Biowaiver and Dissolution Profile Comparison

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Biowaiver

Outline:

1. Introduction
2. Biopharmaceutics Classification System (BCS)
3. Methodology
4. Dissolution profile comparison
5. Request for biowaivers (Thai FDA)

Introduction

- Biowaivers are waivers of clinical bioequivalence studies
- Save time and cost compared to clinical trials
- FDA, EMA, PMDA, WHO

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
BP

www.fda.gov/cder/guidance

WHO Technical Report Series, No. 937, 2006

Annex 8

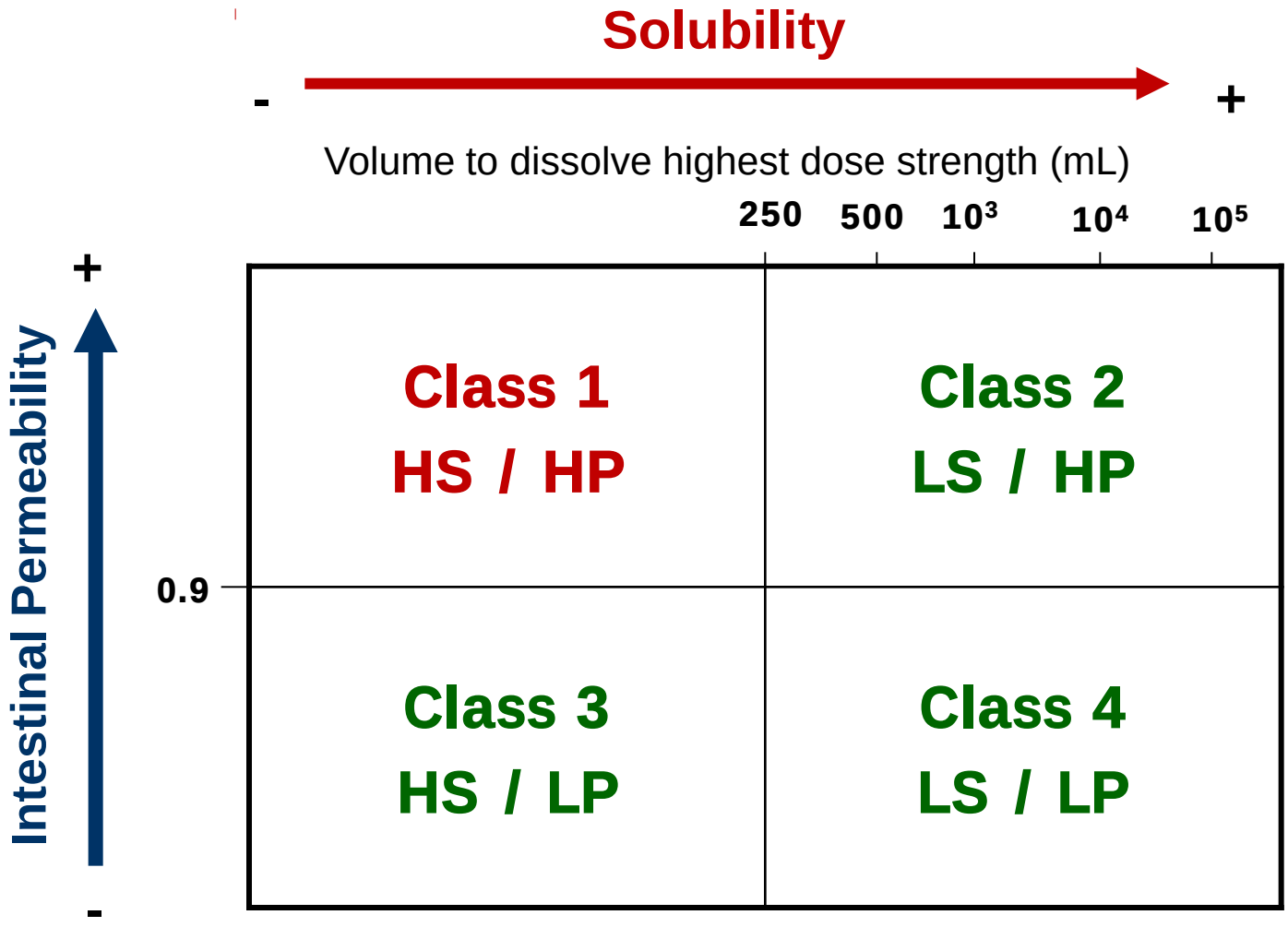
Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms

www.who.int

Biopharmaceutics Classification System (BCS)

