Utilization of Dissolution in Regulating Dose Proportional Formulations

A comparison of different regulatory approaches

Prof.Dr. A.Atilla HINCAL
IDE Pharmaceutical Consultancy Ltd Co
Founder & General Manager
Professor Emeritus, Hacettepe University, Ankara, TR

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Presentation Overview

- *Introduction*
- *Proportionality related informations in the different guidelines and some examples :*
  - i. **EU :** EMA: CPMP/EWP/QWP
    Example: For a proportional product *"Public Assesment Report Decentralised Procedure/UK/H"*
  - ii. **USA :** CFR - DHHS - FDA - CDER
  - iii. **WHO :** Technical Report
  - iv. **Canada:** HC
  - v. **South Africa:** SDAC
- *Conclusion*

Introduction

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INTRODUCTION

- 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* characteristics/results.

INTRODUCTION

Dissolution testing can serve several purposes

a) Quality assurance

- To get information on the test batches used in BA/BE studies and pivotal clinical studies to support specifications for quality control
- To be used as a tool in quality to demonstrate consistency in manufacture
- To get information on the reference product used in BA/BE studies and pivotal clinical studies (same for the proportionality of different strenghts)

INTRODUCTION

Dissolution testing can serve several purposes

b) Bioequivalence surrogate inference

- To demonstrate similarity between reference products from different member states
- To demonstrate similarities between different formulations of an active substance and the reference medicinal product
- To collect information on batch to batch consistency of the products to be used as basis for the selection of appropriate batches for the in vivo study

INTRODUCTION

Levodopa/Carbidopa/Entacapone Combination Products

Public Assesment Report - Decentralised Procedure/UK/H/5568/001-006/DC

	Different Strengths Combination Product	Proportionality
1	50 mg/ 12.50 mg/ 200 mg film coated tablets	4/1/fixed quantity
2	75 mg/ 18.75 mg/ 200 mg film coated tablets	4/1/fixed quantity
3	100 mg/ 25.00 mg/ 200 mg film coated tablets	4/1/fixed quantity
4	125 mg/ 31.25 mg/ 200 mg film coated tablets	4/1/fixed quantity
5	150 mg/ 37.50 mg/ 200 mg film coated tablets	4/1/fixed quantity
6	200 mg/ 50.00 mg/ 200 mg film coated tablets	4/1/fixed quantity

Proportionality Related Informations in the Different Guidelines and Some Examples

European Medicines Agengy

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE, EMA,London, 20 January 2010 Doc. Ref.: CPMP / EWP / QWP / 1401 / 98 Rev. 1 / Corr **

4. Main Guideline Text

4.1 Design, Conduct and Evaluation of BE studies

- The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths (see sections 4.1.4, 4.1.5 and 4.1.6).

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

4. Main Guideline Text

4.1 Design, Conduct and Evaluation of BE studies

4.1.6. Strength to be investigated

- If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below.
- The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.
- In case of non-linear pharmacokinetics (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations.

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

4.1.6. Strength to be investigated

- In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered. In order to assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically. Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%.
- If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, *in vivo* bioequivalence studies for the other strength(s) can be waived.

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

4.1.6. Strength to be investigated

General biowaiver criteria

The following general requirements must be met where a waiver for additional strength(s) is claimed:

a. the pharmaceutical products are manufactured by the same manufacturing process,

b. the qualitative composition of the different strengths is the same,

4.1.6. Strength to be investigated

General biowaiver criteria

- c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
- If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) **or** i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

4.1.6. Strength to be investigated

General biowaiver criteria

i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content

ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed

iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing (see section 4.2).

4.1.6. Strength to be investigated

Linear pharmacokinetics (11)

- For products where all the above conditions a) to d) are fulfilled, it is sufficient to establish bioequivalence with only one strength.
- The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble (see Appendix III), selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Further, if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration of the highest strength, a higher dose may be selected (preferably using multiple tablets of the highest strength). The selected dose may be higher than the highest therapeutic dose provided that this single dose is well tolerated in healthy volunteers and that there are no absorption or solubility limitations at this dose.

4.1.6. Strength to be investigated

Non-linear pharmacokinetics

- For drugs with non-linear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the BE study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above.
- For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or a strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that conditions a) to d) above are fulfilled and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength in the linear range).

4.2. In vitro dissolution tests

- General aspects of *in vitro* dissolution experiments are briefly outlined in Appendix I including basic requirements how to use the similarity factor (*f2*-test).

