This case study presents the issues addressed when designing and constructing a pharmaceutical production facility in Eastern Europe.

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Developing a New Pharmaceutical Facility in Eastern Europe

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Introduction

This article presents a case study of the issues to be addressed when designing and constructing a new pharmaceutical production facility in Eastern Europe. Solutions to the expected difficulties were developed which overcame the differences between Eastern and Western European methods and standards. This applied particularly to cGMP, regulatory issues, construction time, cost, quality, available materials, codes, culture, contractual ethos, and language.

The Brief

The requirement was to design and build a new tablet production plant on an existing pharmaceutical site in Bulgaria to produce approximately three billion tablets per year for large volume generic formulations of plain or coated types with possible addition of hard gelatine capsules and effervescent tablets at a later date.

Key criteria were to:

- have the facility in production as soon as practically possible
- create flexible space with a capability for expansion
- provide cost effective construction with low maintenance and energy costs
- provide an efficient and pleasant professional working environment
- provide visible confirmation of the operating company's commitment to activities in Bulgaria
- comply with cGMPs binding on Bulgarian pharmaceutical manufacturers from April 2003 and subsequent MCA requirements
- ensure all local authority requirements with respect to planning, en-

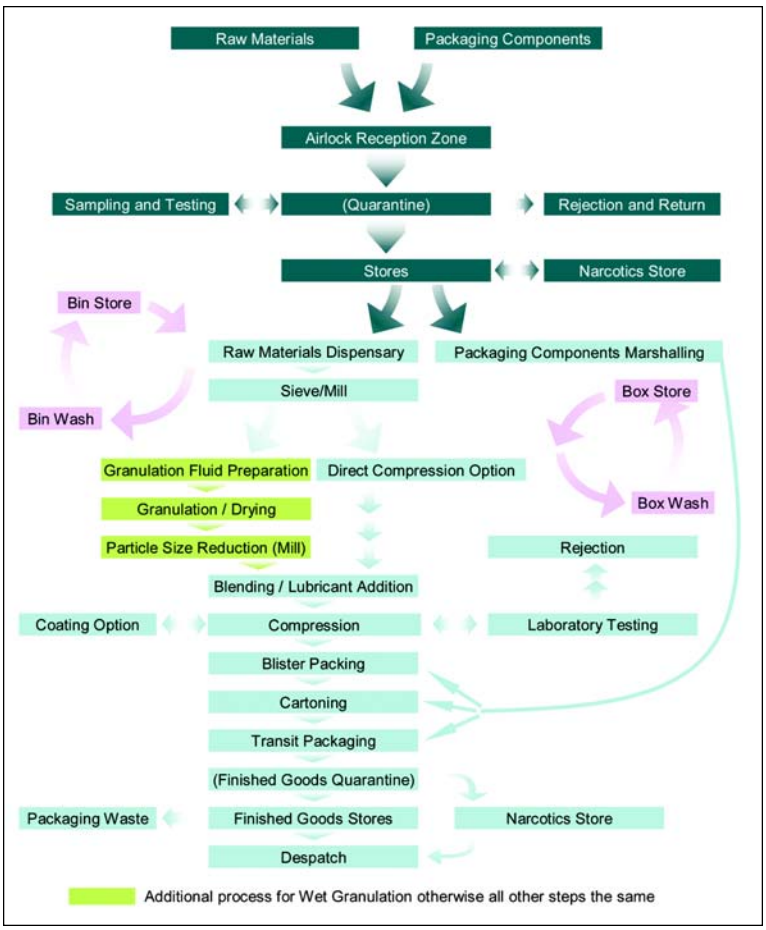

Figure 1. Production of coated or non coated tablets by direct compression and wet granulation.

vironment, approvals, health and safety, etc. are understood and aim to comply

The Strategy

Owing to their limited in-house resource, the operating company (based in Iceland) chose to employ an international company, specializing in pharmaceuticals (based in London), which could both design and support the construction of the project. Expertise in pharmaceutical projects was the key ingredient and the single source would ease and minimize lines of communication and reduce the possible conflicts of split responsibilities.

