Introduction

Dr. Shorooq Abukhamees

What is Quality

- Quality: in simple words is the essential nature of a thing and the totality of its attributes which bear upon its fitness for its intended purpose

Sterility is always an essential quality?

What is Quality

- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. [ICH Q6A]

- The degree to which a set of inherent properties (of a product, system, or process) fulfills requirements [ISO 9000 / ICH Q9 and Q10].

➢Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness.

➢Achieving quality means achieving these characteristics for a product

Slide credit: Dr. Isra Dmour and Prof. Nizar Al-Zoubi

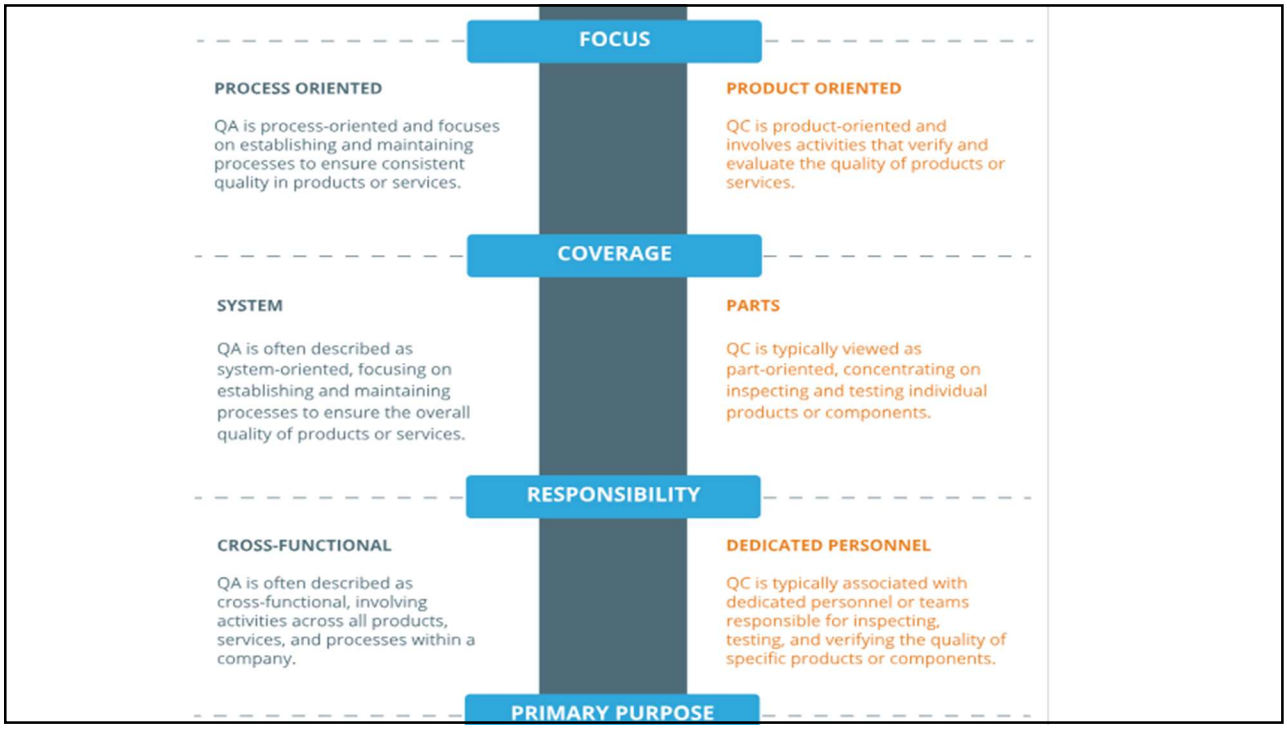
Quality, Quality Control and Quality Assurance

