23.11.3 Choice of Agent

The ideal sterilant would have the following properties:

rapidly lethal against all micro-organisms, highly penetrative, non-aggressive to metals or polymers, rapid elimination of residues and harmless to humans.

A sterility assurance level of 10^6 of better should be achieveable. A variety of methods are available and include the use of ethylene oxide, formaldehyde, paracetic acid, hydrogen peroxide or chlorine dioxide.

The agent of choice will be determined by a number of and equipment-related factors. For pharmaceutical applications in isolators the sterilants in most general use are peracetic acid and hydrogen peroxide.

23.11.4 Gas Contact

To ensure their effectiveness, the sterilant vapours must be in contact with all contaminated surfaces. The following points should be considered:

* Equipment should be raised appreciably above worktops, and efforts made to provide point contact of supports.

* Components should not be laid on worktops or other solid surfaces. Wire baskets or racking can be utilised to approximate point contact support. Wherever possible, containers and components should be suspended farce point contacts (eg. wire hooks), to allow free circulation of sterilant around all items. If necessary components should be rotated or repositioned during processing to ensure all surfaces are exposed to the gaseous sterilant.

* Glove/gauntlet fingers should be fully extended, and supported well clear of the worktop in such a way that the glove/sleeve materials are not unduly folded.

Critical validation issues associated with the sterilisation process should include the concentration of the sterilent, uniform distribution of sterilent, contact times, temperature aeration post sterilisation, condensate remonvals and residue as well as the frequency of sterilisation.

23.11.5 Microbiological Validation

Biological indicators (BI) can be used to confirm the effectiveness of the selected conditions and standard patterns. The test organisms should be selected to represent a known challenge to the process. In practice Bacillus subtilis (var niger) is frequently used, at a concentration of 10^6 - 10^7 spores per strip.

Initial tests should concentrate on establishing approximate death curves for the test organism, and/or progressively increasing sterilant contact time until the target lethality is achieved. The process contact time and sterilant vapour concentration should then be selected to include an acceptable safety margin, which makes allowance also for the compatibility of equipment and with the sterilant. Once process conditions have been established, the cycle/loading pattern should be validated by performing replicate cycles, again using BI's in worst case positions. Positive controls should be performed and the recovery conditions verified. When some degree of occlusion is unavoidable such that the diffusion path of gas is greater than 1 or 2 ram, the actual lethality delivered can be investigated by direct inoculation of the surfaces and estimation of survivors. Positive controls should be used for other techniques and recovery conditions verified as being effective.

23.11.6 Routine Cycle Monitoring

The correct loading of the isolator prior to gassing should be the subject of properly documented control, and it is good practice for isolator access doors to be locked once correct loading has been checked. The gas generator's airflow and sterilant dispenser flow are often pre-set by the manufacturer, but if this is not the case their correct adjustment should also be formally documented. The generator should ideally allow these parameters, as well as sterilant injection time, to be recorded for each cycle, as happens with steam sterilisers. If the generator does not feature computer or chart recording of data, the parameters should be manually recorded at regular intervals, and documented for each cycle.

TABLE 3

DEFINITION OF AIR QUALITY CATEGORIES 1-V.
COMPARISON WITH EQUIVALENT INTERNATIONAL STANDARDS

CATEGORIES OF BACKGROUND ENVIRONMENT OF ISOLATOR	STANDARDS OF BACKGROUND ENVIRONMENT						NEAREST INTERNATIONAL STANDARDS				
	Particle Count (Particles M^{-3})				Viable Micro-organisms		European GMP	Current British Standard BS5295:1989	Previous British Standard BS5295:1976	US Federal Standard 209E	
	0,5uM	5 uM	10 uM	25 uM	Airborne viable count (colonies M^{-3})	Settle plate (colonies per plate)	GRADE	CLASS	CLASS	CLASS	
I	35	0			5	1 per 2 Plates	A	A	1	1	
	350	0					B	B		10	
	3,500	0						C	2	100	
	35,000	200						D		1,000	
	350,000	2,000	450				C	E	3	10,000	
II	3,500,000	20,000	4,500	500	50	5	D	F		100,000	
III	NS	200,000	45,000	5,000	100	10		G	4		
IV	NS	NS			500	50		H			
V	NS	NS			NS	NS		J			

CHAPTER 24

AEROSOLS & METERED DOSE INHALERS

24.1 PRINCIPLE

The manufacture of pressurized aerosol products for inhalation with metering valves requires special consideration because of the particular nature of this form of product. It should be done under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

24.2 GENERAL

24.2.1 There are presently two common manufacturing and filling methods as follows:

24.2.1.1 Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is put into the container, the valve crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

24.2.1.2 One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature, or both. The suspension is then filled directly into the container in one shot.

