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This case study focuses on the plan, design, and construction of the unique concept and layout of Roche's biotech facility, MAB Building 95, Overall Winner of the 2009 Facility of the Year Awards.

Case Study: Project Execution Strategy for MAB Building 95, Overall Winner, 2009 Facility of the Year Awards

by Rochelle Runas, ISPE Technical Writer

Introduction

Nestled tightly in the middle of a busy residential area in Basel, Switzerland is Roche's MAB Building 95. Distinguished by its state-of-the-art architecture, the facility was conceived for the commercial production of therapeutic Monoclonal Anti Bodies. The successful plan, design, and construction of the building's unique concept and layout, in a challenging location, garnered the 2009 Facility of the Year Award for Overall Winner.

Now in its fifth year, the Facility of the Year Awards (FOYA) program, co-sponsored by ISPE, INTERPHEX, and Pharmaceutical Processing magazine, spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers. Roche's MAB Building 95 was selected as Overall Winner among four other FOYA Category Winners. This year's FOYA winners were chosen from submissions for innovative facilities built in Belgium, France, India, Italy, Ireland, England, Germany, Japan, the Netherlands, Spain, Switzerland, and the United States.

This article is a case study on the MAB Building 95 project, which was delivered in 35 months, six weeks ahead of schedule, and nine percent under budget.

Project Business Driver

The $370 million MAB Building 95 project, which took place 2004 to 2007, was delivered as an ultra fast track project to provide additional production capacity for bevacizumab (API of Avastin®), a successful new cancer medication. The primary project business driver was to make the product available to patients as quickly as possible.

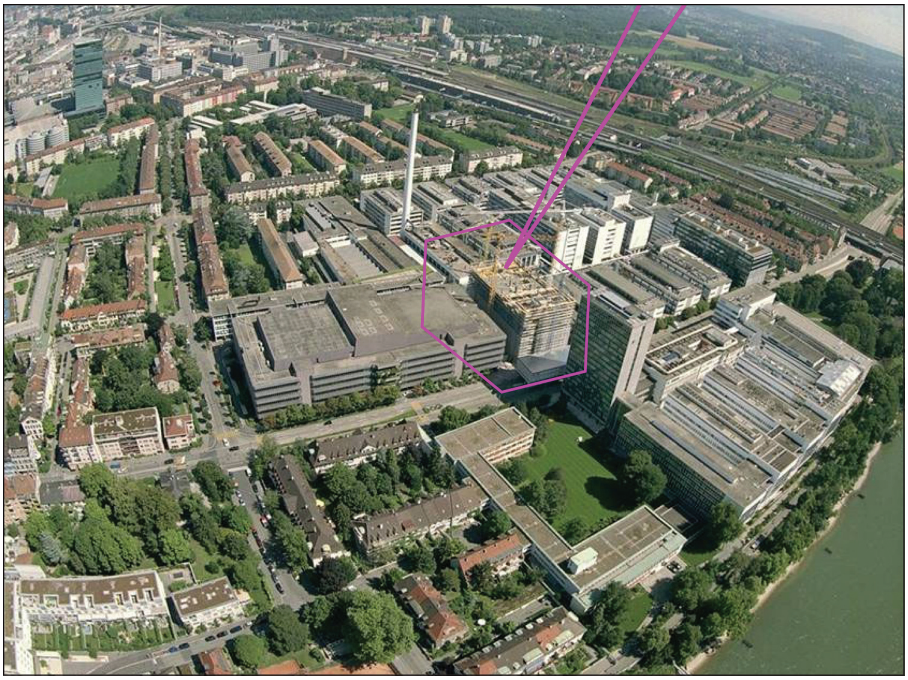
"These new medicines bring the patient large advantages," said Erich Hochuli, Head of Roche Biotech Production Basel. "They work more purposefully and have fewer side effects."

Roche's MAB Building 95 by night.

