ICH, WHO AND SUPAC GUIDELINES

ICH GUIDELINES

INTRODUCTION:

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

A BRIEF HISTORY OF ICH:

Prior to 1960s there were not many controls over introduction of new drugs and also over the assurance of the quality by the manufacturer over his established drug products. Some stray tragic incidents in some countries like USA and India triggered the introduction of exacting drug laws to ensure the quality, safety and efficacy of the drug.

Around 1970s the pharmaceutical industry started getting global but the registration of medicines remained a national responsibility. Although the laws of all the countries were based on the same fundamental obligations to evaluate the quality, safety and efficacy the detailed technical requirements differed from country to country. So the companies had to duplicate many time consuming and expensive test procedures, in order to market new products, internationally. All this resulted in unnecessary expenses and long delays in introducing new drugs.

So a necessity to harmonize or make uniform, the testing procedures and regulatory requirements of different countries was felt and the result is the birth of ICH in April **1990**..

Initiation of ICH

The birth of ICH took place at a meeting in April 1990, hosted by the EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH. The ICH Steering Committee which was established at that meeting has since met at least twice a year, with the location rotating between the three regions.

Format of Applications

A target for the first phase of ICH activities was to remove redundancy and duplication in the development and review process, such that a single set of data could be generated to demonstrate the quality, safety and efficacy of a new medicinal product. The long-term goal of developing a harmonised format has led to the creation of the ICH Guideline M4, *The* ***Common Technical Document (CTD)***. The CTD provides a harmonised format and content for new product applications. The ***Electronic Common Technical Document (eCTD)*** was developed subsequently by the M2 Expert Working Group. This specification document allows for the electronic submission of the CTD from applicant to regulator and provides a harmonised technical solution to implementing the CTD electronically. The eCTD has begun to be implemented across the ICH partner and observer regionsGuidelines

Objectives of ICH:

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

TOPICS OF ICH:

Four Broad Categories - **QSEM**

- **Quality (Q)**: those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)
- **Safety (S)**: those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)
- **Efficacy (E)**: those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)
- **Multidisciplinary (M)**: cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)

Regulatory Public Consultation of ICH Guidelines

Step 2 of the ICH process is reached when the ICH Steering Committee agrees, based on the report of the EWG, that there is sufficient consensus on the technical issues for the draft guideline or recommendation to proceed to the next stage of regulatory consultation. The consensus text approved by the Steering Committee is signed off by the Steering Committee as the *Step 2* Final Document.

Under *Step 3* of the ICH process, the *Step 2* Guideline is subjected to regulatory consultation in the 3 ICH regions according to national/regional procedures. Comments received from regulatory consultation are considered by the EWG for incorporation into the final *Step 4* Harmonised Tripartite Guideline which will be for regulatory implementation (*Step 5*) in the 3 ICH regions

Please find below a list of the *Step 2* ICH Guidelines currently undergoing regulatory consultation in the 3 ICH regions:

Categories of ICH Harmonisation Activities

The ICH harmonisation activities fall into 4 categories (see Table below). The original Formal ICH Procedures involved a step-wise progression of guidelines. This process has evolved to include maintenance activities (Maintenance Procedure), as an essential part of the ICH procedure.

In addition to the maintenance activity, it is also important to have procedures in place to enable the modification of existing guidelines (Revision Procedure), as well as to assist in their implementation (Q&A Procedure).

Category	Type of procedure	Technical Discussion Group	Explanation	Example
1	Formal ICH procedure	EWG	Development of a new guideline	M5 (Data Elements and Standards for Drug Dictionaries
2	Q&A procedure	IWG	Creation of Q&As to assist the implementation of existing guidelines	CTD-IWG
3	Revision procedure	EWG	Revision/Modification of existing guidelines	E2B(R3)
4	Maintenance procedure	EWG	Adding Standards to existing guidelines and/or recommendations	Q3C(R3) M2 Recommendations

Structure of ICH

ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

The focus of ICH has been on the technical requirements for medicinal products containing new drugs. The vast majority of those new drugs and medicines are developed in Western Europe, Japan and the United States of America and therefore, when ICH was established, it was agreed that its scope would be confined to registration in those three regions.

ICH is comprised of Six Parties that are directly involved, as well as three Observers and IFPMA. The Six Parties are the founder members of ICH which represent the regulatory bodies and the research-based industry in the European Union, Japan and the USA. These parties include the EU, EFPIA, MHLW, JPMA, FDA and PhRMA.

The Observers are WHO, EFTA, and Canada (represented by Health Canada). This important group of non-voting members acts as a link between the ICH and non-ICH countries and regions.

ICH is operated via the ICH Steering Committee, which is supported by ICH Coordinators and the ICH Secretariat.

ICH PARTIES:

European Commission - European Union (EU)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
Ministry of Health, Labour and Welfare, Japan (MHLW)
Japan Pharmaceutical Manufacturers Association (JPMA)
US Food and Drug Administration (FDA)
Pharmaceutical Research and Manufacturers of America (PhRMA)

ICH Steering Committee

ICH is administered by the ICH Steering Committee which is supported by the ICH Secretariat. The ICH Steering Committee (SC) was established in April 1990, when ICH was initiated. The Steering Committee, working with the ICH Terms of Reference, determines the policies and procedures for ICH, selects topics for harmonisation and monitors the progress of harmonisation initiatives. The Steering Committee meets at least twice a year with the location rotating between the three regions.

Since the beginning, each of the six co-sponsors has had two seats on the ICH Steering Committee (SC) which oversees the harmonisation activities. IFPMA provides the Secretariat and participates as a non-voting member of the Steering Committee.

The ICH Observers, WHO, Health Canada, and the European Free Trade Association (EFTA) nominate non-voting participants to attend the ICH Steering Committee Meetings.

OVERVIEW OF ICH GUIDELINE:

1) QUALITY:

Q1A(R2)	STABILITY TESTING IN NEW DRUGS AND PRODUCTS(REVISED GUIDELINE)
Q1B	PHOTOSTABILITY TESTING
Q1C	STABILITY TESTING:NEW DOSAGE FORMS
Q1D	BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS
Q1E	EVALUATION OF STABILITY DATA
Q1F	STABILITY DATA PACKAGE FOR REGISTRATION IN CLIMATIC ZONES III AND IV
Q2A	DEFINTIONS AND TERMINOLOGY:ANALUTICAL VALIDATION
Q2B	METHODOLOGY
Q3A	IMPURITY TESTING IN NEW DRUG SUBSTANCES
Q3B	IMPURITIES IN DOSAGE FORMS: ADDENDUN TO THE GUIDELINE ON IMPURITIES IN NEW DRUG SUBSTANCES
Q3C	IMPURITIES:RESIDUAL SOLVENTS
Q4	PHARMACOPOEIAL HARMONIZATION
Q5A	VIRAL SAFETY EVALUATION
Q5B	GENETIC STABILITY
Q5C	STABILITY OF BIOTECHNOLOGY PRODUCTS
Q5D	CELL SUBSTRATES
Q6A	SPECIFICATIONS, TEST PROCEDURES, AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND PRODUCTS
Q7A	GMP FOR ACTIVE PHARMACEUTICAL INGREDIENTS
Q8	PHARMACEUTICAL DEVELOPMENT
Q9	QUALITY RISK MANAGEMENT
Q10	PHARMACEUTICAL QUALITY SYSTEM

2) SAFETY:

S1A	GUIDELINE ON THE NEED FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS
S1B	TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS
S1C(R2)	DOSE SELECTION FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS
S2(R1)	GUIDANCE ON GENOTOXICITY TESTING AND DATA INTERPRETATION FOR PHARMACEUTICALS INTENDED FOR HUMAN USE
S3A	NOTE FOR GUIDANCE ON TOXICOKINETICS: THE ASSESSMENT OF SYSTEMIC EXPOSURE IN TOXICITY STUDIES
S3B	PHARMACOKINETICS:GUIDANCE FOR REPEATED DOSE TISSUE DISTRIBUTION STUDIES
S4	DURATION OF CHRONIC TOXICITY TESTING IN ANIMALS (RODENT AND NON RODENT TOXICITY TESTING)

S5(R2)	DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY
S6(R1)	ADDENDUM TO ICH S6: PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S6	PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S7A	SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS
S7B	THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS
S8	IMMUNOTOXICITY STUDIES FOR HUMAN PHARMACEUTICALS
S9	NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS

3) EFFICACY:

E1	THE EXTENT OF POPULATION EXPOSURE TO ASSESS CLINICAL SAFETY
E2A	CLINICAL SAFETY DATA MANAGEMENT
E2B(R2)	MAINTENANCE OF THE ICH GUIDELINE ON CLINICAL SAFETY DATA MANAGEMENT
E2B(R3)	REVISION OF THE ICH GUIDELINE ON CLINICAL SAFETY DATA MANAGEMENT DATA ELEMENTS FOR TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS
E2C(R1)	CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS
E2D	POST-APPROVAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING
E2E	PHARMACOVIGILANCE PLANNING
E2F	DEVELOPMENT SAFETY UPDATE REPORT
E3	STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
E4	DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION
E5(R1)	ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA
E6(R1)	GUIDELINE FOR GOOD CLINICAL PRACTICE
E7	STUDIES IN SUPPORT OF SPECIAL POPULATIONS:GERIATRICS
E8	GENERAL CONSIDERATIONS FOR CLINICAL TRIALS
E9	STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E10	CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS
E11	CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION
E12	PRINCIPLES FOR CLINICAL EVALUATION OF NEW ANTIHYPERTENSIVE DRUGS
E14	THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
E15	DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES
E16	GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE:

	CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS

4) MULTIDISCIPLINARY;

M2 (R2)	ELECTRONIC TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS MESSAGE SPECIFICATION
M3(R2)	GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
M4	ORGANISATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE
M4E(R1)	THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:EFFICACY
M4Q(R1)	THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:QUALITY
M4S(R2)	THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE:SAFETY
M5	DATA ELEMENTS AND STANDARDS FOR DRUG DICTIONARIES

Safety, Efficacy and Multidisciplinary are not covered here..as we are much concerned with Quality Guidelines.