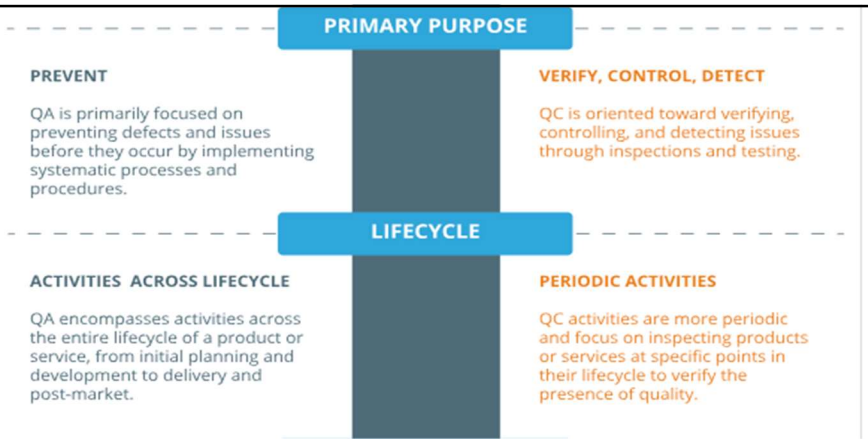
- **Quality control**:
- The regulatory process through which industry measures actual quality performance, compares it with standards, and acts on the difference.

- **Quality assurance**:
- Provision to all concerned the evidence needed to establish confidence that the activities relating to quality are being performed adequately.

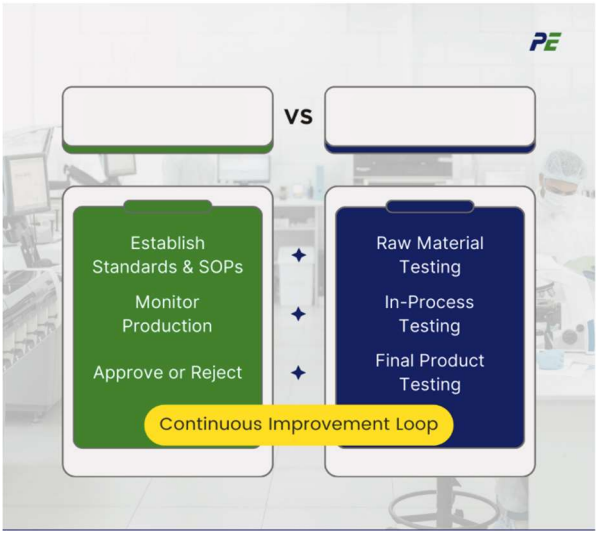
Slide credit: Dr. Isra Dmour and Prof. Nizar Al-Zoubi

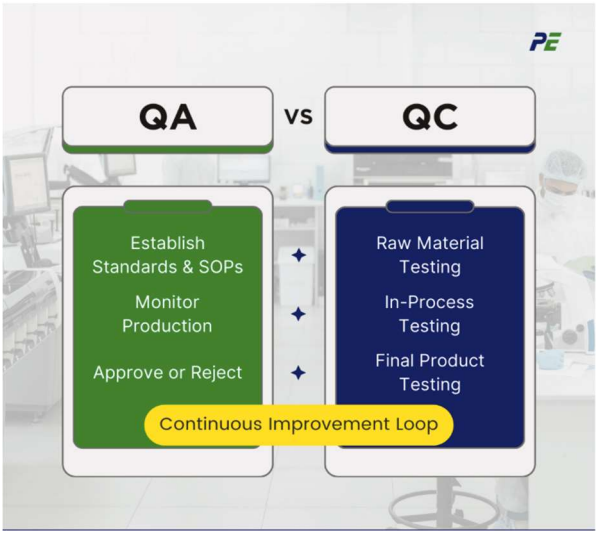

QUALITY CONTROL
VS
QUALITY ASSURANCE
DEFINITION
Quality Assurance (QA) is a framework that utilizes systematic approaches to ensure the quality of products and services.
DEFINITION
Quality Control (QC) is a framework for testing and controlling quality in products and services using systematic approaches.
Quality Assurance (QA)
Quality Control (QC)
NATURE
PROACTIVE
QA is typically proactive, focusing on establishing processes and procedures to prevent issues before they occur.
REACTIVE
QC is more reactive, involving activities that detect and correct issues in the product or service lifecycle.
FOCUS


FOCUS
PROCESS ORIENTED
QA is process-oriented and focuses on establishing and maintaining processes to ensure consistent quality in products or services.
PRODUCT ORIENTED
QC is product-oriented and involves activities that verify and evaluate the quality of products or services.
COVERAGE
SYSTEM
QA is often described as system-oriented, focusing on establishing and maintaining processes to ensure the overall quality of products or services.
PARTS
QC is typically viewed as part-oriented, concentrating on inspecting and testing individual products or components.
RESPONSIBILITY
CROSS-FUNCTIONAL
QA is often described as cross-functional, involving activities across all products, services, and processes within a company.
DEDICATED PERSONNEL
QC is typically associated with dedicated personnel or teams responsible for inspecting, testing, and verifying the quality of specific products or components.
PRIMARY PURPOSE



