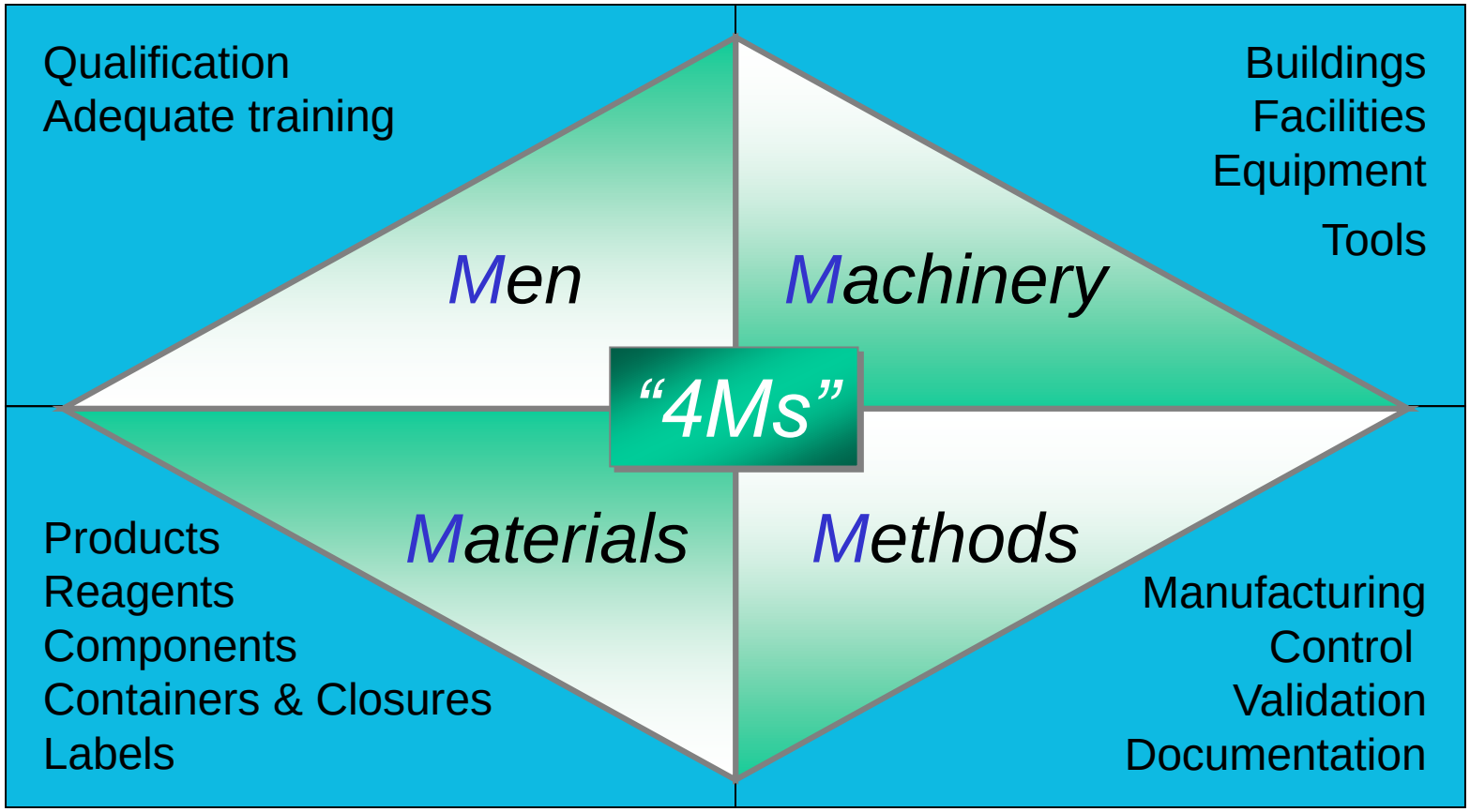
CGMP
for
21st Century : A Risk-based Approach (Quality by Design)

Chung Keel Lee, Ph.D.

Special Advisor to the Minister, MFDS
Professor, EWU/SNU
Advisor, WHO
Chair, ISPE Korea

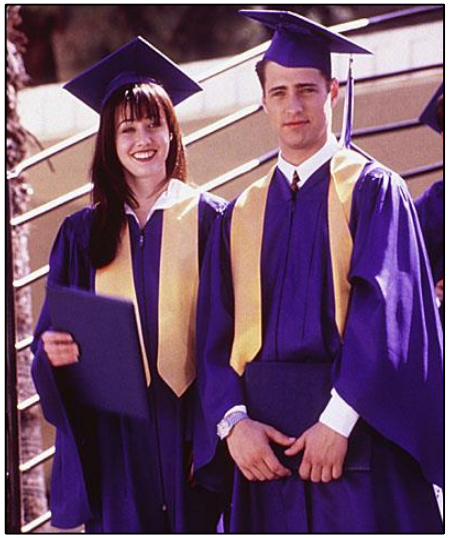
Four Basic Elements of CGMP

- "4Ms"



Four Basic Elements of CGMP

- Men : Organization & Personnel

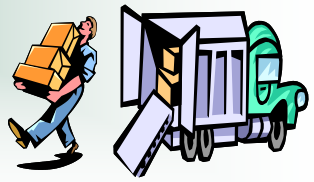


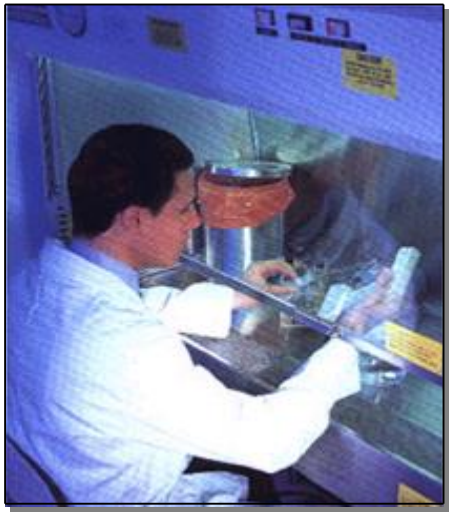
- Qualification
- Training
- Personnel Responsibilities
- Independence

