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A Review Article on Quality Management System

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ABSTRACT :

In the pharmaceutical industry, there are hazards connected with every process and product. An excessive amount of time and resources are used in the process of maintaining product quality throughout its life cycle. According to contemporary guidelines, risk is defined as the product of two factors: the likelihood that harm will occur and the severity of that harm. A risk-based approach to quality management is made possible by the Quality Risk Management (QRM) approach, which was developed by regulatory agencies and uses established management tools in conjunction with statistical tool support. This guarantees that resources are allocated quickly and efficiently to the areas that need them the most. By evaluating and comparing current data from a quality viewpoint to manage product quality, manufacturing processes, validation, and compliance within a risk-based Quality Management System, QRM increases risk awareness and speeds up the discovery of possible problems. Furthermore, quality risk management enhances decision-making in the event that a quality issue emerges. It ought to contain systematic procedures intended to coordinate, support, and enhance risk-based scientific decision-making. In order to achieve effective and efficient quality management and compliance through QRM, this article outlines practical methods for analyzing the threats to the quality system and offers help along the way.

Keywords: ICH Guideline, QRM, QMS

INTRODUCTION [1]

ICH Stand for "International Conference on Harmonization" of Technical Requirements for Registration of pharmaceuticals for human use.
ICH is a joint initiative involving both Regulators and research –based industry initiative of the Europe, Japan and US for the scientific and technical discussions of the testing procedures; required to assess and ensure the Safety, Quality, and Efficacy of the medicines.
ICH was establishment in April 1990, as a joint regulatory/industry project to improve, through harmonization, the efficiency of the process, for development and registering new medicinal products in Europe, Japan and US.
ICH guideline is intended for bringing together the regulatory authorities and pharmaceutical industries together for the discussion of the scientific and technical aspects of drug registration.

Purpose of ICH

The basic purpose of ICH are-

- To monitor, update and increase the international harmonization of Technical Requirements.
- To ensure Safety, Efficacy and Quality of medicines that must be developed and registered in the most efficient and cost effective manner.
- To promote and protect public health from an international perspective.
- To prevent unnecessary duplicate of clinical trials in humans.
- To minimize the use of animal testing without compromising the safety and effectiveness.
- To improve the efficiency of global drug development. [1]

Objective:

- More economic use of human, animal and material resources.
- Elimination of unnecessary delay in the global development and availability of new medicines.
- Maintaining safe guards on Quality, safety, efficacy and regulatory obligations to protect public health.

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GOAL

1. To discuss and establish common guidelines by bringing together three ICH regions: EU, USA, japan
2. To make information available on ICH, ICH activities & ICH guidelines

This is to any country or company that is requests information & to promote mutual understanding of guidelines in order to facilitate harmonization processes regionally & globally and to strengthen the capacity of drug regulatory authorities & industry to utilize them.