- based on aqueous solubility and intestinal permeability
- 3 factors governing the rate and extent of drug absorption from IR products
    1. Solubility
    2. Intestinal permeability
    3. Dissolution

Biopharmaceutics Classification System (BCS)



Criteria for Classification

1. **Solubility**

- Highly soluble: highest dose strength is soluble in ≤ 250 mL aqueous media over a pH range of 1-7.5, 37 ± 1°C

2. **Permeability**

- Highly permeable: extent of absorption in humans ≥ 90 %

3. **Dissolution (3 media)**

- Rapidly dissolving: NLT 85 % la. dissolves in 30 min
- Very rapidly dissolving: NLT 85 % la. dissolves in 15 min

Criteria for Classification

1. **Solubility**

- Highly soluble: highest dose strength is soluble in ≤ 250 mL aqueous media over a pH range of 1-7.5 (1.2 – 6.8), 37 ± 1°C

2. **Permeability**

- Highly permeable: extent of absorption in humans ≥ 90% (85%)

3. **Dissolution (3 media)**

- Rapidly dissolving: NLT 85% la. dissolves in 30 min
- Very rapidly dissolving: NLT 85% la. dissolves in 15 min

Methodology

1. **Solubility class**

- pH-solubility profile of the test drug substance at 37 ± 1°C in aqueous media pH 1-7.5
- pH = pKa, pKa + 1, pKa – 1
- shake-flask method
- using validated stability-indicating assay

Methodology

2. Permeability class

- **PK studies in humans**

  Mass balance

  Absolute bioavailability studies

- **Intestinal permeability methods**

(1) in vivo perfusion studies in humans
(2) in vivo or in situ perfusion studies in animals
(3) in vitro permeation experiments with excised human or animal intestinal tissue
(4) in vitro permeation experiments across epithelial cell monolayers

Methodology

3. Dissolution characteristics and profile similarity

- **Medium (900 mL 0.1 N HCl, pH 4.5, pH 6.8)**

  FDA: - USP Apparatus I, 100 rpm

  - USP Apparatus II, 50 rpm

  WHO: - USP Apparatus II, 75 rpm

- **Similarity factor (f_2) calculation**

Additional considerations for requesting a biowaiver

- **Excipients**
- **Risk Assessment**
- **BCS-based biowaivers are NOT applicable for the following:**
  1. Narrow therapeutic index drugs; digoxin, theophylline, warfarin
  2. Products designed to be absorbed in the oral cavity; sublingual or buccal tablets

Dissolution Profile Comparison

Dissolution Profile Comparison

GUIDELINES

FOR

THE CONDUCT OF BIOAVAILABILITY

AND BIOEQUIVALENCE STUDIES

Adopted from

ASEAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY

AND BIOEQUIVALENCE STUDIES

www.fda.moph.go.th/drug

Dissolution Profile Comparison

- **APPENDIX II: Dissolution testing**
- **Purposes:**

1. **QA:**
   - get information on test batches used in BA/BE studies
   - QC
2. **BE surrogate interference**
   - demonstrate similarity between reference products and different formulations

Dissolution Profile Comparison

Difference factor (f_1)

- difference in percent dissolved between reference and test at various time intervals

$$f_1 = \left[\sum_{t=1}^{n} |R_t - T_t| / \sum_{t=1}^{n} R_t \right] \times 100$$

Similarity factor (f_2)

- comparison of closeness of two comparative formulations

Similarity Factor (f_2)