4.2.1. *In vitro* dissolution tests complementary to bioequivalence studies

- The results of *in vitro* dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

4.2. In vitro dissolution tests

4.2.1. *In vitro* dissolution tests complementary to bioequivalence studies

- Unless otherwise justified, the specifications for the *in vitro* dissolution to be used for quality control of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product (see Appendix I).
- In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails. However, possible reasons for the discrepancy should be addressed and justified

4.2.2. In vitro dissolution tests in support of biowaiver of strengths

- Appropriate *in vitro* dissolution should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous section (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of *in vitro* dissolution (see App. I) should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) [i.e. batch(es)] used for bioequivalence testing.

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

APPENDIX I

Dissolution testing and Similarity of Dissolution Profiles

1.General aspects of dissolution testing as related to bioavailability

- Testing on product quality
- Bioequivalence surrogate inference

2.Similarity of dissolution profiles

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE,

EMA,London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

- **APPENDIX III**
- **IV.Drug Product**
  - *IV.2 Excipients*
- **Fixed Combinations (FCs)**
- BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I or III and the excipients fulfil the requirements outlined in section IV.2. Otherwise *in vivo* bioequivalence testing is required.

Public Asses Report - Decentralised Procedure/UK/H/5568/001-006/DC

Example: Levodopa/Carbidopa/Entacapone Proportional Combination Products

	Different Strengths Combination Products	Proportionality
1	50 mg/ 12.50 mg/ 200 mg film coated tablets	4/1/fixed quantity
2	75 mg/ 18.75 mg/ 200 mg film coated tablets	4/1/fixed quantity
3	100 mg/ 25.00 mg/ 200 mg film coated tablets	4/1/fixed quantity
4	125 mg/ 31.25 mg/ 200 mg film coated tablets	4/1/fixed quantity
5	150 mg/ 37.50 mg/ 200 mg film coated tablets	4/1/fixed quantity
6	200 mg/ 50.00 mg/ 200 mg film coated tablets	4/1/fixed quantity

Compositions of entacapone/levodopa/carbidopa 200/100/25 mg tablet formulations *(in the first pilot absorption study)*

Name of ingredient	**Formulation 1** (wet granulation, all in one)	**Formulation 2** (compaction granul. all in one)
	mg/Tablet	**mg/tablet**
Entacapone	200.0	200.0
Levodopa	100.0	100.0
Carbidopa monohydrate	27.0	27.0
Microcrystalline cellulose	75.0	180.0
Macrogol. 6000	-	90.0
Maize Starch	75.0	-
Sodium starch glycolate	27.0	-
Croscarmellose sodium	-	30.0
Povidone	36.0	-
Microcrystalline cellulose	49.2	-
Colloidal silicon dioxid	1.8	-
Magnesium stearate	9.0	13.0
Theoretical weight of the core tablet	*600.0*	*640.0*
Coating	*HPMC-coating containing color pigments*	*HPMC-coating containing color pigments*
Theoretical weight of the coated table	*619.5*	*660.0*
Manufacturing of granules	*All the active substances were high shear granulated together*	*All the active substances were high shear granulated together*

Compositions of entacapone/levodopa/carbidopa 200/100/25mg tablet formulations (*separate carbidopa in the formulations*).

Name of ingredient	Formulation 3 mg	Formulation 4 mg
Entacapone	200.0	200.0
Levodopa	100.0	100.0
Carbidopa monohydrate	27.0	27.0
Maize Starch	85.0	75.0
Mannitol	86.1	44.0
Croscarmellose sodium	23.7	20.0
Povidone	39.7	36.0
Magnesium stearate	8.5	8.0
Theoretical weight of the core tablet	*570.0*	*510.0*
HPMC-coating containing colour pigments	*17.0*	*15.0*
Theoretical weight of the coated tablet	*587.0*	*525.0*

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A formulation of entacapone/levodopa/carbidopa in amounts of 200mg/100mg/10mg

Name of ingredient	Formulation 5	Formulation 6
	mg	mg
Entacapone	200.0	200.0
Levodopa	150.0	50.0
Carbidopa monohydrate	40.5	13.5
Maize starch	105.0	65.0
Mannitol	113.0	59.5
Croscarmellose sodium	28.5	17.7
Povidone	46.6	31.9
Magnesium stearate	10.5	6.5
Core weight	694	444

Core tablets are coated with colored HPMC-coating to the weight gain of 2-3%.