ICH GUIDELINES

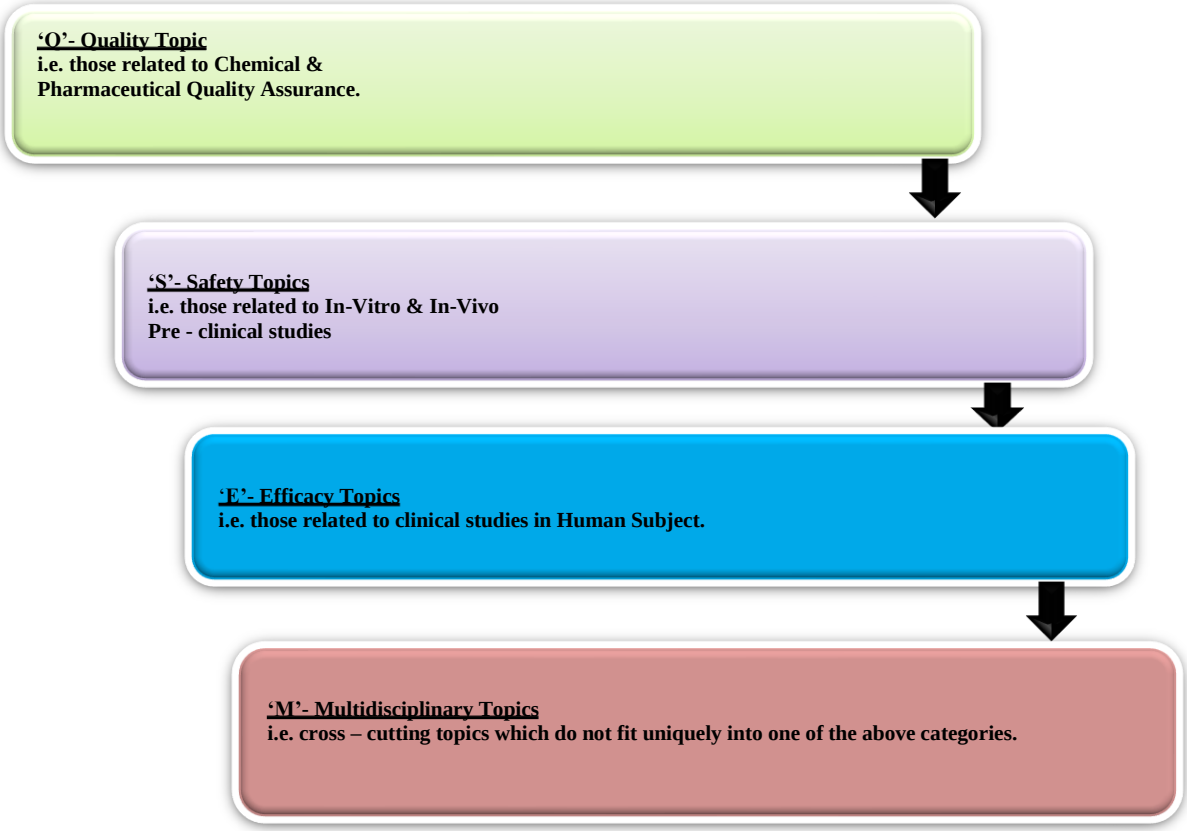

Figure 1: ICH Guideline

Quality guidelines:

Harmonization achievement in the quality area include pivotal milestones such as the conduct of stability studies defining relevant threshold for impurities testing and a more flexible approach to pharmaceutical quality based on good manufacturing practice (GMP) risk management.

It includes the following guidelines:

Q1:	**STABILITY**
Q2:	**ANALYTICAL VALIDATION**
Q3:	**IMPURITIES**
Q4:	**PHARMACOPOEIAS**
Q5:	**QUALITY OF BIOTECHNOLOGICAL PRODUCTS**
Q6:	**SPECIFICATIONS**
Q7:	**GMPs**
Q8:	**PHARMA. DEVELPOMENT**
Q9:	**QRM**
Q10:	**PHARMA. QUALITY SYSTEM**
Q11:	**DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES**
Q12:	**LIFECYCLE MANAGEMENT**
Q13:	**CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS**
Q14:	**ANALYTICAL PROCESS DEVELOPMENT**

Safety guidelines:

ICH has produced a comprehensive set of safety guidelines to uncover potential risks like carcinogenicity, genotoxicity.

S1:	**CARCINOGENICITY STUDIES**
S2:	**GENOTOXICITY STUDIES**
S3:	**TOXICOKINETICS AND PHARMACOKINETICS**
S4:	**TOXICITY TESTING**

S5:	**REPRODUCTIVE TOXICOLOGY**
S6:	**BIOTECHNOLOGICAL PRODUCTS**
S7:	**PHARMACOLOGY STUDIES**
S8:	**IMMUNOTOXICOLOGY STUDIES**
S9:	**NON-CLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS**
S10:	**PHOTOSAFETY EVALUATION**
S11:	**NON-CLINICL PEDIATRIC SAFETY**
S12:	**NON-CLINICAL BIO-DISTRIBUTION STUDIES FOR GENE THERAPY PRODUCTS**

3. Efficacy guidelines:

It concerned with the design, conduct, safety and reporting of clinical trials.

