ICH Q10/WHO TRS
A Regulatory Perspective

Presentation by:

Dr. A. Ramkishan
Asst. Drugs Controller (India)
Govt. of India

Contents of Presentation

- Introduction
- History of WHO GMP TRS guidelines
- A Unique approach for ICH
- ICH Quality Vision
- GMPs & ICH
- Structure & Content of ICH
  - Introduction
  - Scope
  - Objectives
  - Fundamentals of QM
  - QM Elements
- Challenges
- Conclusions
- References

Snapshot - Indian Pharmaceutical Industry

- Industry size : Rs.1.2 Lakh Cr approx. (20 Bn USD) ;Industry is growing @ 20% p.a
- Domestic Market : 58Thousand Cr (approx.) (11.6 Bn USD)
- Exports :Rs. 47 Thousand Cr approx. (10.3 Bn USD)
- Imports: 3.2 Bn USD

3rd Largest in world in terms of Volume & ranks 13th in terms of Value

Export of Biotech products & Biopharmaceuticals ~US $1.36 Bn

Manufacturing Facilities 172 US FDA Approved

Largest Number of Manufacturing Facilities outside US

US Pharmacopoeia has office in Hyderabad, India

USFDA has country office in Delhi

153 EDQM certified facilities

Drugs from India are exported to more than 200 countries

Vaccines from India are exported to more than 151 countries

CDSCO – Geographical Location of 6 Zonal Offices

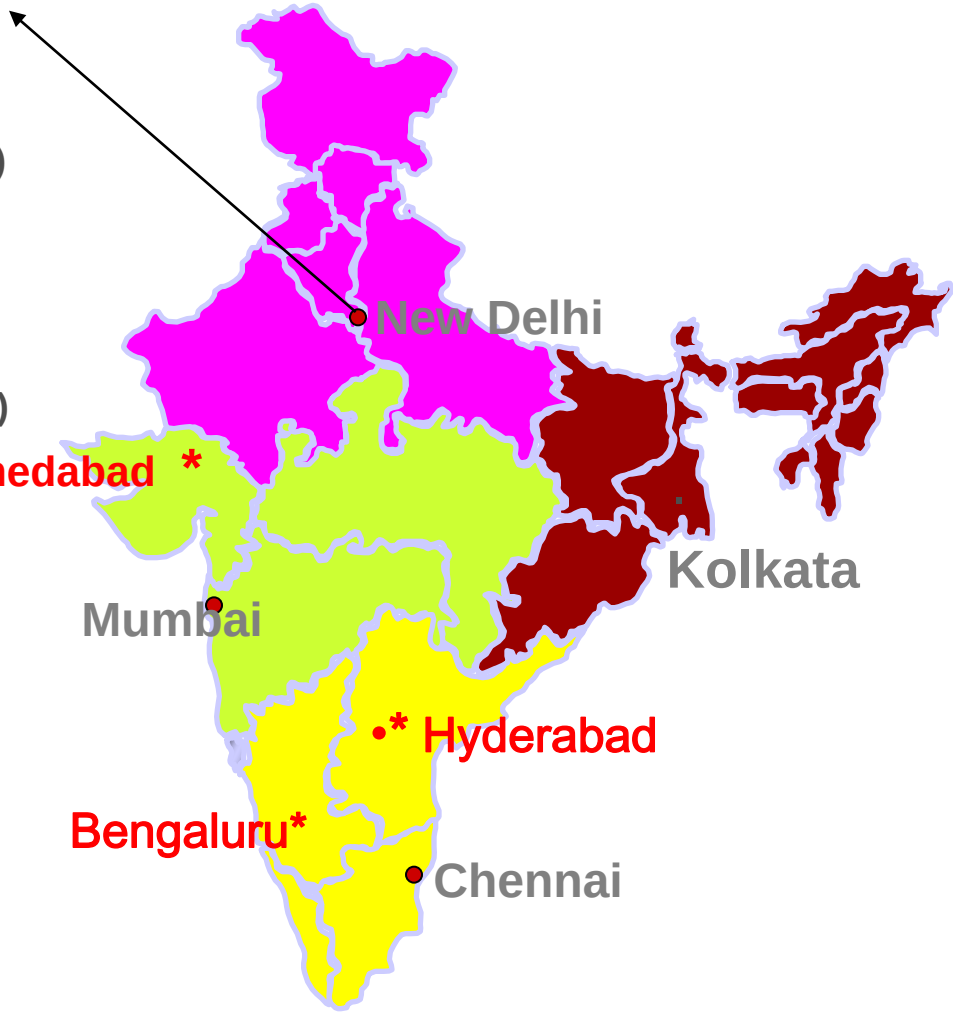
CDSCO, HQ

CDSCO North Zone (**Ghaziabad**)