Four Basic Elements of CGMP

- Materials
  - Raw materials
    - Receipt
    - Quarantine
    - Sampling
    - Testing
    - Release
    - Retesting
  - Cell Banking
  - Products
  - Container & Closures
  - Labels

Untested Components,
Drug product Containers
& Closures

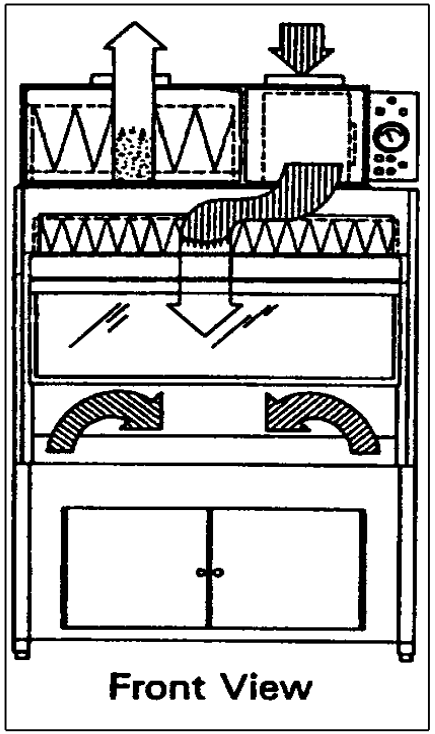


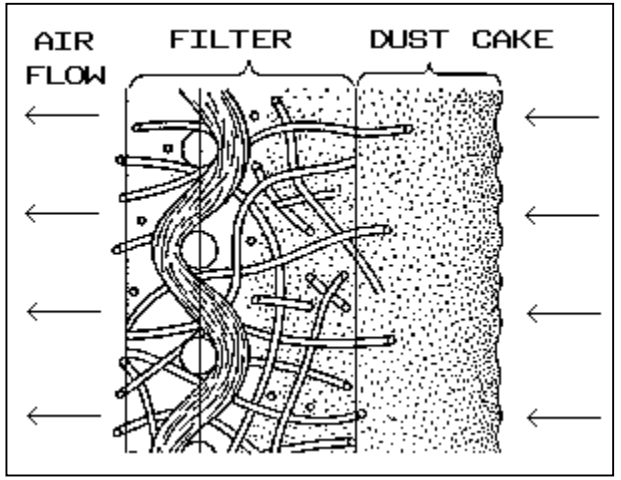


Four Basic Elements of CGMP

- Machinery
  - Building Design
  - HVAC System
  - PW/WFI System
  - Clean Steam System
  - Washing & Toilet Facilities
  - Laminar Flow Hoods

HEPA filter





3 Occupancy States

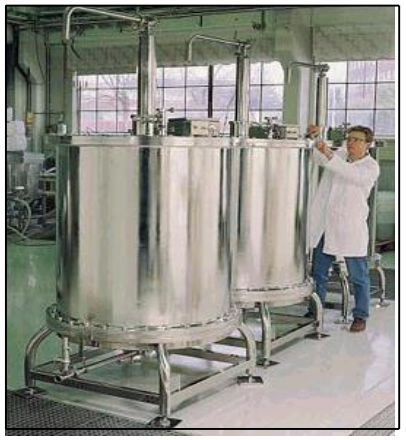
- As-Built condition
  - Where the installation is complete with all services connected and functioning but with no equipment & personnel present.
- At-Rest condition (Static)
  - Where the installation is complete with equipment installed and operating but with no personnel present.
- Operational condition (Dynamic)
  - Where the installation is functioning with the specified No. of personnel present & equipment operating.

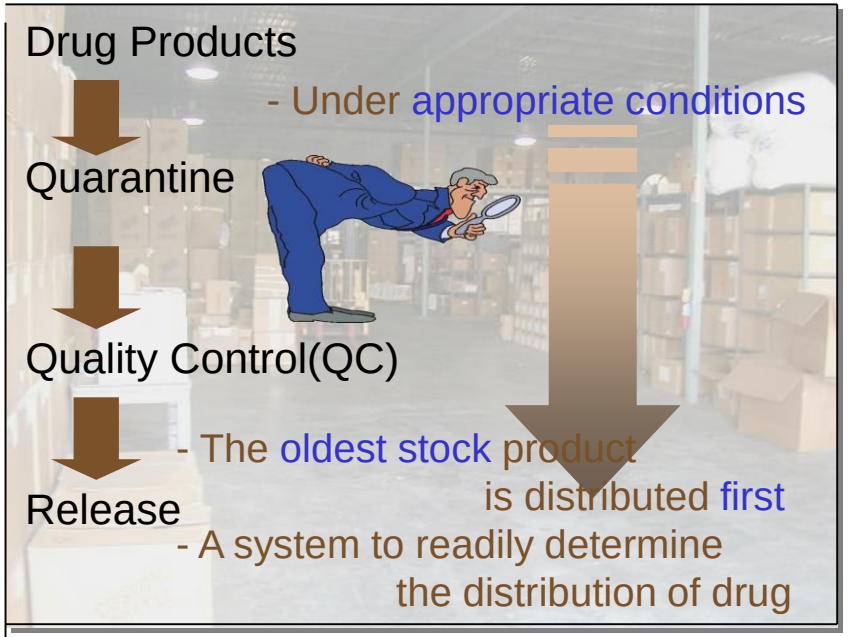
Comparison of Air Cleanliness Classifications