It was agreed that the management language would be English, and that at site level, the language would, of necessity, be Bulgarian.

The concept proposals, preliminary drawings, and specifications would be designed to meet UK standards and would be in English. The detailed engineering drawings also would be produced as for the UK, but a Bulgarian consultant would modify them to meet local requirements.

Similarly, to gain the operating company's board approval and to move the project ahead quickly, cost and time targets were to be set as though it were a UK project, but it was acknowledged that Bulgarian costs may be less and the time requirement may be longer than in the UK. These targets would be adjusted when more information became available.

The implementation of the work was based around tendering 45 individual sub-contract packages to allow sequential progress and reduce the time period required for a single contractor tender. It also was considered that the risks involved in using one contractor would be mitigated.

The Concept

Optional design layouts were developed to produce combinations of possible process and packaging options for an initial output of two billion 500 mg tablets. Initially, products were

Figure 2. Concept layouts.

to be solvent based followed subsequently with aqueous based.

The variances developed were based on the following:

- Two billion 13 mm (500 mg) tablets by direct compression - uncoated
- Four billion 7-9 mm (250 mg) tablets by direct compression - uncoated
- 1.5 billion 10 mm (250mg) tablets by wet granulation
- One billion coated tablets
- 1.5 billion tablets in blister packs - minimum of 10 tablets per carton

The above figures were dependent on achieving good Overall Equipment Efficiencies (OEE) and this was difficult to determine in Bulgaria. In practice, during start-up, the learning curve involved would influence the OEE.

The capacity of the plant was to be doubled with the introduction of additional process equipment. However, it was initially based on two shifts: seven hour days x five days over 250 working days per year.

To develop the processes, generic production procedures as depicted in Figure 1 were used to establish the outline requirements.

An optimum layout as indicated in Figure 2 was agreed based on the operating and design company's experience of the needs in Iceland and the UK while ensuring full compliance to regulatory requirements. The Bulgarian operators and engineers agreed with the layout and flow arrangements. Nevertheless, based on their experiences in Eastern Europe, they believed the facility should be 20% larger than the planned 4,600 sq.m. (49,725 sq.ft.) solution. This was their view on most elements of the design – large 'built in' factors of safety.

The agreed scheme allowed for a sampling booth, two dispensing booths, two granulation and fluid bed dryer suites, blending, six tablet press suites, two coating suites, one capsule filling suite, automatic IBC wash station, four blister packaging, cartoning and over-wrapping suites, and generous work in progress areas with design for future expansion.

The Preliminary Design

To keep the project moving quickly, a decision was made to undertake preliminary engineering using UK design standards, but modified to take into account the known Bulgarian standards at that time.

A review was made of Bulgarian methods, capabilities, and their ability to meet known Western standards. Although masonry was the normal form of construction for the building envelope, steel and metal cladding were available at reasonable cost, although not commonly used. This was considered desirable for speed and flexibility for the future. Internal finishes were available to meet the required cGMPs. However, application techniques were yet to be explored.

Basic Bulgarian design codes were incorporated into the preliminary design, such as seismic codes, floor, roof and wind loadings, summer and winter dry and wet bulb conditions.

The concept design was developed using the information obtained, but maintaining the operational and cGMP features.

All production areas were designated to Class 100,000. However the design was to consider achieving Class 10,000 in the future without involving any major modification to the construction, fabric, or finishes.

Pressure regimes were established whereby movement of air through the various areas satisfied the requirements for containment of powders and elimination of risk of cross contamination. At the same time, all designated clean areas for dispensing, production, and packaging were maintained at positive pressure (10Pa) relative to external atmospheric pressure, thereby preventing ingress of unclean air from outside.

