GMP Design of Pharmaceutical Facilities

Process design
Layouts and Flow Diagrams
OSD Facilities
Biopharma and Aseptic facilities
Speaker - Leonid Shnayder, Ph.D, P.E.

- Industry Professor in Pharma Manufacturing and Engineering (PME) Program at Stevens Institute of Technology

- Work experience:
  - Pharmaceutical Process Development and Optimization
  - Design of Pharma Plants (Process Engineer)
    - Designed plants for Merck, Pfizer, Sanofi-Pasteur, Amgen etc.
  - Teaching in the PME program at Stevens
Speaker - Leonid Shnayder, Ph.D, P.E.

- Courses taught:
  - Intro to Pharma Manufacturing
  - Validation in Pharma Manufacturing
  - GMP in Pharma Facilities Design
  - Manufacturing of Biopharmaceutical Products
  - Manufacturing and Packaging of Oral Solid Dosage Products
  - Statistical Methods in Pharma Manufacturing

- Leonid.Shnayder@stevens.edu
PME Program at Stevens Institute of Technology

• Master of Science in Pharma Manufacturing degree
  • 10 courses (5 “foundation” plus 5 elective courses)
  • All PME courses are offered in both on-campus and online delivery modes. It is possible to earn the degree entirely online
  • Applicants must have Bachelor’s degree in science, pharmacy or engineering

• Graduate Certificates
  • Pharmaceutical Manufacturing
  • Validation, Compliance and Quality
  • 4 courses each
Current Good Manufacturing Practices (cGMP)

- cGMP is a set of regulations published by the US Food and Drug Administration (FDA)
- Most national and international agencies regulating pharma industry have similar regulations or guidelines
- cGMP regulations cover many aspects: organization and personnel, building and facilities, equipment, control of components, production controls, packaging and labeling controls, laboratory controls etc.)
- We’ll discuss aspects related to building and facilities and equipment
GMP Requirements Highlights

• Building shall be of suitable size, location and construction, easily cleanable and maintainable
• Building shall be designed to prevent equipment and material mix-ups and contamination
• Separate areas shall be provided for different operations
• Provide adequate control of air pressure, microorganisms, dust, humidity and temperature as appropriate
• Written procedures required for cleaning and sanitation
Process design considerations

• Basic unit operations
• Process configuration
• Equipment requirements
• Process utility requirements
• Waste treatment
• Process control
• Facility requirements
• Facility layout and process flows
• Cleaning of equipment and piping
Process Design Tools

- Process description
- Block Flow Diagrams (BFD)
- Process Flow Diagrams (PFDs)
- Piping and Instrumentation Diagrams (P&IDs)
- Material and energy balances
- Process and utility equipment list
- Utility requirements table
- Instrument list
- Equipment specifications and/or Data Sheets
- Piping specs
Block Flow Diagram – Tablet Manufacturing

1. Active Ingredient
2. Raw Material
3. Raw Material
4. Excipient
5. Raw Material
6. Raw Material
7. Raw Material
8. Raw Material
9. Lubricant
10. Raw Material
11. Purified Water/Solvent

Weigh

Mill/Sift

Gran Solution Prep

Granulation

Dry

Mill

Blend

Blend

Compress

Coat

Coating Solution Prep

Purified Water/Solvent
Block Flow Diagram and its Uses

• BFD identifies major process operations and their relationships to each other

• BFD can be useful for:
  • Determining the needs for process rooms/areas
  • Visualizing relationships between different rooms
  • Creating a conceptual building layout or “bubble diagram”
  • Identifying major process equipment needed

• BFD is used at very early project stages
• BFD can be considered as a precursor to a PFD – Process Flow Diagram
Process Flow Diagrams (PFD’s)

- PFD’s are graphical representations of the manufacturing process based on manufacturing instructions.
- PFD’s are reference tools that support manufacturing and assist engineers and constructors with developing facilities and equipment design requirements.
- There are no universal standards for PFD’s. Each company uses its own methodology and symbology.
- All PFD’s contain at a minimum the following basic information:
  - Material balance and material streams based on formulation and batch size.
  - Graphical representation of the major steps in the manufacturing process.
  - Identification of the equipment used in the manufacturing process.
Process Flow Diagram
Process Flow Diagrams

- PFDs may be used to describe only the main manufacturing steps or (better) include the support operations, such as liquid as solid waste treatment, exhaust gas treatment, generation and distribution of purified water and other utilities.

- PFD is a document generated early in a project – usually during “conceptual design” stage, and may be updated to reflect changes incorporated at later stages.

- PFDs may be used for developing preliminary equipment list and sizing of the major equipment.

- PFDs help architects to allocate appropriate spaces for all process operations and develop logical plant layout.

- PFDs are also used as a basis for more detailed process drawings called P&IDs – Piping and Instrumentation Diagrams.
Material Flow Diagram

First Floor Plan

SK-1a

Viral Vaccine Manufacturing - Material, Product & Waste Flow
Portable Equipment Flow Diagram

First Floor Plan

SK-3a

Viral Vaccine Manufacturing - Clean / Dirty Equipment Flow

Legend:
- Clean / Dirty Equipment Flow
  - Clean Equipment
  - Dirty Equipment
  - Hand-off

STEVENS INSTITUTE of TECHNOLOGY
• Facility design and layout must satisfy:
  • Process requirements
  • Personnel flows
  • Material flows (raw materials and products)
  • Equipment layout requirements
  • Operational access requirements
  • Maintenance access requirements
• Facility should be designed around process needs!
Building Materials
Clean Room Features

• Walls and floors designed for easy cleaning, resistant to wear and cleaning chemicals
• Coved floor and wall corners
• Minimize horizontal piping, ducts, equipment surfaces where dust can accumulate
• Lighting is supplied by sealed fixtures, often incorporated into ceiling HEPA filter modules.
Clean Room Features (cont’d)

• Typical clean room finishes include:
  • Epoxy terrazzo floors
  • Epoxy painted walls
  • Suspended drywall or plaster ceiling, painted for easy cleaning

• Clean rooms can be built at the site or purchased as modules from a vendor
Examples of Modular Clean Rooms

• Clean room may be purchased as a vendor supplied and installed module
Building Materials and Finishes - Summary

• Materials and Finishes are selected for suitability within every select environment in the facility.

• A very informed basis of understanding is required to properly select materials and finishes. Knowledge of the manufacturing process(s), SOP’s, staff activities and maintenance needs for all areas within the facility are vital to a successful solution.
Manufacturing of Solid Dosage Products

Guiding Principles for Facility Design
Guiding Principles for Regulatory Compliance

• Facility Criteria
  • Facilitate operations
  • Provide adequate space
  • Provide the proper flow of materials
  • Provide control of materials
  • Prevent contamination of materials and products

• Processes
  • Perform as required by the applications approved by the regulatory agency
  • Are demonstrably under control
  • Will not contaminate
  • Have procedures for proper operation and record keeping
Guiding Principles for Regulatory Compliance

• Environmental
  • Provide suitable conditions of temperature, humidity, and particulate control
  • Prevent cross contamination
  • Prevent microbial growth or infestation

• Facilities and Equipment
  • Surfaces that will not contaminate
  • Provide ease of cleaning and maintenance
Contamination and Level of Protection Criteria

• Potential Contamination Sources
  • HVAC Systems
  • Process equipment cleanliness
  • Room construction issues
  • Containerization and transport of materials
  • Personnel
  • Infiltration from other areas
Unit Operations in Solid Dosage Manufacturing
Unit Operations and Equipment Applications

- Dispensing and Weighing
- Sifting and Classifying
- Milling
- Granulation
- Drying
- Blending
- Compression
- Encapsulation
- Coating
Dispensing