E1:	**CLINICAL SAFETY FOR DRUG USED IN LONG TERM TREATMENT**
E2:	**PHARCOVIGILANCE**
E3:	**CLINICAL STUDY REPORTS**
E4:	**DOSE –RESPONSE STUDIES**
E5:	**ETHNIC FACTORS (THE IN ACCEPTABILITY OF FOREGINE CLINICAL DATE)**
E6:	**GOOD CLINICAL PRACTICE**
E7:	**CLINICALTRIALS INGERATRIC POPULATION**
E8:	**GENERAL CONSIDERATIONS FOR CLINICAL TRIALS**
E9:	**STATISTICAL PRINCIPLES FOR CLINICAL TRIALS**
E10:	**CHOICE OF CONTROL GROUP OF CLINICAL TRIALS**
E11:	**CLINICAL TRIALS IN PEDIATEIC POPULATION**
E12:	**CLINICAL EVALUATION BY THERAPEUTIC CATEGORY**
E14:	**CLINICAL EVALUATIONS**
E15:	**DEFINITIONS IN PHARMACOGENETICS**
E16:	**QUALIFICATION IN GENOMICS BIOMARKERS**
E17:	**MULTI-REGIONAL CLINICAL TRIALS**
E18:	**GENOMIC SAMPLING**
E19:	**SAFETY DATA COLLECTIONS**
E20:	**ADAPTIVE CLINICAL TRIALS**

4. Multidisciplinary guidelines:

Some highlights of this guideline are:

M1:	**ICH MEDICAL TERMINOLOGY**
M2:	**ELECTRONIC STANDARD**
M3:	**NONCLINICAL SAFETY STUDIES**
M4:	**COMMON TECHNICAL DOCUMENT(CTD)**
M6:	**GENE THERAPY**
M7:	**MUTAGENIC IMPURITIES**
M10:	**BIOANALYTICAL METHOD VALIDATION**
M12:	**DRUG INTERACTION STUDIES**

QUALITY RISK MANAGEMENT [2]

The quality component plays a critical role in the life cycle of any pharmaceutical product. A comprehensive approach known as quality risk management (QRM) can be used to assess, control, and communicate the risk of quality variation in pharmaceutical products. In ICH guideline Q9, it is mentioned. They are referred to as facilitators because they are a method or tool that offers the means to accomplish a goal. Since QRM is so important, an entire ICH guideline (Q9) has been devoted to it.

Information is arranged through a quality risk management procedure in order to facilitate risk decisions made during the risk management process. It entails identifying hazards as well as analysing and assessing the risks connected to those hazards' exposure (ICH Q9).

The QRM system should guarantee that the degree of effort, formality, and documentation of the QRM process is proportionate with the amount of risk, and that the assessment of the risk to quality is founded on scientific knowledge, expertise with the process, and finally relates to the protection of the patient.

The application of a quality risk management system can be done both in advance and after the fact.

PRINCIPLE [2, 3]

The following are the general guidelines for quality risk management in the pharmaceutical sector, as stated in the internationally harmonized guideline ICH Q9 Quality Risk Management (4, 5).

1. Risk assessment should not be used to decide whether to comply with applicable laws or regulations; rather, it should be used to evaluate how to assure compliance and to establish the ensuing priority for action.
2. Risk management is only possible if it is recognized, evaluated, taken into account for additional mitigation, and shared. The four phases of an efficient QRM process, as outlined in ICH Q9, are embodied in this principle:

   -Risk assessment - Risk control- Risk communication - Risk review
3. All the quality risk evaluations must be based on scientific and process-specific knowledge and ultimately linked primarily to the protection of the patient.
4. Risk assessment is based on the strong understanding of the underlying science, applicable regulations, and related processes involved with the risk under analysis.
5. Effective risk management requires the potential impact of the risk, and ownership of the results of any risk- management assessment.