The possibility of manufacturing effervescent tablets meant certain production areas required a low humidity environment. This was achieved by incorporating regenerative chemical dehumidifiers on systems serving the specified areas.

The cleanroom pressures, temperatures, and humidities were designed to be monitored by a Validated Building Management System which would have the capacity to monitor and record all room data for a year's operation. The system was designed to provide a separate "back up" facility.

The central pure water system was designed to provide pure water to USP24 standard to serve clean-in-place systems, IBC automatic wash station, laboratories, and small parts wash areas.

To minimize operational cost of the air conditioning systems, the ratio of fresh air to re-circulated air was selected at 20% to 80%. To avoid any cross contamination with this high percentage of re-circulated air, filters were installed on the return air systems in addition to the main EU 11-HEPA filters on the supply systems.

Estimating the cost of the building, services, and process equipment was based on UK costs although it was recognized that the cost of the building should be less than the equivalent in the UK so a comfort factor was built in.

All new production and packaging equipment was sourced and costed from Western Europe suppliers.

Similarly, a design and construction program was produced as though the facility were to be designed and constructed in the UK, which would give a challenging target for Bulgarian sub-contractors.

Based on the 30 preliminary drawings, the cost plan and program produced, the board members of the operating company were able to confidently make an informed decision that the proposed solution would meet their business plan requirements for the Bulgarian facility.

Local Authority Requirements

In order for the UK staff to understand the local authority approval process, considerable time and effort was devoted to the subject as some of the materials, methods, and techniques used in Western Europe were not generally available in Eastern Europe. Importing material was not an easy option as it would take time for them to be accepted by local authorities. This caused several difficulties throughout the project, requiring very careful discussion and negotiations

with local and national authorities. Some examples are listed later in this article under Observations and Recommendations.

In Bulgaria, there are explicit approval stages known as Protocol 1 to 17. Each Protocol needs to be completed sequentially and the authorities will not accept parallel execution. Whereas in the UK, once planning permission is granted, construction work can progress awaiting building regulation approval - although at risk. In Bulgaria, one would be penalized with a fine if this process was followed. However, with some careful tactics and negotiations, the UK company was able to move quicker than the normal process.

The process is very complicated, and one should not rely purely on reading material.