FDA	Descriptive		Class 100	Class 10,000	Class 100,000	ND	
	In Operation	≥ 0.5μm /ft^3	100	10,000	100,000	ND	
		Action Level CFU/m^3	1	10	100	ND	
EU, WHO, PIC/S	Descriptive		A	B	C	D	ND
	At Rest	≥ 0.5μm /m^3	3,520	3,520	352,000	3,520,000	
		≥ 5μm /m^3	20	29	2,900	29,000	
	In Operation	≥ 0.5μm /m^3	3,520	352,000	3,520,000	ND	
		≥ 5μm /m^3	20	2,900	29,000	ND	
		CFU/m^3	< 1	< 10	< 100	< 200	
ISPE	Descriptive		Grade 5	Grade 7	Grade 8	CNC+	CNC
ISO	Descriptive		ISO. 5	ISO. 7	ISO. 8	ISO. 9	
	In Operation	≥ 0.5μm /m^3	3,520	352,000	3,520,000	35,200,000	
		≥ 5μm /m^3	20	2,930	29,300	293,000	

Four Basic Elements of CGMP

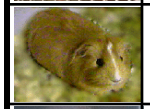
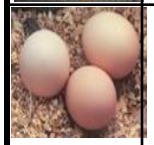
- Methods
  - Production
  - Sampling & Testing
  - Environmental Monitoring
  - Packaging & Labeling
  - Validation
  - Documentation
  - Storage





Testing for adventitious agents

- In vivo tests
  - Test methods

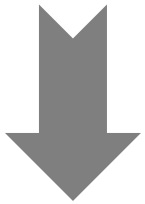
Test Systems		Observation Period(days)	Number of Animals	Route Inoculation	Inoculation Per Animal(mL)
	Suckling mouse	14 14(subpass)	20 5(subpass)	i.c./ i.p.	0.01/0.1
	Adult mouse	21	20	i.c./ i.p.	0.03/0.5
	Guinea pig	42	5	i.c./ i.p.	0.1/5.0
	Rabbit	30	5	i.d./ s.c.	1.0/2.0
	Embryonated chicken egg	3 3(subpass) 9 9(subpass)	10 10(subpass) 10 10(subpass)	allantoic yolk sac	0.5 0.5

Process Validation

- Validated Support Systems/Processes
  - HVAC, WFI/PW, Steam, Compressed air, Dust collection…
  - Cleaning, Sterilization, Depyrogenation, Decontamination…
- Manufacturing Processes
  - Critical production processes impacting on :
    - Product quality
    - Reproducibility of the process
  - Parameters
  - Range of variability
  - Justified sampling plan
  - Testing via validated methods
  - Consistency : 3 consecutive lots (full production scale)

Latest GMP Trends

- Introduction
  - 2002 : Pharmaceutical CGMP Initiative for the 21st Century-A Risk Based Approach



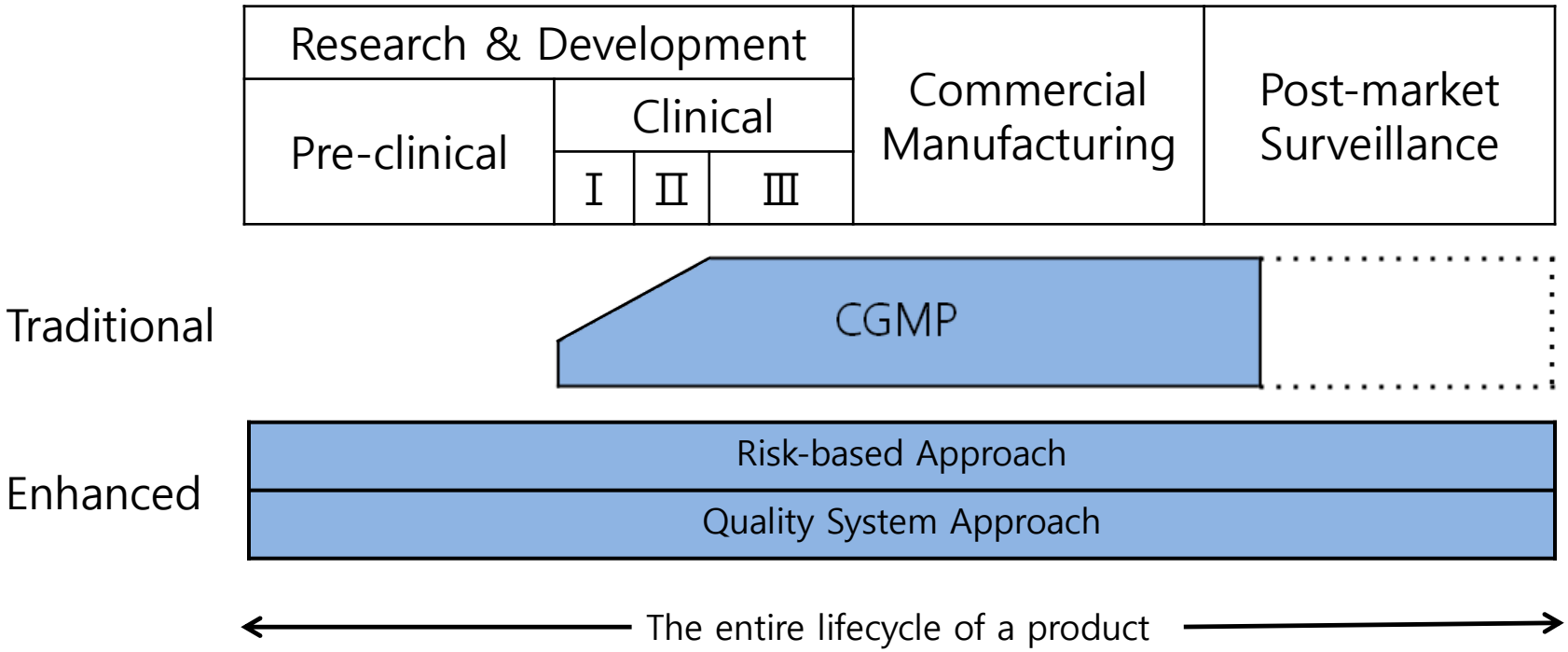
The Pharmaceutical Quality for the 21st Century-A Risk Based Approach