INGREDIENT	PROPORTIONAL STRENGTH FORMULATIONS' DEVELOPMENT STUDIES (mg/tablet)					
	1	**2**	**3**	**4**	**5**	**6**
Entacapone	200.0	200.0	200.0	200.0	200.0	200.0
Levodopa	100.0	100.0	100.0	100.0	150.0	50.0
Carbidopa monohydrate	27.0	27.0	27.0	27.0	40.5	13.5
Microcrystalline cellulose	75.0	180.0	--	--	--	--
Macrogol. 6000	--	30.0	--	--	--	--
Maize Starch	75.0	--	85.0	75.0	105.0	65.0
Mannitol	--	--	86.1	44.0	113.0	59.5
Sodium starch glycolate	27.0	--			--	--
Croscarmellose sodium	--	30.0	23.7	20.00	28.5	17.7
Povidone	36.0	--	39.7	36.0	46.6	31.9
Microcrystalline cellulose	49.2	--	--	--	--	--
Colloidal silicon dioxid	1.8	--	--	--	--	--
Magnesium stearate	9.0	13.0	8.5	8.0	10.5	6.5
Theoretical weight of the core tablet	600.0	640.0	570.0	510.0	694	444
Coating	*	*	17.0	15.0	*	*
Theoretical weight of the coated table	619.5	660.0	587.0	525.0	2-3%	2-3%

INGREDIENT	PROPORTIONAL STRENGTH FORMULATIONS' DEVELOPMENT STUDIES (mg/tablet)								
	1	2	3	4	5	6	7	8	9
Entacapone	200.0	200.0	200.0	200	200	200	200	200	200
Levodopa	150.0	100.0	50.0	150	100	50	150	100	50
Carbidopa monohydrate	40.5 (37.5)	27.0 (25.0)	13.5 (12.5)	37.5	25.0	12.5	37.5	25.0	12.5
Microcrystalline cellulose	--	--	--	--	--	--			
Macrogol. 6000	--	--	--	--	--	--			
Maize Starch	105.0	75.0	65.0	105.0	70.0	35.0	195.0	130.0	65.0
Mannitol	113.0	44.0	59.5	113.0	75.3	37.7	178.5	119.0	59.5
Sodium starch glycolate	--		--	--	--	--	--	--	--
Croscarmellose sodium	28.5	20.0	17.7	28.5	19.0	9.5	53.1	35.4	17.7
Povidone	46.6	36.0	31.9	46.6	31.1	15.5	95.7	63.8	31.9
Microcrystalline cellulose	--	--	--	--	---	--	--	--	--
Colloidal silicon dioxid	--	--	--	--	--	--	--	--	--
Magnesium stearate	10.5	8.0	6.5	10.5	7.0	3.5	19.5	13.0	6.5
Core tablet theor Weight	694,0	510.0	444.0	691.1	527.4	363.4	929.3	686.2	443.1
Coating	*	15.0	*						
Theoretical weight of the coated table	2-3%	525.0	2-3%						

U.S.
Department of Health and Human Services (DHHS)
Food and Drug Administration (FDA),
Center for Drug Evaluation and Research (CDER)

U.S. Department of Health and Human Services(DHHS);Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Related Guidences

- CFR (Code of Federal Regulations) Title 21, Volum 5, april 1, 2014, 21CFR320.22
- Guidance for Industry;Dissolution Testing of Immediate Release Solid Oral Dosage Forms; U.S. DHHS;FDA; Center for Drug Evaluation and Research (CDER); (CDER);August 1997;BP 1
- Guidance for Industry; Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation; U.S. DHHS;FDA; Center for Drug Evaluation and Research (CDER); (CDER) November 1995 CMC 5
- Guidance for Industry; Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System; *DRAFT GUIDANCE ;* U.S. DHHS;FDA; (CDER);(CDER), May 2015 Biopharmaceutics Revision 1
- Guidance for Industry; BE studies with PK endpoints for drugs submitted under an ANDA; U.S. DHHS;FDA; (CDER);(CDER), December 2013, Biopharmaceutics
- Guidance for Industry ; Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations, *DRAFT GUIDANCE;* U.S. DHHS;FDA; Center for Drug Evaluation and Research (CDER);(CDER); March 2014 Biopharmcaeutics
- Guidance for Industry; SUPAC-MR: Modified Release Solid Oral Dosage Forms;Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation;U.S. DHHS;FDA; Center for Drug Evaluation and Research (CDER);September 1997 ;CMC 8