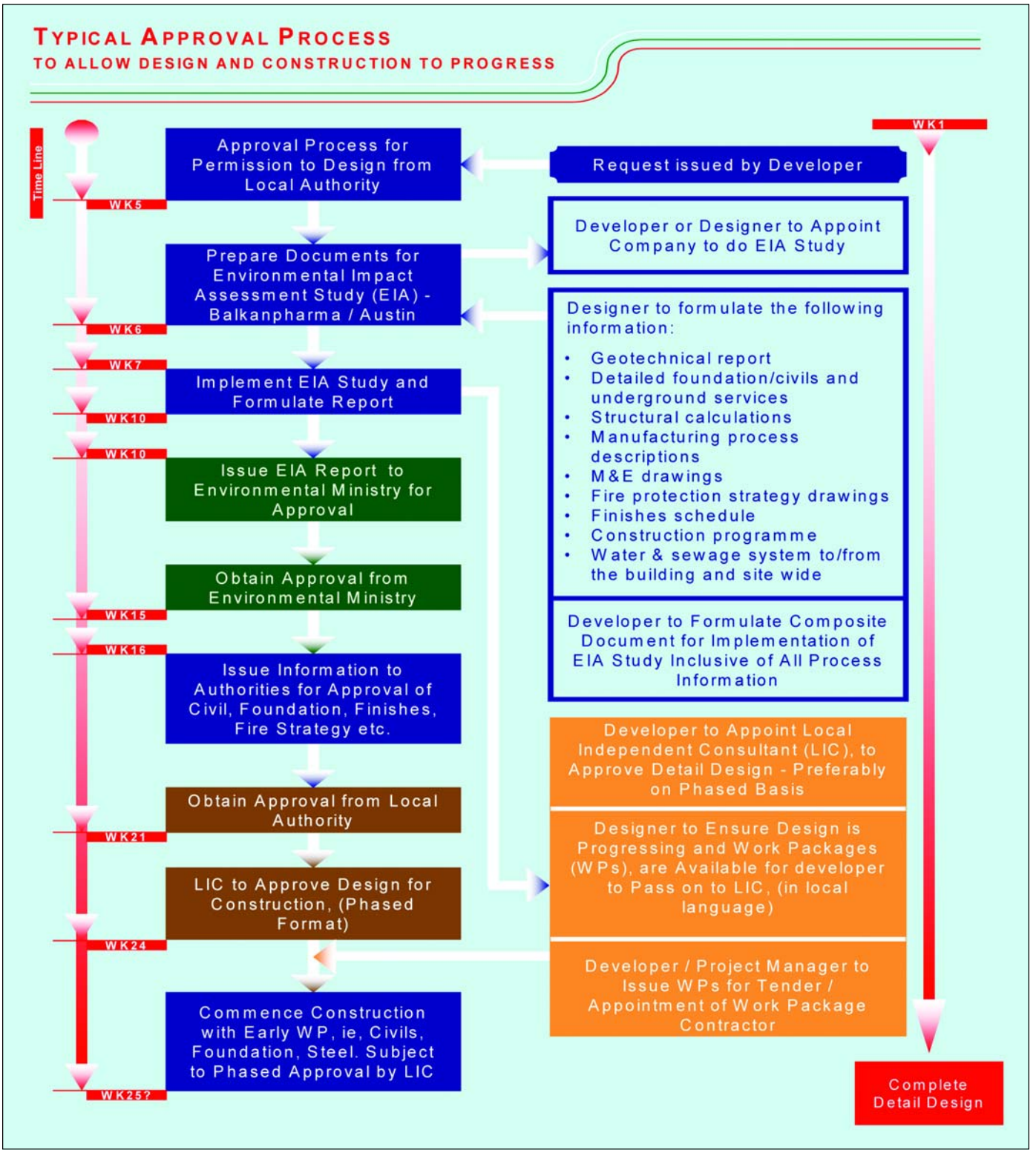

Figure 3. Typical approval process.

Before one considers all protocols in detail, Protocol 1 is the most significant - ***"Permission to Design"*** and ***"Permission to Build"*** is required from the local authority. This process is described in Figure 3 and is usually initiated by the developer.

Preconstruction Stage Approval Process

Once Protocol 1 has been obtained, which could take up to six months, the construction process begins. This is where the requirements must be understood in detail.

Scheduled below is each protocol with information needed. This has been extracted from their National Regulation No 7 -22.05.2001 - statements and protocols issued during the building period.

Protocol No 1 - the site is handed over and accepted by the Contractor and the design is approved for execution. Formal permission is granted from the Mayor's office issued by the Chief Architect.

Protocol No 2 - building site is allowed to formally open to allow building lines and levels to be agreed.

Protocol No 3 - the site book/diary certified from the National Building Supervision Directorate is issued for recording all future activities.

Protocol No 4 - formal hand over/acceptance of all technical documentation.

Protocol No 5 - statement for the building terrain certifying and complying with the detail drawings setting out base building coordinates.

Protocol No 6 - statement certifying soil category and actual excavating working levels.

Protocol No 7 - statement for acceptance of the actual building/assembling works by levels and details.

Protocol No 8 - statement for acceptance of the foundation works for construction.

Protocol No 9 - statement for acceptance of the shuttering, reinforcement and welded works.

Protocol No 10 - deviations from the design dimensions according to Regulation No 3 for the acceptance of the concrete works.

Protocol No 11 - statement for the acceptance and transfer of equipment.

Protocol No 12 - statement for determining the building condition in case of stopping.