Now, Place QA and QC in the proper place:





History and the need for regulatory bodies

- Thalidomide prescribed late 1950s to early 1960s


ADVERTISEMENT BRITISH MEDICAL JOURNAL JUNE 24, 1961

this child's life

may depend on the safety of 'Distaval'

Consider the possible outcome in a case such as this—had the bottle contained a conventional barbiturate. Year by year, the barbiturates claim a mounting toll of childhood victims. Yet it is simple enough to prescribe a sedative and hypnotic which is both highly effective . . . and outstandingly safe. 'Distaval' (*thalidomide*) has been prescribed for over three years in this country, where the accidental poisonings rate is notoriously high; but there is no case on record in which even gross overdosage with 'Distaval' has had harmful results. Put your mind at rest. Depend on the safety of

'DISTAVAL'

THE DISTILLERS COMPANY (*Biochemicals*) LIMITED

Regulatory authorities Examples

1. **Jordan: JFDA** established in 2003
2. **USA**: The **Food and Drug Administration** (**FDA**).
3. **Europe**: The **European Medicines Agency** (**EMA**)
4. **UK**: The **Medicines and Healthcare products Regulatory Agency** (**MHRA**).

Quality can impact safety and efficacy!

- Quality measures during development and manufacturing mitigate risks and ensure that only safe and effective drugs reach the market. Comprehensive documentation throughout the development process is required to support this.

The roles of Jordan Medicines Regulator Drug Directorate in the JFDA

➢ The responsibilities include but not limited to:

1. Responsible for the registration of medicinal products (chemical and biological) whether locally manufactured or imported, and their follow-up after registration and re-registration.
2. Evaluates post approval changes for all medicinal products to facilitate medicines registration for medical security.
3. Pricing and re-Pricing of drugs
4. Approval of the importation of drugs
5. Receiving and evaluating all clinical studies protocols carried in Jordan and supervising and following up the clinical studies decisions.
6. Inspection
7. Product testing
8. Pharmacovigilance

Example of the roles of international Medicines Regulator FDA

- The FDA, in addition to dosage forms, is also concerned about the drug development process, the protection of the human subjects during the drug testing phase, and post marketing drug safety.

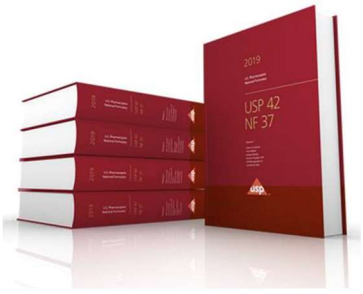
You cannot test quality into a product

- Means that simply performing tests on a pharmaceutical product after it is manufactured does not guarantee its quality. Instead, **quality must be built into the product during its development and manufacturing process**. In other words, testing is essential to confirm that the product meets the necessary standards, but it cannot **create** quality if the product was not developed, formulated, or manufactured properly in the first place. The processes, materials, and controls used in manufacturing must be designed in such a way that the product consistently meets quality standards.

- This idea is central to **Quality by Design (QbD)**, which emphasizes designing processes that inherently ensure quality, rather than relying solely on testing the final product.

Standards for pharmaceutical manufacturing

- Pharmacopoeias contribute to the overall control of the quality of medicinal products by providing authoritative statements of the standards that pharmaceutical substances and finished products are expected to meet, and provide definitive testing methods.



BP Monograph
Medicinal and Pharmaceutical Substances

- British Pharmacopoeia Volume I & II
- Monographs: Medicinal and Pharmaceutical Substances

Magnesium Trisilicate

General Notices

(Ph. Eur. monograph 0403)
Action and use
Antacid.
Preparations
Magnesium Trisilicate Mixture
Chewable Compound Magnesium Trisilicate Tablets
Compound Magnesium Trisilicate Oral Powder
Ph Eur

DEFINITION
It has a variable composition corresponding approximately to $Mg_2Si_3O_8,xH_2O$.
Content
- — *magnesium oxide* (MgO; M_r 40.30): minimum 29.0 per cent (ignited substance),
- — *silicon dioxide* (SiO_2; M_r 60.1): minimum 65.0 per cent (ignited substance).