CFR (Code of Federal Regulations) Title 21, Volum 5, april 1, 2014, 21CFR320.22

PART 320 -- BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Subpart B--Procedures for Determining the Bioavailability or Bioequivalence of Drug Products Sec. 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in 320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (f) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

CFR (Code of Federal Regulations) Title 21, Volum 5, april 1, 2014, 21CFR320.22

(d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

i. The bioavailability of this other drug product has been measured;

ii. Both drug products meet an appropriate in vitro test approved by FDA; and

CFR (Code of Federal Regulations) Title 21, Volum 5, april 1, 2014, 21CFR320.22

iii. The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

iv. Paragraph (d) of this section does not apply to delayed release or extended release products.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the BA of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

CFR (Code of Federal Regulations) Title 21, Volum 5, april 1, 2014, 21CFR320.22

(i) The BA of the other product has been measured; and

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo BA or BE if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo BA if deferral is compatible with the protection of the public health.

(f) FDA, for good cause, may require evidence of in vivo BA or BE for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the BA or BE of the drug product.

[57 FR 17998, Apr. 28, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

USA-FDA Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER August 1997

IV.Setting Dissolution Specifications

Dissolution profile comparison

1. For accepting product sameness under SUPAC-related changes,

2. To waive bioequivalence requirements for lower strengths of a dosage form,

3. To support waivers for other bioequivalence requirements.

In the future, a two-time point approach may be useful, both to characterize a drug product and to serve as quality control specification.

USA-FDA Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER August 1997

V. DOCUMENTATION OF BA AND BE

An in vivo study is generally recommended for all solid oral dosage forms approved after 1962 and for *bioproblem* drug products approved before 1962. Waiver of in vivo studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) *the drug product is in the same dosage form, but in a different strength;* (2) *this different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and* (3*) the new strength meets an appropriate in vitro dissolution test.*

This guidance defines *proportionally similar* in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, exactly half that of a tablet of 100-mg strength, and twice that of a tablet of 25-mg strength).

USA-FDA Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER August 1997

V. DOCUMENTATION OF BA AND BE

- Active and inactive ingredients are not in exactly the same proportion between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
- For high potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ± 10 % of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
- Exceptions to the above definitions may be possible, if adequate justification is provided.

USA-FDA Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER August 1997

VII.BIOWAIVERS

- In addition to routine quality control tests, comparative dissolution tests have been used to waive bioequivalence requirements (biowaivers) for lower strengths of a dosage form. For biowaivers, a dissolution profile should be generated and evaluated using one of the methods described under Section V in this guidance, "Dissolution Profile Comparisons." Biowaivers are generally provided for multiple strengths after approval of a bioequivalence study performed on one strength, using the following criteria:
  - *For multiple strengths of IR products with linear kinetics, the bioequivalence study may be performed at the highest strength and waivers of in vivo studies may be granted on lower strengths, based on an adequate dissolution test, provided the lower strengths are proportionately similar in composition (21 CFR 320.22(d)(2)). Similar may also be interpreted to mean that the different strengths of the products are within the scope of changes permitted under the category "Components and Composition," discussed in the SUPAC-IR guidance. In all cases, the approval of additional strengths is based on dissolution profile comparisons between these additional strengths and the strength of the batch used in the pivotal bioequivalence study.*

FDA Guidance for Industry Immediate Release Solid Oral Dosage Forms, Center for Drug Evaluation and Research (CDER), November 1995 (Level 1)

Type of Excipient	Percent Excipient (W/W) out of total target dosage form weight
Fillers	±5.00
Disintegrants	
Starch	±3.00
Others	±1.00
Binders	±0.50
Lubricants	
Calcium or Magnesium stearate	±0.25
Others	±1.00
Glidants	
Talc	±1.00
Others	±0.10

Immediate-Release Products: Capsules and Tablets

General Recommendations

- For product quality BA and BE studies, we recommend that where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study be performed. We also recommend that in vivo BE studies be accompanied by in vitro dissolution profiles on all strengths of each product.
- For ANDAs, we also recommend that the BE study be conducted between the test product and reference listed drug using the strength(s) specified in *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*.
- *Waivers of In Vivo BE Studies (Biowaivers)*
  - INDs, NDAs, and ANDAs: Preapproval
- When the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BA or BE testing has been conducted, an in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength.