• Small Volume Dispensing
  • Down Flow Laminar Flow Hoods
  • Dedicated Rooms with Environmental Controls

• Large Volume Dispensing
  • Silos
  • Super Sacks
  • Pneumatic Conveyance and Weigh Systems
  • Gravity Transfer and Weigh Systems
Technical Considerations for API Dispensing Systems

• APIs typically handled in small amounts
• Occupational Exposure Limits
• Handled in a Controlled or Contained Environment:
  - Dust collection systems for benign materials
  - Down flow booths for low toxicity materials
  - Closed systems with split valve technology for high toxicity materials
  - Glove Box Isolators for the most toxic materials

• Personal Protection Equipment
Other Design Considerations

• Storage and handling of materials in bulk containers (IBC), drums, bags, etc
  • Partials inventory (Unused material in drums to be returned to inventory)

• Material Handling Equipment

• Staging and Put Down Areas

• Wash Areas and Equipment Storage
  • Pallet washers
  • IBC washers
Sifting and Classifying

Purpose:
• De-lumping of powders
• Improve particle size distribution - removal of oversized and undersized particles

Equipment:
• Vibratory screen sifters
• Manual sieves
Milling

- Used for:
  - Particle size reduction
  - Change particle shape
  - De-lumping
Wet Granulation

• High Shear Granulation
  • High dispersion
  • Improved homogeneity
  • Good for small quantities of actives
Wet Granulation cont’d

- Fluid Bed Granulation
  - Control of particle size
  - Materials that can not withstand high shear
  - Granules dried in same machine
Drying

• Reduce moisture content of granules to 2-5%

• Methods
  • Fluid Bed Dryers
  • Tray Dryers (ovens)
Blending

• Combine granulation with excipients and lubricants
  • Excipient - typically lactose
  • Lubricants - typically magnesium stearate added to improve flow properties

• Convection mixing
  • Use of paddles or blades to achieve mixing
  • Ribbon blenders, Orbital screw blenders, planetary mixers, etc.

• Diffusion Blenders
  • Use of Tumbling Action
  • V Blenders, Cone Blenders, Bin Blenders
Tablet Compression

- Blend (powder or granules) is filled into die cavities
- Material is compressed into tablets
Encapsulatin

• Capsules
  • Hard gelatin capsules filled with solids
  • Final blend must be uniform
  • Better for products with high API content
  • Filling done by volume, so constant bulk density is important
Coating

- Coatings: Aqueous or Solvent Based
  - Film coating
    - Thin film (2 to 5 mils)
    - Clear or with colorant
  - Sugar coating
    - Heavy - may reach 50% of tablet weight
  - Enteric coatings
    - Delay dissolution until the tablet reaches the intestinal tract
  - Bead Coating
    - Time and sustained release products
Coating

- Process entails application of protective coatings to tablets
  - Coatings are applied in solution. May be water or solvent based
  - Multiple cycles of solution application and drying may be needed.
  - Multiple layers of coatings are applied to obtain the desired result

- Equipment Used in the Process
  - Open Coating Pans (Conventional Pans)
  - Perforated Coating Pans: Batch or Continuous Process
  - Wurster Columns (Fluid Bed Processors) – used for coating beads or granules
Facility Layout

• Facility layout must:
  • Provide short and logical routes for material and personnel flow
  • Avoid cross-flows whenever possible
  • Provide means of separation for quarantined, released and rejected materials
  • Provide sufficient space for each operation, including staging, washing and other ancillary areas
  • Help prevent cross-contamination
Layout of Mixing and Granulating Areas

- Easy movement of materials into separate processing rooms
- Minimize cross-contamination potential
- Air pressure in the corridor is higher than in the process rooms for product containment

Figure 14. Layout of mixing and granulating areas.
Design Considerations for OSD - Summary

- HVAC
  - Air Filtration
  - Negative room pressurization
  - Dealing with dust generation:
    - Dust collection
    - Closed processing

- Cleaning
  - Containers must be moved to wash area for cleaning
  - Risk of spreading contaminants through the facility
  - May provide wash or vacuum cleaning capability inside process room
BioPharmaceutical Manufacturing Facilities

Biopharmaceutical Processes and Facilities
Room classification
What is Biopharmaceutical Technology?

• Processes using microorganisms or animal cells for synthesis of products
• Isolation and purification technology for biologically derived compounds
• Modern biotechnology uses genetically engineered cells or microbes
• Products include drugs, vaccines and other high value compounds
• Many biotech drugs are proteins
Figure 8.2 Principal functional areas and flows of the process core and support of an API plant using mobile equipment in purification. CS = clean steam; GMOs = genetically modified organisms; WFI = water for injection; and AP = purified water (aqua purificata).
Building Design Considerations

• Operational Efficiency
• Operational Safety
• Protection of Product from contamination
• Protection of Personnel
• Protection of Facility
• Maintainability
Program Design Considerations

- Equipment Arrangements
- Material Flow
- Personnel Flow
- Product Flow
- Waste Flow
- Adjacencies
- Segregation
- Flexibility
- Expandability
Single Product Facility with Minimal Segregation
Single Product Facility with Moderate Segregation
Multi-Product Facility with Moderate Segregation
Layout Considerations - Summary

• Adjacency of related spaces
• Logical and simple flow of personnel, portable equipment and materials
• Avoid where possible “clean” and “dirty” equipment and personnel passing through the same corridors, gowning areas etc.
• “Air locks” are used at major separation points where maintaining pressure differential is important
• Cleaner spaces usually are located in the middle of a facility, and surrounded by areas of lower classification
## Classification of Clean Rooms

<table>
<thead>
<tr>
<th>Grade</th>
<th>Particles/m³ ≥0.5 µm</th>
<th>ISO Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>In operation</td>
</tr>
<tr>
<td>A</td>
<td>3,520</td>
<td>3,520</td>
</tr>
<tr>
<td>B</td>
<td>3,520</td>
<td>352,000</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>C</td>
<td>352,000</td>
<td>3,520,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3,520,000</td>
<td>Not defined</td>
</tr>
</tbody>
</table>
HVAC Techniques

• Air filtration, including “High Efficiency Particulate Air” filters (HEPA filters)
• Directional flow or air
• Pressure relationships within and between adjacent spaces
• Humidification (used mostly in winter in cold climates), dehumidification (mostly in summer)
• Heating and cooling to maintain constant temperature
Air Filtration

• The low particulate counts in classified rooms are achieved by continuous recirculation of room air with HEPA filters in the recirculation loop.

• The cleaner the room needs to be, the higher recirculation rate required.

• The degree of recirculation is commonly expressed as number of room air changes per hour (air flow rate divided by the room volume).
Air Filtration

• Guidelines for required number of air changes:
  • 240-480 changes/hr for Class A rooms
  • 60-90 changes/hr for Class B rooms
  • 20-40 changes/hr for Class C rooms

• These numbers are not regulations, just guidelines. They vary in different sources.

• Actual number of particles observed depends on activity level – people present, dust-generating operations etc. Easier to achieve low particulates in static (no activity) than in dynamic conditions
Air Pressurization

• In general, rooms of higher class (cleanest) have positive air pressure as compared to adjacent spaces.
• Airlocks are used to separate clean process rooms from corridors and adjacent rooms.
• Airlocks and gowning rooms are normally negatively pressurized compared to the process room and positively to corridor.
Air Pressurization

• Exception can be made in case the product or its component is hazardous (i.e. live virus), in which case containment consideration may require clean room to be negatively pressurized.