Protocol No 13 - acceptance of the completed metal construction corrosion protection.

Protocol No 14 - determine status of all hidden works: concrete foundations, back fill, lintels, masonry, cavity insulation, heat insulation, vapor barriers, internal/external doors, windows, etc. Statement for the building construction acceptance.

Protocol No 15 - statement to confirm the building is ready to be accepted for use. This includes:

- completing 72 hours running test on all systems including mechanical, electrical, drainage, process and production equipment, lifts, etc. and certificate of conformance of any specialist material
- written permission to use imported materials not in accordance with relevant Bulgarian standards and protocol from the licensed Bulgarian laboratory for the imported materials approved by the Ministry of Building
- approved detail drawings and statement of compliance with the design parameters
- Results from 72 hours test on all services. Acceptance Certificate for completion of all works from the relevant authorities including the incoming services supply company, the Regional Inspectorate for Environment and Waters etc.
- statements of completion from the Main Contractor
- proof of ownership and permission to build on territory of someone else's property – if applicable
- environmental impact assessment
- card for assessment of influence on site environment in comparison with the original samples taken at the start
- certificate for achieving the set design parameters within the whole facility
- statement from Occupational Health and Safety Authorities allowing the building to go into operation
- statement from the Fire Fighting Emergency Regional Service
- document issued by the Cadastre Agency (Local County) for building survey, underground technical systems, and equipment survey in attendance with the Cadastre Agency

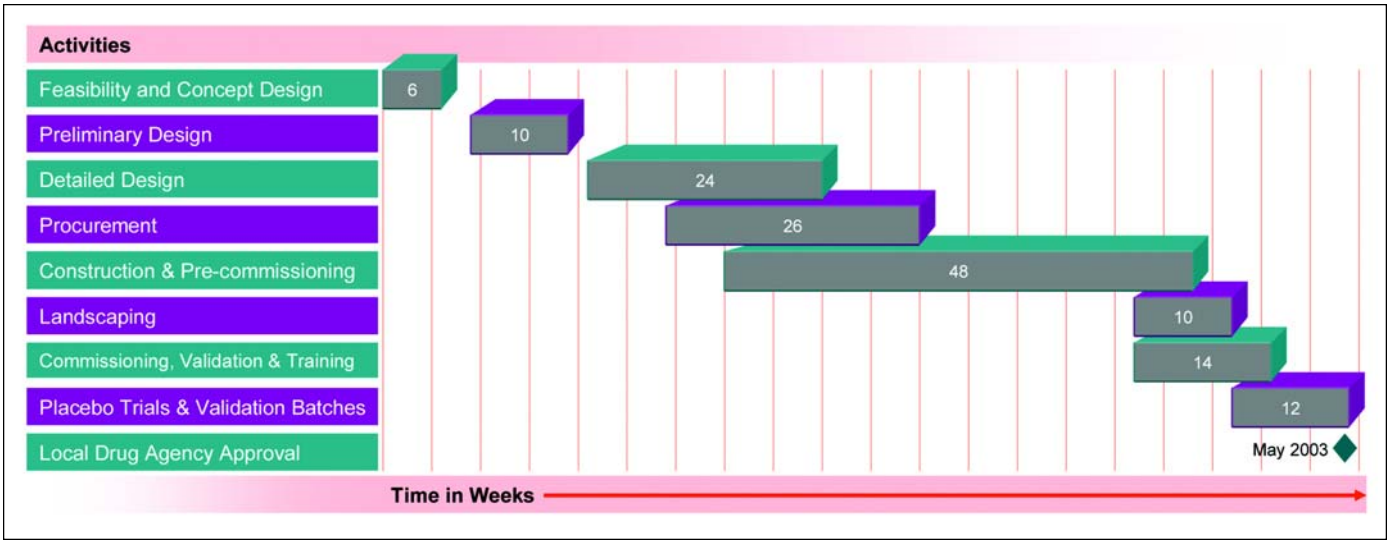

Figure 4. Time schedule for key activities.