Latest GMP Trends

- The Goals of the Initiative
  - To encourage the early adoption of new technological advances by the pharmaceutical industry
  - To facilitate industry application of modern quality management techniques including implementation of quality systems approaches, to pharmaceutical production & quality assurance
  - To encourage implementation of risk-based approaches for both industry & agency (NRA)
  - To ensure that regulatory review, compliance & inspection policies are based on state-of-the-art pharmaceutical science
  - To enhance the consistency & coordination of FDA's drug quality regulatory programs, by integrating quality systems approaches into Agency's review & inspection activities

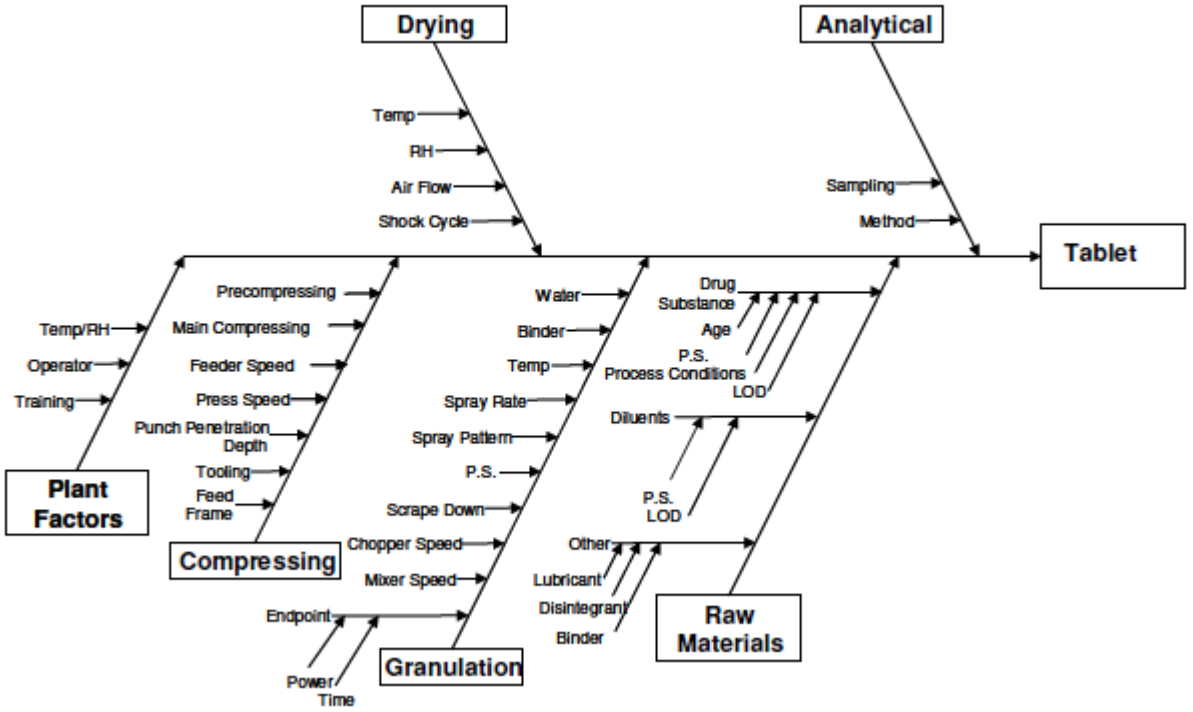
Latest GMP Trends

- Traditional vs. New Enhanced Approach



Latest GMP Trends

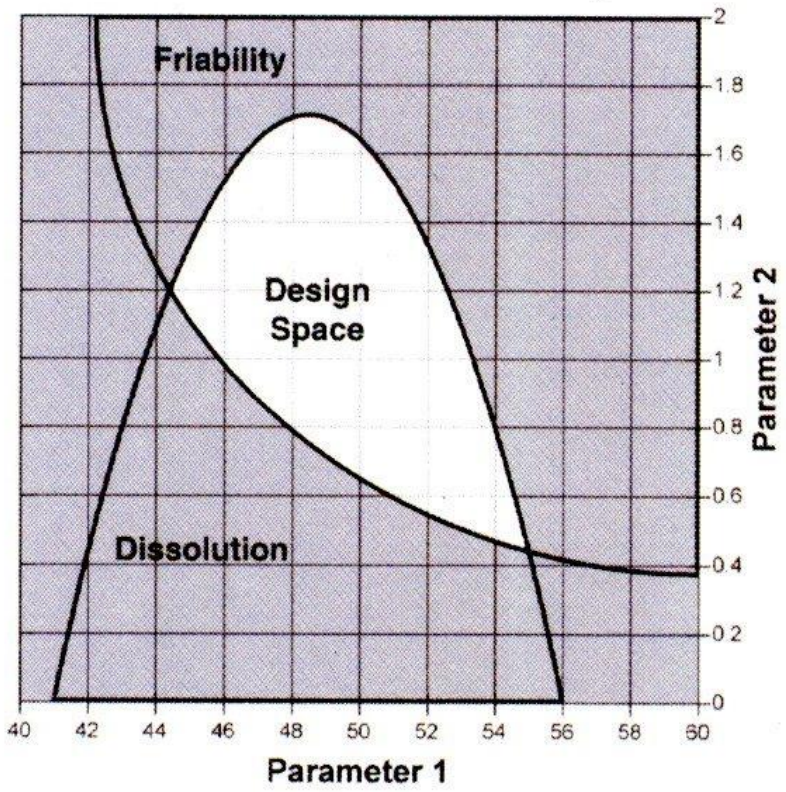
- Ishikawa (Fishbone) Diagram (risk assessment tool)