In addition, the Roche Basel site is being transformed from its traditional chemicals and pharmaceuticals production background to a center of excellence for biologics and pharmaceuticals. Roche representatives say MAB Building 95, the first large production biotech facility in Basel, is the nucleus for this future.

The MAB Building 95 project was running in parallel to Roche's Biologics IV center project in Penzberg, Germany. "We were facing a lot of challenges in the

"The confines of the MAB Building 95 project site, where a chemical production plant once stood, restricted the size of the construction plot to 60 by 30 meters with no available lay-down areas."



Aerial view of MAB Building 95 under construction.

MAB project, but one was very specific: running two investments of this size and complexity in parallel," said Horst Hohler, Head of Roche Pharma Global Engineering. "There are many reasons why MAB was so successful. Most important, however, has been the excellent cooperation and communication within the integrated highly motivated project team." Closely coordinated, both projects seemed to have benefited from the shared experience. The Biologics IV center won the 2008 Facility of the Year Award for the Project Execution category.

Project Overview

Roche's Basel site, continuously occupied by Roche since 1896, lies close to the heart of the historic city, bounded by the River Rhine on the west and urban housing on the other three sides. A major commercial route to the German border runs through the site.

The confines of the MAB Building 95 project site, where a chemical production plant once stood, restricted the size of the construction plot to 60 by 30 meters with no available lay-down areas. Despite the many challenges posed by this small and unique footprint, the project produced a multiproduct facility, 40 meters tall with eight floors aboveground and two floors underground, allowing for the simultaneous production of two different products. It comprises 6 x 12.5 m^3 fermentation capacity plus two downstream processing lines for purification, and associated utilities, laboratories, and offices.

MAB Building 95 has a 100% glass façade on all four sides. For such a challenging architectural task, the project team turned to Herzog & deMeuron, Roche's long term architectural partner and world-renowned for their work on the Beijing National Stadium (a.k.a. Bird's Nest) for the 2008 Olympic Games, the Allianz Arena in Germany, and the Tate Modern in London, among others.

Process Overview

Because the priority business driver was to make innovative new Monoclonal Anti Bodies available to growing patient groups as quickly as possible, when setting project goals, teams focused their attention on the robustness of the process and minimizing supply risk rather than process innovation. Therefore, the production process to manufacture MABS is well established with the process arrangement based on proven, reliable, and successful technology.

The MAB installation achieves multiple line arrangements by the utilization of solid piping spool pieces and transfer panels. The configuration can be changed quickly with minimal effort and minimal operations disturbance. By using fixed piping instead of valves, the

Benchmarking Survey Data – The Building

Height between Floors Production	5.0 m
Building Footprint (Aboveground Floors)	60 x 30 m
Building Footprint (Belowground Floors)	60 x 37 m
Building Height from Ground Level	40.0 m
Usable Area Production	ca 5,600 m^2
Usable Area Laboratory / Office	ca 1,400 m^2
Total Building Area	19,500 m^2
Total Volume	100,000 m^3
Glass Façade	8,400 m^2
Connected Load – Electricity	ca 3.7 MW
Connected Load – Cooling Energy	ca 11 MW
Connected Load – Steam	ca 16.500 kg/h
Handled Air (Installed Volume)	ca 550.000 m^3/h
Number of Air Handling Units	23

risk of accidental cross-contamination is eliminated. Thus, the facility is truly multiproduct, enabling parallel production of two different products with campaign volume and duration configurable in wide ranges.

Process lines, operated via recipes, are highly automated and fully controlled by a Distributed Control System (DCS). The Manufacturing Execution System (MES), which is linked to the Roche Enterprise Resource Planning System (SAP), was phased in as the processes reached stability.