QRM Cover the topics such as:

- FDA, EU/PICs/TGA, ICH Q9-Pharmaceutical risk management;
- The principle of risk management (analysis, control, and management); and
- Regulatory advice for applying risk management in pharmaceuticals.
- The creation of a risk management master plan; risk analysis and control
- applications in design and development; risk analysis and risk to quality management systems and CAPA systems;
- Risk assessment and management of product complaints; risk analysis and compliance in pharmaceutical operations audits and compliance;
- Hazards analysis and Critical Control Point (HACCP) in production and process control;
- Application of risk principles in commissioning, qualification, and process validation;

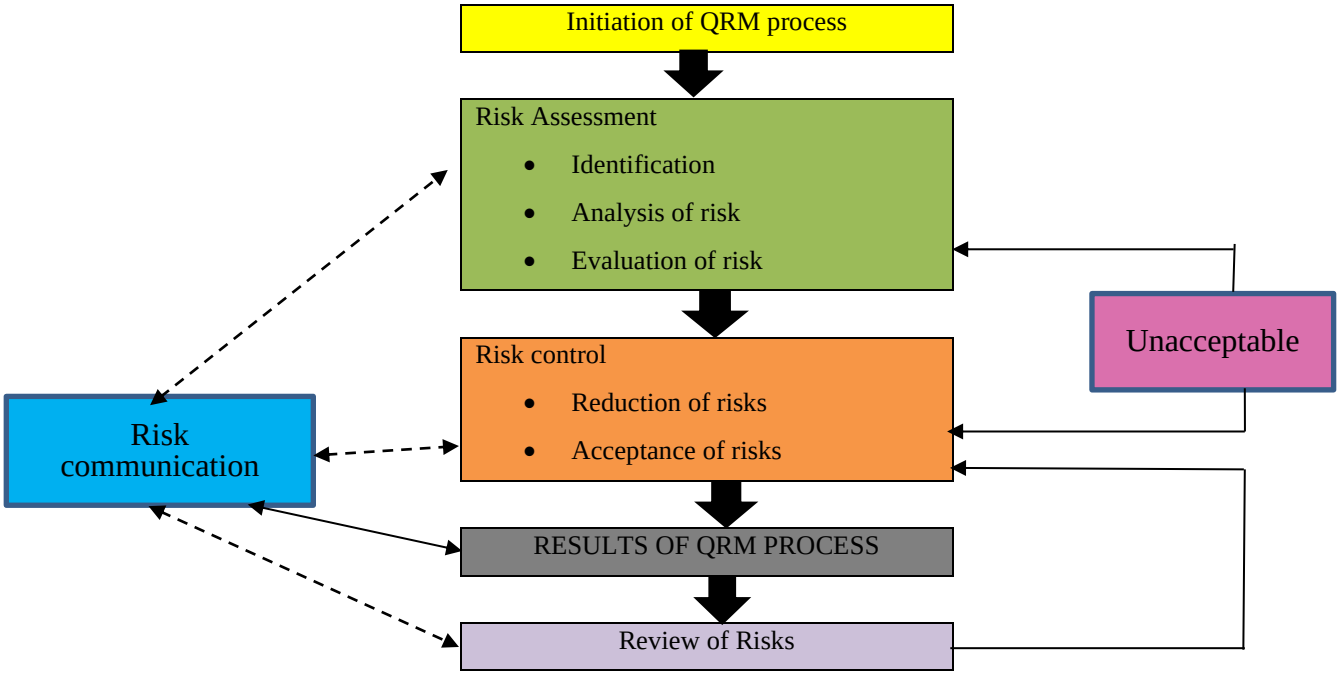

Fig 2: Component of QRM

QUALITY RISK MANAGEMENT PROCESS OVERVIEW [1, 2, 5, 6, 7]

The QRM program consists of four major components:

- Risk Assessment
- Risk Control
- Risk Communication
- Risk Review

All the QRM methods (as described in Table: 1) should address the mentioned four basic components.

Quality Risk Assessment	Quality risk control	Quality Risk Communication	Quality Risk Review
Quality Risk Identification	Quality Risk Reduction	Documentation and communication of the outcome or result to stakeholders	Review Events
Quality Risk Analysis	Quality Risk Acceptance		
Quality Risk Evaluation			

Table 1: QRM Process Model

1. QRM Initiation:

The initiating phase of QRM systematic process involves understanding the risk event by defining and agreeing the context, the scope and tolerability criteria for the QRM, together with any underlying assumptions. It should involve all the stakeholders, all the relevant information is assembled and shared. The scope clearly establishes the boundaries of the process, system project or activity being assessed.

To initiating process of QRM the following plan can be followed.

- Type of risk and problem
- Questions regarding risks
- Information regarding quality and potential hazards
- Information of background and raw data
- Assessment of required resources.
- Specification of time limit

QUALITY RISK ASSESSMENT [8, 9, 10]

A systemic method of gathering data to assist in making a risk decision inside a risk management process is quality risk assessment. It entails identifying risks and analysing and assessing the dangers connected to exposure to those risks. (ICH Q9)

The evaluation procedure needs to answer issues like: What could go wrong?

What does probability mean?

What effects will it have on the quality of the product?

How and what kind of failure will be found?

The process of quality risk assessment also looks for ways to make processes better. A risk owner must be identified in the risk assessment's report in order to guarantee the managed risk's documentation and CAPA implementation.

Quality Risk Identification:

The process of identifying risks involves using information to pinpoint potential dangers or hazards. Historical data, theoretical analysis, and well-informed opinions are among the sources of information used to assess risk. Patient safety, product non-conformity, and suitability for use, specification, and adulteration are among the risks that need to be taken into account.

The initial step in this process is to choose the best group of technical specialists to analyse the risk. This will be done through meetings and brainstorming sessions to gather important data needed for analysis, response, and risk management. This stage involves recording the risk identifier, risk description, risk indicator, risk type (such as safety, technical, or commercial), risk identification stage, etc.

Quality Risk Analysis:

During quality risk analysis a detailed understanding of the probability that the identified risk will occur shall be estimated. It can also include detectability.

Probability of Occurrence	
High	Likely to occur
Medium	May occur
Low	Unlike to occur
Remote	Very unlikely to occur

Table 2: A simple quality risk analysis tool

The key activities to be performed during risk analysis include to understand the impact risk, to rank the significance of risk (by scoring 1 to 5, where 1=low & 5=high), to calculate the risk score (Risk Score=Severity x Probability), colour code the risk based on score (define Red, Blue and Green, unacceptable risk =Blue, Intolerable= Red).

Quality Risk Evaluation:

Quality risk evaluation includes comparison of identified and analysed risk against pre-defined acceptance criteria and consideration of probability, severity and detectability. The complete risk assessment shall result in an overall risk value expressed as either

- A qualitative description of a range of risk using description such as high medium or low.
- A quantitative description of risk expressed numerically on probability scale of 0 to 100 percent.

Detectability: Likelihood that the fault will be noted before harm occurs.

- **High** – when the control is likely to detect the negative event or its effects
- **Medium**-when the control may detect the negative event or its effects
- **Zero**-when no detection control in place

Quality Risk Definitions:

Intolerable (marked in RED): Work to eliminate the negative event or introduce detection controls is required as a priority.

Unacceptable (marked in BLUE): Work to reduce the risk or controls the risk to an acceptable level is required.

Acceptable (marked in GREEN): The risk is acceptable and no risk reduction or detection controls are required.

Where,

Severity: Is the impact on patient safety, product quality and data integrity.

Probability: Is the likelihood of the fault occurring.

Risk =Probability ×Severity			
Severity ⇨ Probability ⇩	High	Medium	Low
High	Unacceptable	Intolerable risk	Intolerable risk
Medium	Acceptable risk	Unacceptable risk	Intolerable risk
Low	Acceptable risk	Acceptable risk	Unacceptable risk
Remote	Acceptable risk	Acceptable risk	Acceptable risk

Table 3: Risk Table with Risk Acceptable Criteria

Quality Risk Evaluation Tools:

Numerous instruments are available for determining and evaluating the risks associated with hazards. To achieve every requirement, a variety of tools and approaches must be used.

Severity level if event occurs	
Critical	Serious GMP non-compliance patient injury possible
Moderate	Significant GMP non-compliance impact on patient possible
Minor	Minor GMP non-compliance no patient impact

Table 4: A simple Quality Risk Evaluation Tool

QUALITY RISK CONTROL:

Depending on the activities importance and trend, the technical team may need to put in more work to ensure that hazards are appropriately addressed. "Actions implementing risk management decision," which include risk acceptance and reduction (if appropriate), are referred to as quality risk control. Question like "Is the risk acceptance without further action?" must be addressed by risk control. & how can risk be minimized, controlled, or eliminated?