24.3 PREMISES AND EQUIPMENT

24.3.1 Manufacture and filling should be carried out as far as possible in a closed system.

24.3.2 Where products or clean components are exposed, the area should be fed with treated filtered air, and should be entered through airlocks.

24.3.3 Suitable systems should exist to determine required environment conditions and to monitor and control these conditions, e.g. temperature controls and propellant loss.

24.4 PRODUCTION AND QUALITY CONTROL

24.4.1 Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing should recognise this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

24.4.2 All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.

24.4.3 Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. Containers should be fed to the filling line in a clean condition or cleaned on line immediately before filling.

24.4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

24.4.5 When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition.

24.4.6 Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

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UPDATE HISTORY

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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

ADDENDUM 6

DISSOLUTION TESTING

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

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~ DISSOLUTION TESTING

1. INTRODUCTION

This guideline describes the setting of dissolution specifications as a quality control requirement and also describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing.

Although intrinsic dissolution of the active pharmaceutical ingredient (API) is an important consideration when formulating solid oral dosage forms, the dissolution behaviour of solid oral dosage forms provides important information to ensure drug product quality. Hence, dissolution testing has been established as an extremely valuable tool to monitor batch-to-batch consistency and the primary utility of a dissolution test is therefore to establish dissolution specifications for relevant drug products for the purposes of quality assurance.

Dissolution testing can also be useful in providing information on drug product quality following certain post-approval changes made to the product, such as changes in formulation, manufacturing process, site of manufacture and the scale-up of the manufacturing process. The various classes of changes where dissolution can be used in support of a bio-waiver are described in the MCC's document on major and minor changes.

In addition, where solid oral dosage forms have been proportionally formulated in different strengths and the drug follows linear kinetics, dissolution data can be used in support of a bio-waiver for lower strengths of such dosage forms provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

Drug absorption from oral dosage forms depends on adequate release of the active pharmaceutical ingredient (API) from the product. Physico-chemical factors such as dissolution or solubility of the drug under physiologic conditions and its permeability through the membranes of the gastrointestinal tract play pivotal roles in this respect. Due to the critical nature of these factors, dissolution of a drug product *in vitro* can, in certain instances, be relevant to anticipate the *in vivo* performance.

2. SETTING DISSOLUTION SPECIFICATIONS FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS

2.1 Objectives

i. To provide general recommendations for dissolution testing and setting dissolution specifications for quality control.

ii. To obtain information on test batches used in bioavailability/ bioeqivalence studies and pivotal clinical studies to support specifications for quality control.

iii. To be used as a tool in quality control to demonstrate batch-to-batch and lot-to-lot consistency during manufacture.

2.2 Dissolution Specifications

Primarily, *in vitro* dissolution specifications are used to ensure batch-to-batch consistency and to indicate potential problems of bioavailability.

i. For new drug products, dissolution specifications must be based on data obtained from acceptable clinical, pivotal bioavailability, and/or bioequivalence batches.

ii. In the case of multi-source pharmaceutical products the dissolution specifications are generally the same as the reference product.

These specifications should be confirmed by comparison of the dissolution performance of the multi-source pharmaceutical product and reference product from an acceptable bioequivalence study.

If the dissolution performance of the multi-source pharmaceutical product is substantially different from that of the reference product and the *in vivo* data remain acceptable, a different dissolution specification for the multi-source pharmaceutical product may be set.

iii. Once dissolution specifications are set, the drug product should comply with those specifications throughout its shelf life.

Setting dissolution specifications for multi-source pharmaceutical products may be classified in three categories as described below.

2.2.1 Drug Product Dissolution Test Available in an Acceptable Pharmacopoeia

In this instance the quality control dissolution test should be the test described in the BP, USP or EP. Use of any other pharmacopoeia must be justified and acceptable to the MCC.

It is recommended that a dissolution profile be generated by taking samples at 15-minute intervals or less using the specified pharmacopoeial method for test and reference products (12 units each).

Additional dissolution data may also be required when scientifically justified e.g. when the pharmacopoeia does not specify a dissolution test for all API's in a combination product.

2.2.2 Pharmacopoeial Drug Dissolution Test Not Available

Comparative dissolution testing using test and reference products under a variety of test conditions is recommended.

The test conditions may include different dissolution media (pH 1 to 6.8), addition of surfactant, or use of an official basket or paddle apparatus with varying agitation.

In all cases, profiles should be generated as previously recommended.