• In such case airlock may be made positive to both process room and to the corridor. This provides both product protection and containment.
Air Pressurization

- Recommended pressure differential between adjacent areas is 10 – 15 Pa, as measured with doors closed.
- When a door opens, pressure differential essentially goes to zero. That is why air locks are installed at critical connection points, and the two doors in an air lock are never opened simultaneously (often enforced by interlocking controls on electrically operated doors).
- Rooms need to be sealed as tight as possible to enable maintaining required pressure differential.
Figure 8.7  Air pressure steps and mapping of ventilation systems. Colored frame = one dedicated air-conditioning system; $P^0 =$ atmospheric pressure; $P^+ =$ overpressure over $P^0$; and $P^{++} =$ overpressure over $P^+$. 
Air Locks – Types

- AL and PAL
- MAL

- **Bubble**
- **Sink**
- **Cascade**
Personnel Air Lock

- Mirror, wash basin, disinfection agent for hands
- Cabinet with gowning suites
- Gowning instruction
- Mirror for self control
- Door to lower room class
- Door to higher room class
- Waste bins for different gowning types
- Optical separation line between clean and less clean area
- Step-over bench for shoe change/shoe cover
Material Air Lock

Figure 8.15  (a) Typical personnel air lock (side view) and (b) procedure for bringing in material through the material air lock (top view).
Figure 17.4  Air Flow Diagram for a Constant-Volume Reheat System. Mix box has (1) 25% filter, (2) 85% filter, (3) heating coil, (4) cooling coil, and (5) fan with inlet vanes or variable-speed motor; (6) humidifier; (7) air-flow monitor; (8) constant-volume control boxes with reheat coil; (9) room terminal HEPA filters; (10) constant-volume boxes.
Air Quality Monitoring

• Number of particles per unit of air volume is tested during facility qualification and routinely. Such testing is done both “at rest” (no activity) and during normal operations. Portable (shown in the picture) or permanently installed particle counters may be used.

Source - www.metone.com
HVAC - Summary

• Clean room classes A, B, C (and sometimes D) are commonly used in biopharma facilities

• To maintain air cleanliness we use:
  • Air recirculation at high flow rates with HEPA filters in the recirculation loop
  • Air pressure differentials between adjacent spaces
  • Air locks for personnel and materials
  • Personnel gowning and access control
  • Air quality monitoring (periodic or continuous)
Single- and Multi-product Plants

• If we have a product with high sales volume, single-product plant is better.

• If we have multiple products with similar technologies and smaller volumes, multi-product plant may be better.

• In multi-product plants:
  • Flexibility must be built into the floor plan.
  • Avoidance of cross-contamination is critical.
  • May operate by campaigns or by parallel processing.
Equipment and Piping Design Concepts

• Most large plants have fixed stainless steel equipment and fixed process piping

• Flexibility can be achieved by using flexible piping (hoses) in addition to the fixed piping

• Many smaller plants use disposable equipment – storage bags, fermentation bags, filters etc.
Plant Design Concepts - Summary

• Three principle variables that are in competition with each other:
  • Investments (capital cost)
  • Operating costs
  • Flexibility

• Different designs may be used for different situations:
  • Multi product versus single product facilities
  • Stainless steel versus disposable (single use) equipment
Aseptic Processing Facilities
Introduction

- Aseptic processing - all the individual components (product, vials & stoppers) are sterilized individually and assembled in a very high quality environment
- Only a small fraction of the final product is tested to confirm its sterility and therapeutic value
- Manufacturer has no direct data other than the design of their process to confirm that the product is safe for human use
Containers for Aseptic Products

Examples:

- Vial (sealed using a rubber stopper and aluminum seal)
- Ampoule (a glass container sealed using heat directly after filling)
- Syringe (sealed with a rubber stopper and a needle cover)
- Plastic bottle (sealed with a plastic cap)
- Blow-Fill-Sealed Bottles (a plastic bottle that is made filled and sealed in one step)
Sterile Dosage Forms

Ampoule

Vial

Prefilled syringe

Blow-fill-seal vials

Bottles
1. Prep Bulk Product
2. Filter Sterilize Bulk Product
3. Wash & Sterilize Stoppers
4. Prep Overseals
5. Assemble Change Parts
6. Wash Vials
7. Depyrogenate Vials
8. Fill Vials
9. Overseal Vials
10. Inspect Vials
11. Package Vials
12. The Background Environment

ISO 5
ISO 8
The Vial Filling Process

- Filling product into vials
- Checking vial weight
  - Manual (destructive) versus automated → cost impact
- Inserting vial stoppers
  - fully
  - partially (half way; used for freeze dried products)
- Over-sealing to secure the stopper
Vial Filling and Stoppering

Vial Filling

Orienting stoppers
Inspect Vials

• Every vial must undergo inspection:
  – manual or automatic
  – may be done in line with the filling process - less scratches – fewer rejected vials
The Vial Filling Process

- The aseptic processing steps (where the product and product contact parts are exposed) are performed in a Class A / ISO5 environment
- The other classes are used for areas with other activities depending on the potential impact of on the process
The Vial Filling Process

• All steps involving clean operators and materials must be separated from dirty operators and waste. This requires separate airlocks and corridors for the clean and dirty activities (unidirectional flows)
• Even with all of these precautions (room pressurization, airflow, airlocks, garbing and treatment of materials) the ISO5 environment is under constant assault by the most contaminated object in the building - the operator
• To minimize the impact of the operator on the process, manufacturers are turning to a new technology – isolators or RABS
The Vial Filling Process

The equipment may be located in:
- Clean Room Environment (Traditional)
- Clean Room Environment & RABS
- Aseptic Filling Isolator
Clean Room
The Vial Filling Process

• Isolators:
  – box around the process
  – access the process via gloves
  – must be decontaminated using automated technology (VHP or H2O2) because the clean zone is very small
The Vial Filling Process

- Advantages of isolators:
  - The operator is removed from the process, so less product risk
  - Can be located in an ISO8 environment
    - Reduced ISO5 area
    - Reduced requirements for the sterile garb
    - Fewer airlocks and material sanitization steps
  - Material and people movement in the facility is simplified
  - Cleaning and cleaning validation reduced
  - Lower long term operation cost than traditional clean room facility
The Vial Filling Process: Isolators or RABS?

RABS

- Concept - to combine the advantages of an isolator with the flexibility of a clean room
- In reality RABS has not solved any of the perceived disadvantages of an isolator.

*Isolators are the future of aseptic processing.*
Factors affecting Aseptic Filling -
Summary

• Success of an aseptic process depends on:
  – Equipment design
  – Process design and controls
  – Facility and Room design
  – HVAC design
  – Clean Rooms/Isolators/RABS
  – Operators: gowning, training, procedures
  – Clean Utilities
References

Questions?
Regulatory requirement for Pharmaceutical facilities

โดย ภญ.พัชรีวรรณ ฝังนิล
กลุ่มกำกับดูแลหลังออกสู่ตลาด สำนักยา
สำนักงานคณะกรรมการอาหารและยา
16 กุมภาพันธ์ 2560
หัวข้อการบรรยาย (1)

• ปัจจัยที่ต้องคำนึงถึงในการออกแบบสถานที่ผลิตยา
• กฎหมายที่เกี่ยวข้อง
• Protection aspects
• นิยามศัพท์สำคัญ
• เทคนิคหลักเลี้ยงการปนเปื้อนข้าม
• Shell-like containment control concept
• Classification of airlock
• Differential pressure
หัวข้อการบรรยาย (2)