Immediate-Release Products: Capsules and Tablets

General Recommendations

- For an NDA, biowaivers of a higher strength will be determined to be appropriate based on (1) clinical safety and/or efficacy studies including data on the dose and the desirability of the higher strength, (2) linear elimination kinetics over the therapeutic dose range, (3) the higher strength being proportionally similar to the lower strength, and (4) the same dissolution procedures being used for both strengths and similar dissolution results obtained. We recommend that a dissolution profile be generated for all strengths.
- If an appropriate dissolution method has been established (see section III.D.), and the dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength, then dissolution profiles in one medium are usually sufficient to support waivers of in vivo testing. Otherwise, dissolution data in three media (pH 1.2, 4.5, and 6.8) are recommended.

World Health Organization

Technical Report

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

9.3 Biowaivers based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

9.3.1 Proportionally similar formulations

- For the purpose of this guidance proportionally similar formulations can be defined in two ways, based on the strength of dosage forms.
  - All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has all the active and inactive ingredients exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

- For a high potency API, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit), the total weight of the dosage form remains nearly the same for all strengths (within ± 10% of the total weight), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering essentially only the amount of the API(s).

9.3.2 Qualification for biowaiver based on dose-proportionality of formulations

- A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the multisource product at one strength has been shown in in vivo studies to be bioequivalent to the corresponding strength of the comparator product. The second requirement is that the further strengths of the multisource product are proportionally similar in formulation to that of the strength studied.

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability”

- When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to that of the strength studied on a percentage released against time basis, the biowaiver procedure can be considered for the further strengths.
- As in the case of biowaivers based on the BCS, a biowaiver based on dose-proportionality of formulations should be considered only when there is an acceptable benefit–risk balance in terms of public health and risk to the individual patient, as discussed in section 9.2.

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"

9.3.3 Dissolution profile comparison for biowaivers based on dose-proportionality of formulations

- As for biowaivers based on the BCS, a model independent mathematical approach (e.g. F_2 test) can be used for comparing the dissolution profiles of two products. The dissolution profile of the two products (multisource test) and comparator (reference)) should be measured under the same test conditions.
- The dissolution sampling times for both multisource and comparator product profiles should be the same:
  - *for example for immediate-release products 10, 15, 20, 30, 45 and 60 minutes;*

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"

- *for example for 12 hour extended-release products 1, 2, 4, 6 and 8 hours; and*
- *for example for 24 hour extended-release products 1, 2, 4, 6, 8 and 16 hours.*
- *Only one time-point should be considered after 85% dissolution from the comparator product.*

- An f_2 value of 50 or greater (50–100) reflects equivalence (less than 10% difference) of the two curves, and thus equivalence of in vitro performance of the two products. To allow the use of the mean data, the coefficient of variation should not be more than 20% at the earliest time-point (e.g. 10 minutes in the case of the example given for im- mediate-release products), and should not be more than 10% at other time-points.

WHO Technical Report Series No 937, 2006, Annex 7, Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"

9.3.3.1 Immediate-release tablets

- Different strengths of a multisource formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:
  - » *all strengths are proportionally similar in formulation (see definition above);*
  - » *an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength, unless a lower strength is chosen for reasons of safety); and*
  - » *the dissolution profiles for the different strengths are similar.*

- As for the biowaiver based on BCS, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended
- in section 9.2, the profile comparison with an f test is unnecessary.

CANADA

HEALTH CANADA

Health Canada Policy Issue - From the Drugs Directorate
Bioequivalence of Proportional Formulations : Solid Dosage Forms

Excipient type	Difference in percent of core weight
Filler	5 %
Disintegrant	
Starch	3%
Other	1 %
Binder	0.5 %
Lubricant	
Ca or Mg stearate	0.25 %
Other	1 %
Glidant	
Talc	1 %
Other	0.1 %

Table 7 The proportion of each ingredient is calculated as a percentage (w/w) of the total core weight. Therefore the percentages shown in Table 9 for excipients (in an example of a range of proportional formulations) are calculated as:
(Weight of excipient/total core weight) X 100

Health Canada Policy Issue - From the Drugs Directorate
Bioequivalence of Proportional Formulations : Solid Dosage Forms

Strength	25 mg		50 mg		100 mg	
	mg	%	mg	%	mg	%
Drug	25	25	50	25	100	25
Excipient 1	40	40	80	40	160	40
Excipient 2	25	25	50	25	100	25
Excipient 3	3.5	3.5	7	3.5	14	3.5
Excipient 4	3.0	3	6	3	12	3
Excipient 5	3.5	3.5	7	3.5	14	3.5
TOTAL	100	100	200	100	400	100