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

where

n = the number of dissolution time points

R_t = mean % drug dissolved of the reference product at time t

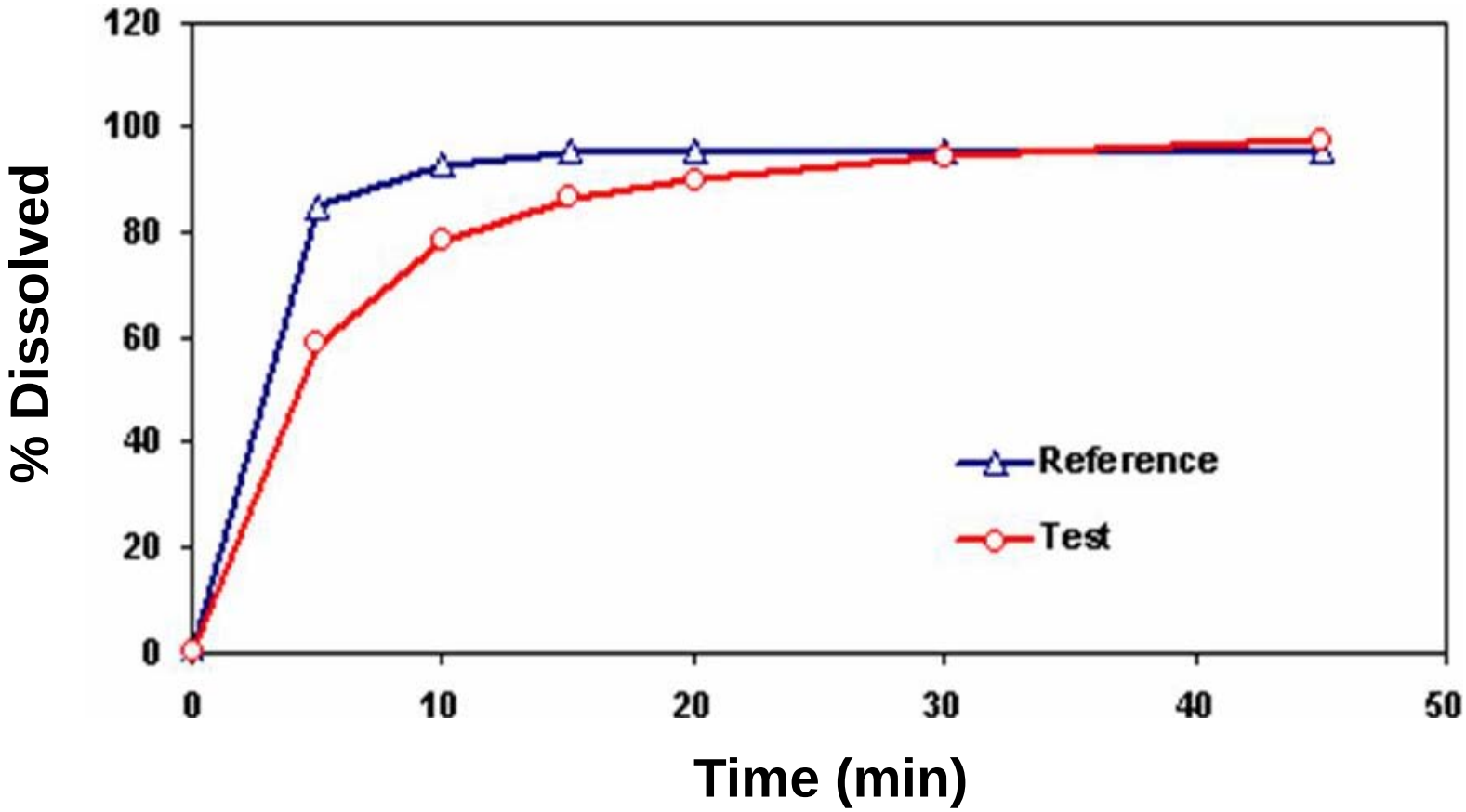
T_t = mean % drug dissolved of the test product at time t

Evaluation of f_2

Evaluation of similarity is based on the conditions of

- 12 individual values for every time point for each formulation
- minimum of three time points (zero excluded)
- Dissolution measurements under exactly the same condition
- Same dissolution time points for both profiles
- Only one measurement should be considered after 85% dissolution of both products
- To allow use of mean data, %CV at the earlier time points should not be more than 20%, and at other time points should not be more than 10%

Example


% Dissolved
120
100
80
60
40
20
0
0
10
20
30
40
50
Time (min)
Reference
Test

Acceptance Criteria

- **Dissolution profiles of the two formulations are considered similar if f_1 value is between 0 and 15, and f_2 value is between 50 and 100.**

- **In case of *very rapidly dissolving products*, dissolution profiles may be accepted as similar.**

Criteria for Classification

1. Solubility

- Highly soluble: highest dose strength is soluble in ≤ 250 mL aqueous media over a pH range of 1-7.5, 37 ± 1°C