- Type of “Clean area”
- Cleanroom condition
- การแบ่งประเภทห้องสะอาด (EN/ISO 14644-1)
- ขีดจำกัดสำหรับการตรวจติดตามจุลินทรีย์ของบริเวณสะอาดระหว่างปฏิบัติงาน
- การปฏิบัติงานในแต่ละระดับความสะอาด
- ตัวอย่างแบบแปลนสถานที่ผลิตยาแต่ละประเภท
ปัจจัยที่ต้องคำนึงถึงในการออกแบบสถานที่ผลิตยา

• กฎหมาย ระเบียบ หลักเกณฑ์ เงื่อนไข ที่สำนักงานคณะกรรมการอาหารและยากำหนด
• ประเภทของผลิตภัณฑ์ยาที่ต้องการผลิต (คุณสมบัติเฉพาะ รูปแบบ)
• กระบวนการผลิต และเทคโนโลยีที่ใช้
• เครื่องมือ/อุปกรณ์การผลิตสำคัญ ที่ต้องใช้ในกระบวนการผลิต
• สภาวะแวดล้อมการผลิต (อุณหภูมิ ความชื้น ความดันอากาศ ระดับความสะอาดของห้องและบริเวณผลิต)
• ระบบสนับสนุนการผลิต (ระบบอากาศ (เช่น HVAC system, De-dusting system, Compressed air) ระบบน้ำ ระบบกำจัดของเสีย)
กฎหมายที่เกี่ยวข้อง (1)

- ประกาศกระทรวงสาธารณสุข เรื่อง การกำหนดรายละเอียดเกี่ยวกับหลักเกณฑ์และวิธีการในการผลิตยาแผนปัจจุบันและแก้ไขเพิ่มเติมหลักเกณฑ์และวิธีการในการผลิตยาแผนปัจจุบันตามกฎหมายว่าด้วยยา พ.ศ. 2559
  - รัฐมนตรีว่าการกระทรวงสาธารณสุข ลงนาม 18 พฤศจิกายน 2559
  - ประกาศในราชกิจจานุเบกษา วันที่ 14 กันยายน 2559
กฎหมายที่เกี่ยวข้อง (2)

ประมวลสาระบาง GMP พ.ศ.2559 (ต่อ)

- ให้ยกเลิก

(1) ประกาศกระทรวงสาธารณสุข เรื่อง การกำหนดรายละเอียดเกี่ยวกับหลักเกณฑ์และวิธีการในการผลิตยาแผนปัจจุบันสำหรับยาซึ่งวัตถุตามกฎหมายว่าด้วยยา พ.ศ. 2549

(2) ประกาศกระทรวงสาธารณสุข เรื่อง การกำหนดรายละเอียดเกี่ยวกับหลักเกณฑ์และวิธีการในการผลิตยาแผนปัจจุบันตามกฎหมายว่าด้วยยา พ.ศ. 2554
กฎหมายที่เกี่ยวข้อง (3)

ประมวลกรอบแนวทาง GMP พ.ศ. 2559 (ต่อ)
- สอดคล้องตาม PIC/S Guide to GMP for Medicinal Products
  PE 009-12 Issued date 1 October 2015
- เนื่องจากครอบคลุมทั้งยาเคมี ยาชีววัตถุ และยาแผนโบราณ
- เอกสารแนวทางประกอบประกาศฯ ประกอบด้วย
  (1) ส่วนที่ 1 (Part I) : 9 หมวดหลัก
  (2) ส่วนที่ 2 (Part II) : หลักเกณฑ์และวิธีการในการผลิต
    สารออกฤทธิ์ทางเภสัชกรรม
  (3) ภาคผนวก 16 ภาคผนวก (Annexes)
    จัดเรียงตามรูปแบบของ PIC/S โดยหากมีการแก้ไขเนื้อหา
    สามารถแก้ไขแต่ละส่วนได้ โดยไม่กระทบเนื้อหาส่วนอื่น
กฎหมายที่เกี่ยวข้อง (4)

ประกาศกระทรวง GMP พ.ศ.2559 (ต่อ)
- ตัวอย่างเนื้อหาในส่วนที่เกี่ยวข้องกับการออกแบบสถานที่ผลิตที่เหมาะสม เช่น
  (1) ส่วนที่ 1 (Part I)
    - หมวด 3 : อาคารสถานที่และเครื่องมือ
    - หมวด 5 : การดำเนินการผลิต
  (2) ส่วนที่ 2 (Part II) : หลักเกณฑ์และวิธีการในการผลิต
    สารออกฤทธิ์ทางเภสัชกรรม
  (3) ภาคผนวก (Annexes)
    - ภาคผนวก 1 : การผลิตยาปราศจากเชื้อ
    - ภาคผนวก 2 : การผลิตผลิตภัณฑ์ยาชีววัตถุสำหรับใช้ในมนุษย์
    - ภาคผนวก 3 : การผลิตเภสัชภัณฑ์รังสี
Protection aspects

GMP Manufacturing Environment

- Product Protection
  - Contamination (Product & Staff)
- Personnel Protection
  - Prevent contact with dust
- Environment Protection
  - Avoid duct discharge

- Protect from Product (cross-contamination)
- Prevent contact with flames
- Avoid fume discharge

- Correct temperature & humidity
- Acceptable comfort conditions
- Avoid effluent discharge

SYSTEM

SYSTEM VALIDATION
นิยามศัพท์สำคัญ (1)

การปนเปื้อนช้ำ (Cross-contamination)

• การปนเปื้อนของวัตถุดิบหรือผลิตภัณฑ์ด้วยวัตถุดิบหรือผลิตภัณฑ์ชนิดอื่น

แอร์ล็อค (Air lock)

• บริเวณปิดสนิทที่มีประตู 2 ทางหรือมากกว่า ซึ่งกันกันกลางอยู่ระหว่างห้องหรือบริเวณที่มีระดับความสะอาดแตกต่างกัน เพื่อวัตถุประสงค์ในการควบคุมการไหลของอากาศระหว่างห้องหรือบริเวณเหล่านี้ เมื่อมีการเปิดประตู แอร์ล็อคมีการออกแบบและใช้สำหรับเป็นทางเข้า-ออกของคนและสิ่งของ
นิยามศัพท์สำคัญ (2)

บริเวณสะอาด (Clean area)

- บริเวณที่มีการควบคุมการปนเปื้อนของอนุภาคและจุลินทรีย์ในสภาพแวดล้อมให้อยู่ในเกณฑ์ที่กำหนด การก่อสร้างและการใช้งานจะต้องทำในลักษณะที่ลดสิ่งปนเปื้อนที่จะนำเข้าไปที่จะเกิดขึ้น หรือที่ถูกกักอยู่ในบริเวณนั้น

บริเวณกักเก็บ (Contained area)

- บริเวณที่สร้างขึ้นและติดตั้งระบบอากาศ และการกรองอากาศที่เหมาะสม และใช้งานในลักษณะเพื่อให้บรรลุวัตถุประสงค์ในการป้องกันสภาพแวดล้อมภายนอกจากการปนเปื้อนโดยสาร ซึ่งวัตถุจากภายนอกบริเวณนั้น
เทคนิคหลักเกี่ยวกับการเปิดปิดชั่ว (1)

ประกาศกระทรวง GMP พ.ศ.2559 (หมวด 5 ข้อ 19)

➢ ดำเนินการผลิตในบริเวณแยกต่างหาก ซึ่งเป็นข้อกำหนดสำหรับผลิตภัณฑ์พวกโมโนซิลลิน วัคซีนที่มีชีวิต ผลิตภัณฑ์แบคทีเรียที่มีชีวิต และผลิตภัณฑ์ซิววัตถุบางชนิด หรือทำการผลิตโดยการแยกเวลาผลิต หลังจากนั้นให้ท่านสมะสะอาดอย่างเหมาะสม