The dissolution specifications should be set based on available bioequivalence and other data. In addition, the method used must be justified and validated.

2.2.3 Special Cases.

For poorly water soluble drug products (e.g. glyburide), dissolution testing at more than one time point, and preferably a dissolution profile, is recommended for quality control purposes. Alternatively, the use of the USP apparatus 4 (Flow-Through Method) should be considered for the development of dissolution specifications for such products.

3 *IN VITRO* DISSOLUTION TESTING IN SUPPORT OF A BIO-WAIVER (Bioequivalence Surrogate Inference)

3.1 Immediate Release Drug Products with Class 1 API's

3.1.1 Objectives

To provide recommendations for requesting a waiver of *in vivo* bioequivalence studies for immediate release (IR) solid oral dosage forms where the API is classified as Class 1 according to the Biopharmaceutics Classification System (Reference 1).

3.1.2 Classification Criteria

In the Biopharmaceutics Classification System (BCS) an API is classified as having high or low solubility and high or low permeability.

i. An API is considered to be *highly soluble* when the highest dose strength is soluble in ≤250mL of aqueous buffer over the pH range of 1.0 to 8.0.

ii. An API is considered to be *highly permeable* when the extent of absorption in humans is determined to be greater than 90% of an administered dose in the absence of documented instability in the gastrointestinal tract, or whose high permeability has been determined experimentally (Reference 1) and reported in the literature.

According to the BCS, a Class 1 API is both *highly soluble* and *highly permeable*.

An immediate release (IR) dosage form can be classified as either rapidly or slowly dissolving and is considered *rapidly dissolving* when not less than 85% of the label amount of the API dissolves within 30 minutes using USP Apparatus 1 at 100rpm (or Apparatus 2 at 50rpm) in a volume of 900mL, or less, in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

3.1.3 Requirements for Bio-Waivers for Immediate Release Drug Products

When an immediate release drug product is *rapidly dissolving* and contains a Class 1 API i.e. the API is both *highly soluble* and *highly permeable*, a bio-waiver for the multi-source product may be granted on the basis of acceptable dissolution data.

Dissolution should be greater than 85% in 30 minutes in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

3.2 Proportionally Similar Dosage Forms

When a bio-waiver is requested for lower strengths of drug products which are proportionally formulated (see Guideline for Bioavailability and Bioequivalence....), the following dissolution testing is required:

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer
   - pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described below for each of the three media.

   Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

   An f_2 value $\geq$ 50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in □15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

iv. Dissolution data in support of bio-waivers for higher strength proportionally similar dosage forms will not normally be considered. However, is a successful biostudy was carried out on a lower strength for reasons of safety (see Guideline for Bioavailability and Bioequivalence....), then dissolution testing on higher strengths will be considered.

3.3 Comparison of a Foreign Reference Product with a Reference Product Registered and Marketed in South Africa

As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in South Africa.

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer

- pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described in section 3.4 for each of the three media.

Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

An f_2 value ≥50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in □15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

3.4 Comparison of Dissolution Profiles

A dissolution profile comparison may be carried out using a simple model independent approach to assess overall profile similarity as well as similarity or differences at each dissolution sample time point.

This approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Reference 2). The difference factor (f_1) calculates the (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |] / [\Sigma_{t=1}^{n} R_t]\}. 100$$

Where *n* is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t.
The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50. \log\{[1+ (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5}.100\}$$

A specific procedure to determine difference and similarity factor is as follows:

1. Determine the dissolution profile of two products (12 units each) of the test and reference products.

DISSOLUTION TESTING

2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, the f_1 values up to 15 (0 – 15) and f_2 values greater than 50 (50 – 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The following recommendations should also be considered:

1. The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both profiles should be the same (e.g., 15, 30, 45, 60 minutes).

2. Only one measurement should be considered after 85% dissolution of both the products.

3. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.

4 Dissolution Testing Requirements For Minor And Major Amendments To The Formulation Of Pharmaceutical Products And Related Manufacturing Procedures Including Their Site Of Manufacture.

When amendments are made to pharmaceutical products, manufacturing procedures and other associated processes including change of site their impact on quality must be demonstrated. The following describes the use of dissolution testing as an indicator of quality which may be applicable as describe below.

The following dissolution tests are recommended:

DISSOLUTION TESTING

4.1 Types of Dissolution Test

4.1.1 Case A Dissolution Testing

Dissolution testing should be conducted as a release test according to the original submission or in accordance with compendial requirements for that product.

4.1.2 Case B Dissolution Testing

Dissolution testing should be conducted as a multi-point test in the application/ compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached for the proposed and currently registered formulation.