- letter of appointment from the employer confirming the staff employed, inclusive of log for health and safety induction for all staff

- statement from the Chief Architect of the municipality for law conformity, validity of issued construction documents, and conformity of performance with the above documents, and for compliance with the requirements of Article 68, Article 178, Paragraph 3 of the Law of Territory Management

- statement from the designers confirming compliance of their respective design to the finished works

Protocol No 16 - (where applicable) Certificate for establishing the suitability of the building for use. This certificate is drawn up by the employees assigned by the chief of National Construction Control Directorate or authorized by him/her employee whose name is included in the Letter of Appointment for State Acceptance Commission in line with Ordinance No 6 of 2001 for issuing Permission to Use the Building in Republic of Bulgaria.

Protocol No 17 - (where applicable) Certificate of completing any non compliances/defects based on the decisions of State Acceptance Commission under Protocol 16.

The operating company's in-house engineering resources assisted with this complete process.

Detail Design and Construction

The detailed design drawings and specifications were produced in the UK with support from two Bulgarian architectural technicians to assist translation of codes into English.

The authorities stipulate that all designs by foreigners must be certified by local designers and a local independent supervisor must ensure correct implementation of work on site in compliance with local codes and maintain a fully itemized site diary of all events.

A local consultant in Bulgaria was employed through the detail design process to assist in converting the necessary information into Bulgarian for local authority approvals, and assist with interpretation where necessary to ensure the designs met with the local codes and standards.

The operating company and UK design company agreed that no compromises should be made on material and equipment selection, and that they would be in line with what would be used in Western Europe. However, the operating company requested that every effort must be made to source as much material locally as possible.

The complete project was overseen by the UK company's project manager on a visiting basis throughout the detail design, procurement, construction, commissioning, and validation with a "very hands on" approach with the operating company's project manager supervising the 'day to day' issues on site.

The detail design was prepared in 45 packages to allow early start on site and provide better control of subcontractors although this caused difficulties with local authority approvals. However, the situation was managed.

To assist the project with professional procurement services, a quantity surveyor was needed. In Bulgaria, quantity surveying is not a recognized profession. However, an expatriate quantity surveyor was sourced and hired to assist with the procurement, cost reporting, and administer the tender process.

Each work package was tendered individually. The companies were selected by placing several advertisements in local and national newspapers inviting them to formally show their interest. Short lists of six companies were selected for each package by interviewing up to eight companies. The selection criteria included review of their past experience, management capability, engineering and technical expertise, labor skills, resources availability, responsiveness, ability to work with English drawings and specifications, quality of past work and documentation, demonstration of team working, financial status, cost etc.

The final selection was undertaken by the operating company with assistance from the UK company's project manager.

Each sub-contract package was managed in the same manner as in the UK. The process for tendering, procurement, cost control and monitoring, valuations etc. was accomplished using the UK company's standard procedures extending to changes, variations, and settlement of final account with each individual contractor.

An expatriate construction manager and a building services engineer were assigned full time on site to assist the progress and coordination of the work to the proper quality standards and program. In addition, each discipline designer from the UK attended the site regularly to assist with monitoring quality, coordination, checking specifications of installation, providing training where necessary on construction methods to be employed, and liaising with authorities when allowed.

It was found that the Bulgarian operatives can produce good quality work if properly supervised, but productivity was low. This was overcome by increasing the labor force and maintaining a high level of management on site. Toward the end of the construction period, a few key tradesmen, in particular electricians, ductwork, and pipe work installers, were sent from the UK to protect the program.

Installation work of mechanical, electrical, and process works was organized by the UK company with final commissioning of the mechanical systems being undertaken by a UK company, overseen by a local commissioning company because commissioning engineers must be certified by the local authorities.