Benchmarking Survey Data – The Process

Main Equipment/Number of Apparatus	305
Number of All Equipment	963
Number of Process Units	200
PFDs	125
P&IDs	318
Rs	10,070
Isometric Drawings	8,100
Number of Pipe Runs	6,750
Piping Process	ca. 43,000 m
I/O (Number of)	ca. 15,000
Number of Instruments (Sensors and Valves)	ca. 12,000
Computer Human Interfaces (CHI)	110
Length Building Electrical Wiring	ca. 75,000 m
Length Automation Electrical Wiring	ca. 440,000 m

Building Concept and Layout

The production process dictated equipment arrangement and layout, which the architecture had to balance against the overall aesthetics of the building and the restricted site footprint. With its vertical process arrangement, MAB Building 95 is often described as a high-rise production.

Utilizing a top down process flow resulted in the tank farm with all media and buffer tanks located on the second top floor. This makes MAB Building 95 the only production building with liquid storage 35 m above ground. This unique layout, providing liquid flow under gravity (with support from pressurized nitrogen when necessary), works well and saved many pumps – beneficial for the facility's sustainability, investment costs, and maintenance effort and costs, said representatives from Roche.

The West side of the building is occupied by the fermentation process with designated laboratories and process service rooms located in the northwest. The East side of the building is occupied by the purification process with designated laboratories and process service rooms located in the northeast.

The layout of the building is symmetric for all aboveground production floors. The central supply shaft services all floors with utilities, HVAC, electrical wiring, and process piping. The two belowground floors accommodate API storage cold rooms, utility units, CIP units, HVAC, as well as changing rooms, MCC rooms, and central computer server rooms. The top floor (eighth) accommodates solely HVAC. All production rooms are class C/D cleanrooms following cGMP zone classifications.

Process Arrangement

Fermentation:

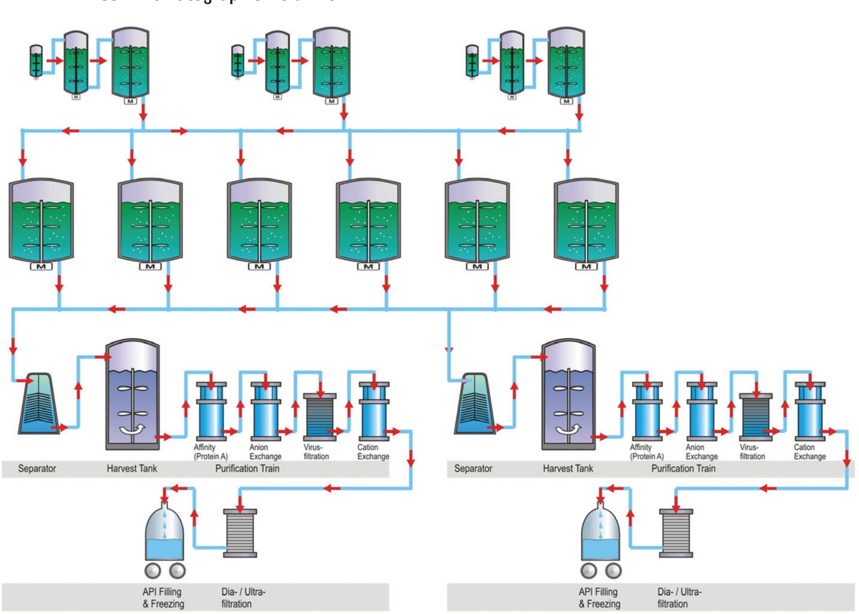
- Cell Banking
- Inoculum Trains
- Fermenters, 14 m³ each (cap. 12.5 m³)
- Two Disc Separators
- Two Harvest Tanks

Purification:

- Two Independent Purification Lines, each with:
  - Three Chromatographic Columns
  - Ultrafiltration
  - Cryo Vessels

Utilities:

- Purified Water, WFI, Clean Steam
- CIP, SIP (Closed Loop, Fully Automated)
- HVAC, Autoclaves
- Utilities supply is located in the basement and top floor and supplied through a central utility shaft.

