions able to execute and document each batch defined by a recipe. Normally the recipe is downloaded from a higher level system, e.g. a MES system, which receives the necessary data for the reporting upon batch completion.

As outlined in fig. 5 the great advantage by using standardized process modules that very different total solution can be established by repeated use of a limited number of standardized process modules.

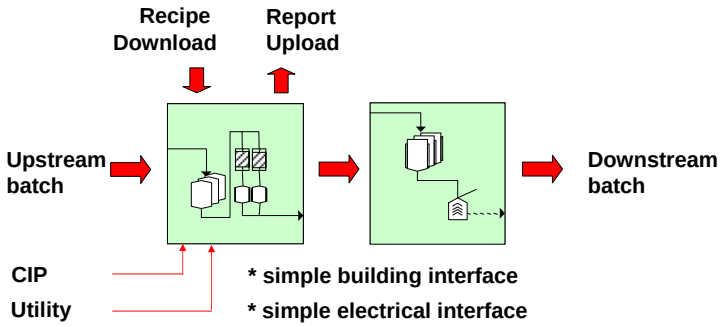

Fig. 4 The main building block is the process module

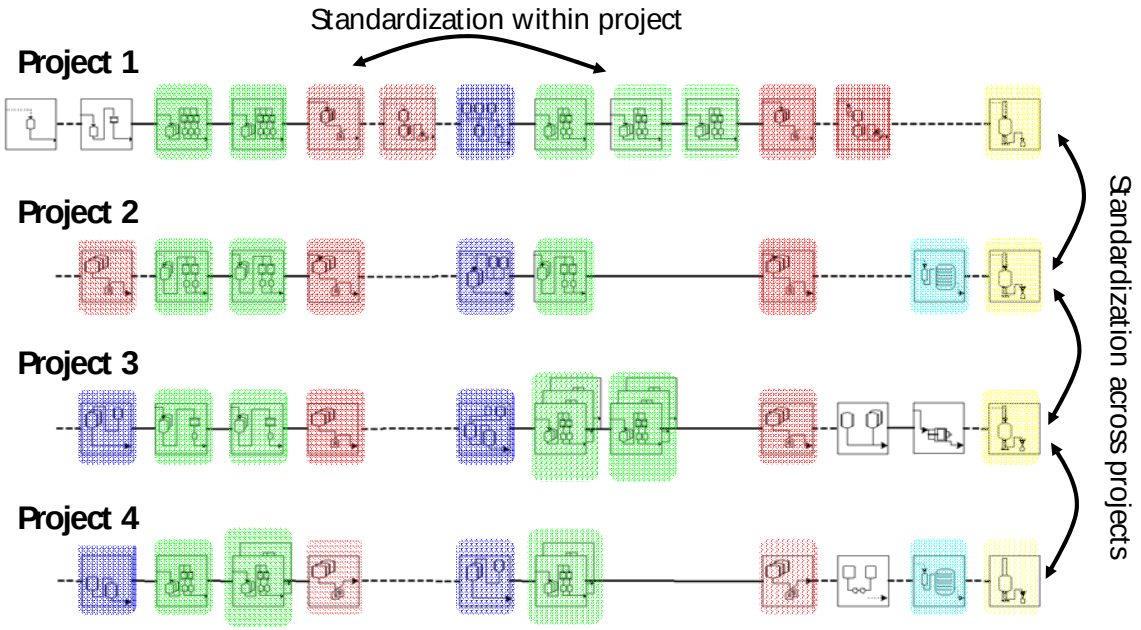

Fig. 5 Standardization of process modules within the project and across projects

The Automation Execution Framework

In order to implement projects fast and efficient it is necessary to operate with predefined project activities, each supported by document templates, specifications, guidelines and support tools.

An example of a general Automation Project Activity Model (A-PAM) is outlined in fig. 6.

The purpose of the A-PAM model is to ensure fast, efficient and predictable implementation of automation solutions and continuously improve performance by the collection of experiences and good practices from executed projects, and making this information available for coming projects in a usable and effective manner.