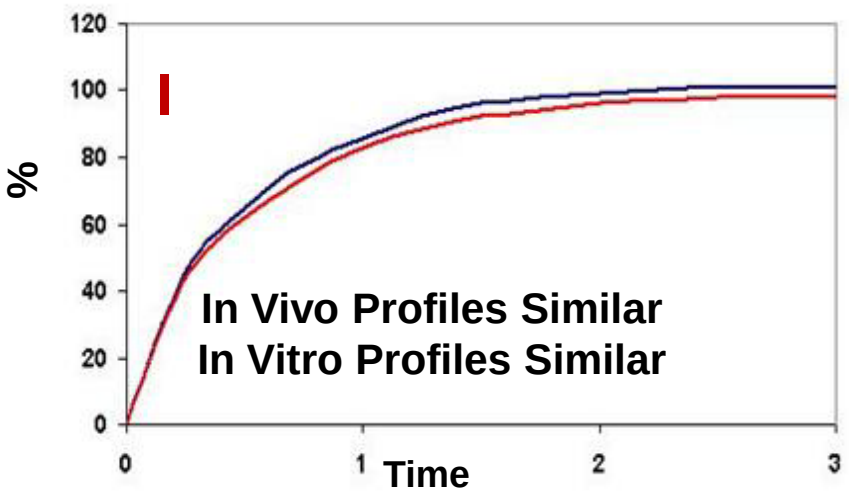
2. Permeability

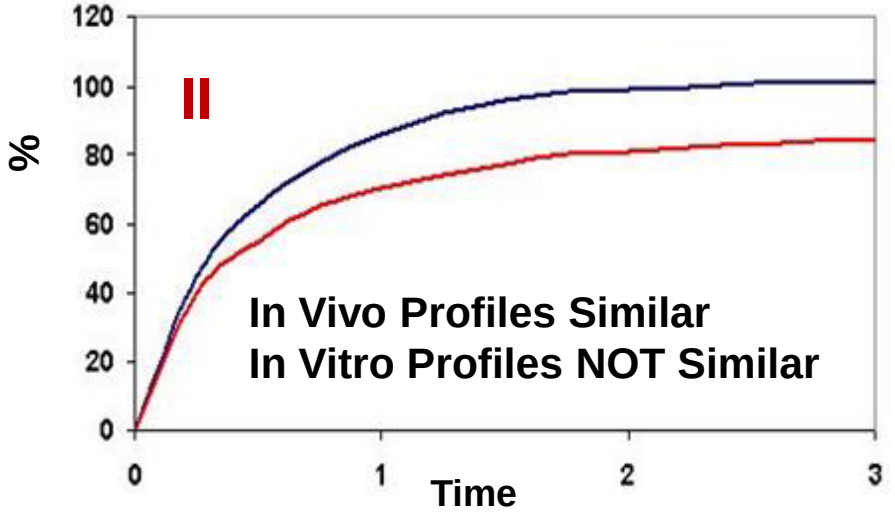
- Highly permeable: extent of absorption in humans ≥ 90 %