CHARACTERS
Appearance
White or almost white powder.
Solubility
Practically insoluble in water and in ethanol (96 per cent).
IDENTIFICATION

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More Examples (USP and BP)

What is ICH?

- International Conference on Harmonization of Technical Requirements for registration of Pharmaceuticals for human use"

ICH
harmonisation for better health

Introduction

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use is an initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development.
- ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.

ICH Mission

- To make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

The Need to Harmonize

- For most countries, the 1960s and 1970s witnessed a rapid development in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products.
- The industry, at the time, was becoming more international and seeking new global markets; however, the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally.
- Realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s.

Initiation of ICH

- Harmonization of regulatory requirements was pioneered by the EC, Europe, in the 1980s, as the EC, Europe moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible.
- At the same time there were discussions between Europe, Japan and the US on possibilities for harmonization. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialize.
- Soon afterwards, the authorities approached International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonization, and ICH was conceived.

Purpose of ICH

➢ Promotion of public health through international harmonisation that contributes to:

- Prevention of unnecessary duplication of clinical trials and post market clinical evaluations.
- Development and manufacturing of new medicines. while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.
- Reduction of unnecessary animal testing without compromising safety and effectiveness.

ICH Guidelines

- ICH has developed over 50 harmonised Guidelines aimed at eliminating duplication in the development and registration process, so that a single set of studies can be generated to demonstrate the quality, safety and efficacy of a new medicinal product. These Guidelines also include the Common Technical Document (CTD), which describes the common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.
- In addition, the ICH is working to facilitate international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI) that will meet the requirements of the pharmaceutical companies and regulatory authorities. A product of this has been the Electronic Common Technical Document (eCTD), which allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator.

ICH Guidelines

➢ **Quality Guidelines: Q1 – Q14**

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

ICH Guidelines

➢ **Safety Guidelines: S1 – S12**

Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

ICH Guidelines

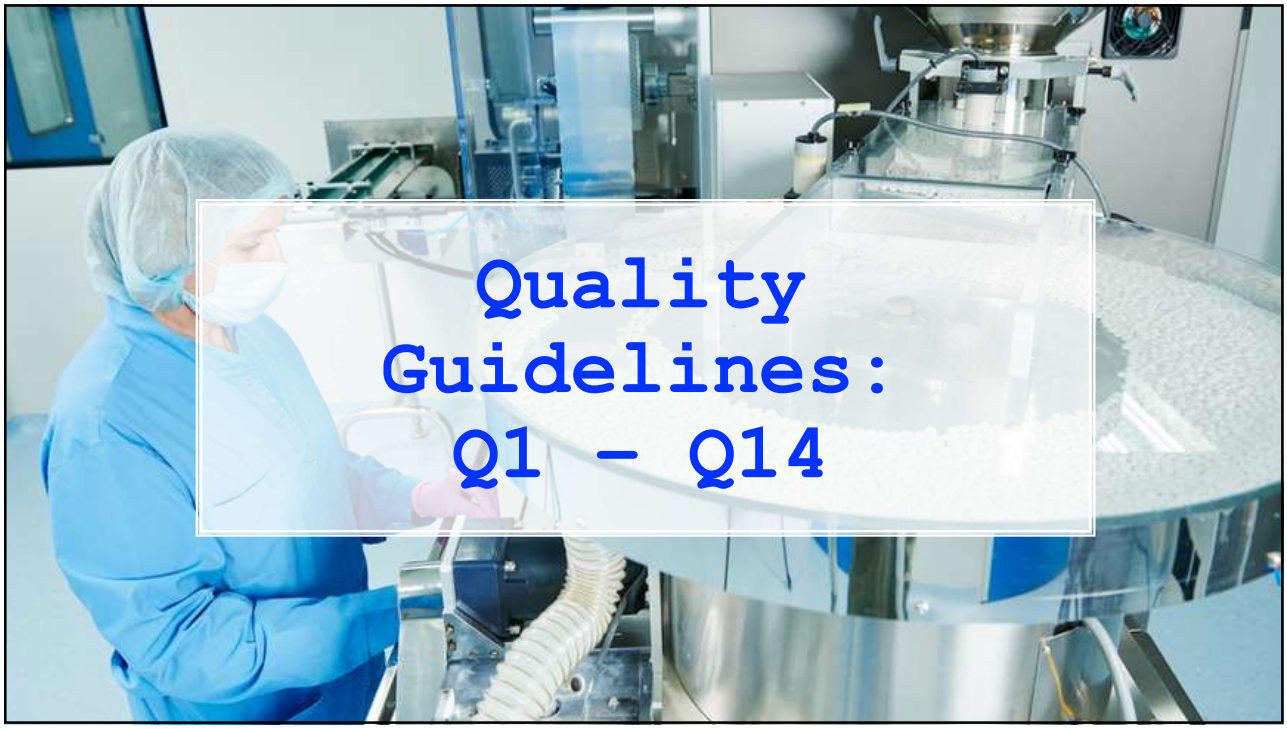
➢ **Efficacy Guidelines: E1 – E22**

Concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ genomics techniques to produce better targeted medicines.

ICH Guidelines

➢ Multidisciplinary Guidelines: **M1 – M15**

Concerned topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).



- Stability
- Analytical validation
- Impurities
- Regulatory acceptance
- Quality of biotechnological products
- Specifications
- Good manufacturing practice
- Pharmaceutical development
- Lifecycle management

- Stability
- Analytical validation
  - ICH Q1A (R2) Stability testing of new drug substances and drug products
  - ICH Q1B Photostability testing of new active substances and medicinal products
  - ICH Q1C Stability testing: requirements for new dosage forms
  - ICH Q1D Bracketing and matrixing designs for stability testing of drug substances and drug products - Scientific guideline
  - ICH Q1E Evaluation of stability data
  - ICH Q1F Stability data package for registration in climatic zones III and IV
- Lifecycle management

- Stability
- **Analytical validation**
- Impurities
  - ICH Q2(R2) Validation of analytical procedures
  - ICH Q14 Analytical procedure development
- Specifications
- Good manufacturing practice
- Pharmaceutical development
- Lifecycle management

- Stability
- Analytical validation
- **Impurities**
- Regulatory acceptance
  - ICH Q3A (R2) Impurities in new drug substances
  - ICH Q3B (R2) Impurities in new drug products
  - ICH Q3C (R9) Residual solvents
  - ICH Q3D Elemental impurities
- Pharmaceutical development
- Lifecycle management

- ICH Q4B Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions
- ICH Q4B Annex 1 Residue on ignition/sulphated ash
- ICH Q4B Annex 2 Test for extractable volume in parenteral preparations
- ICH Q4B Annex 3 Test for particulate contamination: sub-visible particles
- ICH Q4B Annex 4A Microbiological examination of non-sterile products: microbial enumeration tests
- ICH Q4B Annex 4B Test for microbiological examination of non-sterile products: tests for specified microorganisms - Scientific guideline

- Impurities
- **Regulatory acceptance**
- Quality of biotechnological products

- ICH Q4B Annex 4C Test for microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use - Scientific guideline
- ICH Q4B Annex 5 Disintegration test
- ICH Q4B Annex 6 Uniformity of dosage unites general chapter
- ICH Q4B Annex 7 Dissolution test
- ICH Q4B Annex 8 Sterility test
- ICH 4 QB Annex 9 Tablet friability
- ICH Q4B Annex 10 Polyacrylamide gel electrophoresis
- ICH Q4B Annex 11 Capillary electrophoresis
- ICH Q4B Annex 12 Analytical sieving
- ICH Q4B Annex 13 Bulk density and tapped density of powders
- ICH Q4B Annex 14 Bacterial endotoxins tests

- Stability
- Analytical validation
- Impurities
- Regulatory acceptance
- **Quality of biotechnological products**

- ICH Q5A(R2) Guideline on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin - Scientific guideline
- ICH Q5B Analysis of the expression construct in cell lines used for production of rDNA-derived protein products - Scientific guideline
- ICH Q5C Stability testing of biotechnological/biological products
- ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products - Scientific guideline
- ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products - Scientific guideline

- ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances - Scientific guideline
- ICH Q6B Specifications: test procedures and acceptance criteria for biotechnological/biological products - Scientific guideline