The UK company was involved in the validation process from the onset by assisting with writing the User Requirement Specification, Validation Master Plan, chairing Design Qualification reviews, and preparing all Installation and Operational Qualification - Validation Protocols. The on-site activities were supported by the operating company's personnel to ensure cGMP compliance in association with their quality department.

The operating company's Quality Department was involved in the complete process from the start as this was their first facility that would go through the full validation process. This proved to be vital training for them. Although they had good theoretical knowledge of the requirements, they appeared to lack experience in the actual process.

On completion of the facility, the UK company supported the operating company in planning all key activities required in attaining a functional facility including local drug agency approval, management of training, placebo and validation batches, variation licenses, and planning for a MCA inspection.

Observations and Recommendations

1. There are excellent engineering skills in Eastern Europe, but their normal design standards are generally quite conservative. Western European skills can bring more finesse and higher technical inputs to the design

Figure 5. Granulation and fluid dryer suite.

2. It is important that good relationships are developed with the relevant authorities and encouragement of their input will strengthen the project team.

3. The approval process is complicated and extensive. Any one considering a project in Eastern Europe must understand the requirements for each stage.

4. Language can cause misunderstandings. Therefore, it is important that the team is appropriately strengthened with bilingual personnel.

5. Prepare well defined engineering drawings and specifications. Do not leave anything to interpretation.

6. The need for a good strong project and construction manager is a key requisite and everything must be closely followed – checked and double checked. Do not leave anything to chance.

7. Productivity is lower in Eastern Europe, but this can be overcome by increasing the number of operatives. Strong supervision on site is essential.

8. The professional team must be open minded and proactive to deal with issues and perceived barriers as they arise and not get frustrated. Local companies have a set way of working in their country which has not been challenged by western society in the past.

9. Some locals were initially apprehensive about working with western organizations, and particularly about being supervised by UK employees. However, experience demonstrated that with a careful tactical approach and sensi-

Figure 6. Completed facility.

tivity about remuneration differentials, this could be overcome.

10. Daily and weekly monitoring of short and long term program was a mandatory task as reliance could not be placed purely on reported progress by contractors.

11. Working to a budget, program and ensuring quality was a new concept for the locals and required constant reminding from the management team.

12. Local materials are worth investigating if time is available as they are cost effective. However, quality is questionable.

13. The site was purported to be a clear brown field site, yet more than 100 hundred barrels of contaminated waste and a nuclear fall out shelter were found in the ground. These were not identified in the topographic and geotechnical investigations by local companies.

14. The Fire Authority would not accept boarded structural columns to obtain the fire resistance. Hence, they had to be concrete encased. In some areas, solutions offered for fire protection were not acceptable. However, after considerable negotiations and justification, some were finally accepted.

15. The local consultant let the process down in some aspects of approvals due to their lack of experience and knowledge of their own regulations.

16. The water supply quality was found to be inconsistent and unreliable. Therefore, a 50 micron "back wash" prefilter was installed, although original samples did not highlight any issues.

17. The actual management of quality on site was a major issue. The following are simple examples of this:

    (a) Two courses of blue bricks were specified; these were not available in the format required with the setting out of the building and in the finish required. They were subsequently ordered from the UK to avoid delays to the project. On arrival, it was found the contractors had limited brick laying skill.

    (b) Blocks for walls are of different construction and sizes; fair-face block work was not an option because the mortar joint detail could not be achieved to the quality required. Hence walls had to be rendered. This had considerable impact on the setting out.

    (c) Concrete mixing plant was not efficient and the floor slabs had to be laid in several small sections and took considerable amount of coordination, engineering, and time.

    (d) The steel work grade specified was European. However, the contractor did not order the specified quality and quantity. This caused some delay.

    (e) Items such as safety wear, door seals, and ceiling clips were all difficult to obtain locally.

    (f) The contractors were not used to complying exactly with specifications, e.g., all external doors had to be changed twice as they were delivered to the wrong specification and color. All ceiling tiles had to be replaced for the same reason.