➢ ให้มีการกรองอากาศที่หมุนเวียนหรืออากาศที่นำกลับเข้ามาใหม่เพื่อลดความเสี่ยงของการปนเปื้อนจากอากาศ
เทคนิคลักษณะการป้องเป็นข้าม (2)

➢ เก็บเครื่องแต่งกายสำหรับใช้ปฏิบัติงานไว้ภายในบริเวณที่ทำการผลิตผิวภายนอกที่มีความเสี่ยงเป็นพื้นที่ทำให้เกิดการป้องเป็นข้าม

➢ ใช้วิธีการทำความสะอาดและการกำจัดสิ่งปนเปื้อนที่มีประสิทธิผล เนื่องจากการทำความสะอาดเครื่องมือที่ไม่มีประสิทธิผลมักเป็นแหล่งเกิดการป้องเป็นข้าม

➢ ใช้ "ระบบปิด" ในการดำเนินการผลิต

➢ มีการทดสอบสารตกค้างและใช้จัดแสดงสถานะสะอาดติดที่เครื่องมือที่ผ่านการทำความสะอาดแล้ว
Shell-like containment control concept
Classification of airlock (1)

**Typical Pressure Cascade Airlock**

- **P3**: HEPA filtered supply air
  - Class 100,000 ISO 8
  - $P = 0.05'' = 12.5 \text{ Pa}$
  - ROOM 1

- **P2**: Airlock Pressure
  - Class - at rest same as 10K room at rest
  - ROOM 2

- **P1**: Class 10,000 ISO 7
  - $P = 0.15'' = 37.5 \text{ Pa}$
Classification of airlock (2)

Sink airlock

Bubble airlock
**Differential pressure**

**Design Condition** (15Pa differential)

- **Tablets Compr.**
  - 15Pa ± 3Pa

- **Tablets Compr.**
  - 15Pa ± 3Pa

- **Encapsulation**
  - 15Pa ± 3Pa

**Production Corridor**

- **Air Lock**
  - 30Pa ± 3Pa
  - 15Pa

**Image of room pressure gauge indicating normal, alert and action parameters**

**Maximum Differential** (21Pa differential)

- **Tablets Compr.**
  - 12Pa

- **Tablets Compr.**
  - 12Pa

- **Encapsulation**
  - 12Pa

- **Production Corridor**
  - 33Pa
  - 12Pa

**Minimum Differential** (9Pa differential)

- **Tablets Compr.**
  - 18Pa

- **Tablets Compr.**
  - 18Pa

- **Encapsulation**
  - 18Pa

- **Production Corridor**
  - 27Pa
  - 18Pa
Type of “Clean area”
1. Conventional
(Non-unidirectional flow or turbulently ventilated)
2. Unidirectional flow (Laminar flow)
3. Mixed flow
4. Isolators
Perforated plate diffuser
(recommended)

Reduced induction of air

Return Air

PERFORATED PLATE DIFFUSER
(recommended)

Image of supply air perforated plate grille

Image of return air perforated plate grille

Food and Drug Administration
Swirl diffuser (recommended)
Induction diffuser
(not recommended)
Cleanroom condition (1)

- The “as built” state is the condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel presents.
Cleanroom condition (2)

- The “at rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present.

ประกาศกระทรวง GMP พ.ศ.2559

- สถานะ “ไม่มีการปฏิบัติงาน” เป็นสถานะที่มีการติดตั้งระบบและเปิดใช้งาน พร้อมทั้งมีการทำงานของเครื่องมือผลิต แต่ไม่มีผู้ปฏิบัติงานอยู่ในบริเวณนั้น
Cleanroom condition (3)

- The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

การกำศกระทรวง GMP พ.ศ.2559

- สถานะ “กำลังปฏิบัติงาน” เป็นสถานะที่มีการเปิดใช้งานระบบที่ติดตั้งไว้ตามวิธีการใช้ที่กำหนด พร้อมทั้งมีผู้ปฏิบัติงานกำลังปฏิบัติงานตามจำนวนที่ระบุ
Cleanroom condition (4)
ตารางแสดงระดับของสารสนเทศ (EN/ISO 14644-1)

<table>
<thead>
<tr>
<th>ระดับ</th>
<th>ลำดับ</th>
<th>ไม่มีการปฏิบัติงาน (at rest)</th>
<th>กำลังปฏิบัติงาน (in operation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 ไมโครเมตร</td>
<td>5.0 ไมโครเมตร</td>
<td>0.5 ไมโครเมตร</td>
</tr>
<tr>
<td>A</td>
<td>3,520</td>
<td>20</td>
<td>3,520</td>
</tr>
<tr>
<td>B</td>
<td>3,520</td>
<td>29</td>
<td>352,000</td>
</tr>
<tr>
<td>C</td>
<td>352,000</td>
<td>2,900</td>
<td>3,520,000</td>
</tr>
<tr>
<td>D</td>
<td>3,520,000</td>
<td>29,000</td>
<td>ไม่ระบุ</td>
</tr>
</tbody>
</table>
ชิดจำกัดสำหรับการตรวจติดตามจุลินทรีย์ของบริเวณและอุตสาหภัณฑ์ปฏิบัติงาน

| ระดับ | การสัมผัสตัวอย่างอาหาร (โคลนี/ลูกบาศก์เมตร) | การรายงานอาหารเพาะเชื้อ (เส้นผ่านศูนย์กลาง 90 มิลลิเมตร) โคลนี/4 ชั่วโมง(ข) | จำนวนผลิตสัมผัส (เส้นผ่านศูนย์กลาง 55 มิลลิเมตร) โคลนี/จำนวน พิมพ์ถุงมือจำนวน 5 นิ้ว โคลนี/ถุงมือ |
|-------|---------------------------------|---------------------------------|-----------------|-----------------|
| A     | <1                              | <1                              | <1              | <1              |
| B     | 10                              | 5                               | 5               | 5               |
| C     | 100                             | 50                              | 25              | -               |
| D     | 200                             | 100                             | 50              | -               |

หมายเหตุ
(ก) เป็นค่าเฉลี่ย
(ข) อาจรายงานอาหารเพาะเชื้อแต่ละจำนวนให้สัมผัสผลิตภัณฑ์น้อยกว่า 4 ชั่วโมง
### การปฏิบัติงานในแต่ละระดับความสะอาด

<table>
<thead>
<tr>
<th>ระดับ</th>
<th>การปฏิบัติงานสำหรับผลิตภัณฑ์ที่เตรียมโดยกระบวนการปราศจากเชื้อ</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>เตรียมและบรรจุโดยกระบวนการปราศจากเชื้อ</td>
</tr>
<tr>
<td>C</td>
<td>เตรียมสารละลายก่อนทำการกรอง</td>
</tr>
<tr>
<td>D</td>
<td>การดำเนินการกับส่วนประกอบหลังการล้าง</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ระดับ</th>
<th>การปฏิบัติงานสำหรับผลิตภัณฑ์ที่ทำให้ปราศจากเชื้อในขั้นตอนสุดท้าย</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>บรรจุผลิตภัณฑ์เมื่อมีความเสี่ยงกว่าปกติ</td>
</tr>
<tr>
<td>C</td>
<td>เตรียมสารละลายเมื่อมีความเสี่ยงกว่าปกติ และการบรรจุผลิตภัณฑ์</td>
</tr>
<tr>
<td>D</td>
<td>เตรียมส่วนประกอบสำหรับการบรรจุ</td>
</tr>
</tbody>
</table>
ตัวอย่าง
แบบแปลนสถานที่ผลิตยาแต่ละประเภท
Penicillin non-sterile critical area
Typical suit of rooms for terminally sterilized product

- Terminal Autoclave
- Unidirectional Clean Zone
- Clean Filling Room
- Solution Preparation Area
- Clean Change Area
- Equipment and Component Preparation Area
- Component Entry Airlock
- Pass over Bench
- Personnel Movement
- Material Movement

0 Datum + + + + 15 Pa
++ + 30 Pa +++ + 45 Pa
Typical suit of rooms for aseptic filling
Thank you for your attention
PLANNING OF PHARMACEUTICAL FACTORIES
CONCEPT AND IMPLEMENTATION
PEOPLE AND PLANNING

A Quote:

“You do not really understand something unless you can explain it to your grandmother.”