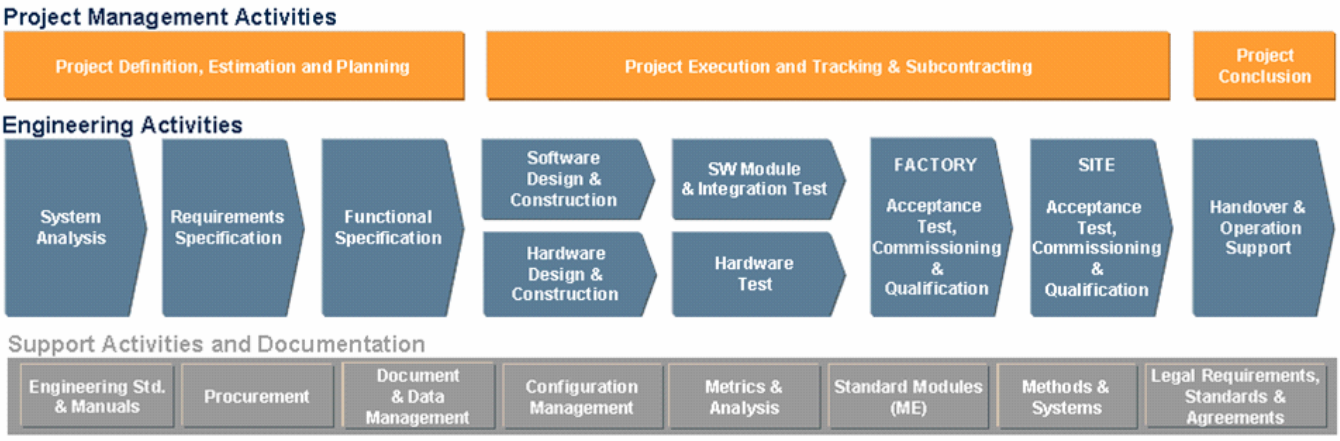

Fig. 6 The Automation Project Activity Model (A-PAM) based on GAMP4 terms

The A-PAM model, which is based on GAMP4, comprises 3 parallel activities:

The project management activities describe how to specify, execute and handover the project in close collaboration with the customer and subcontractors.

The engineering activities describe how to step by step to specify, design, implement, test and document the solution in compliance with predefined standards and procedures.

The support activities describe how to support the project organization e.g. by provision of pre-defined standard automation modules and how to collaborate with subcontractors/partners about the implementation.

All activities defined in the A-PAM model is supported by predefined document templates, specifications and guidelines based on previous experience including illustrative examples on how to do things.

Very important is the predefined transition requirement between the project activities stating which documents have to be completed/available before you are allowed to proceed to the next activity. This is especially important if you want to handover some of the project to a subcontractor.

The full benefit of the A-PAM model is gained by using it from the very beginning to the very end of each project and also during the preparation of project proposals and project evaluations. Using the predefined structures of project phases and process modules provides a splendid basis for systematic recording and re-use of experiences, both in terms of cost estimating and time scheduling.

The Automation Engineering Tools

The fast project implementation must be supported by efficient project management and engineering tools. Fig. 7 outlines a number of tools, which can help managing complex automation engineering projects.