In Quality Guidelines Q1A,Q1B,Q1C,Q1D and Q3 Topics are already covered in Stability Studies(SEM-I)

Q1E: EVALUATION OF THE STABILITY DATA

1. INTRODUCTION

1.1 OBJECTIVES OF THE GUIDELINE

- This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline “Q1A(R) Stability Testing of New Drug Substances and Products” (here after referred as the parent guideline) to propose a retest period/shelf life in a registration application.
- This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by “available data from the stability study under the long-term storage condition” (hereafter referred to as long-term data).

1.2 BACKGROUND

- The guidance on the evaluation and statistical analysis of stability data provided in the parent guideline is brief in nature and limited in scope.
- The parent guideline states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for **batch poolability be performed using a level of significance of 0.25.**

- However, the parent guideline includes few details and does not cover situations where multiple factors are involved in a full- or reduced-design study.

1.3 SCOPE OF THE GUIDELINE

- This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products.

2. GUIDELINES

2.1 GENERAL PRINCIPLES

- The design and execution of formal stability studies should follow the principles outlined in the parent guideline.
- A systematic approach should be adopted to the presentation and evaluation of stability information, which should include, as necessary, physical, chemical, biological and microbiological test characteristics.
- All product characteristics likely to be affected by storage, e.g. assay value or potency, content of products of decomposition, physicochemical properties (hardness, disintegration, particulate matter, etc.), should be determined; for solid or semi-solid oral dosage forms, dissolution tests should be carried out.
- Test methods to demonstrate the efficacy of additives, such as antimicrobial agents, should be used to determine whether such additives remain effective and unchanged throughout the projected shelf-life.
- Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. The assay methods chosen should be those indicative of stability.
- The tests for related compounds or products of decomposition should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity.

2.2 DATA PRESENTATION

- Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application.
- A checklist similar to that used in the WHO survey on the stability of pharmaceutical preparations included in the WHO Model List of Essential Drugs (Appendix 1) can be used to determine the other stability characteristics of the product.

1. Tabulate and plot stability data on all attributes at all storage conditions and evaluate each attribute separately.
2. No significant change at accelerated conditions within six (6) months.
3. Long-term data show little or no variability and little or no change over time.

STABILITY PROTOCOL AND REPORT

1. Batches tested
2. General information
3. Container/closure system
4. Literature and supporting data

5. Stability-indicating analytical methods
6. Testing plan
7. Test parameters
8. Test results
9. Other requirements (post-approval commitments)
10. Conclusions

Result sheets must bear date and responsible person signature / QA approval

The batches should be representative of the manufacturing process and should be manufactured from different batches of key intermediates.

ILLUSTRATIVE DATA OF CAPSULE/TABLET STABILITY BATCHES

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)	20	100	100
Batch size (number of units)			
Primary packing materials			
Date of initial analysis			
Batch number of the API			

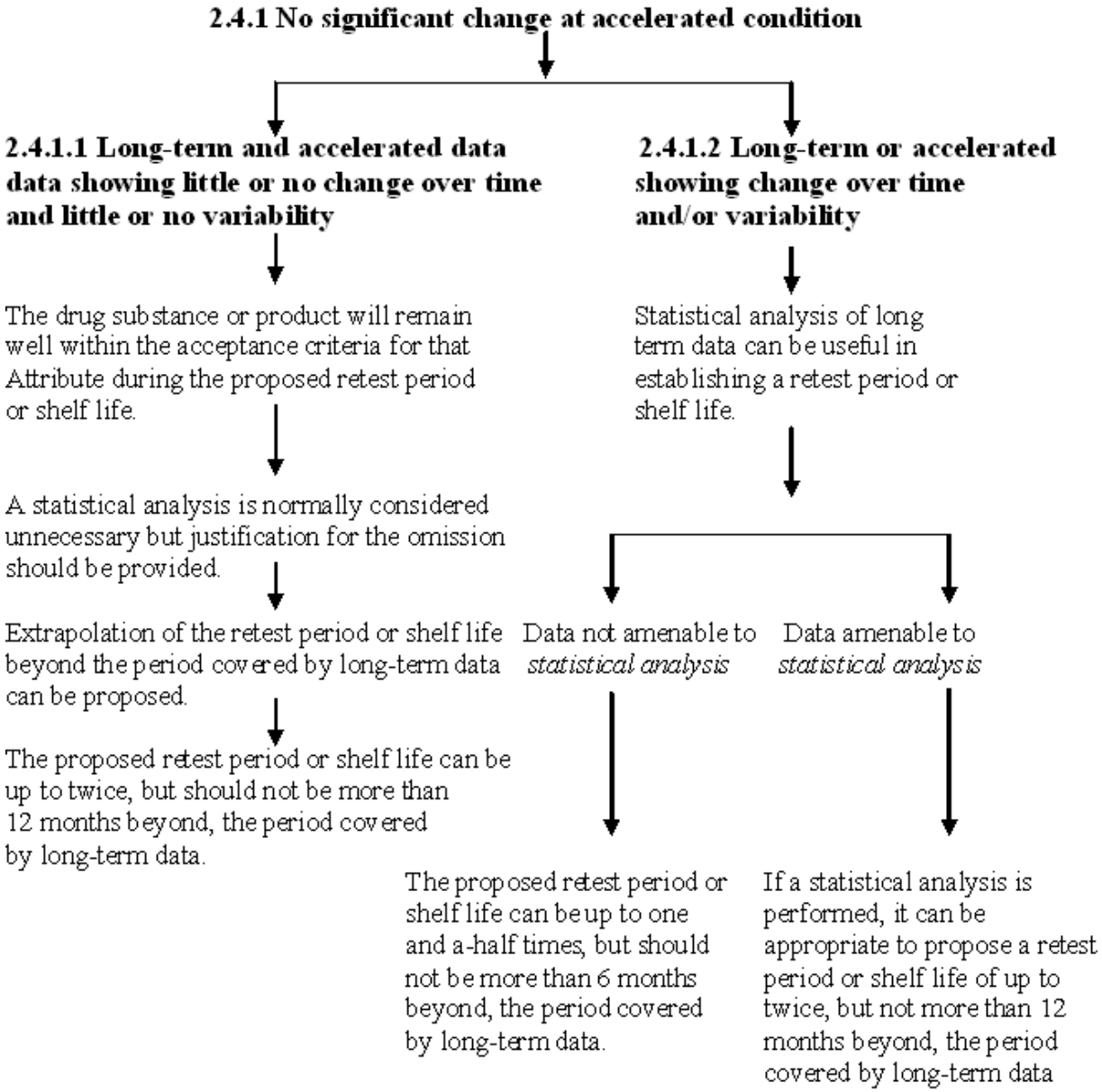
2.3 EXTRAPOLATION

- **Extrapolation** is the practice of using a known data set to infer information about future data.
- Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition.

2.4 DATA EVALUATION FOR RETEST PERIOD OR SHELF LIFE ESTIMATION FOR DRUG SUBSTANCES OR PRODUCTS INTENDED FOR ROOM TEMPERATURE STORAGE

2.4.1 No significant change at accelerated condition

- Where no significant change occurs at the accelerated condition, the retest period or shelf life would depend on the nature of the long-term and accelerated data.



2.4.2 Significant change at accelerated condition

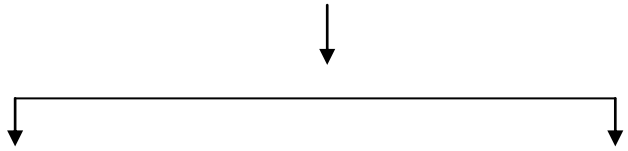
- Where significant change* occurs at the accelerated condition, the retest period or shelf life would depend on the outcome of stability testing at the intermediate condition, as well as at the long-term condition.

***Note**: The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change:

- Softening of a suppository that is designed to melt at 37ºC, if the melting point is clearly demonstrated,
- Failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking.

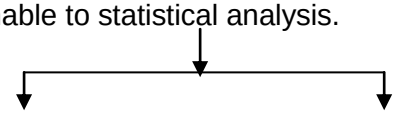
However, if phase separation of a semi-solid dosage form occurs at the accelerated condition, testing at the intermediate condition should be performed. Potential interaction effects should also be considered in establishing that there is no other significant change.

2.4.2 Significant change at accelerated condition



2.4.2.1 No significant change at condition

The extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.