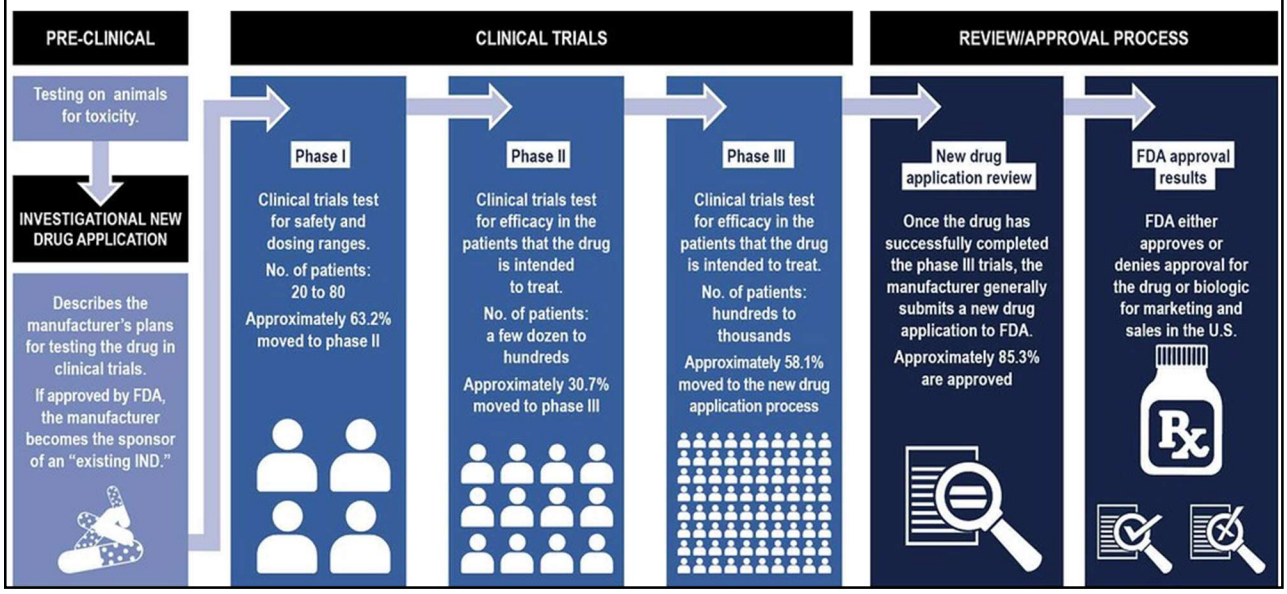
- Quality of biotechnological products
- **Specifications**
- Good manufacturing practice
- Pharmaceutical development
- Lifecycle management

- Stability
- Analytical validation
- Impurities
- Regulatory acceptance
- Quality of biotechnological products
- Specifications
- **Good manufacturing practice**
- Pharmaceutical development

- ICH Q7 Good manufacturing practice for active pharmaceutical ingredients

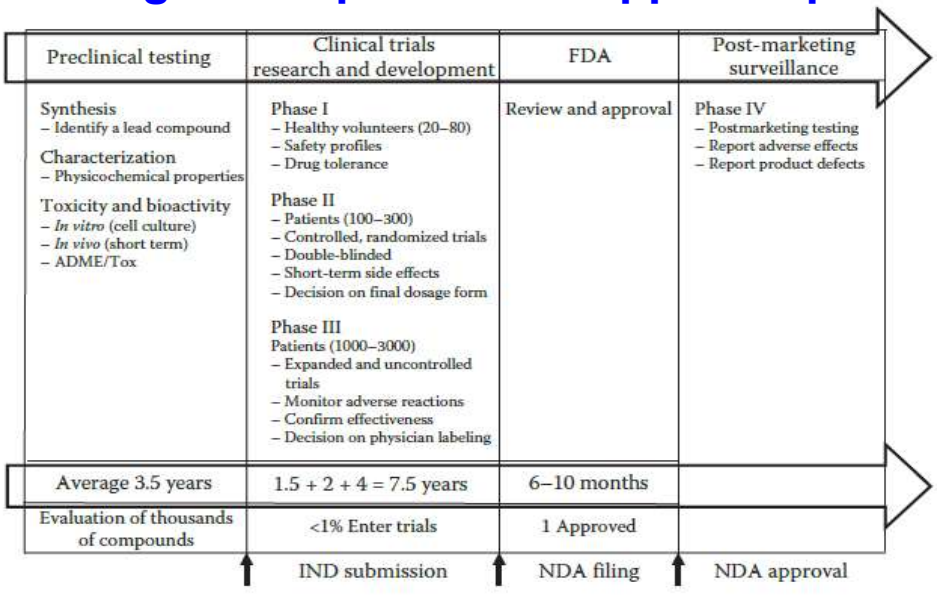
- Stability
  - ICH Q8 (R2) Pharmaceutical development
  - ICH Q9 Quality risk management
  - ICH Q10 Pharmaceutical quality system
  - ICH Q8, Q9 and Q10 - questions and answers
  - ICH Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) - Scientific guideline
  - ICH guideline Q13 on continuous manufacturing of drug substances and drug products - Step 2b
- Specifications
- Good manufacturing practice
- **Pharmaceutical development**
- Lifecycle management

