Case Study:
Shanghai Johnson & Johnson Pharmaceutical Plant
Programming
Shanghai Johnson & Johnson Pharmaceutical Plant
Background

- History
  - 1994 Import Tylenol® products
  - 1995 JV with Shanghai #1 biochemical and pharmaceutical company (SJJP)
  - 1996 Constructed a liquid manufacturing and solid dose packaging facility
  - 2000 Solid dose manufacturing addition
Business Drivers

- High population and high GDP growth rate
  - 1.2 Billion population
  - 7-9.5% Growth in GDP for last four years

- Projected growth in OTC market
  - 2000  $ 2.8 Billion
  - 2010  $15+ Billion
Business Drivers

• Expiration of import license for solid bulk
• New reimbursement policy eliminates products from sub-standard plants
• Cost savings to produce locally
• Alleviate domestic capacity constraints
Original Project Scope

• Budget of $12.5 million
• Produce solid dose dry blends facility
  – Small expansion to existing facility
  – Upgrade and qualify existing facility utilities
  – Install and qualify compression coating & printing equipment
  – Validate products
Final Project Scope

- Budget of $12.5 million
- Construct a solid dose manufacturing facility
  - Add fluid bed & high shear granulation
  - Upgrade USP 23 Water and add clean steam
  - Qualify and commission facility & utilities
  - Tech transfer of solid dose processing
  - Develop and validate products
Challenges to Project Scope

• Changes in government import policy
• Pharmaceutical Bureau enforcement of GMP procedures for new facilities
• Chinese government drive for capital and technology investment
Additional Project Challenges

- Delay in management approval
  - Proposals to use existing J&J assets
  - Evaluate existing contract manufacturing laws
- No extension on date for GMP certification
Additional Project Challenges

- Continuous input from governmental agencies
  - Shanghai Health Ministry (2 Bureaus)
  - Shanghai Pharmaceutical Bureau
  - Beijing Health Ministry
  - Beijing Pharmaceutical Bureau
  - Shanghai Building Bureau
We Succeed Within Original Budget

- Acquired excess J&J assets
- Adapted program to fit a prefab building
- SJJP personnel were trained at McNeil
- Leveraged McNeil qualification expertise
- J&J compliance training was an ongoing activity
Major Achievements

• From ground breaking to GMP certification - completed in 14 months
  – Use of McNeil facility and validation standards
  – Creative scheduling of construction and qualification activities
  – Good design & field management
  – Good construction team

• Project was completed under budget
Designing Pharmaceutical Facilities in the Global Market Place

Design

Shanghai Johnson & Johnson Pharmaceutical Plant

October 2000
Building Design Concept

- Three main functional suites linked by a primary circulation corridor
Building Design Concept

- Three main functional suites linked by a primary circulation corridor
- Improved material flow/personnel flow
- Future expansion
- Isolation of "new" and "old" structure
Construction Elements

- 3 meter x 2.7 meter module
- Prefabricated metal building system shell
- CMU interior partitions with plaster finish
- Pile supported structural slab-on-grade foundation
Environmental Systems

HVAC:

- Chilled water cooling
- Low pressure "amine-free" steam for preheat, humidification and process equipment
- Constant volume terminal reheat air handling system
- Facility Management System
- Personal computer-based, networked, DiDC system
Environmental Systems

Plumbing/Process:

- Oil-free compressed air
- USP purified water
- Wet-pipe sprinkler
Environmental Systems

Electrical:

- 10 kV primary service
- Automatic power factor correction
- 220/380 volt, 3-phase power distribution
- 220/380 volt, 3-phase lighting
- Diesel-engine driven standby power
Compliance

- McNeil Consumer Healthcare Manufacturing Facility Guidelines
- Johnson+Johnson Guidelines for Design and Construction of Production Facilities, Manufacturing Operations and Clean Rooms
- USA 21 CFR Parts 210, 211 - Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs
- PRC National Pharmaceutical Supervisory Administration Pharmaceutical Good Manufacturing Practice Guidelines
药品生产质量管理规范
（1992年修订）

第一章 总 则

第一条 根据《中华人民共和国药品管理法》第九条及《中华人民共和国药品管理法实施办法》第二十六条规定，特制定《药品生产质量管理规范》（简称《规范》）。

第二条 本《规范》是药品生产企业管理生产和质量的基本准则。适用于药品制剂生产的全过程及原料药生产中影响成品质量的关键工艺。

第二章 人 员

第三条 药品生产企业必须配备一定数量的与药品生产相适应的具有医药专业知识、生产经验及组织能力的各级管理人员和技术人员。

第四条 负责生产和质量管理的企业领导人必须具有大专以上或与之相当的学历，并具有药品生产及质量管理的经验，能够按《规范》的要求组织生产，对《规范》的实施和产品质量负全部责任。

第五条 药品生产和质量管理的部门负责人应受过高等专业教育或具有相当学历，必须具有药品生产和质量管理的实践经验，有能力对药品生产和质量管理中的实际问题作出正确的判断和处理。
Production areas may require more lighting. Production workshop areas should have emergency lighting installed.

**Article Fourteen:** To meet product quality requirements, spaces may be divided into areas of different cleanliness levels. Air in the factory rooms must be measured for particle and bacteria counts, and the results must be recorded.