Data not amenable to statistical analysis

The proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data

Data amenable to statistical analysis

The proposed retest period or shelf life can be up to one-and-half times, but should not be more than 6 months beyond, the period covered by long-term data

2.4.2.2 Significant change at intermediate intermediate condition

The proposed retest period or shelf life should not exceed the period covered by long-term data

2.5 DATA EVALUATION FOR RE-TEST PERIOD OR SHELF LIFE ESTIMATION FOR DRUG SUBSTANCES OR PRODUCT INTENDED FOR STORAGE BELOW ROOM TEMPERATURE

2.5.1 Drug substances or products intended for storage in a refrigerator

2.5.2 Drug substances or products intended for storage in a freezer

2.5.3 Drug substances or products intended for storage below -20° C

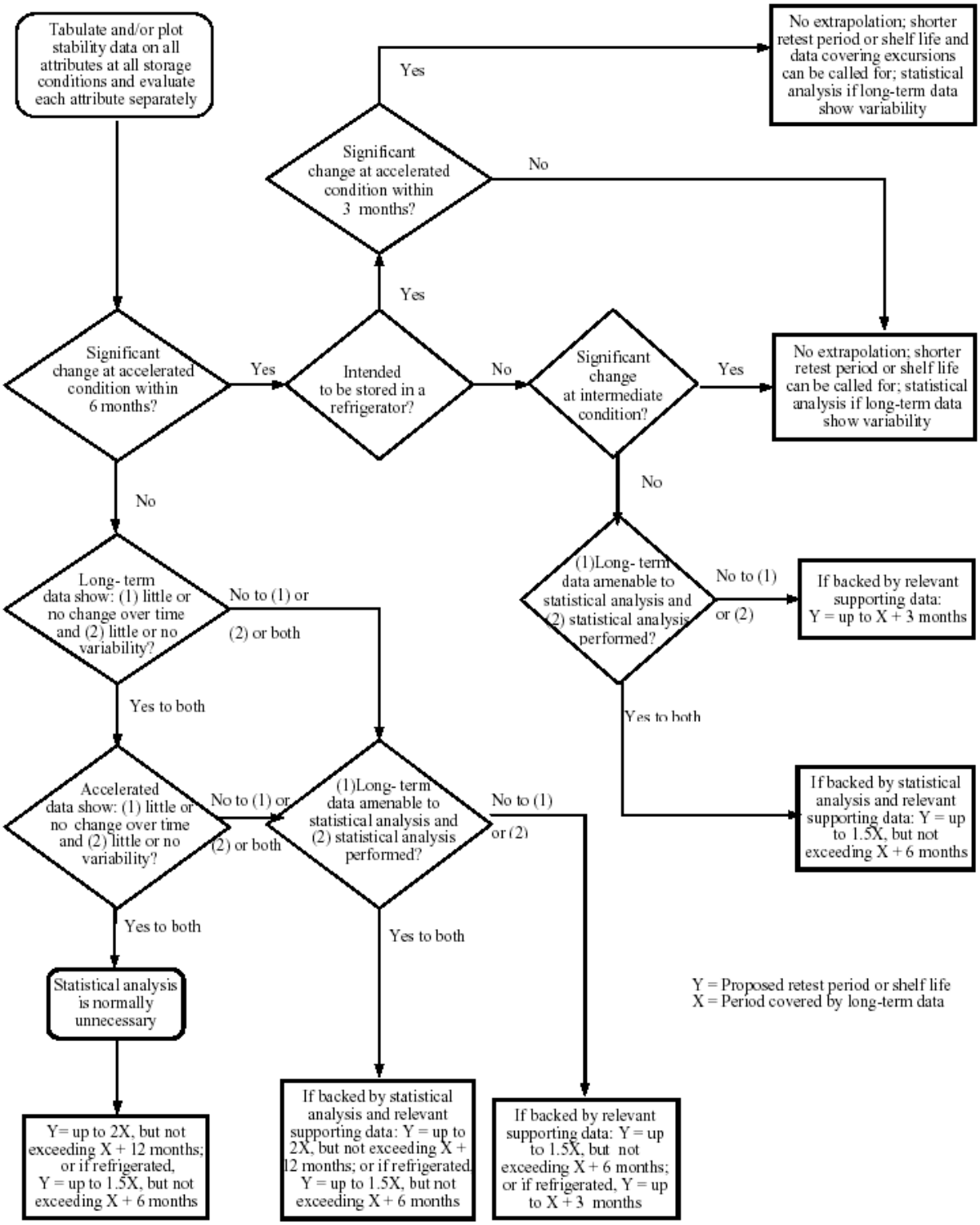
2.6 GENERAL STATISTICAL APPROACHES

- Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application.

- The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances.
- The same statistical method should also be used to analyze data from commitment batches to verify or extend the originally approved retest period or shelf life.
- **Regression analysis** is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life.
- The relationship between **an attribute and time** can be **represented by a linear or non-linear function on an arithmetic or logarithmic scale.**
- In some cases, a non-linear regression can better reflect the true relationship.
- An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by **determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion.**
- For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion.
- For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the acceptance criterion.
- For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.

3. APPENDICES

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



Q1F: STABILITY DATA PACKAGE FOR REGISTRATION IN CLIMATIC ZONES III AND IV.

1. INTRODUCTION

1.1 OBJECTIVES OF THE GUIDELINE

- This guideline describes outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in Climatic Zones III and IV.

1.2 BACKGROUND

- A product's shelf life should be established according to climatic conditions in which the product is to be marketed.
- Storage conditions recommended by manufacturers on the basis of stability studies are meant to guarantee the maintenance of quality, safety and efficacy throughout the shelf-life of product.
- Temperature and humidity determine the storage conditions and so they greatly affect the stability of drug product.
- Climatic conditions in countries where the product is to be marketed should be carefully considered during drug development phase. So the world has been divided into four climatic zones based on prevalent annual climatic conditions.

DEFINITION & STORAGE/TEST CONDITIONS FOR FOUR CLIMATIC ZONES

Climatic zones	Definition	Storage / Test conditions	Examples
I	Temperate Climate	21°C ± 2°C and 45% RH ± 5% RH	Northern Europe, Canada
II	Mediterranean & subtropical climate	25°C ± 2 °C and 60% RH ± 5% RH	Southern Europe, Japan, US
III	Hot dry climate	30°C ± 2°C and 35% RH ± 5% RH	Egypt, Sudan
IV	Hot & Humid climate	30°C ± 2°C and 75% RH ± 5% RH	Central Africa, South Pacific

%RH = Relative Humidity

1.3 SCOPE OF THE GUIDELINE

- This document is an annex to the parent guideline and recommends the long-term storage condition for stability testing of a new drug substance or drug product for a registration application in territories in Climatic Zones III and IV.

2. GUIDELINES

2.1 CONTINUITY WITH THE PARENT GUIDELINE

The following sections of the parent guideline can be considered common to any territory in the world and are not reproduced here:

Stress testing ,Selection of batches ,Container closure system ,Specification ,Testing frequency ,Storage conditions for drug substance or product in a refrigerator ,Storage conditions for drug substance or product in a freezer ,Stability commitment ,Evaluation ,Statements/labeling

2.2 STORAGE CONDITIONS

2.2.1 General Case

- For the "General case" (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

TYPE OF STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
LONG TERM	30°C ± 2°C / 65% RH ± 5% RH	12 MONTHS
ACCELERATED	40°C ± 2°C / 75% RH ± 5% RH	6 MONTHS

- No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV. Thus, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in Q1E are applied.

2.2.2 Aqueous-based drug products packaged in semi-permeable containers

- For aqueous-based drug products packaged in semi-permeable containers (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

TYPE OF STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
LONG TERM	30°C ± 2°C/35% RH ± 5% RH	12 MONTHS
ACCELERATED	40°C ± 2°C/ NOT MORE THAN 25 % RH ± 5% RH	6 MONTHS

- As described in the parent guideline, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio. (see table below for examples).
- **The ratio of water loss rates at a given temperature is calculated by the general formula (100 – reference % RH)/ (100 – alternative % RH).**

ALTERNATIVE RELATIVE HUMIDITY	REFERENCE RELATIVE HUMIDITY	RATIO OF WATER LOSS RATES AT A GIVEN TEMPERATURE
65% RH	35% RH	1.9
75% RH	25% RH	3.0

- Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

2.2.3 Tests at elevated temperature and/or extremes of humidity

- Special transportation and climatic conditions outside the storage conditions recommended in this guideline should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover extremely hot & dry conditions and at 25°C/80% RH to cover extremely high humidity conditions.
- Stability testing at a high humidity condition, e.g., 25°C/80% RH is recommended for solid dosage forms in water-vapour permeable packaging, e.g., tablets in PVC/ aluminum blisters, intended to be marketed in territories with extremely high humidity conditions in Zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapour, e.g. aluminum/aluminum blisters, stability testing at a storage condition of extremely high humidity is not considered necessary.

2.3 Additional Considerations

- If it cannot be demonstrated that the drug substance or drug product will remain within its acceptance criteria when stored at 30°C ± 2°C/65 % RH ± 5 % RH for the duration of the proposed retest period or shelf life, the following options should be considered: (1) a reduced retest period or shelf life, (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

Q4B	**EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS**
Q4B ANNEX 1	ON RESIDUE ON IGNITION/SULPHATED ASH GENERAL CHAPTER
Q4B ANNEX 2	TEST FOR EXTRACTABLE VOLUME OF PARENTERAL PREPARATIONS GENERAL CHAPTER
Q4B ANNEX 3	TEST FOR PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES GENERAL CHAPTER
Q4B ANNEX 4A	MICROBIOLOGICAL EXAMINATION OF NON-STERILE PRODUCTS: MICROBIAL ENUMERATIONS TESTS GENERAL CHAPTER
Q4B ANNEX 4B	MICROBIOLOGICAL EXAMINATION OF NON-STERILE PRODUCTS: TEST FOR SPECIFIED MICRO-ORGANISMS GENERAL CHAPTE
Q4B ANNEX 4C	MICROBIOLOGICAL EXAMINATION OF NON-STERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE GENERAL CHAPTER
Q4B ANNEX 5	DISINTEGRATION TEST GENERAL CHAPTER
Q4B ANNEX 6	UNIFORMITY OF DOSAGE UNITS GENERAL CHAPTER
Q4B ANNEX 7	DISSOLUTION TEST GENERAL CHAPTER

Q4B ANNEX 8	STERILITY TEST GENERAL CHAPTER
Q4B ANNEX 9	TABLET FRIABILITY GENERAL CHAPTER
Q4B ANNEX 10	POLYACRYLAMIDE GEL ELECTROPHORESIS GENERAL CHAPTER
Q4B ANNEX 11	CAPILLARY ELECTROPHORESIS GENERAL CHAPTER
Q4B ANNEX 12	ANALYTICAL SIEVING GENERAL CHAPTER

WHO GUIDELINES

(Under Global Regulatory Requirements)

Introduction:

- The World Health Organization is the United Nations specialized agency for health.
- It was established on 7 April 1948.
- WHO is governed by 192 Member States through the World Health Assembly.
- All countries which are Members of the United Nations may become members of WHO.
- The Executive Board is composed of 32 members technically qualified in the field of health.
- Members are elected for three-years.
- The Organization is headed by the Director-General, who is appointed by the Health Assembly on the nomination of the Executive Board.
- WHO Member States are grouped into six regions.
- Each region has a regional office.
- Regional offices are in-
- Africa, America, Southeast Asia, Europe, Eastern Mediterranean, Western Pacific

Functions of WHO:

WHO has four main functions:

- To give worldwide guidance in the field of health.
- To set global standards for health.
- To cooperate with governments in strengthening national health programs.
- To develop and transfer appropriate health technology information.