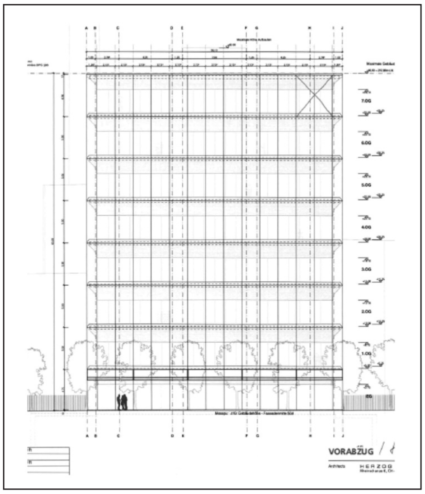


Design Process in 3D CAD

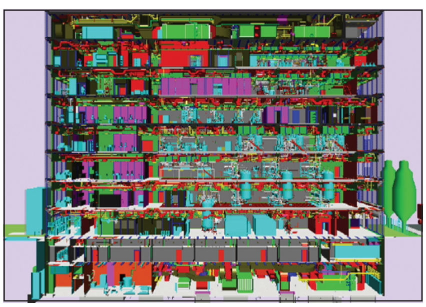
Everything that was to be built for MAB Building 95 was first modeled in an all inclusive 3D CAD model. The starting point – the architectural drawings, were transferred from 2D CAD systems into the 3D CAD model. With that, the building dimensions were defined. This meant that any change in building dimensions triggered an even greater number of changes in other disciplines,

"We established the sacred line, Change is evil,"

- Daniel Riekert, MAB Building 95 Project Manager



Architectural drawing.



West side (fermentation) in 3D CAD.

increasing the model size. "We established the sacred line, Change is evil," said MAB Building 95 Project Manager Daniel Riekert.

In the next design phase, equipment was modeled and equipment layout was optimized. The 3D model provided an efficient tool to not only make quick changes in the layout, but also to obtain immediate feedback on the consequences. The most critical area with the highest installation density was the central service shaft.

Once equipment arrangement was established, piping was planned. This was solely done using the electronic tools of the 3D CAD system. Isometrics planning involved paper only once: at the end for the plots to go to manufacturing and construction. All piping was modeled for process and utility systems, independent of size. State-of-the-art 3D CAD systems have multiple layers, each to accommodate a different design discipline. The project team used 25 layers. Because the model grew so complex and dense, only up to two layers could be shown at once for visualization.

Parallel to piping, HVAC ducting, sanitary routing, and electrical wiring routing were modeled.

Finally, the interior walls and hanging ceilings were included, a unique challenge for the project team as every wall or ceiling penetration had to be equipped with a GMP qualified sealing.

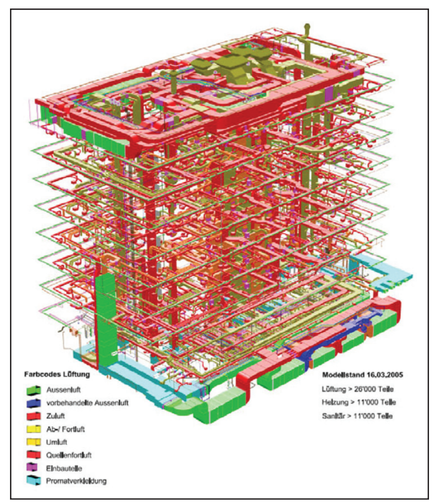
"The power and efficiency of the 3D CAD model ultimately becomes apparent as one imagines to overlay all the discipline layers," said Riekert. "It is the only tool that allows reliably arranging everything properly and identifying upfront clashes that become more costly to remediate the later they are identified."

Integrated Project Schedule

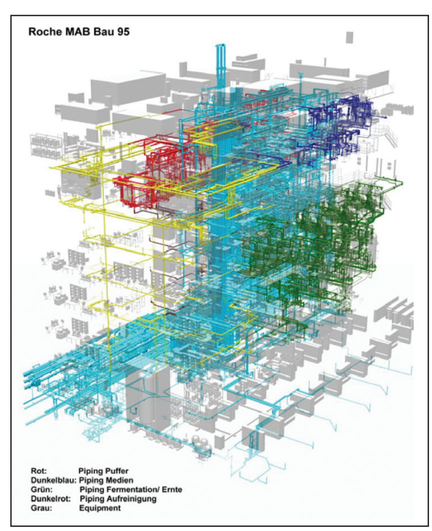
Since the facility had to be arranged vertically and all systems are fully integrated (piping as well as automation), the normal option of sequential completion proved to be too slow when modeled in the schedule. This forced the project team to develop the strategy and tactics necessary to complete the whole facility as a single entity, i.e., work on everything in parallel.