    (g) Local pipe/ductwork fabrication and quality of material inclusive of insulation appeared dubious. The quality of installation was also not to a good standard.

    (h) The wall finishes took more than four attempts to get to an acceptable level of quality.

    (i) All antistatic floors had to be re-laid by using a British contractor as the specification could not be achieved.

    (j) The welding on the medium temperature hot water and chilled water pipe work was poor such that a high level of resistance was encountered on the system and the pumps had to be increased in duties to avoid delay to the program.

Results

Despite the inherent difficulties of designing and constructing a facility of this type in Eastern Europe, with a positive

attitude by the team, the problems were overcome to produce an excellent facility.

Speed was a key factor and the critical time schedules met are seen in Figure 4. The overall budget cost was not exceeded. Savings were made on local contracts such as ground works, civils, steelwork, cladding, and finishes. There was an overspending on process equipment such as granulation, tablet machines, blender, blister lines, pure water plant etc. Site supervision was overspent, primarily because of the extensive checks required.

The overall cost of completion was 7.5% below the agreed budget, i.e., just more than $1 million under the $15 million budget. This was achieved by preparing good quality engineering documentation for tendering, pre-selection of companies to be invited to tender, post tender interviews to ensure compliance – technically, financially, and availability of resources; good negotiating and buying skills on the packages and a pro-active client to allow the UK company to effectively design and assist them in management of the project, yet making themselves available to respond efficiently and make decisions when required.

The quality goals were in most cases accomplished and have met cGMP standards.

However, anyone considering a similar project in the future must employ more on-site dedicated supervisors to monitor day to day installation and material quality.

The granulation/fluid bed dryer suite and external view of the facility are shown in Figures 5 and 6 respectively to demonstrate the quality achieved.

The facility has obtained its operating license from the Bulgarian Drug Agency and is in the process of being prepared for an MCA inspection for products made for the European market.

Safety standards imposed on site were in accordance with UK's Construction Design and Management regulations. These were stipulated as part of the appointment of contractors. In reality, they were difficult to impose as the correct form of Personal Protective Equipment was not readily available and there was no motivation by subcontractors to obtain them. However, the safety record on site was better than the average UK site.

Highlights of the Project

- first cGMP compliant facility design in Bulgaria
- first facility to be inspected by the MCA in Bulgaria
- first substantial pharmaceutical project in Bulgaria over the last 12 to 15 years
- facility complete within 12 months from starting on site
- facility ready for manufacturing within six months of completion of construction
- first facility validated to EU standards in Bulgaria
- probably the best pharmaceutical facility in Bulgaria if not in Eastern Europe
- quality of the finished project was generally very good and comparable to the best in the UK
- completed project cost $1 million below the $15 budget
- several cultural problems overcome successfully
- several political problems with approvals addressed successfully
- facility - available for PQ/production 18 months from the first operation on site
- formal opening ceremony achieved 12 months from the first ground breaking
- benchmark set for future pharmaceutical facilities in Eastern Europe
- pro-activeness by the operating company gave the UK company better control and management of the overall project
- the operating company managed very professionally
- safety statistics on site better than a comparable project in UK

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About the Author

Prakash Davda is the Deputy Managing Director of The Austin Company of UK Limited based in London, UK. Davda has more than 20 years of experience in the design and construction of high tech facilities throughout the UK. Throughout the last 10 years, he has been heavily involved in project activities for laboratories, pilot plants, production units, and warehousing for the pharmaceutical industry within the UK. He held the post of Principle in Charge for the Bulgarian project and managed the design, construction, commissioning, validation, and start-up teams. Davda is a member of the Institute of Electrical Engineers, The Chartered Institution of Building Services Engineers, and obtained his Masters in economics and management from The Bartlett School of Graduate (University College London) in 1995. He can be contacted by tel: +44-208-371-9000 or by email: prakash.davda@austin.co.uk.

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