Research tools of WHO:

WHO research tools include,

WHOLIS: World health organization database available on net, all publication since 1948.

WHOSIS: A guide to epidemiological and statistical information available from WHO.

WHO stability guidelines:

- Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms.
- It is for the stability testing of final drug products that are well established (e.g. generics) and are in conventional dosage forms (e.g. tablets).
- The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety, and efficacy throughout the shelf-life of a product.
- The effect on products of the extremely adverse climatic conditions existing in certain countries to which they may be exported calls for special consideration.
- In a stability study, the effect on the product in question of variations in temperature, time, humidity, light intensity and partial vapor pressure are investigated.
- For reconstituted product: “in use” stability data must be submitted to support the recommended storage time and conditions.
- Intended market: Stability testing should take into account the intended market and the climatic conditions in the area in which the drug products will be used.
- Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:
    - Zone I: Temperate.
    - Zone II: Subtropical, with possible High Humidity.
    - Zone III: Hot/Dry.
    - Zone IV: Hot/Humid.

Design of stability studies:

Test samples:

1) For registration purposes, test samples of products should contain fairly stable active ingredients and should be from two different production batches.

2) Should be representative of the manufacturing process.

3) Should be manufactured from different batches of API, if possible.

4) Suggested sampling schedule:

- One batch every other year for formulations considered to be stable, otherwise one batch per year;
- One batch every 3-5 years for formulations for which the stability profile has been established, unless a major change has been made

Test conditions:

Accelerated studies:

For less stable drug substances, if limited stability data are available: then duration of the accelerated studies for zone II should be increased to 6 months.

Accelerated stability testing of products containing relatively stable active ingredients.

Storage temp. (°C)	Relative humidity (%)	Duration of studies (months)
	Zone IV- For hot climatic zones or global market	
40±2	75±5	6
	Zone II - For temperate and subtropical climatic zones:	
40±2	75±5	3

Alternative Storage condition:

1) Storage for 6 months at a temp of at least 15 °C above the expected actual storage temp & appropriate RH.

2) Storage at higher temp may also be recommended, e.g. 3 months at 45-50 °C and 75% relative humidity (RH) for zone IV.

3) Where significant changes occur in the course of accelerated studies, additional tests at intermediate conditions should be conducted, e.g. 30 ± 2 °C and 60 ± 5% RH.

Real-time studies:

For registration purposes, the results of real time studies of at least 6 months' duration should be available at the time of registration***.***

Frequency of testing and evaluation of test results:

For accelerated studies:

0, 1, 2, 3 and, when appropriate, 6 months;

For real-time studies:

0, 6 and 12 months, and then once a year.

For on-going studies:

- For the confirmation of the provisional shelf-life: 6-months.
- For well established products : 12 months.

Highly stable formulations:

First 12 months and then at the end of the shelf-life.

Less stable drug substances:

Every 3 months in the first year, every 6 months in the second year, and then annually

Analytical methods:

- Analytical methods should be validated or verified .
- All product characteristics likely to be affected by storage should be determined.
- Tests for related compounds or products of decomposition should also be validated.

Stability report:

Provides details of the design of the study, as well as the results and conclusions.

WHO Guidelines On Sampling Of Pharmaceuticals:

Sampling comprises of the operations designed to select a portion of a material for a defined purpose. All operations related to sampling should be performed with care, using proper equipment and tools.

Purpose of Sampling:

- Prequalification
- Acceptance of consignments
- In-process control
- Inspection for customs clearance, deterioration, adulteration

Classes and Types of Materials:

- Starting materials
- Primary and secondary Packaging Materials
- Intermediates
- Pharmaceutical products

Controls to Be Applied To the Sample:

- Checking the identity of a material;
- Performing complete pharmacopoeial or analogous testing;
- Performing special/specific tests.

Sampling Operation and Precautions:

- Procedure should be such that any non-uniformity of the material can be detected
- Non-homogeneous portions of the material or bulk should be sampled and tested separately\
- Composting of the samples from the diff. portions should be avoided, since it can mask contamination
- For Finished drug products the sampling procedure must take account
    - Official and non-official tests (for dosage forms)
    - Non-official tests could include testing for adulteration, counterfeiting, etc.

Storage and Retention:

- Container used to store a sample shouldn't interact with the sampled material nor allow contamination, should protect from light, air, moisture, etc., as req. by the storage directions for the material sampled
- Samples should be stored in accordance with the storage conditions as specified for the respective API, excipient or drug product
- Closures and labels should be preferably of such a kind that unauthorized opening can be detected.
- Samples must never be returned to the bulk.

Sampling for Regulatory Purposes:

Additional samples for regulatory testing and verification purposes should be provided. e.g. duplicate testing and parallel testing by different regulatory laboratories and by the consignee of the product.

Sampling Plans for Starting Materials, Packaging Materials and Finished Products:

Starting Material:

<u>The "n plan</u>"

Used only when material

1) is uniform &

2) Supplied from a recognized source

FORMULA: $n = 1+\sqrt{N}$

Where, N is the number of sampling units

According to this plan, original samples are taken from N sampling units selected at random

n-plan is not statistically based and should be used only as a guiding principle.

"n plan" is not recommended for use by control laboratories of manufacturers.

The "r plan"

Used when material

1) is non-uniform &

2) Supplied from source that is not well known

FORMULA: $r = 1.5\sqrt{N}$

Where, N is the number of sampling units

According to this plan samples are taken from each of the N sampling units of the consignment and placed in separate sample containers & tested.

If the results are in agreement, r final samples are formed by appropriate pooling of the original samples.

If these results are in agreement, the r samples are combined for the retention sample.

Guidelines on Good Manufacturing Practices (GMP): Validation

- Focuses mainly on the overall concept of validation and is intended as a basic guide for use by GMP inspectors.
- It encompasses details related to :Validation; Qualification ; Calibration and verification
- Other aspects addressed in this guideline include the Validation Team, Validation Master Plan, Validation Protocol (VP), Validation Report (VR), types of validation (Computer Systems Validation; Process Validation; Analytical Validation; Cleaning Validation), Re-validation and Change Control associated with validation.

Guidelines on- Inspection

- Inspection of…..
  - pharmaceutical manufacturers
  - drug distribution channels (products)
- Guidelines for pre-approval inspection
- Quality system requirements for national GMP Inspectorates

- Intended to promote harmonization of pharmaceutical inspection practices among WHO Member States

Objectives:

- Evaluation of the establishment's compliance with GMP requirements
- Evaluation of the procedures and controls implemented in the mfg
- Audit of the completeness and accuracy of the mfg and testing information submitted with the application
- The collection of samples for the validation or verification of the analytical methods included in the application.

Types of Inspection

- **Routine inspection:**
  - Full inspection of all applicable components of GMP

- **Concise inspection:**
  - Eligibility: Manufacturers with a consistent record of compliance with GMP.
  - It is on limited number of GMP requirements selected as indicators of overall GMP performance. It is generally done unannounced.

- **Follow-up inspection:**
  - It is done to monitor the result of corrective actions.
  - It is normally carried out from 6 weeks to 6 months after the initial inspection, depending on the nature of the defects and the work to be undertaken.

- **Special inspection:**
  - Necessary to undertake spot checks following complaints or recalls related to suspected quality defects in products.
  - Special visits may also be made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate. The inspection should preferably be unannounced.

- **Investigative inspection:**
  - This type of inspection is used to assess the performance of a new establishment whose scope of operation was previously unknown. It should also be unannounced.

When Inspections are required?

- New chemical entity
- Drugs of narrow therapeutic range
- Products previously associated with serious adverse effects, complaints, recalls
- Applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

- Products that are difficult to manufacture or test, or that are of doubtful stability
- New applicants or manufacturers

WHO's Guidance on Interchange ability of Medicines

- WHO guideline on registration requirements to established interchangeability for multisource pharmaceutical products (1996 under revision)
- Guidance on selection of comparator products for equivalence assessment of interchangeable generic products
- New draft: BCS classification to limit in vivo tests
- In vitro test methodology for BCS class I drugs

Why Is Bioequivalence Needed?

- Pharmaceutical equivalence does not necessarily mean therapeutic equivalence
- Multisource drug products should conform to the same standards of quality, safety and efficacy required for the reference product and must be interchangeable
- Differences in excipients or manufacturing process may lead to differences in product performance. Also, in vitro dissolution does not necessarily reflect in vivo bioavailability.

What are the ways of demonstrating Therapeutic Equivalence?

- Comparative BA (BE) studies
- Comparative pharmacodynamic studies in humans
- Comparative clinical trials
- *In vitro* dissolution tests

When BE Studies are not needed for Multisource product?

A) An aqueous solution for parenteral use
B) A solution for oral use
C) A medicinal gas
D) A powder for reconstitution as a solution for oral or parenteral use
E) An otic or ophthalmic solution
F) A topical aqueous solution
G) An inhalation product or nasal spray as an aqueous solution

For E, F and G, formulation of multisource product must be similar to reference product.

Also, bioequivalence studies may be waived for compositionally similar strengths when one strength in a range has been studied.

Proportionally Similar Formulations:

Proportionally similar formulations are defined in two ways based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportion between different strengths
(ii) For a high potency API (up to 10 mg per dosage), where the amount of the API in the dosage form is relatively low, the total wt of the dosage form remains nearly the same for all strengths (within ± 10% of the total wt), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering the amount of the API and one or more inactive and inert ingredients.

Design of comparative BA studies:

- Studies should be carried out in accordance with provisions of guidelines on Good Clinical Practice, Good Manufacturing Practice, Good Laboratory Practice
- Most common design is single-dose, randomized, two-way crossover study (non-replicated)
- Other designs possible, e.g. parallel design for drugs with long half-lives, steady-state studies for some non-linear drugs

Factors to consider in the design of a study:

Study formulation should be representative of formulation to be marketed

- Subjects
  - Number
  - Health status
  - Age, weight, height
  - Ethnicity
  - Gender
  - Special characteristics e.g. poor metabolizers
  - Smoking
  - Inclusion/exclusion criteria specified in protocol
- Randomization
- Blinding
- Sampling protocol
- Washout period
- Administration of food and beverages during study
- Recording of adverse events

Bioequivalence standards (acceptance ranges):

- The 90% confidence interval of the relative mean AUC of the test to reference product should be between 80-125%.
- The 90% confidence interval of the relative mean CMAX of the test to reference product should be between 80-125%. Since CMAX is recognized as being more variable than the AUC ratio, a wider acceptance range may be justifiable.
- These standards must be met on log-transformed parameters calculated from the measured data
- If the measured potency of the multisource formulation differs by more than 5% from that of the reference product, the parameters may be normalized for potency.
- TMAX may be important for some drugs

Critical parameters to look into when evaluating dossiers with respect to BE studies

- Is the reference product suitable?
- Was the study design such that variability due to factors other than the product was reduced? Other design issues e.g. sample size, sampling protocol
- Assay validation adequate?
- Pharmacokinetic analysis appropriate?
- Statistical analysis appropriate?
- Acceptance criteria met?

Some statistical considerations:

- **A priority specification of methods**
  - Statistical methods to be used must be specified beforehand in the protocol
- **Number of subjects**
  - Take into consideration error variance of parameter, desired significance level and acceptable deviation from reference product
  - Minimum 12 subjects, Usually 18-24 subjects sufficient.
- **Log-transformation**
  - AUC and CMAX should be analyzed after log-transformation
  - Satisfies assumption of Analysis of Variance (ANOVA model is additive rather than multiplicative)
- **Outliers**
  - Must be valid medical reason to drop outlier from analysis
  - Post hoc deletion of outlier values is generally discouraged

Parametric methods are recommended for the analysis of log-transformed BE measures

Non-parametric methods can be used when the log transformed data is not normal

Pharmacodynamic studies:

Not recommended: for oral product for systemic action due to high within-subject variability

Uses:

- If quantitative analysis of the drug and/or metabolite(s) in plasma or urine can't be made with sufficient accuracy and sensitivity
- If measurements of drug concentration can't be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product.

WHO Model System for Computer-assisted Drug Registration (SIAMED):

Objective of this system is to improve the efficiency of drug regulatory authority (DRA) enabling them to assure that marketing authorizations are consistent with their national drug policy.

Technical information:

Version: FoxPro 2.6 (DOS).

It is a user-friendly system that allows the entry, updating, retrieval and printing of information stored in a related database.

Multi-user version and network support:

SIAMED has been used with the following network operating systems:

- LANtastic 6.0,
- Novell DOS,
- Windows 95 and
- NT4 and Novell NetWare 3.11

What does the model system do?

Information on companies,

- Summary information on inspections carried out at company premises
- Information on medicinal products for which an application has been received or a marketing authorization is issued,
- Status of applications in the evaluation process.
- Decisions such rejection, issuance, cancellation, renewal, and variation to marketing authorizations
- Variations to valid marketing authorizations, automatically keeping history of all variations made.

Provisions and Prerequisites for a Clinical Trial:

Justification for the trial,

- Ethical principles : As per current version of Declaration of Helsinki
- Supporting data for the investigational product:
  - Pre-clinical studies
  - Information about manufacturing procedures
  - compilation of information on safety and efficacy based on previous Clinical data for subsequent trials
- Investigator and site(s) of investigation
- Regulatory requirements

The Protocol:

Clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor.

Protection of Trial Subjects:

Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects.

It is the accepted basis for clinical trial ethics & must be fully followed and respected by all parties.

Ethics committee:

It ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, by previewing trial protocols, etc.

Informed consent:

Principles of informed consent in the current revisions of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects should be implemented in each clinical trial.

Confidentiality:

The investigator must establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects

Recommended guidelines for CROs:

This document provide guidelines to organizations such as organizations Such as contract research organizations (CROS) performing be studies on behalf Of sponsors that are involved in the conduct of *in vivo* BE studies.

This document provides information on:

- Organization and management;
- Clinical phase of a study;
- Bioanalytical phase of a study;
- Pharmacokinetic and statistical analysis; and
- Study report.

Role of the Drug Regulatory Authority

- ❖ Provides the legal framework for clinical trials
- ❖ Have a mandate to review protocols and, where necessary, to protect the safety of subjects, to require protocol revisions and/or termination of trials.
- ❖ Carry out on-site inspections of the clinical trial site.

WHO GMP: Investigational pharmaceutical products for clinical trials in humans:

- The present guidelines supplement both the WHO guide on GMP and the guidelines on GCP for trials on pharmaceutical products . The application of the principles of GMP to the preparation of investigational products is necessary for several reasons:
- To assure consistency between and within batches of the investigational product & thus assure the reliability of clinical trials.
- To assure consistency between the investigational product & the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.
- To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors, or from starting materials and components of inadequate quality.
- To document all changes in the manufacturing process.

WHO's global guidelines – DISTRIBUTION:

- ❖ WHO Certification Scheme for Products Moving in International Commerce (SMACS) new scheme for pharmaceutical starting materials:
  - Model certificate, when inspected by national authority
  - WHO model for self-assessment for manufacture of pharmaceutical starting materials
- ❖ Good Distribution and Trading Practices for pharmaceutical starting materials (GTDP)

- Good Distribution Practices (GDP) (for products in prep.)
- Good Storage Practices (GSP)

Guidelines on the implementation of the WHO certification scheme on the QUALITY OF PHARMACEUTICAL PRODUCTS moving in international commerce:

- The Scheme is an administrative instrument that requires each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State that:
- A specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
- The plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO;
- All submitted product information, including labelling, is currently authorized in the certifying country

Eligibility for participation:

Any Member State intending to participate in the Scheme may do so by notifying the Director-General of the WHO, in writing, of:

- Its willingness to participate in the Scheme;
- Any significant reservations it intends to observe relating to this participation; and
- The name and address of its national drug regulatory authority or other competent authority.
- A Member State may opt to participate solely to control the *import* of pharmaceutical products and active substances. This intention should be stated explicitly in its notification to the WHO
- A Member State intending to use the Scheme to support the *export* of pharmaceutical products should first satisfy itself that it possesses:
  - An effective national licensing system
  - GMP requirements, as recommended by WHO
  - Effective controls to monitor the quality of pharmaceutical products
  - A national pharmaceuticals inspectorate,
  - Administrative capacity to issue the required certificates,

Requesting a certificate:

Three documents can be requested within the scope of the scheme:

a) Certificate of a Pharmaceutical Product (Product certificate)

b) Statement of Licensing Status of Pharmaceutical Product (s)

c) Batch Certificate of a Pharmaceutical Product**.**

WHO pharmaceutical starting materials certification scheme (SMACS): (Guidelines on implementation)

This guidance text, in combination with other recommendations and guidelines issued by WHO, will be an important step towards ensuring the quality and traceability of pharmaceutical starting materials and in assigning the responsibility for specifications within the processes of mfg, storage and distribution of pharmaceutical starting materials.

Objectives:

The Scheme is an administrative instrument that can be used by:

1) A Member State to attest that:

A specific starting material is used in a pharmaceutical product authorized to be placed on the market within its jurisdiction or within another national jurisdiction; and the manufacturing site in which a specific starting material is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO.

2) Manufacturer to attest compliance with a quality assurance system

The newly proposed scheme consists of,

1. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the competent national authority, or, alternatively:

2. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer.

WHO GMP Guidelines for pharmaceutical products:

Main Principles:

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967.

The following points are covered in the recent one.

1. Quality Assurance: Achieved by following GMP, GCP and GLP.
2. GMP

3. Sanitation and hygiene-A high level of sanitation and hygiene should be practised

4. Qualification AND validation

5. Complaints

6. Product recalls

7. Contract production and analysis

- Contract giver
- Contract acceptor- cannot pass it on to a third party without prior approval of a contract giver.

8. Self inspection and quality audits

- Quality audit- is to supplement self inspection, is the assessment of a part of or complete quality system with the specific purpose of improving it.

9. Personnel

10. Training

11. Personal hygiene

12. Premises: Ancillary, storage, weighing, production, quality control areas.

13. Equipment- Be suitable for its intended use; facilitate thorough cleaning; minimize the risk of contamination of products and containers during production; and facilitate efficient and, if applicable, validated and reliable operation**.**

14. Materials

15. Documentation

16. Good practices in production

- Prevention of cross contamination
- Processing operation-work area and equipment are clean before starting new operation
- Packaging operation-particular attention should be given to minimizing the risk of cross contamination.

17. Good practices in Quality control

- Control of starting materials, intermediates, bulk and finished products.

- Test requirements- the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

- Batch record review-Production and quality control records should be reviewed
- Stability studies-Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials.

WHO GMP: Starting Materials:

Active Pharmaceutical Ingredients (Bulk Drug Substances):

1. Explanation**-**The guideline gives procedures and practices that manufacturer should employ to get products having quality and purity appropriate for their use in pharmaceutical products.
2. General consideration- these guidelines are for human as well as veterinary use.
3. Personnel-
4. Equipment-
5. Premises –for cytostatic substances antibiotics etc, there should be separate areas with separate AHU.
6. Documentation-includes master formulae records, batch formulae records and SOP's. Outdated master formulae records should be withdrawn but should be retained for reference.

   Batch records electronically stored should be protected by back up transfer or magnetic tape, microfilm, paper print outs etc.

7. Retention of records and reference samples- of the API, and where necessary of intermediate products, should be retained for at least 1 year beyond the expiry date of the finished product or for a specified period if there is no expiry date.
8. Production-Processing procedures
9. Starting materials- Some may not be tested for compliance because of the hazards involved (e.g., phosphorus pentachloride and dimethyl sulfate). This is acceptable when a batch certificate of analysis is available from the vendor and when there is a reason based on safety or other valid considerations.
10. Intermediate products
11. Packaging
12. Quality control
13. Stability studies- expiry date do not usually need to be set for active pharmaceutical ingredient, if the stability testing does not indicate a reasonable shelf life, then the product can be labeled with an appropriate arbitrary expiry date and should be retested on or before that date.
14. Self inspection and quality audits
15. Storage
16. Complaints defects and rejected samples.

Pharmaceutical Excipients:

1. General considerations –

- An excipient manufacturer should be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance.

- Automated process controls and processing equipment are more likely to be used in an excipient plant than in a plant manufacturing finished dosage forms.

2. Self-inspection

A good starting point for an excipient plant - inspection is a review of the following areas:

- Non-conformance
- Complaint files.
- Change control documentation.

3. Quality Audits

Master formula and batch production records,

- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- Storage areas for rejected products.
- Adequacy of measures taken to preclude contamination of materials in the process.

4. Equipment.

- Use of equipment - Equipment that contains tarry or gummy residues that cannot be removed easily should be dedicated for use with these products only.
- Cleaning programme
- Detailed cleaning procedure
- Sampling plan
- Analytical methods/cleaning limits

5. Materials

- Starting materials –labile products
- Rejected and recovered materials
- Returned excipients

6. Documentation

Specifications, Batch production records , Other documents

7. Good practices in production and quality control -Change control and process validation,

- Good practices in production
- Prevention of cross-contamination
- Control of microbial contamination
- Water systems/water quality

- Packaging operations
- Delivery

8. Good practices in quality control

- Control of starting materials -certificate of analysis from the supplier
- In-process testing
- Quality records and retention samples

Reserve samples should be retained for 1 yr after the expiry or re-evaluation date, or for 1yr after distribution is complete.

- Stability studies

HERBAL medicinal products

1. Glossary

2. General-The control of the starting materials, storage and processing assumes particular importance because of the often complex and variable nature of many herbal medicinal products and the number and the small quantity of defined active ingredients present in them.

3. Premises

- Medicinal plant materials should be stored in separate areas.
- The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light.

4**.** Production area-

- To avoid cross-contamination whenever dust is generated, special precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants.

5. Specifications for starting materials-

- The botanical name, with reference to the authors.
- Details of the source of the plant
- Whether the whole plant or only a part is used.
- When dried plant is purchased, the drying system.
- A description of the plant material based on visual and/or microscopical inspection

. Assay

- Any treatment used to reduce fungal/microbial contamination or other infestation should be documented.

6**.** Qualitative and quantitative requirements

Medicinal plant material: (a) the quantity of plant material must be stated; or (b) the quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity. The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated

7. Specifications for the finished product

If the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined.

8. Processing instructions- The processing instructions should list the different operations to be performed on the plant material.

9. Quality control -Reference samples of plant materials must be available for use in comparative tests.

10. Sampling

11. Stability tests –it must be shown that, substances present are stable and that their content as a proportion of the whole remains constant.

If it is not feasible to determine the stability of each active ingredient, the stability of the product should be determined

Sterile pharmaceuticals products

1. General considerations-

Manufacturing operations are divided here into 2 categories:

1. Terminally sterilized

2. Aseptically sterilized at some or all stages.

2. Quality control –

The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media-fills” runs for aseptically processed products.

Pharmacopoeial methods must be used for the validation and performance of the sterility test.

3. Sanitation –because of limited effectiveness of ultraviolet light it should not be used as a substitute for chemical disinfection.

4. Manufacture of sterile preparations – Limits for microbiological contamination

Grade	Air sample (CFU/m3)	Settle plates (diameter 90mm) (CFU/4 hours)	Contact plates (diameter 55mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

5. Terminally sterilized products-The filling of products for terminal sterilization should generally be done in at least a grade C environment.

6. Sterilization-

The sterilization is carried out by

- Dry heat
- Moist heat
- Radiation
- Filtration
- By gases and fumigants

7. Aseptic processing and sterilization by filtration

The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods.

8. Personnel.

9. Premises- Grade B areas should be designed in such a way that all operations can be observed from outside.

10. Equipment –

A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized. Equipment that has to be taken apart for maintenance should be resterilized after complete reassembly, wherever possible.

11. Finishing of sterile products-

Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

Radiopharmaceutical Products:

1. Scope of this guideline- Manufacturing procedure within the scope of these guidelines includes:

1. The preparation of radiopharmaceuticals in hospital radiopharmacies.
2. The preparation of radiopharmaceuticals in centralized radiopharmacies.
3. The production of radiopharmaceuticals in nuclear centers and institutes or by industrial manufacturers.
4. The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centers.

2. Principles-

Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control may sometimes be retrospective. Therefore a strict adherence to GMP is mandatory.

3. Personnel

1. Person who has academic achievement together with a practical expertise and experience in radiopharmacy and radiation hygiene

2. Can be relied on to observe the appropriate codes of practice and are not subject to any disease.
3. Minimum number of personnel required should be present in clean and aseptic areas when work is in progress.
4. Personnel should be trained in GMP, the safe handling of radioactive materials and radiation safety procedures.
5. Training records

4. Premises and equipment-

1. Specific disposal systems should be mandatory for radioactive effluents.
2. Sinks should be excluded from aseptic areas. Any sink installed in other clean areas should be of suitable material and be regularly sanitized.
3. Separate air-handling units should be used for radioactive and non-radioactive areas.
4. Proper HVAC

5. Production-

1. SOPs must be available for all operating procedures.

2. Specifications for starting materials.

3. Great care should be taken in cleaning, sterilizing and operating freeze-drying equipment used for the preparation of kits.

4. For the measurement of very short half-lives, national central laboratories should be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

5. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

6. Dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and international guidelines.

6. Labelling-

1. All products should be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions.

2. An area of the container should be left uncovered to allow inspection of the contents.

3. Information on batch coding must be provided to the national and/or regional authorities.

7. Production and distribution records-

1. Separate records for the receipt, storage, use and disposal of radioactive materials
2. Distribution records should be kept.
3. The return of radioactive products should be carried out in accordance with international and national transport regulations.

8. Quality assurance and quality control-

1. Quality assurance and/or quality control have the principal responsibilities same as that for any other pharmaceutical product

Biological Products

1. Scope:

Manufacturing procedures within the scope of these guidelines include:

- Growth of strains of microorganisms and eukaryotic cells,
- Extraction of substances from biological tissues, including human, animal and plant tissues (allergens)
- Recombinant DNA (rDNA) techniques,
- Hybridoma techniques,
- Propagation of microorganisms in embryos or animals.

2. Principles

- Biological products are manufactured by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These processes display inherent variability. For this

reason, in the manufacture of biological products full adherence to GMP is necessary.

3. Personnel

- The staff engaged in the manufacturing process should be separate from the staff responsible for animal care**.**
- To ensure the manufacture of high-quality products, personnel should be trained in GMP and GLP in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine**.**
- All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated with appropriate vaccines and, where appropriate, be submitted to regular testing for evidence of active tuberculosis.

4. Premises and equipment.

- Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers. And on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, including, if appropriate, sterilization and washing**.**
- Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished.
- Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.

5. Animal quarters and care.

- Animals shall be accommodated in separate buildings with self-contained ventilation systems.
- The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin.
- The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded.
- Provision shall also be made for animal inoculation rooms, which shall be separate from the postmortem rooms.
- There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals

6. Production.

- Standard operating procedures
- Specifications for starting materials
- Media and cultures shall be added to fermenters and other vessels under carefully controlled conditions to avoid contamination. Care shall be taken to ensure that vessels are correctly connected when cultures are added.
- If possible, media should be sterilized *in situ*. In-line sterilizing filters for routine addition of gases, media, acids, alkalis, defoaming agents, etc. to fermenters should be used consideration should be given to the validation of sterilization methods.

7. Labelling.

- All products shall be clearly identified by labels.
- The information given on the label on the container and the label on the package shall be approved.
- The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.
- The label on the package should show at least the nature and amount of any preservative or additive in the product

8. Lot processing records (protocols) and distribution records

- Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation.

9. Quality assurance and quality control

- In-process controls very important here
- Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.
- Special consideration needs to be given to the quality control requirements arising from production of biological products by continuous culture.

Good Storage Practices for Pharmaceuticals

1. Introduction.

- Involved in the storage, transportation and distribution of pharmaceuticals.
- It is closely linked to other existing guides recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, such as:
  - Good trade and distribution practice (GTDP) of pharmaceutical starting materials.
  - The stability testing of pharmaceutical products
  - The cold chain, especially for vaccines and biologicals;
- The International Pharmacopoeia

This guidance has been prepared in close collaboration with the International pharmaceutical Federation (FIP).

2. Personnel.

- All personnel should receive proper training in relation to good storage practice, regulations, procedures and safety .
- Personnel employed in storage areas should wear suitable protective or working garments appropriate for the activities they perform.

3. Premises and facilities.

- Precautions must be taken to prevent unauthorized persons from entering storage areas.
- Sufficient capacity
- Storage areas should be designed or adapted to ensure good storage conditions.
- Clean, and free from accumulated waste and vermin.

- Receiving and dispatch bays should protect materials and products from the weather.
- The materials or products, and areas concerned should be appropriately identified.
- The “first expired/first out” (FEFO) principle should be followed.

4. Storage requirements.

Storage conditions should be in compliance with the labelling.

Monitoring of storage conditions

- Recorded temperature monitoring data should be available for review.
- All monitoring records should be kept for at least the shelf-life of the stored material or product plus 1 year.

5. **Storage requirements**

- Documentation: written instructions and records
- Labelling and containers
- Receipt of incoming materials and pharmaceutical products
- Stock rotation and control-Periodic stock reconciliation should be performed by comparing the actual and recorded stocks.
- Control of obsolete and outdated materials and pharmaceutical Products

6. Returned goods

- Including recalled goods should be handled in accordance with approved procedures and records should be maintained.
- All returned goods should be placed in quarantine
- Any stock reissued should be so identified and recorded in stock records.
- Pharmaceuticals returned from patients to the pharmacy should not be taken back as stock, but should be destroyed.

7. **Dispatch and transport**

- Materials and pharmaceutical products should be transported in such a way that their integrity is maintained.
- The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order.
- All records should be readily accessible and available on request.

8. **Product recall**

MISCELLANEOUS

WHO action to address Substandard and Counterfeit medicines:

WHO provides support to countries to strengthen,

- Pharmaceutical legislation
- Good Manufacturing Practices (GMP)
- National drug regulatory capacity and performance

- To promote information exchange among drug regulatory authorities –
- To strengthen drug procurement.
- WHO also works with countries to ensure that quality assurance is built into the entire drug supply chain.
- Guidance materials have been prepared for countries in relation to product assessment and registration, distribution of medicines, basic tests and laboratory services.
- Nine GMP training workshops were held in Africa and Asia

ECBS – Expert Committee on Biological Standardization:

The WHO Expert Committee on Biological Standardization is commissioned by WHO

- Its function is to- establish detailed recommendations and guidelines for the manufacturing, licensing, and control of blood products, cell regulators, vaccines and related in vitro diagnostic tests.
- The Expert Committee on Biological Standardization meets on an annual basis since 1947.
- The Expert Committee directly reports to the Executive Board, which is the executive arm of the World Health Assembly.

Technical report series:

- Provide updated information on the establishment, discontinuation and replacement of the WHO International Biological Reference Preparations as well on the adoption of Guidelines and Recommendations.
- The list of international reference standards is available as per name and as per area of work.

International Pharmacopoeia:

- The desire for the unification of terminology and of the strengths and composition of drugs led on to attempts to produce an international pharmacopoeia.
- The work on The International Pharmacopoeia is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations as well as specialists from industry and other institutions.
- The information published in **The International Pharmacopoeia** is collated via a consultative procedure and may thus be regarded as being based on international experience.
- The current edition completes the list of monographs for active pharmaceutical substances. It also includes a number of important general texts, e.g. on the dissolution test, drug nomenclature, general specifications for dosage forms, and many more.

- ❖ The needs of developing countries are taken into account and simple, classical physicochemical techniques are recommended that have been shown to be sound.
- ❖ Whenever possible, classical procedures are used in the analytical methods so that the pharmacopoeia can be applied without the need for expensive equipment.
- ❖ Priority is given to drugs that are widely used throughout the world. High priority is accorded to drugs that are important to WHO health programmes, and which may not appear in any other pharmacopoeias, e.g. new antimalarial drugs.
- ❖ Unlike other pharmacopoeias, the International Pharmacopoeia has no legal status.
- ❖ WHO Member States can adopt it and incorporate it into national legislation, either in part or in whole.

Essential Drugs and Medicines Policy:

WHO gives a list of essential drugs,

- Essential medicines are those that satisfy the priority health care needs of the population.
  They are selected in regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.
- Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.
- The implementation of the concentrationept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility."

Information Support for Pharmaceutical Regulation:

Aim is improving the access of national regulatory and pharmaceutical control authorities, to reliable information management systems, and to provide mechanisms for exchange of independent information on drug quality, safety and efficacy.

Example of taking such initiative is -**ICDRA**

- As a prime example of networking initiatives, the International Conference of Drug Regulatory Authorities (ICDRA) provides an international forum where representatives of national and regional drug regulatory authorities can exchange information and debate drug regulatory matters.

The Global Database on Adverse Drug Reactions-

The data collected are used to generate early warning signals of potential adverse reactions.

- More generally, the programme offers WHO Member States a tool for developing and reporting on activities concerned with adverse drug reaction monitoring. Additionally, the programme provides guidance and training courses on pharmacovigilance.
- WHO also provides information on regulatory matters to Member States through regular publications such as WHO Drug Information, the WHO Pharmaceuticals Newsletter (monthly) and WHO Drug Alerts.
- To provide electronic information support .WHO has developed SIAMED, a model system for computer-assisted drug registration, to help countries harmonize regulatory systems and improve the drug registration efficiency of their drug regulatory authority.

GUIDELINES FOR

SCALE UP AND POST APPROVAL CHANGES

PURPOSE OF GUIDANCE

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the postapproval period, to change: 1) the components or composition; 2) the site of manufacture; 3) the scale-up/scale-down of manufacture; and/or 4) the manufacturing (process and equipment) of an immediate release oral formulation.

The guidance defines: 1) levels of change; 2) recommended chemistry, manufacturing, and controls tests for each level of change; 3) *in vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level of change; and 4) documentation that should support the change. For those changes filed in a "changes being effected supplement" [21 CFR 314.70(c)], the FDA may, after a review of the supplemental information, decide that the changes are not approvable.

This guidance thus sets forth application information that should be provided to CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified postapproval changes.

DEFINITION OF TERMS

A. Batch

A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits [21CFR 210.3(b)(2)].

B. Contiguous Campus

Continuous or unbroken site or a set of buildings in adjacent city blocks.

C. Dissolution Testing

Case A: Dissolution of Q = 85% in 15 minutes in 900 milliliters (mL) of 0.1N hydrochloride (HCl), using the United States Pharmacopeia (USP) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.
Case B: Multi-point dissolution profile in the application/compendia medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently
accepted formulation.
Case C: Multi-point dissolution profiles performed in water, 0.1N HCl,and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60,

and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

D. Drug Product
A drug product is a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients [21 CFR 314.3(b)]. A solid oral dosage form includes tablets, chewable tablets, capsules, and soft gelatin capsules.

E. Drug Substance
An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient [21 CFR 314.3(b)].

F. Equipment
Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

G. Formulation
A listing of the ingredients and composition of the dosage form.

H. Justification
Reports containing scientific data and expert professional judgment to substantiate decisions.

I. New Drug Substance
Any substance that, when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance [21 CFR310.3(g)].

J. Operating Principle
Rules or concepts governing the operation of the system.

K. Pilot Scale
The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale.For solid oral dosage forms this is generally taken to be, at a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger

L. Process
A series of operations and/or actions used to produce a desired result.

M. Ranges
The extent to which or the limits between which acceptable variation exists.

N. Same
Agreeing in kind, amount; unchanged in character or condition.

O. Scale-up
The process of increasing the batch size.

P. Scale-down
The process of decreasing the batch size.

Q. Similar
Having a general likeness.

R. Significant body of information
A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.

S. Validation
Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through the production phase.Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS:

COMPONENTS AND COMPOSITION
This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at Level 3 (defined below), except as described below.

A. Level 1 Changes

1. Definition of Level
Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:
a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges :the total additive effect of all excipient changes should not be more than 5%

2. Test Documentation
a. Chemistry Documentation
Application/compendial release requirements and stability testing.
Stability testing: one batch on long-term stability data reported in annual report.
b. Dissolution Documentation
None beyond application/compendial requirements.
c. *In Vivo* Bioequivalence Documentation
None.

3. Filing Documentation
Annual report (all information including long-term stability data).

B. Level 2 Changes
1. Definition of Level
Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug, milligram/milliliter (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37 + 0.5oC). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. (Example:Compound A has as its lowest solubility at 37 + 0.5oC, 1.0 mg/Ml at pH 7, and is available in 100 mg, 200 mg and 400 mg strengths.

This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL). Permeability (Pe, centimeter per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally).

Examples:
a. Change in the technical grade of an excipient. (Example:Avicel PH102 vs. Avicel PH200.)
b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent
ranges (which represent a two fold increase over Level 1 changes):
The total additive effect of all excipient changes should not change by more than 10%.
.
2. Test Documentation
a. Chemistry Documentation
Application/compendial release requirements and batchrecords.
Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation
Case A: High Permeability, High Solubility Drugs
Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).

Case B: Low Permeability, High Solubility Drugs
Multi-point dissolution profile should be performed in the application/compendia medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs
Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer
media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and
120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

c. *In Vivo* Bioequivalence Documentation
None: if the situation does not meet the description in Case A, Case B or Case C, refer to Level 3 changes.

3. **Filing Documentation**
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Changes
1. **Definition of Level**
Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.

Examples:
a. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in SectionIII.A.1.b.
b. All other drugs not meeting the dissolution criteria under Section III.B.2.b.
c. Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed in Section III.A.1.b.
d. Changes in the excipient ranges of all drugs beyond those listed in Section III.B.1.b.

2. **Test Documentation**
a. Chemistry Documentation
Application/compendial release requirements and batch records.

Significant body of information available:
One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of information not available:
Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

b. Dissolution Documentation
Case B dissolution profile as described in Section III.B.2.b.

c. *In Vivo* Bioequivalence Documentation
Full bioequivalence study. The bioequivalence study may be waived with an acceptable *in vivo/in vitro* correlation has been verified.

3. **Filing Documentation**
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

SITE CHANGES
Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities and do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. Scale-up is addressed in Section V of this guidance. New manufacturing locations should have a satisfactory current Good Manufacturing Practice (CGMP) inspection.

A. Level 1 Changes
1. **Definition of Level**
Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.
2. **Test Documentation**
a. Chemistry Documentation
None beyond application/compendial release requirements.

b. Dissolution Documentation
None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence Documentation-None.

3. **Filing Documentation-**Annual report.

B. Level 2 Changes
1. **Definition of Level**
Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental

conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. **Test Documentation**

a. Chemistry Documentation
Location of new site and updated batch records. None beyond application/compendial release requirements.One batch on long-term stability data reported in annual report.

b. Dissolution Documentation
None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence Documentation-None.

3**. Filing Documentation**
Changes being effected supplement; annual report (longterm stability test data).

C. Level 3 Changes

1. **Definition of Level**
Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation, where needed.

2. Test Documentation

a. Chemistry Documentation
Location of new site and updated batch records. Application/compendial release requirements.
Stability:
Significant body of data available:
One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of data not available:
Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long- term stability data reported in annual report.

b. Dissolution Documentation
Case B: Multi-point dissolution profile should be performed in the application/compendia medium at 15, 30, 45, 60 and 120 minutes or until an

asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

c. *In Vivo* Bioequivalence Documentation-None.

3. **Filing Documentation**
Changes being effected supplement; annual report (long-term stability data).

CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)
Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate agency personnel.

A. Level 1 Changes

1. **Definition of Level**
Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP's; and 3) the same standard operating procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. **Test Documentation**

a. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records in annual report.One batch on long-term stability reported in annual report.
b. Dissolution Documentation
None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence-None.

3. **Filing Documentation-**Annual report (long-term stability data).

B. Level 2 Changes

1. **Definition of Level**
Changes in batch size beyond a factor of ten times the size of the pilot/biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP'S; and 3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

2. **Test Documentation**

a. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.
Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

b. Dissolution Documentation-Case B testing.

c. *In Vivo* Bioequivalence-None.

3. **Filing Documentation**
Changes being effected supplement; annual report (long-term stability data).

MANUFACTURING
Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment
1. Level 1 Changes

a. **Definition of Change**
This category consists of: 1) change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients; and 2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.

b. Test Documentation

i. Chemistry Documentation
Application/compendial release requirements.Notification of change and submission of updated batch records.
Stability testing: One batch on long-term stability.

ii. Dissolution Documentation
None beyond application/compendial release requirements.

iii. *In Vivo* Bioequivalence Documentation-None

.c. **Filing Documentation-**Annual report (long-term stability data).

2. Level 2 Changes

a. **Definition of Level**
Change in equipment to a different design and different operating principles.

b. **Test Documentation**

i. Chemistry Documentation
Application/compendial release requirements.Notification of change and submission of updated batch records.
Stability testing:
Significant body of data available:
One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of data not available:
Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

ii. Dissolution Documentation-Case C dissolution profile.

iii. *In Vivo* Bioequivalence Documentation-None.

c. **Filing Documentation**
Prior approval supplement with justification for change;
annual report (long-term stability data).

B. Process
1. Level 1 Changes

a. **Definition of Level**
This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.
b. **Test Documentation**

i. Chemistry Documentation
None beyond application/compendial release requirements.

ii. Dissolution Documentation
None beyond application/compendial release requirements.

iii. *In Vivo* Bioequivalence Documentation-None.

c. **Filing Documentation-**Annual report.

2. Level 2 Changes

a. **Definition of Level**
This category includes process changes including changes such as mixing times and operating speeds outside of application/validation ranges.

b. Test Documentation

i. Chemistry Documentation
Application/compendial release requirements. Notification of change and submission of updated batch records.

Stability testing: One batch on long-term stability.

ii. Dissolution Documentation-Case B dissolution profile.

iii. *In Vivo* Bioequivalence Documentation-None.

c. **Filing Documentation**
Changes being effected supplement; annual report (longterm stability data).

3. Level 3 Changes

a**. Definition of Level**
This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

b. Test Documentation

i. Chemistry Documentation
Application/compendial release requirements.Notification of change and submission of updated batch records.

Stability testing:
Significant body of data available:
One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Significant body of data not available:
Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

ii. Dissolution Documentation-Case B dissolution.

iii. *In Vivo* Bioequivalence Documentation
In vivo bioequivalence study. The bioequivalence study may be waived if a suitable *in vivo/in vitro* correlation has been verified.

c. **Filing Documentation**
Prior approval supplement with justification; annual report (long-term stability data).

***IN VITRO* DISSOLUTION**
See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12 individual dosage units.
Dissolution profiles may be compared using the following equation that defines a similarity factor (f2):
f2 = 50 LOG {[1+1/n (R-T)] x 100}
n 2 -0.5
t=1 t t
where Rt and Tt are the percent dissolved at each time point. An f2 value between 50 and 100 suggests the two dissolution profiles are similar.

IN VIVO BIOEQUIVALENCE STUDIES

Below is a general outline of an *in vivo* bioequivalence study. It is intended as a guide and the design of the actual study may vary depending on the drug and dosage form.

A. *Objective:*

To compare the rate and extent of absorption of the drug product for which the manufacture has been changed, as defined in this guidance, to the drug product manufactured prior to the change.

B. *Design:*

The study design should be a single dose, two-treatment, two-period crossover with adequate washout period between the two phases of the study. Equal numbers of subjects should be randomly assigned to each of the two dosing sequences.

C. *Selection of Subjects:*

The number of subjects enrolled in the bioequivalence study should be determined statistically to account for the intrasubject variability and to meet the current bioequivalence interval.

D. *Procedure:*

Each subject should receive the following two treatments:
Treatment 1: Product manufactured with the proposed change.
Treatment 2: Product manufactured prior to the proposed change.
Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 above with 240 mL water. Food should not be allowed until 4 hours after dosing. Water may be allowed after the first hour. Subjects should be served standardized meals beginning at 4 hours during the study.

E. *Restrictions:*

Prior to and during each study phase, water may be allowed *ad libitum* except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours prior to each study period and until
after the last blood sample is collected.

F. *Blood Sampling:*

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the Cmax and Tmax during the absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at -20oC or -70oC to maintain sample stability.

G. *Analytical Method:*

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery,

and stability of the samples under the storage and handling conditions associated with the analytical method.

H. *Pharmacokinetic Analysis:*
From the plasma drug concentration-time data, AUC0-t, AUC0-inf, Cmax, Tmax, Kel and t1/2 should be estimated.

I. *Statistical Analysis:*
Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC0-t, AUC0-inf, Cmax) should be calculated, using the two one-sided t-test procedure.

MODIFIED RELEASE ORAL SOLID DOSAGE FORMS:

COMPONENTS AND COMPOSITION — NONRELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in nonrelease controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release. The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3 (defined below), except as described below in Section III.A.1.a. Waiver of bioequivalence testing for a change in composition which involves only a different color, flavor or preservative may be permissible as described in 21 CFR
320.22(d)(4)

A. Level 1 Change

1. Definition of Level
Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Examples:
a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:
.The total additive effect of all nonrelease controlling excipient changes should not be more than 5%.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements.
Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation
None beyond application/compendial requirements
.
c. Bioequivalence documentation-None.

3. Filing Documentation
Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level
Level 2 changes are those that could have a significant impact on formulation quality and performance.
Example: Avicel PH102 vs. Avicel PH200
Examples:
a. A change in the technical grade and/or specifications of a nonrelease controlling excipient.3
b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, greater than those listed above for a level 1 change, but less than or equal to the following percent ranges (which represent a two-fold increase over level 1
changes): The total additive effect of all nonrelease controlling excipient changes should not change by more than 10%.

2. Test documentation

a. Chemistry documentation
Application/compendial product release requirements and updated executed batch records.
Stability: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is
reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed

by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.

Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15,30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendia dissolution testing need be performed (i.e., only in vitro release data by the correlating method need to be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation-None.

3**. Filing Documentation**
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level
Level 3 changes are those that are likely to have a significant impact on formulation quality and performance.
Example:
a. Changes in the nonrelease controlling excipient range beyond those listed in Section III.B.1.b. The total weight of the dosage form may be within or outside the approved original application range.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements and updated executed batch records.
Stability:
Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and longterm stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter, until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

COMPONENTS AND COMPOSITION — RELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in release controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether or not the excipient is critical to drug release. The sponsor should provide appropriate justifications (i.e., mechanism of drug release and manufacturing process) for claiming any excipient(s) as a release controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes exceeding the ranges defined in each of the levels below may be allowed if considered to be within normal batch-to-batch
variation and contained within an approved original application.

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A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Example:
a. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form.
The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements.
Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation
None beyond application/compendial requirements.

c. Bioequivalence documentation-None.

3. Filing Documentation
Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level
Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for a level 2 change would vary depending on whether the product could be considered to have a narrow therapeutic range.
Example: Eudragit RS-100 vs. Eudragit RL-100.
Examples:
a. Change in the technical grade and/or specifications of the release controlling excipient(s).
b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 1 change, but less than or equal to 10% w/w of total release controlling excipient content in the modified release solid oral dosage form.
The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition are based on the original approved target composition and not on the composition based on previous level 1 or level 2 changes. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements and updated executed batch records.
Stability:
! **Nonnarrow therapeutic range drugs:** One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual
report.
! **Narrow therapeutic range drugs**: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in
annual report.

b. Dissolution documentation

! Nonnarrow therapeutic range drugs
Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is
reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.
Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendia dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles

(i.e., for the unchanged drug product and the changed drug product)obtained in each individual medium is appropriate.

! Narrow therapeutic range drugs
Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained in application/compendial medium for the changed drug product and the
biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30,45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

! Nonnarrow therapeutic range drugs: None.
! Narrow therapeutic range drugs: A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation . Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level
Level 3 changes are those that are likely to have a significant impact on formulation quality and performance affecting all therapeutic ranges of the drug.
Examples:
a. Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer).
b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 2 change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form). Total weight of the dosage form may be within or outside the original approved application range.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements and updated executed batch records.

Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation
Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation
A single-dose bioequivalence study . The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation . Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

GUIDELINE FOR REST CHANGES ARE SAME AS FOR IR ORAL DOSAGE FORMS.

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