High emphasis was placed on meticulous planning and scheduling of tasks. Each item in the facility 3D CAD model was linked to an activity in the project schedule. The construction logic was established, reassembling the 3D CAD model from excavation to 100% mechanical completion. This construction logic was transferred to the schedule to confirm the schedule scope. The resulting integrated schedule was used to set specific interrelated design, manufacturing, FAT, delivery, installation dates. Suppliers were fully integrated into team scheduling, synchronized timing, and delivery routes.

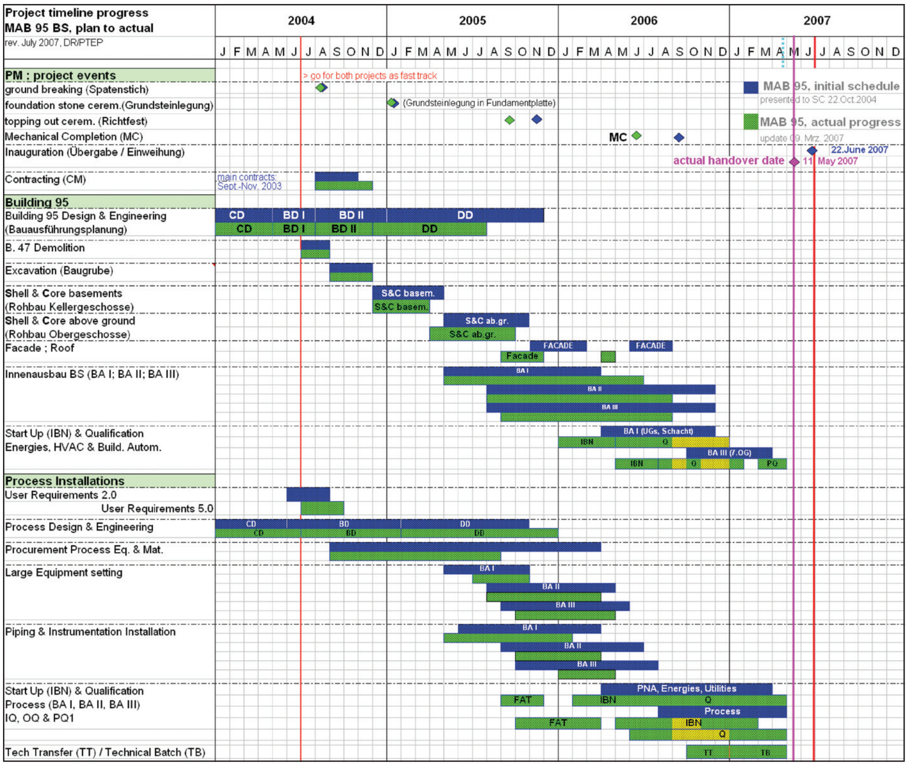
Progress was monitored in real time, down to the pipe spool level, and the schedule was updated daily. Great attention was focused on weekly progress reviews where the achieved physical progress for all disciplines was audited and corrective actions were agreed upon if any schedule slippage was identified. A primary focus for the project team was the synchronization of the interfaces between phases. This assured seamless workflow not only in the distinct project phases, but also through these interface periods. This removed productivity



HVAC layer in 3D CAD.



Equipment and piping layers in 3D CAD.



Project overview schedule.

reduction often seen during funding period activities when a project team is focused on securing funding for the next project phase.