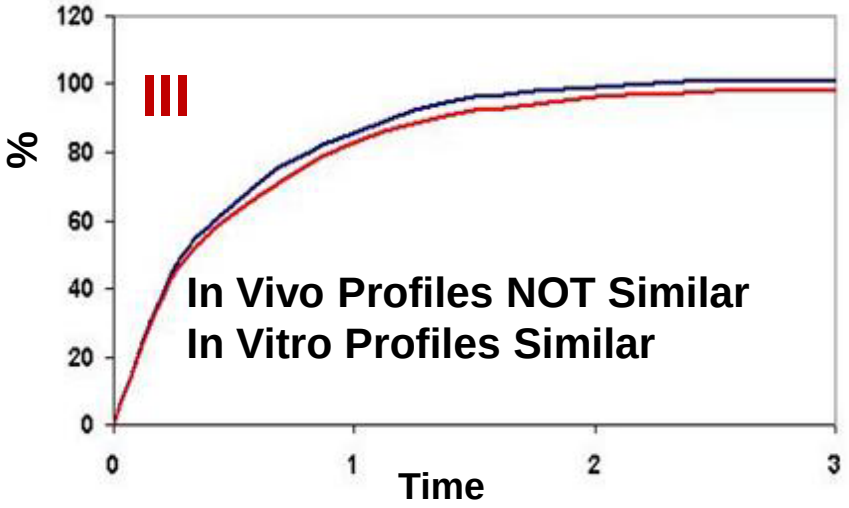
3. **Dissolution (3 media)**

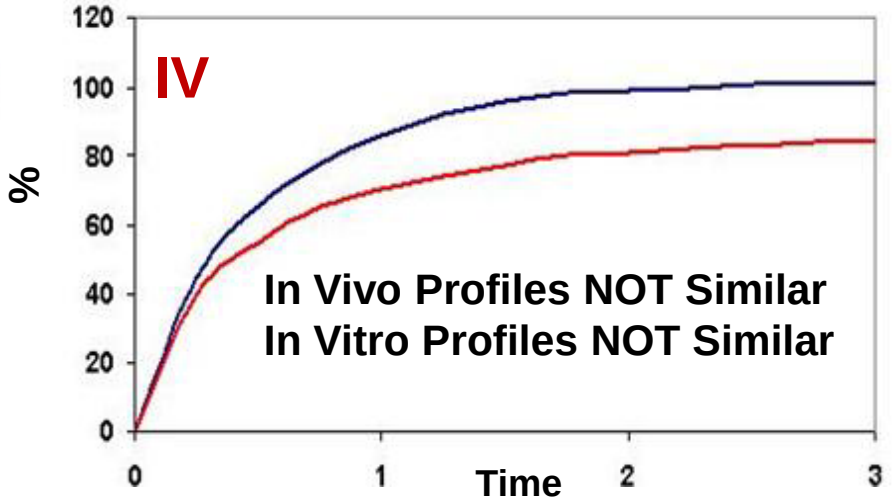
- **Rapidly dissolving: NLT 85 % la. dissolves in 30 min**
- **Very rapidly dissolving: NLT 85 % la. dissolves in 15 min**

Possible Outcomes Scenarios









Dissolution Methods Database

- www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
- **Dissolution Methods Database Search**
- **Available information:**

  - Drug name
  - Dosage form
  - USP Apparatus
  - Speed (rpm)
  - Medium
  - Volume (mL)
  - Recommended sampling times (min)
  - Date updated

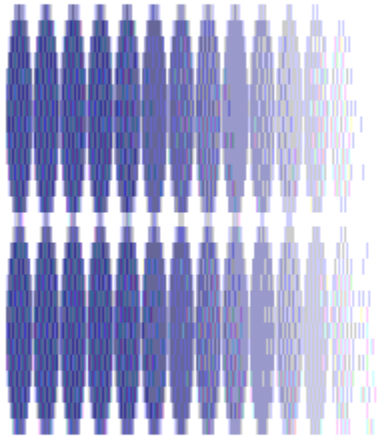
U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration

A-Z Index Search go

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products Tobacco Products

Dissolution Methods



FAQ | Contact Us | CDER Home

FDA-Recommended Dissolution Methods

Search for a Drug by its Generic Name

Enter at least three characters: Submit Clear

Printable List of All Drugs in the Database

Dissolution Methods Disclaimer

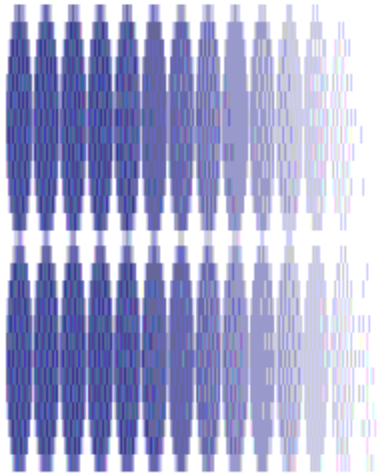
U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration

A-Z Index Search go

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products Tobacco Products

Dissolution Methods



FAQ | Contact Us | CDER Home

FDA-Recommended Dissolution Methods

Search for a Drug by its Generic Name

Enter at least three characters: Glimepiride Submit Clear

Printable List of All Drugs in the Database

Dissolution Methods

Search Results for 'Glimepiride'