Health Canada Policy Issue - From the Drugs Directorate
Bioequivalence of Proportional Formulations : Solid Dosage Forms

- If different strengths have differences in the proportion of ingredients which exceed those in Table , but within the progression of strengths the changes are incremental, a comparative bioavailability study is required on the lowest and highest strengths. Incremental changes are those in which proportions of ingredients increase or decrease successively from the lowest to the highest strengths in the range.
- If different strengths contain different ingredients, or if the differences between formulations exceed those defined in Table and are not incremental within the progression of strengths, comparative bioavailability studies are required on each different formulation.

South Africa
Southern African Development Center
(SDAC)

SADC GUIDELINE FOR BIOAVAILABILITY AND BIOEQUIVALANCE 2007

- **3.10 Proportionally Similar Dosage Forms/Products**
- Pharmaceutical products are considered proportionally similar in the following cases:
- 3.10.1 When all APIs and inactive pharmaceutical ingredients (IPIs) are in exactly the same proportion between different strengths (e.g. a 100 mg strength tablet has all API and IPIs exactly half of a 200 mg strength tablet and twice that of a 50 mg strength tablet).
- 3.10.2 When the active and inactive ingredients are not in exactly the same proportion but the ratios of IPIs to the total mass of the dosage form are within the limits defined by the Post-registration amendment guideline.
- 3.10.3 When the pharmaceutical products contain high potency APIs and these products are of different strengths but are of similar mass.

SADC GUIDELINE FOR BIOAVAILABILITY AND BIOEQUIVALANCE 2007

WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

6.1.2 Different Strength Dosage Forms

- When the drug product is the same dosage form but of a different strength and is proportionally similar (section 2.9 of this guideline) in its API and IPIs, a biowaiver may be acceptable.
- Dissolution profiles are required for all strengths. The f2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f2 value ??50 indicates a
- sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f2 value < 50, it may be necessary to conduct an *in vivo* study. The difference factor, f1, should also be submitted but will not be used as an acceptance criterion (Reference 6).

SADC GUIDELINE FOR BIOAVAILABILITY AND BIOEQUIVALANCE 2007

- **WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES**
- **a) Lower strength** dosage forms
- The demonstration of bioequivalence *in vivo* of one or more of the lower strength(s) may be waived based on dissolution tests (Appendix 2) and an *in vivo* study on the highest strength.
- **b) Higher strength** dosage forms
- Conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength if an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

SADC GUIDELINE FOR BIOAVAILABILITY AND BIOEQUIVALANCE 2007

- **WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES**
- **i) Multisource pharmaceutical products**
- - Linear elimination kinetics has been shown over the therapeutic dose range.
- - The higher strength is proportionally similar to the lower strength.
- - Comparative dissolution on the higher strength of the test and reference products is similar

SADC GUIDELINE FOR BIOAVAILABILITY AND BIOEQUIVALANCE 2007

- **WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES**
- **ii) New Chemical Entities**
- - Clinical safety and/or efficacy studies including dose desirability of the higher strength,
- - linear elimination kinetics over the therapeutic dose range,
- - the higher strength being proportionally similar to the lower strength, and
- - the same dissolution procedures being used for both strengths and similar dissolution results obtained.

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WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

6.2 MODIFIED RELEASE PRODUCT

6.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods described in Appendix 2.

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WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

6.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

a) in the same dosage form but in a different strength, and

b) is proportionally similar in its active and inactive ingredients, and

c) has the same drug release mechanism, an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

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WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

6.2.2 Tablets – Lower strength, *cont'd*

- For sections 5.2.1 and 5.2.2 above, the f2 factor should be used to compare profiles from the different strengths of the product. An f2 value of >50 can be used to confirm that further *in vivo* studies are not needed (Appendix 2).
- The difference factor, f1, should also be submitted but will not be used as an acceptance criterion.

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- **APPENDIX 1**

INTRODUCTION

- 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. 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 biowaiver for lower strengths of such dosage forms, provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

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- ***IN VITRO* DISSOLUTION TESTING IN SUPPORT OF A BIOWAIVER**
- **(Bioequivalence Surrogate Inference)**
- When a biowaiver is requested for lower strengths of drug products which are proportionally formulated, the following dissolution testing is required:
- a) Dissolution of test and reference products should be conducted in each of the following three media:

  · acidic media such as 0,1 N HCl

  · pH 4,5 buffer

  · pH 6,8 buffer

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Biowaivers will be considered under the circumstances detailed below.