The following are highlights of the many activities that ran in parallel and the multiple acceleration programs the project team employed:

- After the project start in July 2004, the building's basic design was accelerated to apply earlier for a construction permit, typically a lengthy process due to site location in a residential zone.
- Demolition of existing building started immediately with excavation work starting two months later.
- Procurement for the building shell trade contractor and the other major building trades started immediately to facilitate an early construction start.
- An extensive procurement program based on competitive bidding was coordinated with the Biologics IV project in Penzberg.
- Exhaustive acceleration program during detail design mainly for piping isometrics, HVAC ducting, and electrical wiring supported an early start of mechanical installations.
- A sophisticated building construction schedule secured six weeks for a basement floor and three weeks for a super structure floor.
- Infrastructure mechanical installation in the basement began, while the concrete for the aboveground floors had yet to be poured.
- Acceleration program for piping and HVAC installation.
- Since all mechanical systems were interconnected, commissioning, start-up, and qualification of utilities and process units were performed in sequence.
- The start-up team was staffed as much as possible with future production crews.
- Introduction of technical batches (non-qualified runs under production conditions) during start-up allowed for early detection of flaws and reduced time for remedial work.

Construction Outside of the Box

The confines of the site made it necessary to rethink construction set-up. Besides just in time materials delivery, all containers for construction staff were placed on top of steel structures, leaving the place underneath free for traffic. Even the sky space above major roads was occupied.

The project team organized and coordinated trades and workforce on the construction site (at peak time, more than 500 workers) to assure uninterrupted workflow and under the pressure of constant competition for space to work. Project sourcing for trades, labor and machinery was Europe-wide. At peak loading, 24 different languages were used on the site. "This put 'tool box' safety talks into a completely new area," said Project Manager Daniel Riekert. "Putting Safety first in team thinking

Construction staff occupied an office that was elevated above the main public roadway.

and enforcing this every day, rewarded the project with just 4 lost time accidents on 1 million workhours, no fatalities and therefore an exceptional safety track record, by factors better than typically seen. Fast track does not mean consessions to Safety, rather it can be done in a compatible manner."

The team established and managed a "just in time" delivery concept of equipment, materials, and pipe spools to the workforce. At peak times, one truck off-loaded every 20 minutes. To reduce congestion in and around the tight project site, cutting-edge communication technology was applied whenever possible in the day-to-day running of the project. Extensive use was made of video conferencing, documentation was exchanged via the Internet prior to joint reviews, site access was restricted to key personnel, and all project participants were encouraged to conduct as much communication as possible through electronic media. This allowed a large reduction in travel time and cost.

Commissioning/ Validation Strategy

Commissioning and start-up was performed by 18 start-up teams and seven support teams, which operated on a seven day/week-two shift model for the majority of the project.

Qualification was performed by seven start-up teams and seven support teams (production staff), which operated on a five day/week-one (extended) shift model for the majority of the project.

The whole facility is based on the modular design concept, which served as the basis for both process and automation design. Through this technique, a "high copy effect" was achieved when implementing the required functionality. This allowed the team to adopt a bracketing concept to the modular design.

The Technical Acceptance Tests (TATs) performed on every installed system were highly standardized and reproducible. This led to a considerable reduction in man-hours and to a significant efficiency increase.

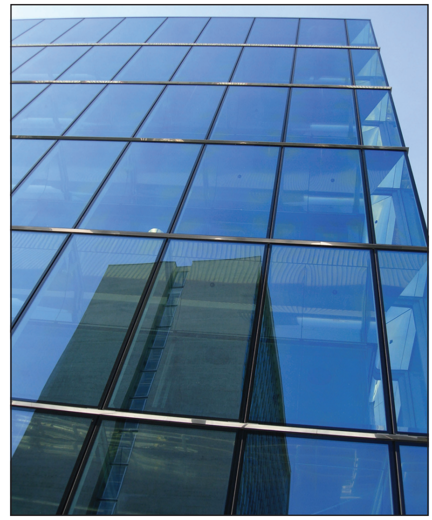
Further efficiency increases and a reduction of qualification timelines were achieved by using documentation from Technical Start-Up and Factory Acceptance Tests (FATs) for the qualification projects. These measures required close coordination of the start-up and qualification teams.