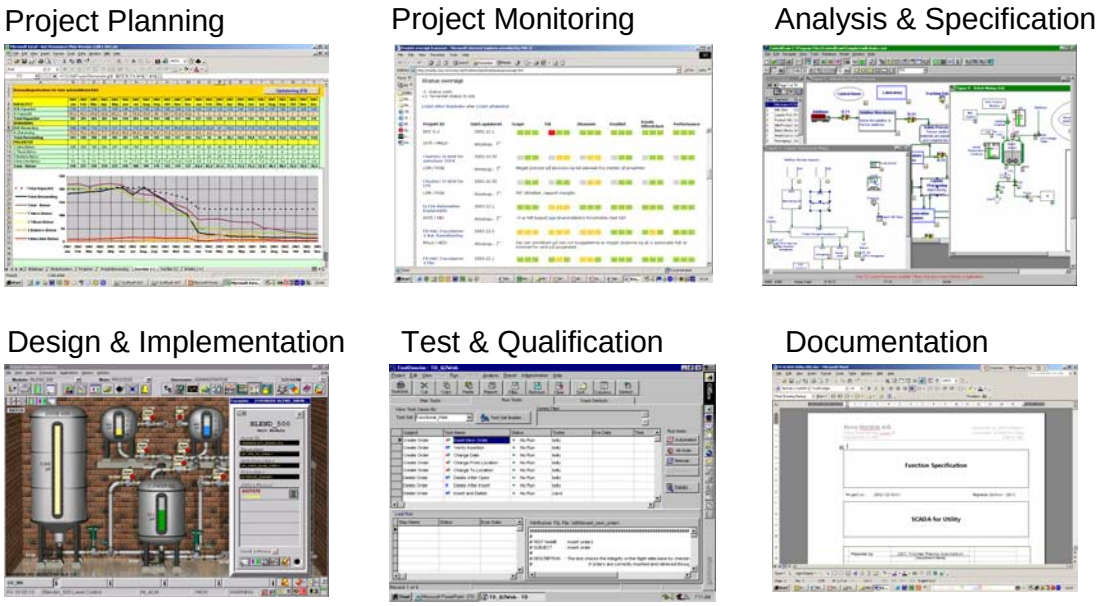

Fig. 7 Examples of computer based project management and engineering tools

Project planning is supported by tools for estimation of necessary amounts of resources and necessary time for each project phase based on past experience. It is implemented around a database comprising key information about each standard module making up the complete solution.

Project monitoring is performed by a web based tool in which the project managers and coordinators can update the current project status for each part of the project and which can provide the management with key information about management of scope, price, time, quality, customer satisfaction and team performance, all illustrated by colors indicating if intervention is necessary (green=OK, yellow=warning, red=alert)

Analysis and specification is supported by a computer-based modeling and specification tool based on ISA S88 comprising a library of predefined equipment modules and procedural elements for fast and easy set up of customized models/specifications.

Design and implementation is supported by predefined design documents for process modules associated with pre-coded and pre-qualified code modules for the most important implementation platforms

Test and pre-qualification of standard software modules is supported by an automated test environment with predefined test procedures and automatic logging of any deviations. This makes it very fast to test and qualify any changes to the software modules and efficiently keeps track of the complete set of software versions.

Documentation is handled by a document management system with a predefined set up of document folders corresponding to the break down in process modules and for each document with predefined attributes for fast retrieval and update.

The Global Supply Network

The process modules for a specific plant may be supplied from a global network of collaborating suppliers as outlined in fig. 8. In the example a local customer in USA needs a new plant and analyses and specifies the requirements for this in collaboration with the main engineering contractor, who has an office close to the customer. The requirement specifications are handed over to a central back office of the main contractor in Europe, where a customized design based on predefined equipment, process and automation modules is defined. The design specifications are then handed over to subcontractors which take care of the implementation. For the automation part the design is accompanied with configurable software modules and configuration guidelines for the chosen system platform. The automation subcontractor (in this case a subcontractor in China) configures and tests the software modules according the standards and hands over the software modules to the equipment subcontractor (in this case a subcontractor in Italy). The equipment contractor which has implemented the process modules based on design specifications from the main contractor will then integrate the solution with the software modules and test the complete solution before shipping it to the customer in USA. Parallel to this the equipment subcontractor has implemented and installed the building modules based on design specifications from main contractor. All modules can now be installed, integrated and tested on-site by the customer. Due to use of the modular engineering approach it has been possible to run all necessary engineering activities in parallel at the most cost efficient places in the world and to establish the new plant faster, cheaper and with better quality compared to traditional sequential implementation of buildings, equipment and automation solutions on-site.