- CQA of the product
- Input variables : materials etc.
- Process parameters : temp., time, humidity etc.
- Multidimensional combination & interaction → Design Space
- Real time release (test)
- Quality by Design → Regulatory flexibility

Latest GMP Trends

- Design Space



Latest GMP Trends

- US FDA's Guidances with Enhanced Approach (QbD)
  - Sterile Drug Products Produced by Aseptic Processing –CGMP (Sept., 2004)
  - Process Analytical Technology (PAT) : A Framework for Innovative Pharmaceutical Development, Manufacturing & Quality Assurance (Sept., 2004)
  - Quality Systems Approach to Pharmaceutical CGMP Regulations (Sept., 2006)
  - Process Validation : General Principles & Practices (Jan., 2011)

Latest GMP Trends

- Sterile Drug Products Produced by Aseptic Processing – CGMP (Updated version of 1987 Aseptic processing guideline)
  - Personnel qualification
  - Cleanroom design
  - Process design
  - Quality control
  - Environmental monitoring
  - Review of production records

Latest GMP Trends

- Process Analytical Technology(PAT)
  - Introduction / Scope / Background
  - PAT framework
    - Process understanding
    - Principles & tools
      - PAT tools
      - Risk-based approach
      - Integrated systems approach
      - Real time release
    - Strategy for implementation
  - PAT regulatory approach

Latest GMP Trends

- Quality Systems Approach to Pharmaceutical CGMP Regulations
  - Introduction / Background/CGMP vs. modern Quality Systems
  - Quality systems model
    - Management responsibility
    - Resources
    - Manufacturing operations
    - Evaluation activities
  - Conclusion
    - Implementation of a quality systems model will facilitate compliance with CGMP

Latest GMP Trends

- Process Validation : General Principles & Practices
  - Introduction / Background/Regulatory Requirements
  - Recommendations
    - General considerations for process validation
    - Process design
    - Process qualification
    - Process verification
  - Concurrent release of PPQ batches
  - Documentation
  - Analytical methodology

Latest GMP Trends

- ICH Harmonized Tripartite Guidelines
  - Pharmaceutical Development (ICH Q8:R2) (Aug., 2009)
  - Quality Risk Management (ICH Q9) (Nov., 2005)
  - Pharmaceutical Quality System (ICH Q10) (June, 2008)
  - Development & Manufacture of Drug Substances (ICH Q11) (Nov., 2012)
  - Technical & Regulatory Considerations for Pharmaceutical Product Lifecycle Management (ICH Q12) (July, 2014)

Latest GMP Trends

- Pharmaceutical Development (ICH Q8:R2)
  - This guideline describes the content for pharmaceutical development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.
  - This section provides the knowledge gained through the application of scientific approaches & quality risk management to the development of a product & its manufacturing process.
  - The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.
  - Scope
    - This guideline does not apply to IND products but the principles in this guideline are important to consider.

Latest GMP Trends

- Pharmaceutical Development (ICH Q8:R2)
  - Development
    - The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
    - The knowledge gained from pharmaceutical development studies & manufacturing experience provides scientific understanding to support the establishment of the design space, specifications, & manufacturing controls.

Latest GMP Trends

- Pharmaceutical Development (ICH Q8:R2)
  - Development
    - Information from pharmaceutical development studies can be a basis for quality risk management.
    - Quality cannot be tested into products ; i.e., quality should be built by design (Quality by Design).
    - Design space is proposed by the applicant & is subject to regulatory assessment & approval. Working within the design space is not considered as a change.

Latest GMP Trends

- Quality Risk Management (ICH Q9)
  - Quality risk management is a valuable component of an effective quality system.
  - Risk is defined as the combination of the probability of occurrence of harm & the severity of that harm.
  - In relation to pharmaceuticals the protection of the patient by managing the risk to quality should be considered of prime importance.

Latest GMP Trends

- Quality Risk Management (ICH Q9)
  - An effective quality risk management approach can ensure the high quality of the drug product to the patient by providing a proactive means to identify & control potential issues during development & manufacturing.
  - Effective quality management can provide regulators with greater assurance of a company's ability to deal with potential risks, & can beneficially affect the extent of direct regulatory oversight.

Latest GMP Trends

- Quality Risk Management (ICH Q9)
  - This document is to offer a systematic approach to quality risk management & to provide guidance on the principles & some of the tools of quality risk management that can enable more effective & consistent risk-based decisions by both regulators & industry.
  - The use of informal risk management processes can also be considered acceptable. (vs. formal processes)

Latest GMP Trends

- Quality Risk Management (ICH Q9)
  - Risk management methodology
    - Basic risk management facilitation methods : flow charts, check sheets
    - Failure mode effects analysis (FMEA)
    - Failure mode effects, and criticality analysis (FMECA)
    - Fault tree analysis(FTA)
    - Hazard analysis & critical control points(HACCP)
    - Hazard operability analysis (HAZOP)
    - Preliminary hazard analysis(PHA)
    - Risk ranking & filtering
    - Supporting statistical tools

Latest GMP Trends

- Pharmaceutical Quality Management System (ICH Q10)
  - To describe a model for an effective quality management system for the pharmaceutical industry
  - Based upon International Organization for Standardization (ISO) quality concepts
  - Includes GMP regulations
  - Complements pharmaceutical development (ICH Q8) & quality risk management (ICH Q9)

Latest GMP Trends

- Pharmaceutical Quality Management System (ICH Q10)
  - Can be implemented throughout the different stages of a product lifecycle.
  - ICH Q10 applicable to manufacturing sites is currently specified by GMP requirements.
  - The content of ICH Q10 that is additional to current GMP requirements is optional.
  - Implementation of ICH Q10 throughout the product lifecycle should facilitate innovative & continual improvement and strengthen the link between pharmaceutical development & manufacturing activities.

Latest GMP Trends

- Pharmaceutical Quality Management System (ICH Q10)
  - Scope
    - Applies to the systems supporting the development & manufacture of
      - Drug substances : ex) APIs
      - Drug products including biotechnology & biological products
    - Throughout the product lifecycle :
      - Pharmaceutical development
      - Technology transfer
      - Commercial manufacturing
      - Product discontinuation

Latest GMP Trends

- Pharmaceutical Quality Management System (ICH Q10)
  - Relationship to other guidelines
    - Foundation of QC10
      - GMP requirements
      - ICH Q7 (GMP for APIs)
      - ISO quality management system guidelines
    - Q10 augments GMPs.
    - Q10 provides a harmonized model for a pharmaceutical quality system throughout the lifecycle of a product.
    - GMPs do not address all stages of the product lifecycle (e.g., development).
    - Q10 intends to encourage the use of science-and risk-based approaches at each lifecycle stage to promote continual improvement across the entire product lifecycle.

Latest GMP Trends

- Differing Approaches to Pharmaceutical Development

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • PAT tools utilized
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimization and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods

Latest GMP Trends

- Differing Approaches to Pharmaceutical Development

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval • at-, on- & in-line analysis
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	• Reactive to problems • Post-approval changes needed	• Proactive •Continual improvement within design space

Hazard & Risk Analysis in Pharmaceutical Products

(Application of HACCP Methodology to Pharmaceuticals)

A. History of HACCP

1. The Hazard Analysis and Critical Control Point (HACCP)
2. Preventive-based food safety system
3. Pioneered by the “Pillsbury Company” in early 1960’s
4. Assurance against contamination by bacterial & viral pathogens, toxins, chemical or physical hazards
5. FDA recommends the implementation of HACCP in food establishments
6. The National Advisory Committee on Microbiological Criteria for Foods(NACMCF) was established in 1988

B. Use of HACCP for Phamaceuticals

1. **Safety Hazard**
   a. Identification
   b. Assessment
   c. Control

2. **Elements of HACCP Methodology**
   a. Develop a flow diagram of the process
   b. Verify the flow diagram on site
   c. Analyse the critical quality variables
   d. Assess the hazards
   e. Identify measures for their control

C. Definitions

1. **Critical Control Point**
   A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level

2. **Hazard**
   Any circumstances in the production, control and distribution of a pharmaceutical which can cause an adverse health effect

3. **Risk**
   An estimate of the likely occurrence of a hazard

C. Definitions *(continued)*

4. **Critical limit**
   The maximum or minimum value to which a physical, biological, or chemical parameter must be controlled at a critical control point to minimize the risk that the identified product safety hazard may occur

5. **Monitoring**
   A planned sequence of observations or measurements of critical limits designed to produce an accurate record and intended to ensure that the critical limit maintains product safety

D. Principles

1. **The HACCP system is based on 7 principles**

   a. Conduct a hazard analysis

   b. Determine the critical control points (CCPs)

   c. Establish target levels & critical limits

   d. Establish a system to monitor the CCPs

   e. Establish the corrective action to be taken

   f. Documentation

   g. Establish the procedures to verify that the HACCP is working

E. Application

In applying 7 principles 12 stages are recommended.

1. **Assemble a HACCP team (stage 1)**
    a. Research & development
    b. Production
    c. Quality control/assurance
    d. Microbiology
    e. Engineering
    f. Distribution

E. Application *(continued)*

2. Team members should be able to:

a. Conduct a hazard analysis

b. Identify potential hazards

c. Identify hazards which should be controlled

d. Recommend controls & critical limits

e. Devise procedures for monitoring & verification

f. Recommend appropriate corrective action where deviations occur

g. Verify the HACCP plan

E. Application (continued)

3. Describe the product & process (stage 2)

a. Composition
b. Physical / Chemical properties
c. Structure
d. pH
e. Temperatures
f. Method of cleaning
g. Bactericidal / Bacteriostatic treatment