Project Management Approach

High ethical standards were set for project management and leadership. The primary areas of focus were on:

- teamwork and team motivation
- engagement and empowerment of team members
- building an environment of integrity and trust in the team
- working together with contractors and suppliers in a spirit of open team partnership

"No blame, fix the problem," was an overriding principle that led Roche's integrated project team. A Roche philosophy is to take ownership and actively manage project risks instead of delegating them. Support was provided by all parts of the Roche organization and their experts as critical issues surfaced or interfaces were to be managed. The project was able to call for additional support anytime and was given priority. Peer reviews for design and project management were carried out by colleagues from the worldwide Roche engineering network.



Roche's MAB Building 95.

Much effort was invested in project definition (e.g., user requirements) and project execution planning during project initiation, where organizational setup, roles, responsibilities, and execution strategies were defined to support achievement of project goals. Best practice engineering processes were applied in all disciplines.

Key Project Participants

Owner: Roche Biotech Basel
Engineering: Roche Pharma Global Engineering and Roche Basel Site Engineering
Designer/Architect: Herzog & deMeuron, Basel, Switzerland
Main/General Contractor: Linde-KCA, Dresden, Germany
Construction Manager: Bovis Lend Lease, Munich, Germany (Liquidated)

Engineering Subcontractors
Axima – Basel, Switzerland (HVAC, Sanitary in CD, BD)
IB Mayer – Ottobrunn, Germany (HVAC, Sanitary in DD)
ZPF – Basel, Switzerland (Statics)
Emmer – Basel, Switzerland (Façade Planning)
Kiwi – Dübendorf, Switzerland (Electro Planning)
IP Hage – Neckartenzlingen, Germany (Cleanroom Planning)
P. Burkart – Schindellegi, Switzerland (3D CAD Isometric Planning)
CTE – Liestal, Switzerland (Automation, DCS Planning)
Penta-Electric – Basel, Switzerland (Automation, DCS Planning)
Netzhammer – Basel, Switzerland (Automation, DCS Planning)
Etavis – Basel, Switzerland (Automation, DCS Planning)
onoff – Basel, Switzerland (Automation, MES Planning)
Penta-Electric – Basel, Switzerland (Automation, MES Planning)

Third Party (Qualification)
LSMW – Stuttgart, Germany
VTU – Graz, Austria

Current project control best practices are standard processes in Roche and are successfully applied in all Roche projects. Special efforts were made on controlling the scheduling of critical path items and on the enabling of early commissioning of 100% completed systems. Together with focused acceleration programs, these were the most important planning measures for schedule reduction.

Sophisticated resource planning including the application of different shift-models ensured staffing levels, avoidance of work overload, especially on the user side and automation, and enabled recruitment of the plant operatives to be complete early in the project.

Since the production group had to be established from scratch by recruiting knowledgeable operators, some of whom were new to biotechnology and without specific experience, intensive training programs were established. In cooperation with the Zürich College in Wädenswil, training was provided in theoretical background, and experience with large scale production was shared by colleagues from Roche Penzberg and Genentech.