Albert Einstein
PRESENT SCENARIO:
The Globalization & Open Market Policy has proved to be a boon for the industries, but has generated need for a globally acceptable manufacturing facility.

There are many flourishing manufacturing facilities, but not all are in compliance with the various regulatory standards.

NEED FOR A FACILITY:
Rapid change in manufacturing technology & various regulatory compliances to upgrade for better solution in line with cGMP.

With globalization, the need for a compliant facility has become a statutory necessity.
If you have decided to build a new factory ..... or to revamp an existing one .... ...be aware that planning is not easy and that it is not a smooth way...
PARTICIPANTS TO THE PLANNING PROCESS

Forecasts for x years → Objectives Budget → Company internal approvals

<table>
<thead>
<tr>
<th>Technology</th>
<th>Logistics</th>
<th>Building services</th>
<th>Building technology</th>
</tr>
</thead>
</table>

Planning → Execution

Approvals (pharmaceutical) ← Approvals (non-pharmaceutical)

Internal Planner Authorities
Represented works for a pharmaceutical plant:

- up to 80 different works
- more than 15 engineering specialties
- client representatives

<table>
<thead>
<tr>
<th>Category</th>
<th>downstairs</th>
<th>upstairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site / building prep + structure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roof + facade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Building services</td>
<td></td>
<td></td>
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<tr>
<td>Interior + finishing works</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process related systems, Logistics + Warehousing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacists, Architects, Engineers, Specialists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Client representatives</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Schedule Example

<table>
<thead>
<tr>
<th>Activity</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
</tr>
<tr>
<td>Project Organisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection and Evaluation Basic Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concept / Masterplan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection and Ordering Equipment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documents Construction Permit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of Contractors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detailed Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Construction Permit</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Construction / Implementation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Equipment Installation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Training of Personnel</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Qualification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production Start</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Activities can start in parallel.
<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>General laws + regulations</strong></td>
</tr>
<tr>
<td>2</td>
<td><strong>Pharmaceutical regulations, EU, FDA, PIC/S, WHO, requirements of pharmacy inspectors, product registration ...</strong></td>
</tr>
<tr>
<td>3</td>
<td><strong>Labour and environmental requirements...</strong></td>
</tr>
<tr>
<td>4</td>
<td><strong>Norms</strong> ISO, ATEX, etc...</td>
</tr>
<tr>
<td>5</td>
<td><strong>Specific guidelines, (Biosafety, Fed Std, OSHA) for conception, planning, operation ...</strong></td>
</tr>
<tr>
<td>6</td>
<td><strong>Company standards, planning conditions (quantities, technologies, products, deadlines, budget ...)</strong></td>
</tr>
</tbody>
</table>

**NORMS, REGULATIONS AND REQUIREMENTS**

Diagram showing a pyramid with levels labeled from 1 to 6, each corresponding to different types of regulations and requirements.
PLANNING STEPS

- Feasibility Concept
  - Process / Equipment
  - GMP and Hygiene Zoning
  - Quantitative data
  - Layout

- Basic Design
  - Refining of elements
  - Calculations
  - Functional tendering
  - Layouts 1:100

- Detail Design
  - Complete detailing for all disciplines
  - Layouts 1:20, 1:50
  - Tendering

- Execution
PLANNING MODELS

CONVENTIONAL MODEL

Feasibility Concept → Basic Design → Detail Design → Execution

IMPROVED MODEL

Conceptual design → Basic Design → Detail Design → Execution

Not to scale
FEASIBILITY VERSUS CONCEPTUAL STUDY

Feasibility

- Static
- Dominated by economical criteria
- No project alternatives:
- Yes / No only
- No influence on schedule of subsequent phases

Conceptual Study

- Includes the feasibility study
- Dynamic / prospective
- Dominated by technical criteria
- Project alternatives are generated
- User oriented
- Choices possible
  - Costs
  - Technology
  - Organisation
- Reduces time spent on subsequent phases, while increasing their precision
It pays to invest into a strong conceptual design

- Low initial costs
- Early clarification of main issues
- Powerful decision tool
- Possibility to develop alternatives
- “Freewheeling”
PLANNING SEQUENCE AND ITERATION PROBLEMS

- Planning Task Start
- Task Definition
- Targets Requirements
- Analysis
- Conceptual Design with Alternatives
- Basic Design
- Detail Design
- Execution

Easy:  
Difficult:
The cheapest and most promising Phase is the Conceptual Phase!
POSSIBILITIES OF COST MINIMISATION

The best and cheapest chance to minimise cost of investment and operation is in Phase 1!

- **Basic Design**
  - Factory size
  - Factory organization
  - Technology
  - GMP

- **Conceptual Design**
  - Small teams
  - Brainstorming
  - Alternatives
  - New ideas

- **Detail Engineering**

- **Execution**

Costs saving potential
DETERMINATION OF COSTS
in relation to the planning stage

The better the concept, the higher the precision

Feasibility
Conceptual design

Basic design

Detail design

Execution
Supervision
Documentation

Cost estimation

Cost calculation

Tender documents
Offers

Final quotations

PRICE PAID
PRECISION OF COSTS in relation to the planning stage

Feasibility Conceptual design
± 30%

Basic Design
± 20%

Detail Design
± 10%

Execution Supervision Documentation
± 5%

Cost estimation
The better the concept, the higher the precision

Cost calculation
Tender documents Offers

Final Quotations
DETERMINATION OF COSTS
in relation to the planning system

- Feasibility
  Conceptual design

- Basic design

- Detail design
  General planner: good control

- Execution
  Supervision
  Documentation

Turnkey price: poor control
TARGETS OF PHARMACEUTICAL FACTORY PLANNING

- Planning of a production plant
  - future oriented
  - flexible
  - economical in investments and operating costs
  - GMP conform
  - conform to local / international regulations

- High motivation of staff by high quality of working place
- Efficient planning
- Adequate quality standard (value for money)
- Architecture compatible with local surroundings
The Purpose of the Conceptual Design is to arrive to:

- Layout
- General Factory Organisation Procedures
- Hygiene Concept
- Technology Concept
- Air Handling and Utilities Concepts

which can be successfully presented to Authorities for a Pre-Approval Design Review

and to get a high degree of safety about:

- Investments
- Schedule
PRELIMINARY CONTACT WITH AUTHORITIES
PRE-APPROVAL DESIGN REVIEW

US FDA / Europe
• It is not an establishment inspection report
• There are no Inspectional Observations
• It is a “candid dialogue” regarding potential issues (Red Flags)
• The outcome represents the opinion of an inspector, not necessarily that of the FDA
• Agencies act as consultants, not as police

ASIA
• No dialogue
• Inspector can block further work, by imposing his point of view
• No appeal possibility in the practice (respect of authority, fear of later potential problems)
EXAMPLES OF STATEMENTS BY INSPECTORS

• Corridor should not be less than 2,5 m wide
• Preparation of binder should be separated from granulation
• Room for rejected raw materials must be larger to 10 m²
• Rapid doors not acceptable
• Separate building required for hormones, not just complete separation in building, with dedicated HVAC, entrance, utilities, etc.
• Utilisation of barcode system to replace labels unacceptable
• Hygiene classes for degowning: B to D not accepted, should be B to C
• Airlock in front of capping room
• Etc.
Although binder preparation dedicated to the line, and preparation of binder just-in-time, obligation to have separate room and corridor: loss of space, no apparent benefit
New capping systems, with rail crimpers, emit practically no particles, so why additional airlock? Machines are in addition equipped with air extraction at capping point.
Type of “rapid door” frequently utilised in Europe and in the USA in cleanrooms ISO 8, but often rejected in some Asian countries.
HOW TO REACH A GOOD CONCEPTUAL DESIGN RESULT?