### Room Cleanliness Levels and Air Changes

<table>
<thead>
<tr>
<th>Cleanliness Class</th>
<th>Particle Count / Square meter</th>
<th>Live Bacteria Count / cubic meter</th>
<th>Number of Air Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 100</td>
<td>≤ 3,500</td>
<td>0</td>
<td>≤ 5 Vertical flow 0.3 m/sec</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 10,000</td>
<td>≤ 350,000</td>
<td>≤ 2,000</td>
<td>≤ 100 Horizontal flow 0.4 m/sec</td>
</tr>
<tr>
<td>Class 100,000</td>
<td>≤ 3,500,000</td>
<td>≤ 20,000</td>
<td>≤ 500 ≥ 20 changes/hr</td>
</tr>
</tbody>
</table>

(Note: Fed. Std. 209E Table 1 does not identify air changes)

**Article Fifteen:**

Class 100 clean rooms should be used in production where sterile environments are needed, in which the final container may not have any sterilizing agents (before the final fill and seal, it is not necessary to filter out all bacteria), before filling and sealing; for large dose size injectables (≥ 50 ml); when sterilizing agents can be used in the product container filters and filling processes; for packaging and filling of powdered injectables, for sterile raw material chemical powders, refining, drying and packaging.

Class 10,000 clean rooms should be used in production where sterile environments are needed in which the final container may not have sterilizing agent additives. (It is necessary to filter out bacteria before final filling); for compounding of large injectables and compounding, filtering and filling of small dose injectables (< 50 ml); for compounding, filtering and filling of eye drops; for compounding, filtering, and filling of oral medicines (not steam sterilized); for filling and packaging of oils, lotions, creams, etc. without sterilizing agents in the final package; for refining, drying, and packaging of raw material powders.

Class 100,000 clean rooms are used for production in tabletting, encapsulating, chewable production, etc. and for refining, drying and packaging of bulk chemicals.
General vs. Specific

Lighting:
- USA CFR 211.44 “Adequate lighting shall be provided in all areas.”
- Chinese GMP Chapter 3, Article 13, “Factory lighting should not be below 300 lux.”

Cleaning:
- USA CFR 211.42 Facilities should be designed “to facilitate cleaning.”
- Chinese GMP, Chapter 3, Article 10, “Boundaries between ceilings, walls, and floors, should be smooth (coved) to facilitate cleaning.”
Project Execution

Shanghai Johnson & Johnson Pharmaceutical Plant
Overall Project Timeline

- Phase 1 AR Approval: Sept 1997
- Xian Vs Shanghai Decision: Dec ‘97- Sept 98
- Phase 2 AR Approval: Dec 1998
- China Pharm Approval: April 1999
- Building Occupancy Permit: March 2000
- China GMP Certificate: April 2000
- Completion of Stability: August 2000
- In Production: September 2000
Construction Start Dates

- Piling: Dec 1998
- Foundation / Slab: Feb 1999
- Steel Erection: June 1999
- Masonry Walls: July 1999
- Mechanical / Electrical: July 1999
- Long Lead Equipment on site: Sept 1999
- Process Equipment Install: Dec 1999
- System Start Up: Jan / Feb 2000
- Building Occupancy Permit: Mar 2000
- Validation Complete: Apr 2000
Engineering / Contractors:

- Design in USA - Convert in China:
- All Contractors are Chinese except:
  - Electrical / Mechanical - China / Singapore JV
New Technology / Products

• Masonry Block:
  – New Chinese Firm - William Block (Chicago)
    • 1ST time in Minhang
      – Guardhouse / Site Office - Learning Curve
      – Used extensively throughout new plant extension
      – Results: Very Good

• Turf Block:
  – Zoning
    • Chinese requirements: 30% Green Area
    • Results: Satisfied code
New Technology / Products

- Facility Management System (FMS)
  - 1ST System In Minhang
    - Overall control of utilities - Validation
    - PLC Controlled
    - Results: Good - plant still learning
Construction Issues

• Pre - Engineered Building:
  – Contractor ordered wrong gauge for steel siding
    • Informed J&J two weeks after siding due on site
    • Contractor is still working with J&J in Thailand
    • Delayed building enclosure by two months
    • Cultural -- did not want to deliver bad news.
    • Even Managing Director did not know until 2 hours before J&J.
Construction Issues

• Construction Manager
  – Cost prohibitive
  – WWES acted as General Contractor using local China staff plus supplements
    • Used expat employees
    • Multiple local subcontractors - 15 +

• Validation of Facility Systems:
  – 1st Time in Minhang for Facility Systems
  – AHU, Compressed Air, FMS, Dust Collector, and DI Water
### SJJP Phase 3: Overall Cost Summary

<table>
<thead>
<tr>
<th></th>
<th>Budget</th>
<th>Actual</th>
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</thead>
<tbody>
<tr>
<td>Site Work</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Piling/Fdns / Slab</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>PEMB/Finishes</td>
<td>1,600</td>
<td>1,550</td>
</tr>
<tr>
<td>Mechanical/Electrical</td>
<td>3,000</td>
<td>3,500</td>
</tr>
<tr>
<td>Process Installation</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>Spare Parts</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Startup Service / Validation</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>General Conditions</td>
<td>500</td>
<td>550</td>
</tr>
<tr>
<td>Engineering(Bala and LDI)</td>
<td>700</td>
<td>950</td>
</tr>
<tr>
<td>WWES Expat</td>
<td>150</td>
<td>210</td>
</tr>
<tr>
<td>WWES Local</td>
<td>200</td>
<td>210</td>
</tr>
<tr>
<td>Contingency</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>$8,150</td>
<td>$7,980</td>
</tr>
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</table>
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Shanghai Johnson & Johnson Pharmaceutical Plant

Peoples Republic of China
Production: September 2000