4.1.3 Case C Dissolution Testing

Dissolution testing should be conducted as a multi-point test in water, 0.1N HCl and buffer at pH=4.5 and 6.8 for the proposed and currently registered formulations at 15, 30, 45, 60 and 120 minutes or until either 90% of drug from the drug product is dissolved or an asymptote is reached. In the case of poorly soluble drugs, comparisons can be made using alternative compendial methods and media that have been appropriately justified.

4.2 Types of Changes

4.2.1 Minor Changes

In the event that the minor change made is such that there is unlikely to be an effect on the quality and performance of a dosage form then Case A dissolution testing is appropriate.

4.2.2 Intermediate Changes

In the event that the changes made may have a significant impact on the quality and performance of a dosage form then Case B dissolution testing is appropriate. However if the change is made to a product containing a BCS class 1 compound then 85% must be dissolved in 15 minutes in the media used in the application or compendial requirements.

DISSOLUTION TESTING

For low permeability, high solubility drugs, dissolution profiles should be generated in the application/compendial medium as previously described for Case B dissolution testing. For high permeability, low solubility compounds, multi-point dissolution profiles should be carried out according to Case C dissolution testing.

Profiles of the currently used product and the proposed product should be proven similar according to the f_2 requirements as describe in this Guideline.

4.2.3 **Major Changes**

In the case of changes that are highly likely to have a significant impact on formulation quality and performance, *in vivo* bioequivalence testing must be conducted. Case B or Case C dissolution testing may also be required. Biowavers may be considered if a proven *in vitro-in vivo* correlation (IVIVC) has been shown.

5. REFERENCES

1. Guidance for Industry. Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

2. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 5

BIOAVAILABILITY AND BIOEQUIVALENCE DATA REQUIRED AS PROOF OF EFFICACY

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REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

BIOAVAILABILITY/BIOEQUIVALENCE

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1. INTRODUCTION

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies must be submitted with each application for the registration of a medicine.

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

Comparison of therapeutic performances of two pharmaceutical products containing the same active substance is a critical means of assessing the possibility of using either the innovator or a multi-source (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bicequivalence.

The objectives of this guideline are to:

i. Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.

ii. Provide guidance on the design and conduct of studies and the evaluation of data.

iii. Provide guidance when *in vitro* instead of *in vivo* data may be used.

iv. Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

2 DEFINITIONS

2.1 Active Pharmaceutical Ingredient (API)

A substance or compound used or intended to be used in the manufacture of a pharmaceutical product and which is expected to have a medicinal or pharmacological effect when administered.

2.2 Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

2.3 Pharmaceutical Equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in the product performance.

2.4 Therapeutic Equivalence

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

2.5 Bioavailability

Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

2.6 Bioequivalence

Bioequivalence is defined as the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may be used to demonstrate bioequivalence.

2.7 Pharmaceutical Dosage Form

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution etc.) suitable for administration to human and animal subjects.

2.8 Multi-Source (Generic) Pharmaceutical Product

Multi-source pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

2.9 Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

i. When all active pharmaceutical ingredients and inactive components are in exactly the same proportion between different strengths (e.g. a 100mg strength tablet has all active and inactive pharmaceutical ingredients exactly half of a 200mg strength tablet and twice that of a 50mg strength tablet).

ii. When the active and inactive ingredients are not in exactly the same proportion but the ratios of inactive pharmaceutical ingredients to the total weight of the dosage form are within the limits defined by the Guideline for Major and Minor Amendments.

iii. When the pharmaceutical products contain high potency active pharmaceutical ingredients and these products are of different strengths but are of similar weight.

The difference in API content between strengths may be compensated for by weight changes in one or more of the inactive pharmaceutical excipients provided that the total weight of the pharmaceutical product remains within 10% of the weight of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same inactive pharmaceutical excipients must be used for all strengths, provided that the changes remain within the limits defined by the Guideline for Major and Minor Amendments.

Exceptions to the above definitions may be considered provided justification is submitted.

BIOAVAILABILITY/BIOEQUIVALENCE

3. DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as parallel designs for very long half-life substances could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required and must be justified.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80% is covered before 72 hours.

For immediate release dosage forms, studies must be done under fasting conditions, unless food effects influence bioavailability. If the dosage directions specifically state administration with food, both fed and fasted studies are required. For modified release dosage forms the influence of food must be demonstrated to exclude any possibility of dose dumping, hence both fed and fasted studies are required.

3.2 Subjects

3.2.1 Number of Subjects

It is recommended that the number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria.