Unit-4

Industrial Pharmacy 2

B.Pharma 7 Sem Notes

Unit: 4

Quality management systems:

- **Quality management & Certifications: Concept of Quality, Total Quality Management, Quality by Design (QbD), Six Sigma concept, Out of Specifications (OOS), Change control, Introduction to ISO 9000 series of quality systems standards, ISO 14000, NABL, GLP**

Concept of Quality

Quality is one of the most important aspects in any industry, especially in pharmaceuticals, healthcare, and manufacturing. In simple words, quality means how good or suitable a product or service is for its intended purpose.

▸ Definition

Quality can be defined as *"the degree to which a product or service meets the requirements and expectations of the customer."* It is not just about the final product but includes every step of the process, from raw materials to the finished goods.

▸ Key Aspects of Quality

- Fitness for Use: The product should do what it is meant to do.
- Conformance to Specifications: The product should meet all written standards and limits.
- Customer Satisfaction: The end-user should be happy with the product.
- Consistency: The product should be the same every time it is made.
- Reliability: The product should work well throughout its shelf life.

Why Quality Matters in Pharma?
In the pharmaceutical industry, poor quality can directly harm patients.
It can lead to product recalls, legal penalties, and loss of public trust.
Quality ensures safety, efficacy, and purity of medicines.

▸ Dimensions of Quality

Dimension	Meaning
Performance	How well the product does its main job
Durability	How long the product lasts under normal conditions
Reliability	Ability to perform consistently without failure
Aesthetics	How the product looks and feels (packaging, appearance)
Safety	The product should not cause any harm to the user
Compliance	Meeting all regulatory and legal requirements

Total Quality Management (TQM)

Total Quality Management (TQM) is a management approach that focuses on long-term success by making sure every single person in an organization is committed to delivering high-quality work. It is not just about checking quality at the end — it is about building quality into every step.

▸ Definition

TQM is a **structured organizational management approach** that seeks to improve the quality of products and services through ongoing refinements in response to continuous feedback.

▸ Core Principles of TQM

Principle	Explanation
Customer Focus	Everything starts and ends with the customer. Understand what customers need and deliver it consistently.
Total Employee Involvement	Every worker, from top management to the shop floor, participates in improving quality.
Process-Centered	Focus on improving processes (the way work is done), not just outcomes.
Integrated System	All departments work together as one system towards quality goals.
Continuous Improvement	Always look for ways to do things better — this is called Kaizen.
Fact-Based Decisions	Use real data and measurements to make decisions, not guesswork.
Communication	Open and regular communication at all levels of the organization.

▸ Benefits of TQM

- Reduces waste and defects in products.
- Improves customer satisfaction and loyalty.
- Lowers costs through efficiency.
- Creates a culture of continuous improvement.
- Improves employee morale and involvement.

▸ Tools Used in TQM

- Pareto Chart — Identifies the most important problems (80/20 rule).
- Fishbone Diagram (Ishikawa) — Finds root causes of a problem.
- Control Charts — Monitors process stability over time.
- Flowcharts — Maps out the steps in a process.
- Check Sheets — Collects data in a simple, organized way.
- Histograms — Shows the frequency distribution of data.
- Scatter Diagrams — Shows the relationship between two variables.

Quality by Design (QbD)

Quality by Design (QbD) is a modern approach in pharmaceutical development. Instead of testing quality after a product is made, QbD builds quality into the product from the very beginning during the design and development stage.

▸ Definition

According to ICH Q8, QbD is defined as *"a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."*

▸ Key Elements of QbD

Element	Description
QTPP	Quality Target Product Profile — Defines what the final product should look like (dosage form, strength, purity, stability, etc.)
CQA	Critical Quality Attributes — Physical, chemical, or biological properties that must be within limits to ensure quality (e.g., dissolution rate, particle size).
CPP	Critical Process Parameters — Process variables that affect CQAs (e.g., temperature, mixing speed, pressure).
Design Space	The range of input variables and process parameters where quality is guaranteed. Working within design space is not a change.
Control Strategy	A planned set of controls to ensure the process works consistently (in-process testing, PAT, etc.).
Risk Assessment	Identifying and evaluating risks that could affect product quality using tools like FMEA or risk matrices.

▸ QbD vs. Traditional Approach

Traditional Approach	QbD Approach
Quality tested at the end	Quality built into the process
Fixed process, no flexibility	Design space allows flexibility
Reactive: find & fix problems	Proactive: prevent problems
Less understanding of process	Deep process understanding

Six Sigma Concept

Six Sigma is a data-driven quality improvement methodology that aims to reduce defects and variations in any process. The term "Six Sigma" comes from statistics — it means that the process should produce no more than 3.4 defects per million opportunities, which is near-perfect quality.

▸ Origin

Six Sigma was developed by Motorola in the 1980s and later made famous by General Electric (GE) under CEO Jack Welch. It is now used across all industries including pharma, IT, banking, and healthcare.

▸ Core Methodology: DMAIC

The most commonly used framework in Six Sigma is DMAIC, which stands for:

Phase	Full Form	What Happens?
D	**Define**	Identify the problem, customer needs, and project goals.
M	**Measure**	Collect data and measure current performance of the process.
A	**Analyze**	Find the root cause of defects or variations using statistical tools.
I	**Improve**	Develop and implement solutions to fix the root cause.
C	**Control**	Monitor the improved process to make sure improvements last.

▸ Six Sigma Belt System

- **White Belt** — Basic understanding of Six Sigma.
- **Yellow Belt** — Supports projects, understands basics of DMAIC.
- **Green Belt** — Leads smaller projects, uses data analysis tools.
- **Black Belt** — Leads complex projects, coaches Green Belts.
- **Master Black Belt** — Strategic leader, trains all levels, drives company-wide initiatives.

Note
At Six Sigma level, a process produces only 3.4 defects per million opportunities.
This translates to a 99.99966% accuracy rate!

Out of Specifications (OOS)

Out of Specification (OOS) results are test results that fall outside the established acceptance criteria or specifications mentioned in official documents like pharmacopeias, drug master files, or in-house specifications.

▸ Important

- OOS indicates a potential quality issue with the product.
- Regulatory agencies (like the US FDA) strictly monitor how companies handle OOS results.
- Proper OOS investigation prevents defective products from reaching patients.
- Failure to investigate OOS properly can result in warning letters, product recalls, or plant shutdowns.

▸ OOS Investigation Process

When an OOS result is found, a structured investigation is carried out in multiple phases:

Phase I — Laboratory Investigation

- Check if there was any analyst error (wrong dilution, wrong sample preparation).
- Review instrument calibration and performance.
- Verify calculation accuracy.
- Check if proper procedures (SOPs) were followed.
- If a lab error is confirmed, the result is invalidated and retesting is done.

Phase II — Full-Scale Investigation

- If Phase I does not find a lab error, a detailed investigation is launched.
- Manufacturing process is reviewed (raw materials, equipment, environment).

- Additional samples may be tested (retesting and resampling).
- Root cause analysis is performed.
- CAPA (Corrective and Preventive Actions) are implemented.

Important Terms in OOS
OOT (Out of Trend): Results within specification but showing an unusual trend over time.
OOE (Out of Expectation): Results within specification but outside the expected range.
Retesting: Testing the same sample again.
Resampling: Taking a new sample from the same batch and testing it.

Change Control

Change Control is a formal system used in pharmaceutical and regulated industries to manage any change that could affect the quality of a product, process, equipment, or system. It makes sure that changes are properly reviewed, approved, and documented before they are put into action.

▸ Why Change Control is Needed

- To prevent unintended negative effects on product quality.
- To maintain compliance with regulatory requirements (cGMP).
- To keep records of all changes for audits and inspections.
- To allow proper risk assessment before implementing changes.

▸ Types of Changes

Type	Nature	Example
Minor	Low risk, minimal impact on quality	Updating an SOP format
Major	Significant impact on quality or safety	Changing a raw material supplier
Critical	High risk, may require regulatory approval	Changing the manufacturing process itself

▸ Steps in Change Control Process

1. Initiation: A change request is submitted with details and justification.
2. Impact Assessment: The QA team assesses how the change affects quality, safety, and compliance.

3. Approval: The change is reviewed and approved by the Change Control Committee.
4. Implementation: The approved change is put into practice.
5. Review and Closure: After implementation, the change is reviewed for effectiveness and closed.

ISO 9000 Series of Quality System Standards

ISO 9000 is a family of international standards published by the International Organization for Standardization (ISO) that provides guidance and tools for organizations wanting to ensure their products and services consistently meet customer requirements and that quality is continuously improved.

What is ISO?

ISO stands for the International Organization for Standardization. It is based in Geneva, Switzerland, and develops voluntary international standards. ISO has published over 24,000 standards covering everything from technology to food safety to healthcare.

Standards in the ISO 9000 Family

Standard	Purpose
ISO 9000	Fundamentals and Vocabulary — Covers the basic concepts and definitions used in the quality management system.
ISO 9001	Requirements — The main certifiable standard. Specifies what an organization must do to demonstrate its ability to provide products that meet customer and regulatory requirements.
ISO 9004	Managing for Sustained Success — Provides guidelines for improving the overall performance of the organization beyond ISO 9001.
ISO 19011	Auditing Management Systems — Provides guidance on how to plan and conduct internal and external quality audits.

Seven Quality Management Principles (ISO 9001:2015)

- Customer Focus — Meeting and exceeding customer expectations.
- Leadership — Leaders set direction and create conditions for people to achieve quality.
- Engagement of People — Competent, empowered people at all levels are essential.
- Process Approach — Managing activities as processes that are linked together.

- Improvement — Ongoing focus on improving performance.
- Evidence-Based Decision Making — Decisions based on analysis of data.
- Relationship Management — Managing relationships with interested parties (suppliers, partners).

Benefits of ISO 9001 Certification

- Internationally recognized proof of quality.
- Improves customer confidence and trust.
- Helps enter international markets.
- Reduces waste and improves efficiency.
- Provides a framework for continuous improvement.