E. Application (continued)

3. Describe the product & process (stage 2)

h. Drying

i. Screening

j. Mixing

k. Blending

l. Packaging

m. Storage condition

n. The method of distribution & transport where products are thermolabile

E. Application *(continued)*

4. Identify the intended use (stage 3)

a. The expected uses of the product by the consumer

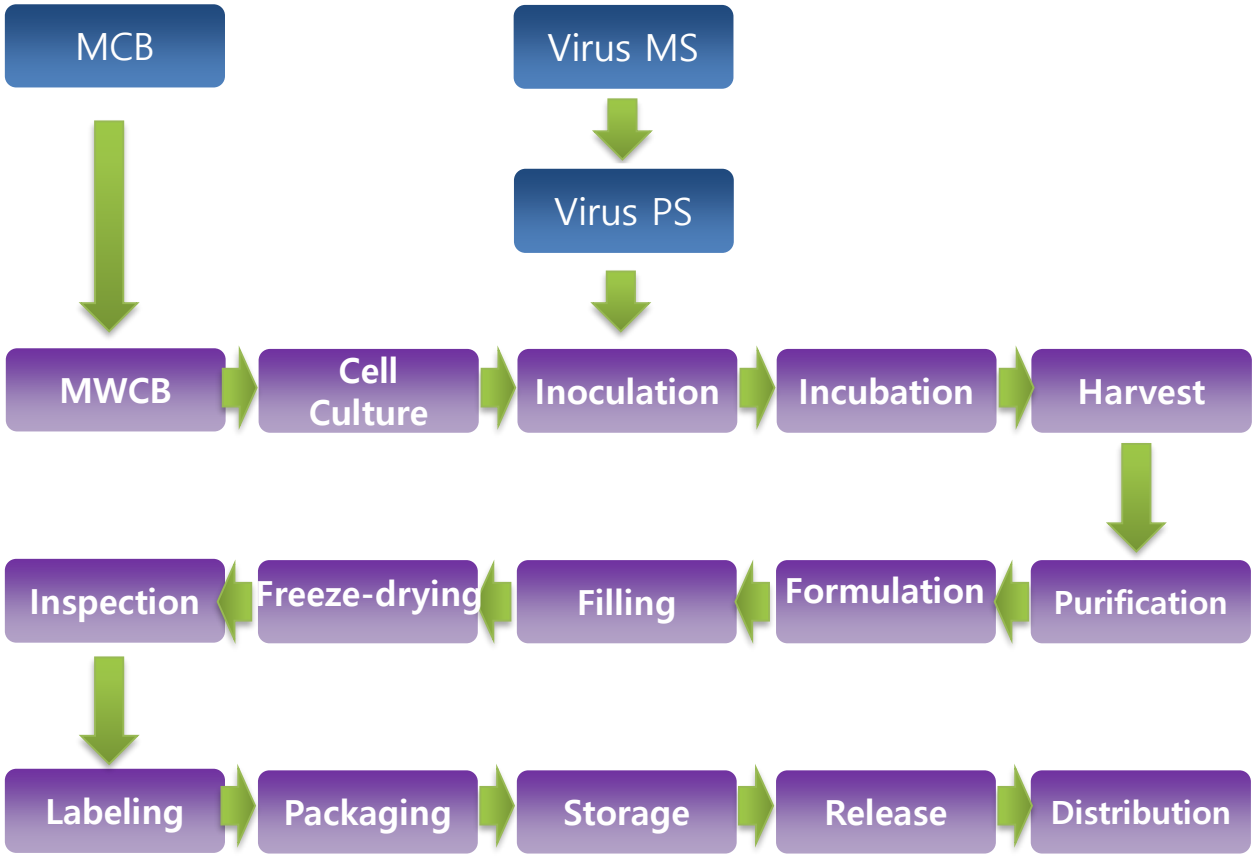
1) Infants

2) Immunocompromised patients

3) Adults

E. Application *(continued)*

5. Construct a flow diagram (stage 4)



E. Application (continued)

6. On-site confirmation of flow diagram (stage 5)

a. During all stages & hours of operation
b. Amendments may be made & should be documented

E. Application *(continued)*

7. **List all potential hazards, conduct a hazard analysis & consider any measures to control identified hazards (stage 6) : Principle 1**

   a. List all the hazards from production, testing & distribution up to the point of use

   b. A hazard analysis
      1) Step 1
         a) Review :
            materials, activities, equipment, storage, distribution, intended use of the product

E. Application *(continued)*

b) Check :

- ✓The probable occurrence of hazards & the severity of their adverse health effects
- ✓The qualitative and/or quantitative evaluation of the presence of hazards
- ✓The survival or multiplication of microorganisms of concern
- ✓The production or persistence in drugs of toxins, chemicals or physical agents
- ✓The conditions leading to the above

E. Application *(continued)*

b. A hazard analysis (continued)