Right team

Good method  Right team

Discipline  Good method  Right team

Good data  Discipline  Good method  Right team

Some fantasy  Good data  Discipline  Good method

Some fantasy  Good data  Discipline

Some fantasy  Good data
A Quote:

“You do not really understand something unless you can explain it to your grandmother.”

Albert Einstein

The idea is to work intensively with a small group of people, possibly detached from their daily chores. These people must have the necessary know-how (or back-ups) and the power of decision.
PEOPLE AND PLANNING

CORE TEAM
- Quality Assurance
- Production Manager
- Process GMP Expert
- Integrated Factory Planning Experts

AD HOC MEMBERS
- Utilities Specialist
- Controller
- Other Specialists
- Logistics
- Engineering
JUDGEMENT ERRORS

Role of Participants: To plan AND to decide

Number of Participants

Large Organisations

Individuals

Concept Team

Number of Participants:
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
There are many planning methods

By Experimenting and Innovating

By Adding Individual Functions

By Cloning Existing Units

By Systematic Planning

By Turnkey Contracting
OPTIMAL PLANNING METHOD

Site, Site selection
Masterplan
General organisation factory
Departments
Functional groups
Equipment, single units

PLANNING FROM INSIDE TO OUTSIDE

PLANNING FROM MACRO TO MICRO

PLANNING FROM IDEAL TO REAL
NEED FOR FOCUSING

- Economy of scale
- Efficiency / Best practice
- Flexibility
- Performance
- Organisation

Analysis of
- Product range
- Process
- Technologies
- Organisation

Conceptional design
- Make or buy
- Specialisation
- Capacity increase
- Technology
- Standardisation
- Regulatory aspects
- Results versus costs

• Requirements
• Vision of client
PLANNING METHOD
DEVELOPMENT OF IDEAL ORGANISATION

Information
- Analysis process
- Analysis of products and production volumes
- Analysis organisation
- Analysis space situation
- Analysis machinery / equipment

Identification
- Identification key problems
- Analysis Material / Information flow
- Identification necessary infrastructure

Strategy
- Plant strategy + Process architecture

Resulting Organisation
- Definition Modules Functional units Vertical Horizontal
- Verification process flow, material flow
- Verification GMP concept
- Calculation necessary space
- Definition of constraints, etc.
- Combination material flows functional inter-dependencies
- B/W-Orientation of factory
- Rough layout development
- Layout alternatives

Evaluation + Selection
- Adaptation Process, machinery + equipment

START
END
PLANNING METHOD
RATIONALISATION, INNOVATION AND OPTIMISATION

Morphological Analysis + Search for Solutions

Capacity and Rationalisation Analysis

Existing Technology

GMP-Concept

Technological Alternatives

Degree of Automation

Investment / Budget

Forecasts, Quantities, Product Mix

Batch Sizes

Galenical Properties

Project-Technology

GMP-Concept

Degree of Automation

Batch Sizes

Foreseen Equipment

Shifts ?

Product Seasonality

Campaign Sizes

Cleaning + Change-over Times

Dimension. Machines (Type/Quantity)

Plant strategy + Process architecture
PLANNING PROCEDURE: CONCEPTUAL DESIGN

Production forecasts / next 6-10 years

- Description of process flows from starting materials until finished product
- Design of the overall flow diagram indicating all GMP-classes

Calculation of material flow quantities

- Definition of process technology
  - Process technology
  - Machinery + equipment
  - Transport systems + containers
- Definition of personnel, shifts, etc.

Design of the ideal layouts + modules for each step

- Ideal layouts peripheral areas
- Ideal layouts personnel areas

Combination of individual layouts to functional units

--> Granulation, tabletting, preparation of liquids, filling ...

Design of the ideal overall total layout

Development of the masterplan for the design on the green field

Development of the integration of the layout into an existing building structure
PLANNING PROCEDURE: CONCEPTUAL DESIGN
FORECASTS

Product lists, quantities

Sorting by galenical forms

Sorting by types ("conventional", toxic, hormones, beta-lactames, etc.)

Strategy for marginal or special products
(quantities, types, galenical forms):
Make or buy
**ABC ANALYSIS**

<table>
<thead>
<tr>
<th>Number of products</th>
<th>Volume of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>A 10</td>
<td>60</td>
</tr>
<tr>
<td>B 30</td>
<td>30</td>
</tr>
<tr>
<td>C 60</td>
<td>10</td>
</tr>
</tbody>
</table>

**Example**

- **Number of products**: 50
- **Total number of units**: 100,000,000
- **Average weight unit (g)**: 0,5

<table>
<thead>
<tr>
<th>Number of products</th>
<th>Volume of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>A 10 5</td>
<td>60 30.000</td>
</tr>
<tr>
<td>B 30 15</td>
<td>30 15.000</td>
</tr>
<tr>
<td>C 60 30</td>
<td>10 5.000</td>
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</table>
### CAPACITY CALCULATIONS

### ABC ANALYSIS

### OPTIMISATION OCCUPANCY EQUIPMENT

<table>
<thead>
<tr>
<th>Abbrev</th>
<th>Damage Form</th>
<th>Unit Weight (g)</th>
<th>Mg new 2004</th>
<th>Gran. amount</th>
<th>Setch (2004)</th>
<th>Gran. kg 2004</th>
<th>Gran. kg 2016</th>
<th>New batch size 2014</th>
<th>Setch (2014)</th>
<th>Total kg 2014</th>
<th>Mg size 2014</th>
<th>%</th>
<th>% cum</th>
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<tbody>
<tr>
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<td>540.0</td>
<td>80.000</td>
<td>251.0</td>
<td>105.0</td>
<td>45.0</td>
<td>23.0</td>
<td>1.9</td>
<td>0.5</td>
<td>1.0</td>
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<td>11</td>
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<tr>
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<td>120.0</td>
<td>60.0</td>
<td>30.0</td>
<td>15.0</td>
<td>1.9</td>
<td>0.5</td>
<td>1.0</td>
<td>6.98</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>CVC</td>
<td>0.030</td>
<td>150.0</td>
<td>20.000</td>
<td>60.0</td>
<td>30.0</td>
<td>15.0</td>
<td>7.5</td>
<td>1.9</td>
<td>0.5</td>
<td>1.0</td>
<td>6.98</td>
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<tr>
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<td>50.000</td>
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<td>10.0</td>
<td>5.0</td>
<td>2.5</td>
<td>1.9</td>
<td>0.5</td>
<td>1.0</td>
<td>6.98</td>
<td>11</td>
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<tr>
<td>EHC</td>
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<td>150.0</td>
<td>25.000</td>
<td>10.0</td>
<td>5.0</td>
<td>2.5</td>
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<td>10.000</td>
<td>5.0</td>
<td>2.5</td>
<td>1.25</td>
<td>0.63</td>
<td>1.9</td>
<td>0.5</td>
<td>1.0</td>
<td>6.98</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table: Batch Size