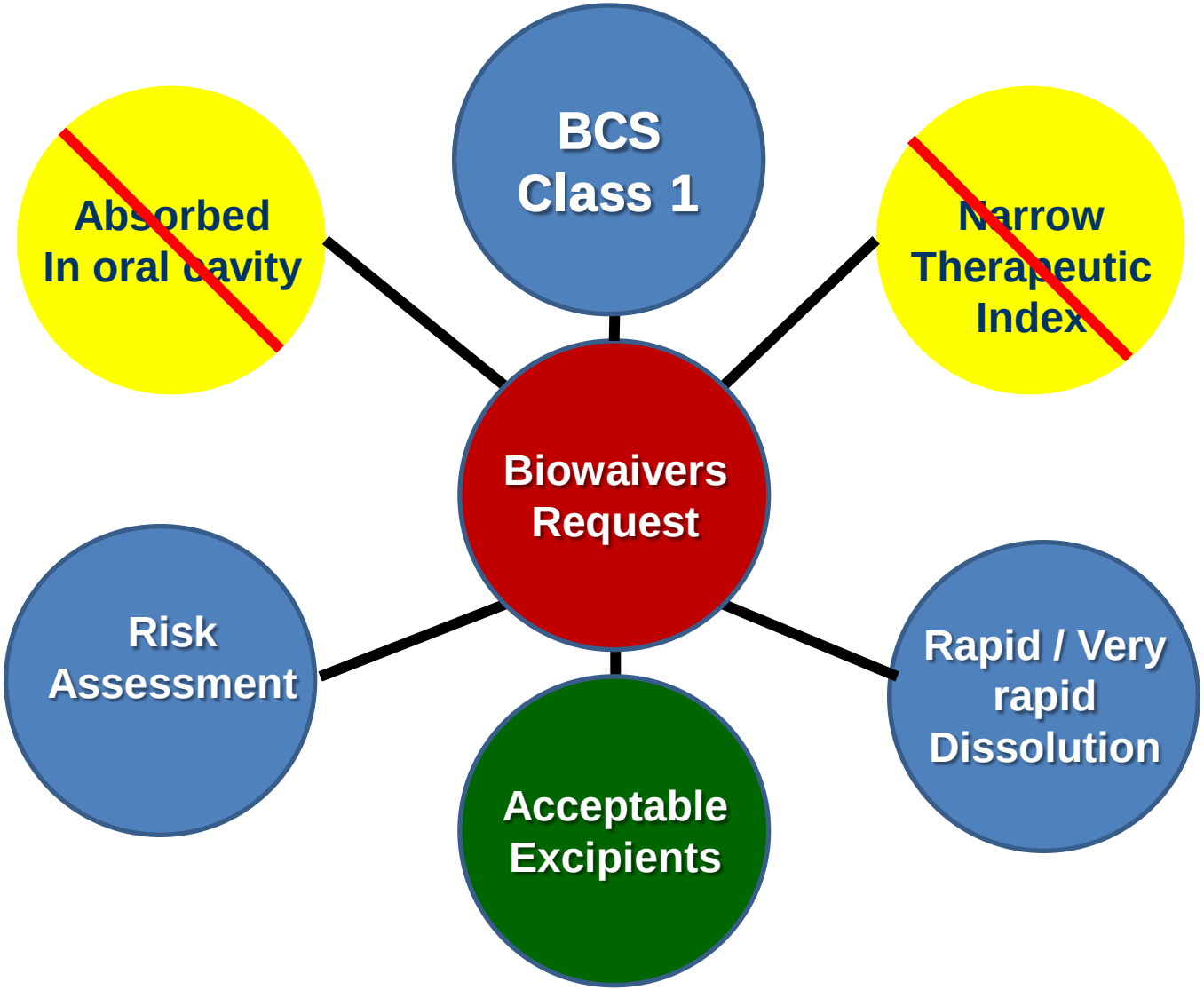
Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Glimepiride	Tablet	II (Paddle)	75	Phosphate Buffer, pH 7.8	900	5, 10, 15 and 30	07/23/2004

Request for Biowaivers

ระเบียบสำนักงานคณะกรรมการอาหารและยา
ว่าด้วยการยกเว้นการศึกษาชีวสมมูลในมนุษย์
สำหรับผลิตภัณฑ์ยารูปแบบของแข็งชนิดรับประทาน
ที่ปลดปล่อยยาทันที
พ.ศ. 2550

www.fda.moph.go.th/drug

Data Supporting a Request for Biowaivers



Data Supporting a Request for Biowaivers

BCS Class 1

High solubility:

- highest dose strength is soluble in ≤ 250 mL aqueous media over a pH range of 1-7.5, 37 ± 1°C
- pH-solubility profile of the test drug substance at 37 ± 1°C in aqueous media pH 1-7.5
- pH = pKa, pKa + 1, pKa - 1