New drug development and approval process



- *New medicines can take upwards of 12 years and costs $2.6 billion (Phrma, 2015)*. The first milestone for any new drug occurs during the research and discovery phase. Some form of experimentation in an R&D lab leads to the development of an active pharmaceutical ingredient (API) that may have therapeutic activity in the human body. If the active ingredient is believed to have real potential, the drug moves into the development stage.
- This early stage of development involves what is known as "preclinical testing," and is carried out in laboratories and animal testing facilities. If the drug performs well during this stage, the company can file an **Investigational New Drug Application (IND)** with the FDA to request permission to begin testing on human subjects. There are three major phases a drug must pass through during human subject testing (clinical studies). If the drug passes through clinical studies successfully, the company can then submit a **New Drug Application (NDA)** to the FDA `seeking approval to market the new product.`

New drug development and approval process



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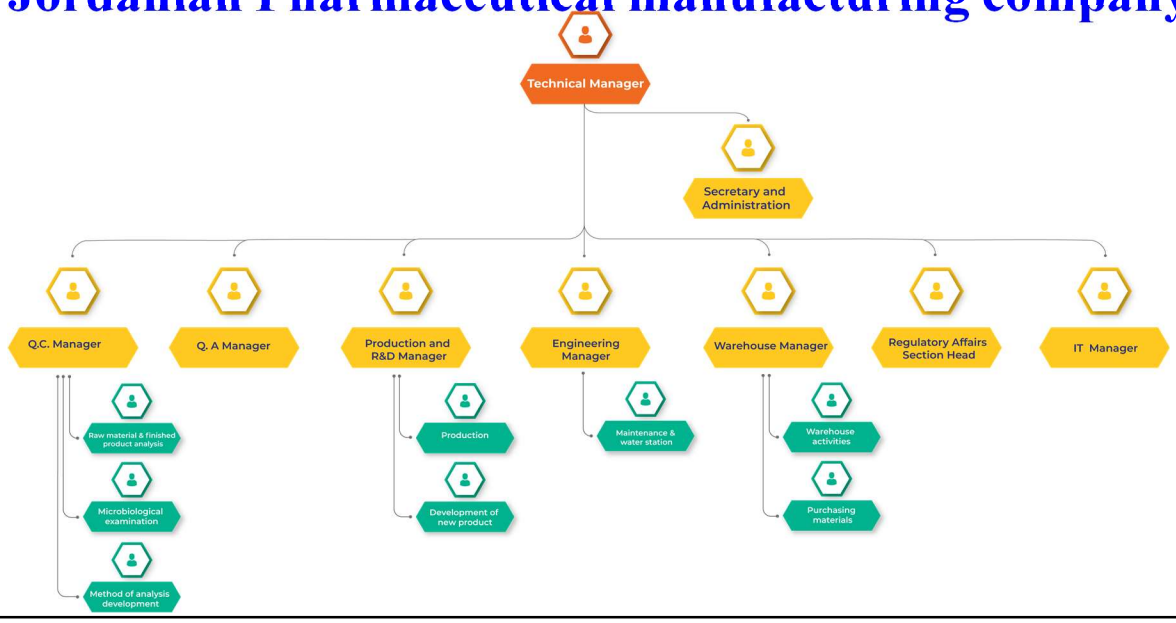
Time course for the development of a new drug (slide credit : Dr. Isra Dmour)

An example of Organizational Chart for a Jordanian Pharmaceutical manufacturing company



Manufacturing process

Raw Materials → Process → Product

Process Variables


Thank you!
Questions?