ISO 14000 — Environmental Management System

ISO 14000 is a family of international standards that helps organizations manage their impact on the environment. While ISO 9000 focuses on product quality, ISO 14000 focuses on environmental quality — making sure that a company's operations do as little harm to the environment as possible.

▸ Standards

Standard	Focus Area
ISO 14001	Environmental Management Systems — Requirements. This is the main certifiable standard.
ISO 14004	EMS — General guidelines on implementation.
ISO 14010	Environmental auditing guidelines.
ISO 14020	Environmental labelling of products.
ISO 14040	Life Cycle Assessment — Evaluating environmental impact from raw material to disposal.

▸ Concepts in ISO 14001

- Environmental Policy: A written commitment by top management to protect the environment.
- Environmental Aspects: Activities that can interact with the environment (e.g., emissions, waste, water use).

- Plan-Do-Check-Act (PDCA) Cycle: Continuous improvement framework applied to environmental management.
- Legal Compliance: The organization must identify and follow all environmental laws and regulations.
- Pollution Prevention: Focus on preventing pollution rather than just treating it.

▸ Benefits of ISO 14000

- Reduces environmental footprint and pollution.
- Ensures compliance with environmental laws.
- Enhances company reputation and public image.
- Can reduce costs through efficient use of resources and waste reduction.
- Opens doors for international business opportunities.

NABL — National Accreditation Board for Testing and Calibration Laboratories

NABL is an autonomous body under the Department of Science and Technology, Government of India. It provides accreditation to testing and calibration laboratories in India, ensuring that their test results are reliable, accurate, and internationally accepted.

▸ What is Accreditation?

Accreditation is the formal recognition that a laboratory is competent to carry out specific tests or calibrations. It is different from certification — certification says you have a system in place, while accreditation confirms your technical competence.

▸ Standards Used by NABL

Standard	Application
ISO/IEC 17025	General requirements for the competence of testing and calibration laboratories.
ISO 15189	Specific requirements for quality and competence of medical laboratories.

▸ Areas of Accreditation

- Biological Testing
- Chemical Testing
- Mechanical Testing

- Electrical Testing
- Medical/Clinical Testing (Pathology labs)
- Calibration of instruments
- Non-Destructive Testing (NDT)
- Radiological and Nuclear Testing

▸ Benefits of NABL Accreditation

- Test results are recognized nationally and internationally (through ILAC and APLAC agreements).
- Increases customer confidence in the laboratory's results.
- Helps laboratories improve their quality management systems.
- Essential for labs providing services to government and pharma sectors.
- Reduces the need for re-testing by different agencies.

NABL at a Glance
Full Form: National Accreditation Board for Testing and Calibration Laboratories
Established: 1998
Governed by: Department of Science and Technology, Government of India
International Recognition: Signatory to ILAC MRA and APLAC MRA

Good Laboratory Practice (GLP)

Good Laboratory Practice (GLP) is a set of principles and guidelines that ensure the quality, reliability, and integrity of non-clinical laboratory studies. These studies are usually conducted to evaluate the safety of chemicals, pharmaceuticals, pesticides, food additives, and other substances before they are tested on humans.

▸ Purpose of GLP

- To ensure that test data is reliable, reproducible, and of high quality.
- To provide a framework for planning, performing, monitoring, recording, and reporting laboratory studies.
- To protect the health of humans, animals, and the environment by ensuring proper safety testing.
- To allow regulatory authorities to verify the quality of submitted data.

▸ Principles of GLP

Principle	Description
Organization & Personnel	Clear management structure, qualified staff, defined roles and responsibilities.
Quality Assurance	Independent QA unit inspects studies to ensure GLP compliance.
Facilities	Labs should have adequate space, proper environmental controls, and separate areas for different activities.
Equipment	All equipment must be properly maintained, calibrated, and validated.
Test Systems	Proper handling and care of biological test systems (animals, cell cultures, etc.).
Test & Reference Items	Proper storage, labelling, handling, and accountability of test substances.
SOPs	Standard Operating Procedures must be written for all routine activities.
Study Plan	Each study must have a detailed written protocol approved before the study begins.
Recording of Data	All raw data must be recorded accurately, promptly, and permanently.
Reporting	A final study report must be prepared summarizing all findings, methods, and conclusions.
Archiving	All raw data, reports, samples, and specimens must be archived safely for future reference.

▸ Difference between GLP & GMP

GLP	GMP
Applies to non-clinical lab studies	Applies to manufacturing of drugs
Focus: Data integrity and reliability	Focus: Product quality and safety
Governed by OECD guidelines	Governed by FDA, WHO, ICH guidelines
Pre-clinical (before human trials)	During drug manufacturing

Regulatory Bodies for GLP

- OECD (Organisation for Economic Co-operation and Development) — International guidelines.
- US FDA — 21 CFR Part 58 for GLP compliance in the United States.
- DST India — National GLP Compliance Monitoring Authority (NGCMA) in India.
- UKAS, MHRA — In the United Kingdom.