2) Step 2

a) A hazard evaluation

ex.) : severity, probability of occurrence

b) Decide which hazards should be addressed in the HACCP plan

c) Decide what control measures exist

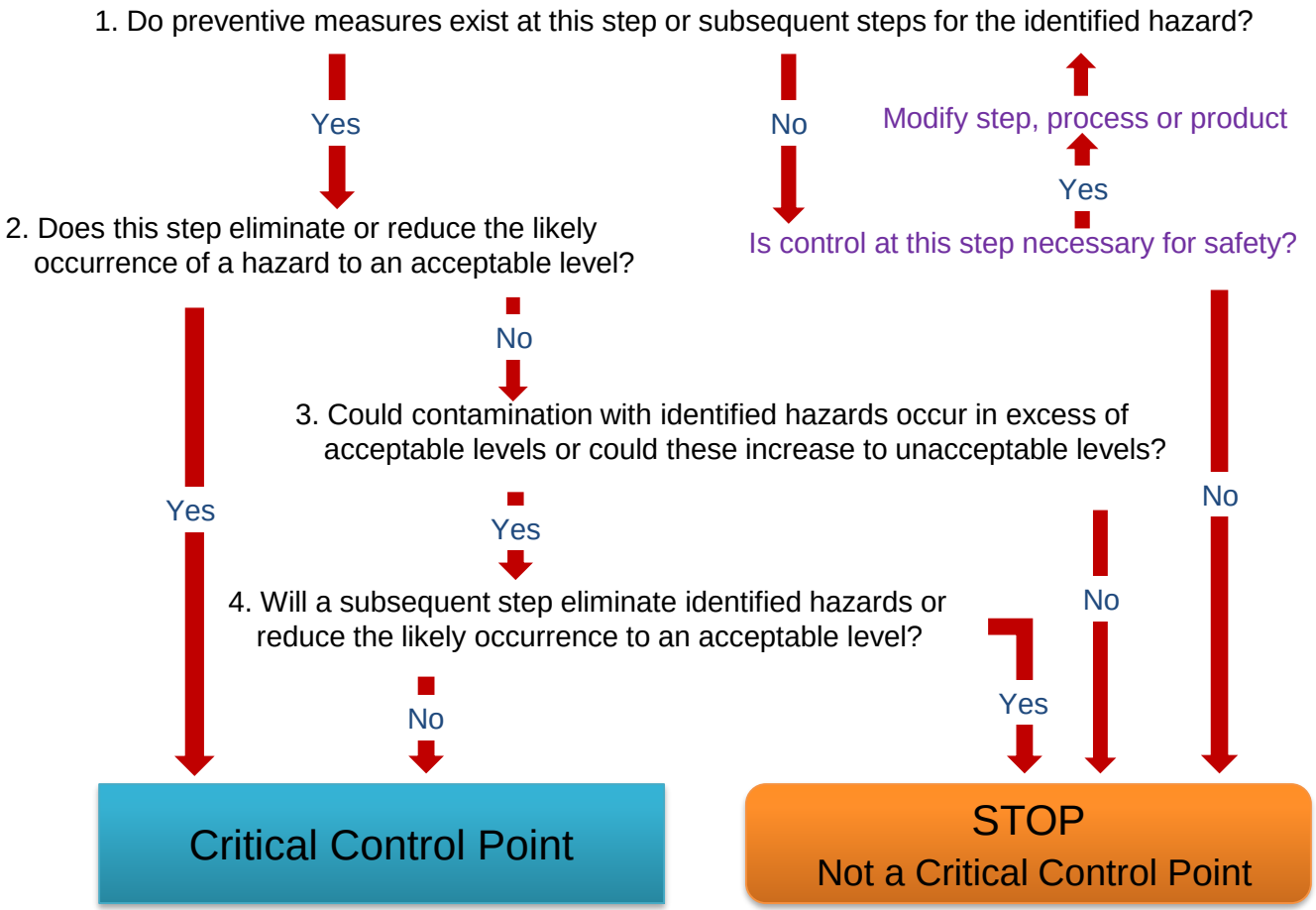
d) Potential hazards to be considered

- ✓ materials & ingredients
- ✓ physical characteristic & composition of the product
- ✓ processing procedures
- ✓ microbial limits
- ✓ premises
- ✓ equipment
- ✓ packaging
- ✓ sanitation & hygiene
- ✓ personnel
- ✓ risk of explosions
- ✓ mix-ups

E. Application *(continued)*

8. Determine critical control points (stage 7) : Principle 2

a. Use decision-tree (CCP Decision Tree Table)



E. Application (continued)

9. Establish critical limits for each CCP (stage 8) : Principle 3

a. Critical limits for each CCP

1) Temperature
2) Time
3) Moisture level
4) pH etc

E. Application *(continued)*

10. Establish a monitoring system for each CCP (stage 9) : Principle 4

a. The scheduled measurement of a CCP relative to its critical limits

b. Physical & Chemical measurements are often preferred

c. The personnel conducting the monitoring : production line supervisors, maintenance staff, QC staff etc.

d. Signatures by monitor & supervisor

E. Application *(continued)*

11. Establish corrective actions (stage 10) : Principle 5

a. Develop specific corrective action for each CCP

b. Corrective actions include :
   1) Determination & correction of the course of non-compliance
   2) Determination of the disposition of the non-compliant product
   3) Record the corrective actions taken

E. Application *(continued)*

12. Establish verification procedures (stage 11) : Principle 6

a. To determine if the HACCP system is working correctly

b. Verification includes :

   1) Review of the HACCP system & its records

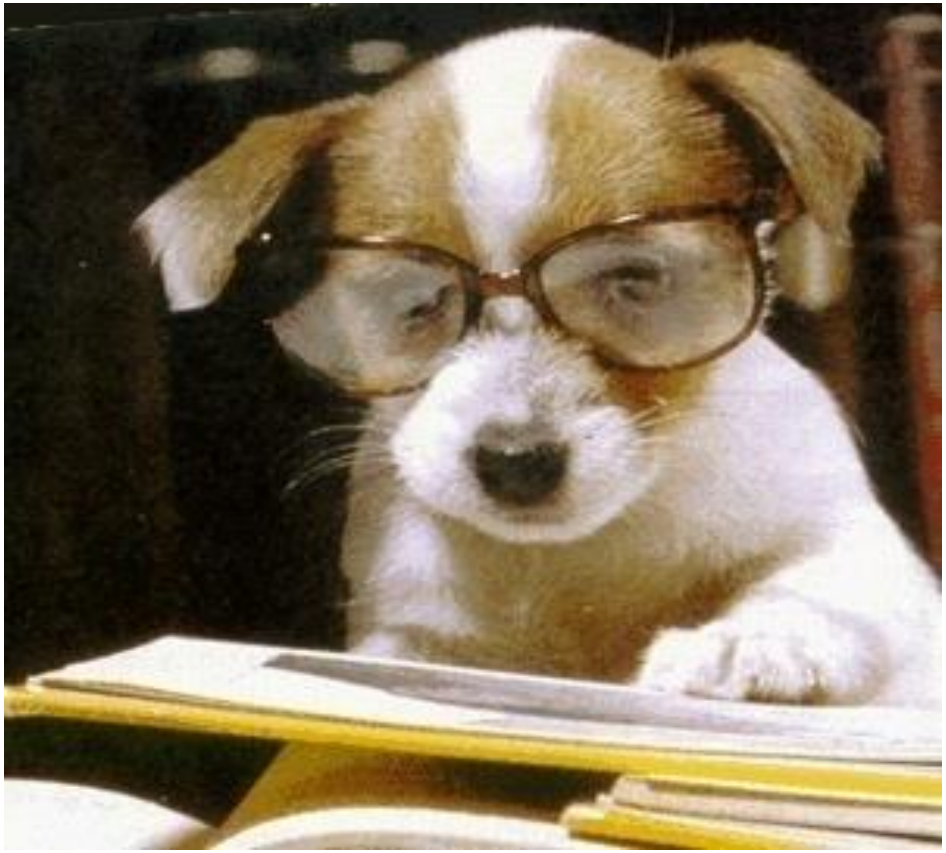
   2) Review of deviations and product dispositions

   3) Confirmation that CCPs are kept under control

c. A periodic comprehensive evaluation of the HACCP system by independent third party

E. Application *(continued)*

13. **Establish documentation & record keeping (stage 12): Principle 7.**
    a. Hazard analysis
    b. CCP determination
    c. HACCP plan
    d. Critical limit determination
    e. CCP monitoring activities
    f. Process steps
    g. Associated hazards
    h. Critical limits
    i. Verification procedures & schedule
    j. Deviation
    k. Associated corrective actions
    l. Modifications to the HACCP system



Thank you~*^^*