- IMMEDIATE RELEASE PRODUCTS
- ……..

- The API is uncomplicated, i.e. it does not exhibit any of the following:
  - A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
  - A steep dose-response relationship.
  - A risk of serious undesired effects.
  - Complicated or variable pharmacokinetics, e.g.:
    - » non linear pharmacokinetics,
    - » variable or incomplete absorption,
    - » an absorption window, i.e. site-specific absorption,
    - » substantial first-pass metabolism (>40 %), or
    - » an elimination half-life of 24 hours or more.

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WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Biowaivers will be considered under the circumstances detailed below.

- IMMEDIATE RELEASE PRODUCTS

- ……..
- In the case of multisource products, the reference product should be a conventional, immediate- release oral dosage form and the test and reference products should exhibit similar dissolution profiles.
- Dosage forms should not be intended for absorption in the oral cavity, e.g. sublingual or buccal tablets.
- BCS base biowaivers are intended only for BE studies. They do not apply to food effect BA studies or similar pharmacokinetic studies.
- The reference product should be a conventional, immediate-release oral dosage form.

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Different Strength Dosage Forms

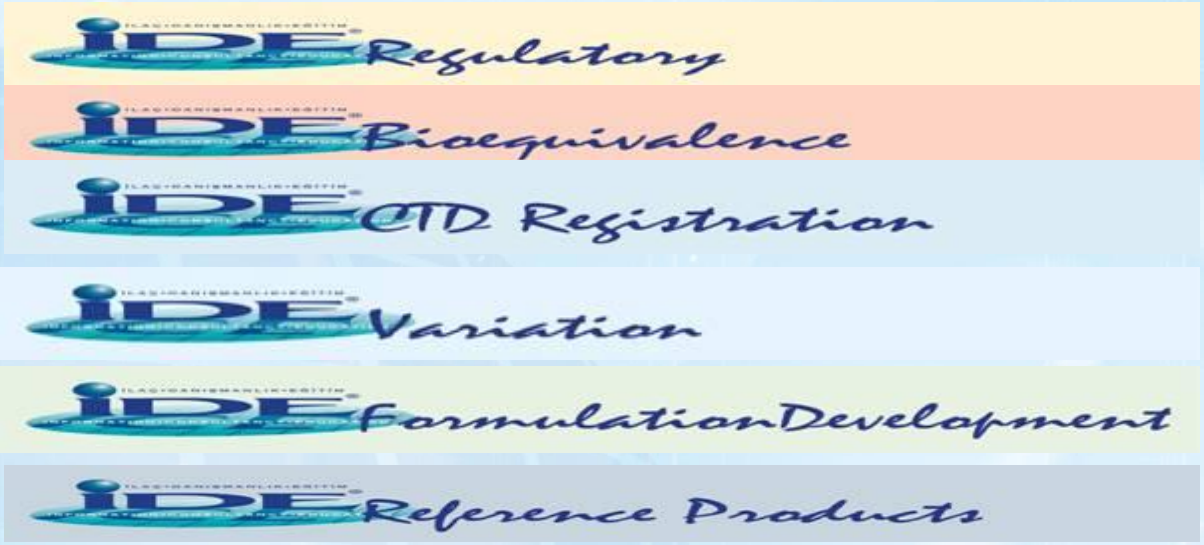
- When the drug product is the same dosage form but of a different strength and is proportionally similar (section 2.9 of this guideline) in its API and IPIs, a biowaiver may be acceptable.
- Dissolution profiles are required for all strengths. The f2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f2 value more than 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f2 value lower than 50, it may be necessary to conduct an *in vivo* study. The difference factor, f1, should also be submitted but will not be used as an acceptance criterion .

Conclusion

Conclusion

- Different Guidelines gave the similar approaches and informations.
- Some of the guidelines can be helpfull to the researchers working in this field with some detail in them.
- It can be understood that the formulators dealing with combination products must pay attention in advance to the combinations that will have or not different strenghts and than the formulators must pay special attention to the proportionalities of th different strenghts which must be within the guidelines acceptance limits.

THANK YOU FOR YOUR ATTENTION



e.mail: atilla.hincal@ide-cso.com