CDSCO West Zone (**Mumbai**)

CDSCO South Zone (**Chennai**)

CDSCO East Zone (**Kolkata**)



New Zonal Offices	**: 2**
Ahmedabad & Hyderabad	
Sub- Zonal Office	**: 5**
Port Offices/Airports	**: 7**
Laboratories	**: 6**

29 States

6 Union Territories

WHAT IS GMP?

- Good manufacturing practices (GMP) is a system for ensuring that products are consistently produced and controlled to quality standards.
- The procedures employed to ensure that the drug product or substance is manufactured under a quality management system and meets the claimed requirements for purity, Identity, safety and quality.
- It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final products. The main risks i. Unexpected contamination of products, causing damage to health or even death. ii. Wrong labels on containers, leading to patients getting wrong medicine. iii. Not enough or too much active ingredients, resulting in ineffective treatment or adverse effects.
- The WHO is a specialized agency of the United nations with the primary responsibility for international health matter and public health. The quality of pharmaceutical has been a concern of the WHO since it's inception. The setting of Global standards is requested in article – II of the WHO constitution which cites as one of the organization functions that it should develop, establish and promote international standards with respect to food, Biological, Pharmaceuticals & similar products.

- GMP covers all aspects of production: from the starting materials, premises and equipment to the training and personal hygiene for staff. Detailed written procedures are essential for each process that could affect the quality of the finished products. There must be system to provide documented proof that correct procedures are consistently followed at each step in the manufacturing of process – every time a products is made.

History of WHO GMP TRS

- WHO TRS 307 (21st Report)-1965
- WHO TRS 418 (22nd Report)-1971
- WHO TRS 463 (23rd Report)-1972
- WHO TRS 487 (24th Report)-1972
- WHO TRS 567 (25th Report)-1975
- WHO TRS 614 (26th Report)-1977
- WHO TRS 645 (27th Report)-1980
- WHO TRS 681 (28th Report)-1982
- WHO TRS 704 (29th Report)-1984

History of WHO GMP TRS conti…

- WHO TRS 748 (30th Report)-1987
- WHO TRS 790 (31st Report)-1990
- WHO TRS 823 (32nd Report)-1992
- WHO TRS 834 (33rd Report)-1993
- WHO TRS 863 (34th Report)-1996
- WHO TRS 885 (35th Report)-1999
- WHO TRS 902 (36th Report)-2002
- WHO TRS 908 (37th Report)-2003
- WHO TRS 917 (38th Report)-2003

History of WHO GMP TRS conti…

- WHO TRS 929 (39th Report)-2005
- WHO TRS 937 (40th Report)-2006
- WHO TRS 943 (41st Report)-2007
- WHO TRS 948 (42nd Report)-2008
- WHO TRS 953 (43rd Report)-2009
- WHO TRS 957 (44th Report)-2010
- WHO TRS 961 (45th Report)-2011
- WHO TRS-2012-- Awaited

WHO GMP TRS 961 New Approaches

- Quality Assurance – new approaches
  - WHO guidelines on Quality Risk Management (QRM)
  - WHO guidelines on Technology Transfer
- Prequalification of quality control laboratories
  - Update of activities
  - Procedure for prequalifying laboratories
  - Update on the WHO guidelines for preparing a laboratory information file

WHO GMP TRS 961 New Approaches Conti..

- Regulatory guidance
  - WHO guidelines for preparing a Site Master File (SMF)
  - Submission of documentation for a multisource (generic) finished products
  - Pharmaceutical development for multisource (generic) pharmaceutical products
  - Bio-pharmaceutics Classification System
  - Development of pediatric medicines
  - Quality requirements for Artemisinin

A Unique Approach

- ICH was created in 1990.
- Agreement between the European Union (EU), Japan & The United States of America (USA) to harmonize Technical Requirements for registration of Pharmaceuticals for human use.
- Joint effort by Regulators & Stake holders.
- ICH expert working groups focusing on Safety, Quality, Efficacy & Multidisciplinary guidelines.

ICH Q10- Vision

- Describe a modern quality system needed to establish and maintain a state of control that can ensure the realization of a quality drug product and facilitate continual improvement over the life cycle of a drug product.
- Promote a paradigm shift from discreet GMP compliance systems at each stage of the product lifecycle to a global QS approach over the entire lifecycle of the product
- And if adopted by industry (on a voluntary basis) would:
- Complement and serves as a bridge between regional GMP regulations.
- Facilitate application of ICH Q8 (Pharmaceutical development), Q9 (Quality Risk Management System)

Vision Conti….

- Links development and manufacturing through the product lifecycle
- Facilitate continual improvement in pharmaceutical manufacturing
- Based upon the well accepted ISO 9000 structure within a pharmaceutical context
- Facilitate ‘appropriate levels of regulatory scrutiny’
- Post approval changes
- Inspections
- Would provide a harmonized model for a Pharmaceutical Quality System that if adopted by industry (on a voluntary basis) would:
- Leverage knowledge and encourage a preventive action culture, which ensures actions are taken before a problem / issue arises

Vision Conti….

- Improve quality monitoring and review (e.g. data evaluation, statistical process control and process capability measurements), which form the basis for continual improvement of processes
- Provide greater assurance that there is no unintended consequence as a result of continual improvement activities

GMPs & ICH Q10-Brief relationship

- Q10 is not a harmonized GMP, Regional GMPs do not currently apply across the product(s) life cycle but
- GMPs do provide guidance on manufacture and control of pharmaceutical products
- GMPs do provide guidance on most of the essential elements of a Quality Assurance System
- GMPs address CAPA but not proactive continual improvement
- GMPs touch on management responsibilities
- GMPs do not address the system needed to bring a quality product to market
- However, GMPs are a critical element of an effective Pharmaceutical Quality System

ICH Q10-Structure & Content

- Introduction
- Scope
- Pharmaceutical Quality System
- Management Responsibility
- Management and Continual Improvement of Product Quality
- Management and Continual Improvement of the Pharmaceutical Quality System

Introduction to ICH Q10 (PQS)

- ICH Q10 was adopted in the year 2008 to establish and implement an effective QA system in order to comply with GMP.
- ICH Q10 describes comprehensive model for an effective pharmaceutical quality system i.e., based on ISO Quality Concepts, Applicable GMP texts and also Pharmaceutical development (ICH Q8) and Quality Risk Management (ICH Q9).
- It enhances the quality and facilitates the innovation and strengthen the link between development of product and manufacturing activities.
- It should be noted that ICH Q10 is optional.

Introduction to ICH Q10 Conti...

ICH Q10

- Pharmaceutical Quality System or PQS
- Current is Step 4, Version dated 4th June 2008
- Recommended for adoption to the regulatory bodies of the European Union, Japan and USA
- PQS is a management system to direct and control a pharmaceutical company with regard to quality (ICH Q10 based on ISO 9000:2005)

Introduction to ICH Q10 Conti...

Regulatory Applicability

- European Medicines Evaluation Agency (EMEA) has adopted ICH Q10 in January 2011
- US FDA issued guidance for Industry - Quality Systems Approach to Pharmaceutical cGMP Regulations - September 2006
- Other agencies are in process of adoption
  - WHO has (indirectly) adopted ICH Q9 since May 2011 (TRS 961, *45th Report*)

Introduction to ICH Q10 Conti...

- ICH Q10 describes a comprehensive approach to Pharmaceutical Quality System
- It includes Good Manufacturing Practice (GMP) regulations
- It is harmonized with ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management”
- It demonstrates Industry & Regulatory to enhance the Quality and Availability of medicines around the Globe in the interest of Public Health

Introduction to ICH Q10 Conti...

- ICH Q10 is not intended to create any new regulatory requirements
- It only helps in maintaining product quality and compliance at all stages of product life cycle
- It helps innovation and continual improvement in the pharma manufacturing
- Regional GMPs do not explicitly address all stages of the product life cycle (e.g., development) and ICH Q10 is intended to encourage the use of science and risk based approaches at each lifecycle stage thereby promoting continual improvement across the entire product life cycle.

Scope to ICH Q10

- ICH Q10 can be implemented throughout the different stages of a product lifecycle which is the scope of ICH Q10 implementation
  I. Development Stage
  II. Technology Transfer Stage
  III. Manufacturing Stage
  IV. Discontinuation Stage

Table I: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

Scope to ICH Q10 Conti...

Pharmaceutical Development:

- Drug substance development;
- Formulation development (including container/closure system);
- Manufacture of investigational products;
- Delivery system development (where relevant);
- Manufacturing process development and scale-up;
- Analytical method development

Technology Transfer:

- New product transfers during Development through Manufacturing;
- Transfers within or between manufacturing and testing sites for marketed products.

Scope to ICH Q10 Conti...

Commercial Manufacturing:

- Acquisition and control of materials
- Provision of facilities, utilities & equipment;
- Production (including packaging and labeling);
- QC and QA
- Release, Storage
- Distribution (excluding wholesaler activities)

Product Discontinuation:

- Retention of documentation
- Sample retention
- Continued product assessment and reporting

Scope to ICH Q10 Conti...

- It applies to the system supporting to the development and manufacture of different various dosage forms through out the product life cycle.

- Pharmaceutical Development
- Technology Transfer
- Quality System
- Production System
- Facilities, Utility & Equipment System
- Laboratory Controls System
- Materials System
- Packaging & Labelling System

The objectives of PQS

(1) ***Achieve Product Realization:*** To establish, implement & maintain a system that allows the delivery of a products with the quality attributes appropriate to meet the needs of patient & other stake holders.

(2) ***Establish & Maintain a State of Control:*** To develop & use effective monitoring & control systems for process performance & product quality, thereby providing assurance of continued suitability and capability of processes. Quality Risk Management (QRM) can be useful in identifying the monitoring and control systems

(3) ***Facilitate Continual Improvement***: To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovation & quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. QRM can be useful for identifying & prioritizing areas for continual improvement.

ICH Q9: QRM-Quality Risk Management

QRM is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating & controlling potential risks to quality. It facilitates continual improvement of process performance & product quality throughout the product life cycle.

QRM can be applied to different aspects of pharmaceutical quality (e.g. Design & content consideration)

PQS Elements

- PQS consists of four elements are:

(1) Process performance & Product quality monitoring system

(2) Corrective & Preventive Action (CAPA) system

(3) Change management system

(4) Management review of process performance & product quality

Process performance & Product quality monitoring system:

- Should use quality risk management to establish the control strategy, which include parameters & attributes related to drug substances/product materials/components/facility/equipment condition/in process control/finished product specification/frequency of monitoring & control
- Should provide the tools for measurement for analysis of parameters & attributes identified in the control strategy
- Should analyze parameters and attribute identified in control strategy to verify continued operation within a state of control
- Should identify source of verification affecting process performance & product quality to reduce or control variations
- Should include feedback on product quality from both internal & external sources
- Should provide knowledge to enhance process understanding.

Corrective And Preventive Action (CAPA):

- Pharmaceutical company should have a system for implementing CAPA resulting from the investigation of complaints, product rejections, non conformances, recalls, deviations, audits, regulatory inspections & findings, trends from process performance & product quality monitoring. The objective of CAPA is determining the root cause of deviation.
- Corrective Action: Action to eliminate the cause of a detectable non-conformity or other undesirable situation. Note: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence (ISO 9000:2005)
- Preventive Action: Action to eliminate the cause of potential non-conformity or other undesirable potential situation. Note: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence (ISO 9000:2005)

Change Management System

- Change Management: A systematic approach to proposing, evaluating, approving, implementing & reviewing changes.

It Should Include

- Quality risk management to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk
- Proposed changes should be evaluated relative to the marketing authorization including design space, to determine whether a change to regulatory filling is required under regional requirements
- Proposed change should be evaluated by expert in contributing their experience and knowledge
- After implementation & evaluation of change should be under taken to conform the change objectives were achieved and there were no deleterious impact on product quality

Should include

- The result of regulatory inspection and findings, audits and other assessments and commitments maid to regulatory authorities.
- Periodic quality reviews, that can include:

1. Measures of customer satisfaction such as product quality complaints and recalls
2. Conclusions of process performance and product quality monitoring.
3. The effectiveness of process and product changes including those arising from CAPA.

- Any follow-up actions from previous management reviews

Applicability OF ICH Q10

- Pharmaceutical Quality System
- Scale-up and Technology Transfer
- Process Validation
- Change Management and Continual Improvement
- Quality Unit (QA/QC) and Batch Release

ICH Q10 PQS

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Discontinuation

Investigational products

GMP

Management Responsibilities

PQS elements

Process Performance & Product Quality Monitoring System

Corrective Action / Preventive Action (CAPA) System

Change Management System

Management Review

Enablers

Knowledge Management

Quality Risk Management

Key Messages – PQS ICH Q10

- It introduces the involvement and role of senior management
- It introduces a product life cycle perspective
- Quality Risk Management and Knowledge Management are enablers for the PQS
- Implementation of PQS provides to enhance assurance of product quality

Conclusions

- ICH Q10 requires an understanding of FDA for the 21st Century, ICH Q8 (Design), ICH Q9 (Risk) as well as ISO 9000 (2005) to maximize benefit
- ICH Q10 is an ISO SYSTEMS approach to GMP
- NOT additional to GMP but integral to GMP
- Covers full life Cycle of a Product
- Objectives: Product Realization, Control & improvement
- Demands Management Team to lead Quality System and which protects public health in respect of product lifecycle.
- As a management team we firmly believe that effective and robust Quality
- Risk Management underpinned by an effective quality system is key to the successful implementation of the new concepts described in ICH Q8, Q9 & Q10.

Conclusions Conti...

- **Scale up and Technology Transfer**
  - Scale-up of manufacturing processes and controls must confirm and support final design space
  - Proof of concept and adaptation of Control Strategy for commercial applicability
- **Process validation**
  - Over the lifecycle rather than a one time event
  - Confirms predictive models at full scale
  - Incorporates QRM Principles and Knowledge Management
  - Part of PQS at commercial manufacturing site

Conclusions Conti...

- **Change Management**
  - Need to consider development information
  - Changes within the design space can be managed internally without prior regulatory notification
  - Changes to Non-Critical process parameters can be managed internally without prior regulatory notification

- **Continual Improvement of the product**
  - Proactive use of trended data
  - Feed expanded knowledge back to Development

Conclusions Conti...

- **Quality Unit and Batch Release**
  - Use of Risk Management within the Quality System
  - Lifecycle responsibility with Cross functional alignment with commercial/R&D
  - Ensure alignment of the site PQS with enhanced development approach (continual improvement of the PQS itself)
  - Maintenance and use of the Design Space and Control Strategy, and predictive models

Challenges

- Trust and Culture Change
  - Industry-Regulatory Trust & Openness in vision
  - Culture change in both for industry & regulatory
- Will the Q10 approach disadvantage small & medium manufacturing units?
- What is the scope of QMS (Site or Enterprise)?
- How many companies will require re-engineering of their QMS?
- How will we eventually adopted?
- Please tell what are the other challenges in implementation of ICH Q10??? (For Audience)

References

- GMP Text for the 21st century www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm
- International Conference on Harmonisation, ICH Q8: Pharmaceutical Development, November 2005. http://www.ich.org/
- International Conference on Harmonisation, ICH Q9: Quality Risk Management, November 2005. http://www.ich.org/
- International Conference on Harmonisation, ICH Q10: Pharmaceutical Quality System, May 2007 & June 2008. http://www.ich.org/
- FDA, Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006. http://www.fda.gov/
- 01 January 2008By:Adrian Kirk Pharmaceutical Technology Europe
- WHO GMP Guidelines TRS 957, TRS 937 & TRS 961-2011.
- Schedule M & Schedule L1 of Drugs & Cosmetics Act 1940 and Rules thereunder.
- QA New Approaches-WHO Guidelines 2011
- Statistical data of Industry from Pharmaexil

Life is like a game & juggling some five balls in the air. They are

Work, Family, Health, Friends & Spirit

You will soon understand that work is a rubber ball. If you drop it, it will bounce back but the other four balls-family, Health, Friends & Spirit are made up of glass. If you drop one of this they will be irrevocably scuffed, damaged, marked, nicked or even shattered. They will never be the same. You must understand that and strive for it.

Work efficiently during office hours and leave on time. Give the required time to your family, friends & have proper rest.

“Value has a value only if its value is valued”

Thank You