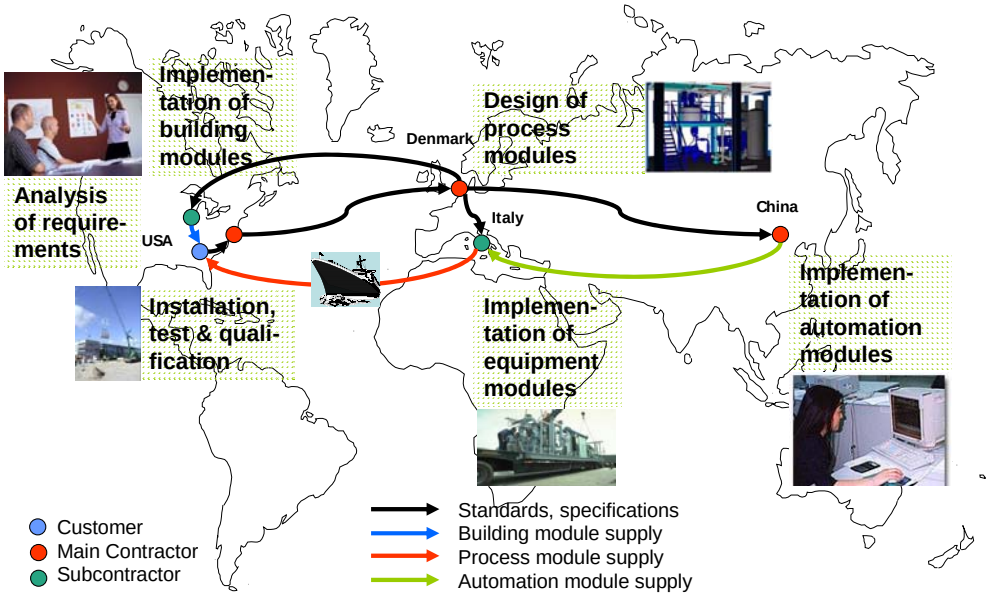

Fig. 8 Example of global network for supply of configurable modules

A Practical Example

An illustrative example of state-of-the-art modular design and engineering is described below.

In 18 months it was possible to establish a new turnkey biotechnology plant for the production of FVIIa, a haemophilia medicine. FVIIa enables the blood to coagulate. FVIIa is approved for treatment of bleeding of inhibitor patients, i.e. patients with haemophilia A or B, who have developed antibodies against coagulation factors VIII or IX that are normally used for treatment of haemophilia patients. The target group is patients for whom there are no alternative treatment possibilities.

Facts
- Biotech API production
- Size: approx. 14,000 m2(150.000 sqft)
- Organization: approx. 100 employees
- Investment: approx. USD 140 million
- Establishment time: 18 months
- Handover: 1st November 2002

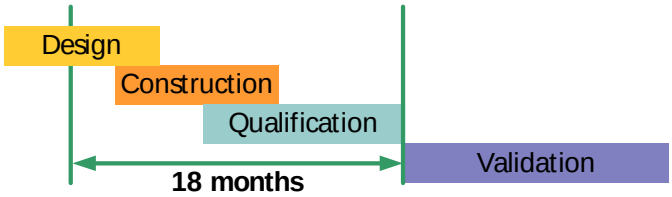

Fig. 9 Overall facts incl. time frame for project implementation

Fig. 10 From a 3D model to final implementation of the pharmaceutical plant

The new plant is a self-supporting unit with own energy supplies. It consists of five building sections comprising an administration building with connecting corridor to process building, utilities, and energy centre. The process building has large glass facades, making the compact building seem light and transparent. Windows and roof sections can be easily dismounted to allow for insertion of equipment modules. The classified clean rooms in the process building have been isolated in separate glass buildings. The quality level is set to comply with the requirements of authorities and client. The modular construction meets the demands to flexibility of a modern facility.

18 Months is twice as fast as normal for a plant for pharmaceutical manufacture of a similar size and complexity. The key to building the plant in 18 months is the modular design right from the start with use of known solutions. The modular design has enabled nearly all process and building units to be manufactured in complete modules. Based on the modular design, vendors have manufactured and pre-tested every single process module including automation. The backbone and pre-qualified standard modules for the automation solution were provided by a system subcontractor. The process modules were transported to production site and lowered into the plant, where the final IQ, OQ, and PQ were performed. Full documentation, including test documentation, was prepared for each process module as part of vendor's delivery.

The modular approach was taken up front in the conceptual design phase where relevant building and process modules were identified from the initial process flow diagrams, please se fig. 11.

Requirements for each module were further detailed during the basic design phases. A full 3D model of the complete plant including models of all process modules were developed in the detailed design phase, please se fig. 12. The subcontractors implemented the process modules on various locations in Europe.

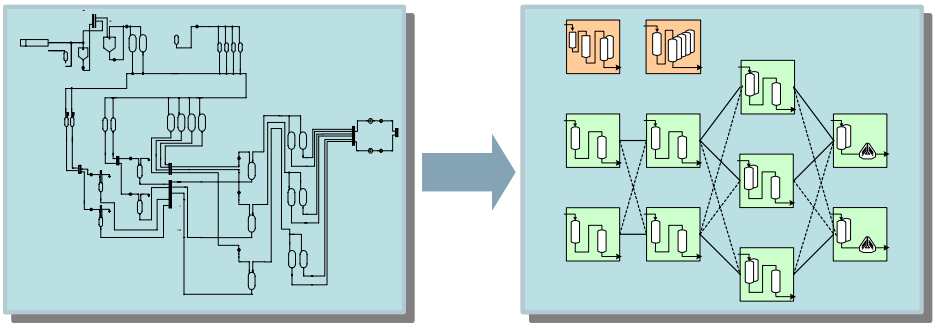

Fig. 11 Process Flow Diagrams transferred into Process Modules

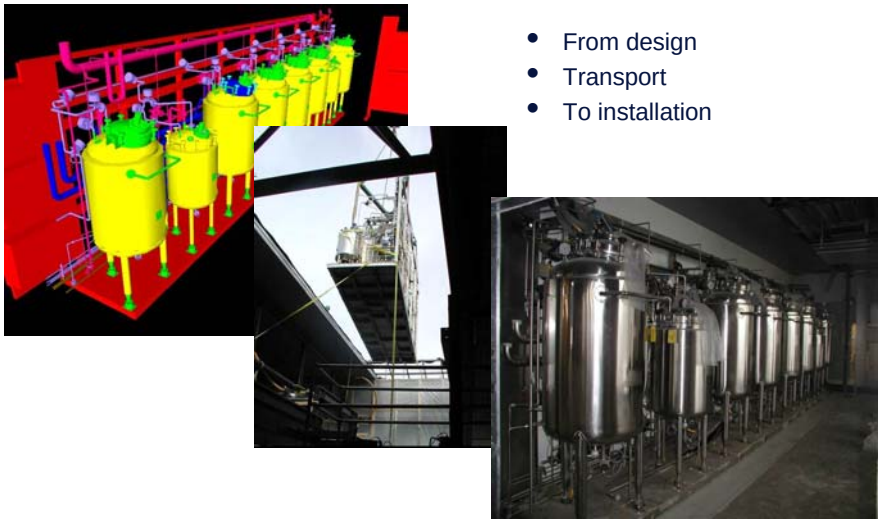

Fig. 12 Example of process module from 3D design to installation

The development of the automation solutions was based on the structured approach described in ISA. S88. As outlined in fig 13 two separate models were developed top down. The equipment model describes the hierarchical break down of the plant into process cells, units, equipment and control modules. The procedural model describes the hierarchical breakdown of the overall manufacturing procedure, into procedures, unit procedures, operations and phases. The linking between the two models is indicated by the arrows. Based on these models the automation solution was implemented and tested bottom up, i.e. implementation, test and qualification of control modules, equipment modules and process modules off site and final integration, test and qualification of the process modules on-site. The pre-qualification of all modules off-site was one of the major contributors to the short implementation time.

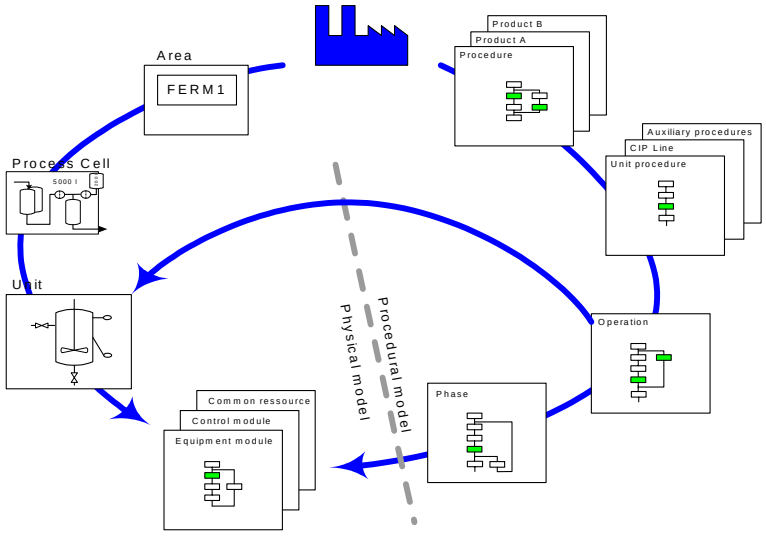

Fig. 13 Modular engineering approach based on ISA S88

Conclusions

The market demand for fast implementation of the necessary manufacturing facilities upon approval of a new drug can be met by fast track engineering based on configurable standard modules.

A modular fast track facility costs approximately the same as a traditional facility. Cost effective production of modules off site counterbalance shipping expenses, added structural steel etc. The structured work packages and streamlined qualification and validation save time and costs in the commissioning and qualification phase.

The prime advantages of a modularised fast track approach are:

- Shorter time to market and therefore faster Return On Investment (ROI)
- Fast track makes it possible to initiate projects later and therefore reduce risk for wrong decisions and scope changes
- Consecutive projects will be cheaper

However it takes more than modularisation to reduce time, risk and cost. The following aspects are very important for a successful fast track implementation:

- Clear strategy and goals
- Create Winning Culture and team spirit
- Clear contractors responsibility
- Firm design package - “Approved for Construction”
- Flexible building conditions
- Building and process modules engineered and established concurrently

Fast track implementation also imposes a number of challenges on the user organization:

- Finalize process design in the short design phase
- Identify known process uncertainties
- Create, hire and train a highly professional team to run the plant in less than 18 month
- Create validation protocols and a quality system including instructions

Our experience with fast track implementation based on modular engineering has shown remarkable results. We have step by step approached an overall goal which was defined 5 years ago: To establish a new pharmaceutical plant within 12 months. The example described in this paper cut down the implementation time from 36 to 18 months and recently we have delivered a complete new pharmaceutical plant in 12 months. The goal was reached.

Acknowledgements

I would like to thank my colleagues Kasper Bonnevie and Klaus Illum for valuable input to this paper

Abbreviations

A-PAM	Automation Project Activity Model
API	Active Pharmaceutical Ingredient
BD	Basic Design
CD	Conceptual Design
CIP	Cleaning in Place
DD	Detailed Design
IQ	Installation Qualification
ISA	Instrument Society of America
ISPE	International Society for Pharmaceutical Engineering
MES	Manufacturing Execution System
OPC	OLE for Process Control
OQ	Operational Qualification
PAM	Project Activity Model
PQ	Performance Qualification
PQ	Process Qualification
PV	Process Validation
ROI	Return On Investment
SIP	Sterilization in Place
XML	eXtensible Markup Language

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