<table>
<thead>
<tr>
<th>Batch size</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
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<td></td>
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<td></td>
<td></td>
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<td>10</td>
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<td></td>
</tr>
</tbody>
</table>

### ABC Analysis:

- **AHC**: 540.0 g, 80.000 Mg (new 2004), 251.0 Gran. amount, 105.0 Setch (2004), 45.0 Gran. kg 2004, 23.0 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.
- **BHC**: 300.0 g, 40.000 Mg (new 2004), 120.0 Gran. amount, 60.0 Setch (2004), 30.0 Gran. kg 2004, 15.0 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.
- **CVC**: 150.0 g, 20.000 Mg (new 2004), 60.0 Gran. amount, 30.0 Setch (2004), 15.0 Gran. kg 2004, 7.5 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.
- **DHC**: 20.0 g, 10.000 Mg (new 2004), 20.0 Gran. amount, 10.0 Setch (2004), 5.0 Gran. kg 2004, 2.5 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.
- **EHC**: 10.0 g, 5.000 Mg (new 2004), 10.0 Gran. amount, 5.0 Setch (2004), 2.5 Gran. kg 2004, 1.25 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.
- **FHC**: 5.0 g, 1.000 Mg (new 2004), 5.0 Gran. amount, 2.5 Setch (2004), 1.25 Gran. kg 2004, 0.63 Gran. kg 2016, 1.9 New batch size 2014, 0.5 Setch (2014), 1.0 Total kg 2014, 6.98 Mg size 2014.

### ISPE Thailand Affiliate Logo
SELECTION OF TECHNOLOGY AND EQUIPMENT

EXAMPLES OF SELECTION FACTORS

• Vision of client
• Properties of products to be processed
• Output requirements
• Degree of automation, sophistication
• Supplier: price, service and serviceability
• Cleanability and maintenance needs
• Space constraints
• Previous experience, available equipment (standardization)
• GMP issues
• Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client: size, degree of sophistication, automated guided vehicles, architecture, budget, future-oriented or not
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Safety of operator
- Vision of client
- Properties of products to be processed:
  eg granulation properties: is a direct compression possible or a dry granulation?
  Aseptic processing or terminal sterilization, ampoules or syringes
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- **Output requirements**
  - High capacity / one shift, low capacity / 2 or 3 shifts
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- **Degree of automation, sophistication**
  fully automated preparation of solutions, with CIP/SIP, equipment for solids with CIP capability, cartoning, palettisation, etc.
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator

![Diagram showing the relationship between number of products and automation possibilities.](image)
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- **Supplier: price, service and serviceability**
- **Cleanability and maintenance needs**
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- **Space constraints**
  Can influence the type or the supplier: eg difference in size between FBG and “one-pot” system
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)

**GMP issues**
Aseptic processing problems: automated loading of freeze-dryer, increased automation, increased sterility assurance level

- Safety of operator
SELECTION OF TECHNOLOGY AND EQUIPMENT

- Vision of client
- Properties of products to be processed
- Output requirements
- Degree of automation, sophistication
- Supplier: price, service and serviceability
- Cleanability and maintenance needs
- Space constraints
- Previous experience, available equipment (standardization)
- GMP issues
- Safety of operator: containment or PPE?

In most cases, several factors will play a role simultaneously
SELECTION OF TECHNOLOGY AND EQUIPMENT
MORPHOLOGICAL ANALYSIS

PROCESS ALTERNATIVES
SELECTION OF TECHNOLOGY AND EQUIPMENT
PROCESS SELECTION
Whereas a **process flow chart** reflects the process only, an **organization flow chart** includes the process, its organization as well as additional elements such as quantities, personnel needs, hygiene zoning, equipment and inter-relationships within the production or between production and related functions.

The process flowchart must be transformed into an organisational flow chart

Organization flow charts exist at different levels, micro- and macro:
- **Micro**: within a department
- **Macro**: within a production unit / plant
PLANNING METHOD
PROCESS FLOWCHART (EXAMPLE: SOLIDS)

Granulation → Binder preparation

Drying

Sieving

Addition lubricants

Blending

Compression
PLANNING METHOD
ORGANIZATION FLOWCHART (EXAMPLE: SOLIDS)
PLANNING METHOD
FLOWS PERSONNEL AND MATERIALS

Selection of alternative ESSENTIAL, later changes practically impossible
RELATIONSHIPS DETERMINATION

- BULK
- CLEAN UTILITIES
- WH
- BULK QC
- QA QC
- CENTRAL LOCKERS
- FORM FILL
- UTIL BLACK
- WS
- QUA R
- PACKAGING

COLOR CODE:
- **Red**: Strong relation
- **Blue**: Weak relation
- **Yellow**: No relevance

**Diagram Elements**
- Arrows indicate the flow of relationships.
PERSONNEL LOCKERS
EXAMPLE LAYOUT

Depend on
• Hygiene zone
• Local regulations
• Company / cultural habits to be considered
IDEAL LAYOUT MATERIAL / PERSONNEL FLOW PLANNING
EXAMPLE SUPPLY ROUTES MATERIALS

2nd Floor
- Grey Area
- Zone C
- Refilling Booth
- Zone C
- Weighing Booth

Maintenance Floor
- Air Lock
  - Black to Grey
- Air Lock
  - Grey to C

1st Floor
- Air Lock
  - Black to Grey
- Grey Area
- Zone C
- LF Booth
  - Solution to be filled

Ground Floor
- i-Point
  - Black Area
- Sampling
- Changing to internal pallets
- Labelling
- Green Area

Basement
- Black Area
- Locker

Zone A / B
Zone C
Zone D
Zone Grey
Zone Black
Zone Green

ISPE Thailand Affiliate
Results

• User oriented working place
• Optimized user identification
• Coordinated equipment layout and access areas
• Tailor-made area, volume and environment
• Modularized interior works
FROM IDEAL MODULE TO FACTORY LAYOUT
From process to space organisation

Step 1

Process Flow Chart is transformed into layout
From process to space organisation
Step 2
OVERVIEW GLOBAL CONCEPT

From process to space organisation
Step 3
EXAMPLE OF CONCEPT FOR SOLIDS PRODUCTION
EXAMPLE OF CONCEPT FOR SOLIDS PRODUCTION

NOTE: SUPPLY LEVEL GRANULATORS BETWEEN 5.40 AND 6.00 M.
LOGISTICS

**Goods IN handling**
- Cleaning
- Administration
- Sampling
- Palletisation
- Etc

**Goods OUT handling**
- Picking
- Commissioning
- Administration
- Etc

**Storage activities**
- Main storage
- Special storages

**Production**

**Exterior**
- Clients
- Logistic centre
GOOD GMP

- Minimized risk of contamination / cross-contamination
- Clear material flows (uni-directional whenever possible)
- Clear personnel flows (uni-directional whenever possible)
- Unambiguous definition of GMP zones
- Separation clean – dirty (washing areas)

Overkill
- Cost issues
- Nice to have
- GMP is not an attribute, no black and white attitudes
A good pharmaceutical factory is a factory that is:

- Pharmaceutically approved (qualification / validation )
- Economical to operate and maintain
- Flexible and adaptable quantity-wise and for new technologies

To design such an excellent pharmaceutical plant, an integrated, multi-disciplinary and experienced team is required.

The objectives, the vision, the method and the involvement of each member of the team will achieve this goal, and not the principle “function follows adding up individual inputs”
Thank You