Major Equipment Suppliers

Equipment Type	Manufacturer	Location
Fermentation	Bioengineering	Wald, Switzerland
Fermenter Vessels	Bioengineering	Wald, Switzerland
Separator	Alfa Laval	Tumba, Sweden
Purification	Millipore	Molsheim, France
CIP, SIP	GEA Dissel	Niedersachsen, Germany
PW-, Pure Steam-Generation	Pharmatec	Wiesbaden, Germany
Filter	Pall	Dreieich, Germany
Filter, Columns	Millipore	Molsheim, France
Filter Stations	Sartorius	Goettingen, Germany
Cryovessels	Stedim	Fribourg, Switzerland
Cryovessels	Zeta	Graz, Austria
Media Prep. Vessels	Mavag	Neunkirch, Switzerland
Buffer Storage Tanks	Glatt	Wiesbaden, Germany
Buffer Storage Tanks	Karasek	Gloggnitz-Stuppach, Austria
Water Tanks	Apaco	Grellingen, Switzerland
Autoclaves	Sauter	Basel, Switzerland
Wash Machines	Sauter	Basel, Switzerland
HTST System	Calorifer	Elgg, Switzerland
Membrane Valves	Gemü	Ingelfingen, Germany
Steam and Condensate	Ramseyer	Flamatt, Switzerland
MCC Cabinets	ABB Swiss	Baden-Dättwil, Switzerland
Trafos	ABB Secheron	Baden-Dättwil, Switzerland
Low Voltage Cabinets	Balzaretti & Frey	Udligenswil, Switzerland
HMI (Human Machine interfaces)	Gecma	Kerpen, Germany
Laboratory Furniture	Renggli	Rotkreuz, Switzerland

Major Trade Contractors

Trade	Contractor	Location
Master Builder	Batigroup	Basel, Switzerland
Facade	Ernst Schweizer	Hedingen, Switzerland
Facade Cleaning Lift	PK Küpfer	Glattbrugg, Switzerland
Piping	MCE	Salzburg, Austria
Insulation	Novisol	Basel, Switzerland
HVAC, Sanitary	Axima	Basel, Switzerland
Steel Structures	Schauenberg	Kirchzarten, Germany
Insulation	Novisol	Basel, Switzerland
Elektro	Selmoni	Basel, Switzerland
Elektro	Etavis	Zürich, Switzerland
Automation, Controls, BMS	Siemens Swiss	Zürich, Switzerland
Cleanroom Systems	Daldrop & Huber	Neckartailfingen, Germany
Doors	Dreier	Kleinlützel, Switzerland
Suspended Ceilings	Isolag	Zürich, Switzerland
Raised Floors	IFM	Buchdorf, Switzerland
Plasterer	Canonica	Basel, Switzerland
Roofing	Marx Flachdach	Muttenz, Switzerland
Fire Alarm System	Siemens Cerberus	Männedorf, Switzerland
Smoke Ventilation Systems	Mistral	Wien, Austria
Floors PVC	Regio	Allschwil, Switzerland
Floors Epoxy	Repoxit	Winterthur, Switzerland
Lifts	Schindler	Ebikon, Switzerland
Painter	Heinrich Schmid	Lörrach, Germany
Painter	Schweizer Söhne	Basel, Switzerland
Carpenter	Tschudin	Basel, Switzerland

Procurement Strategy

The project core team's behavior toward procurement was very cost-conscious. That guiding behavior, coupled with an economy of scale at market, resulted in substantial savings. What was planned was built with no significant changes during execution.

In the competitive bidding process, the Roche team resourced to bid 200 packages in a planned sequence. Packages were split among several suppliers to mitigate risk. Procurement was closely coordinated with Biologics IV, the sister project in Penzberg, Germany running parallel to MAB Building 95. Reimbursable cost contracts with prime contractors and incentives were beneficial.

For the project core team, procurement didn't end with the contract award. A high emphasis was placed on safeguarding timely delivery to the site.

Conclusion

Delivering an ultra fast track biotechnology facility is a huge challenge for a project manager by itself. To combine this challenge with the added dimension of a restricted site footprint, city center construction logistics, residential neighborhood, and a star architect with strong views on design and material selection called for innovative project management techniques. The project team at Roche Pharma Biotech Production Basel shined while delivering an ultra fast-track, completely unique, vertical MAB facility. Every aspect of this project had to be flawlessly executed to accommodate the many challenges of the site, location, and facility design.

"Delivering the project under budget and six weeks ahead of schedule seemed unimaginable when we started," said Riekert. "But the enthusiastic commitment of the project team to rise beyond limitations, delivered a world class project we are very proud of and will keep in best memories."