Risk acceptance and action are part of "implementing risk management decision" (ICH Q9).

The goal of quality risk reduction is to prevent quality risk when it rises over a level that can be tolerated. One way to reduce risk is to Action taken to reduce the likelihood that harm will occur.

Action taken to reduce the likelihood that the intensity of that harm will occur.

Typically, CHANGE CONTROL and CAPA. Consequently, it is necessary to repeat the risk assessment in order to detect and assess any potential Changes to the risk profile.

QUALITY RISK ACCEPTANCE:

Quality risk Acceptance is the decision to accept risk. If risk reduction action taken, follows re-analysis and evaluation. On case to case basis QRM strategy is designed to reduce to an acceptable level depend upon many parameters. The documented results of the QRM process shall be communicated to the relevant stakeholders.

QUALITY RISK REVIEW:

Review or monitoring of output/results of the risk management process considering new knowledge and experience about the risk (ICH Q9) ensure that nothing has changed to affect the QRM assumptions, output and conclusions and to be consider during product review.

QUALITY RISK MANAGEMENT METHODS: [11, 12]

A key early step in the executive of a risk analysis to determine the appropriate risk-assessment method or tools. There is no single best choice for any given assessment process, and the selection of the appropriate risk methodology should be based on the depth of analysis required, complexity of the subject risk of concern, and the familiarity with the assessment tool. The list of generally well-recognized risk-management tools shall be:
Basic risk management facilitation method (flowcharts, check sheet etc.)

- Failure Mode Effect Analysis (FMEA)
- Failure Mode, Effect and Critical Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

POSITIVE AREAS FOR APPLICATION OF RISK MANAGEMENT:

The pharmaceutical sector has highlighted the following possible areas for QRM implementation.

- Documentation (Batch records, SOPs, etc.)
- Instruction (Timetables and Efficiency)
- Defects in quality (complaints, variations, out-of-stock, etc.)
- Compliance Audits
- Regular evaluations (Revalidation evaluation)
- Measures to prevent changes (Impact analysis)
- Development reports (Process and control verification)
- Facilities, equipment, and utilities (parts, maintenance, etc.)
- Material handling, including receiving, delivery, and storage
- Packaging and labelling (including container closure systems)

CONCLUSION :

Quality risk management is a systematic process for assessment, control, communication and review of risk to the quality of the drug product across the product lifecycle. Two primary principles of quality risk management are the evaluation.
Overall, the contribution is positive and helps to protect patient.

1. It also raises awareness of quality risk management, which is already ingrained in corporate and government culture.
2. Constant behavioural modification

- Recognising hazards can be advantageous.

- A lengthily list of dangers that have been recognised and evaluated and controlled provides high quality capability.
- Awareness of quality risks – "Risk –based approach"
- A potential of risks remains – No "zero" risk!

REFERENCES :

1. International Conference on Harmonization of Technical Requirement for Registration of Pharmaceutical Human Use (ICH). Q9 Quality Risk Management. Geneva: ICH; 2005.
2. Scott, C. (2011). Quality by design and the new process validation guidance. *BioProcess International*, *9*, 14-21.
3. Chen, M. (2007). Brief Introduction to the ICH Guidelines. In *Family Health International, Biostatistics Workshop, New Delhi, India. Available at: http://www. hostemostel.Com/pdf/ICH/6. pdf [Last accessed on 2013 January 12]*.
4. Rights are reserved by Sharmada, A., & Kakodkar, S. S. (2015). Pharmaceutical Quality-by-Design (QbD): Basic Principles.
5. Guideline, I. H. T. (2011). Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Q11. *London: European medicines agency.*
6. Regulations, P. C. (2006). Guidance for Industry.
7. Chen, M. (2007). Brief Introduction to the ICH Guidelines. In *Family Health International, Biostatistics Workshop, New Delhi, India. Available at: http://www. hostemostel. com/pdf/ICH/6. pdf [Last accessed on 2013 January 12]*.
8. World Health Organization, & WHO Expert Committee on Specifications for Pharmaceutical Preparations. (2017). Fifty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.