Data Supporting a Request for Biowaivers

BCS Class 1

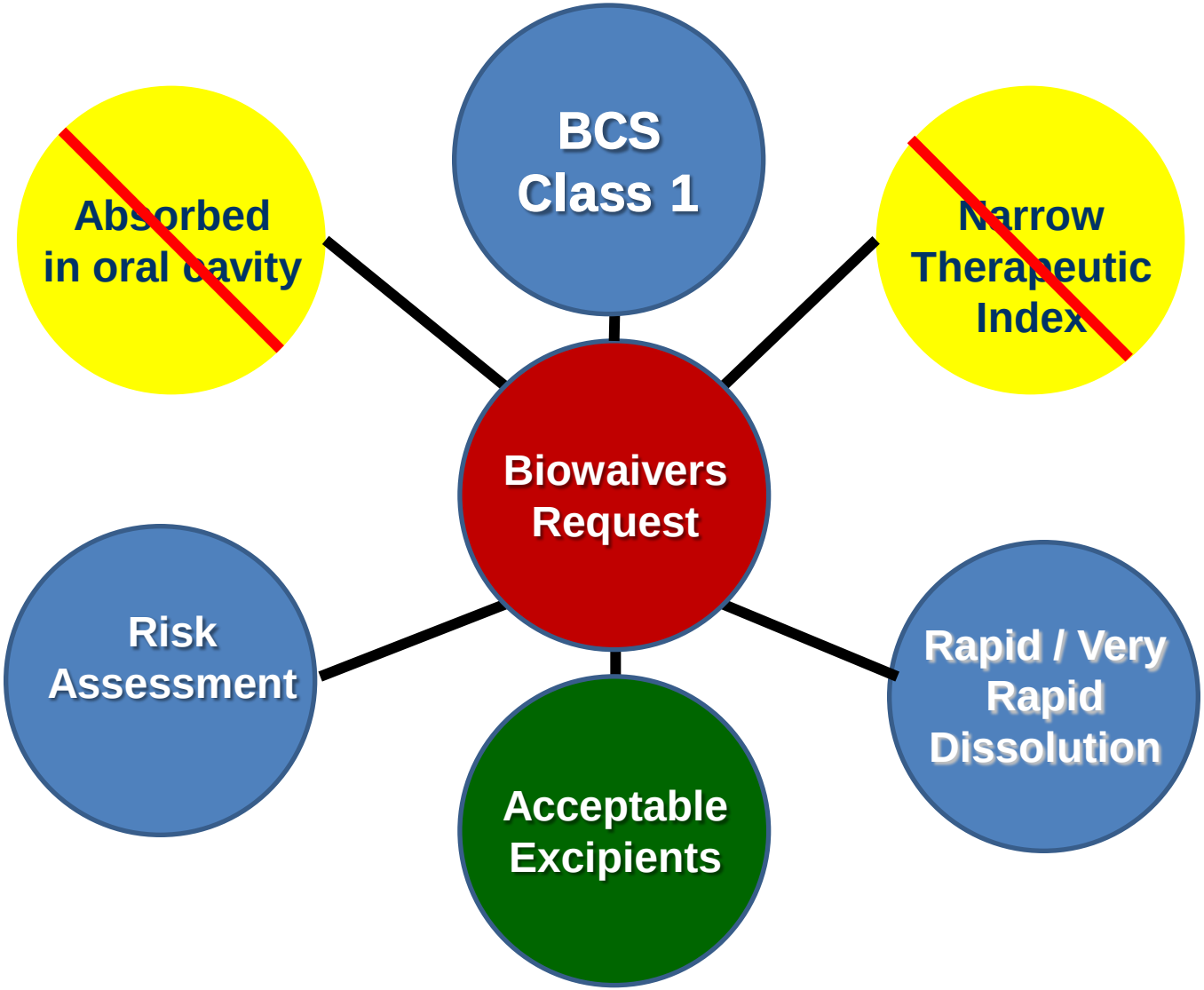
High permeability:

- **fraction absorbed in humans ≥ 85%**
- **PK studies in human:** Mass balance, Absolute bioavailability studies
- **Intestinal permeability methods**

1) in vivo perfusion studies in humans
2) in vitro permeation experiments with excised human or animal intestinal tissue
3) in vivo or in situ perfusion studies in animals
4) in vitro permeation experiments across epithelial cell monolayers

- Suitability of methodology

Data Supporting a Request for Biowaivers



Data Supporting a Request for Biowaivers

Rapidly dissolving

- Medium (900 mL; pH 1.2, pH 4.5, pH 6.8), 37 ± 0.5°C

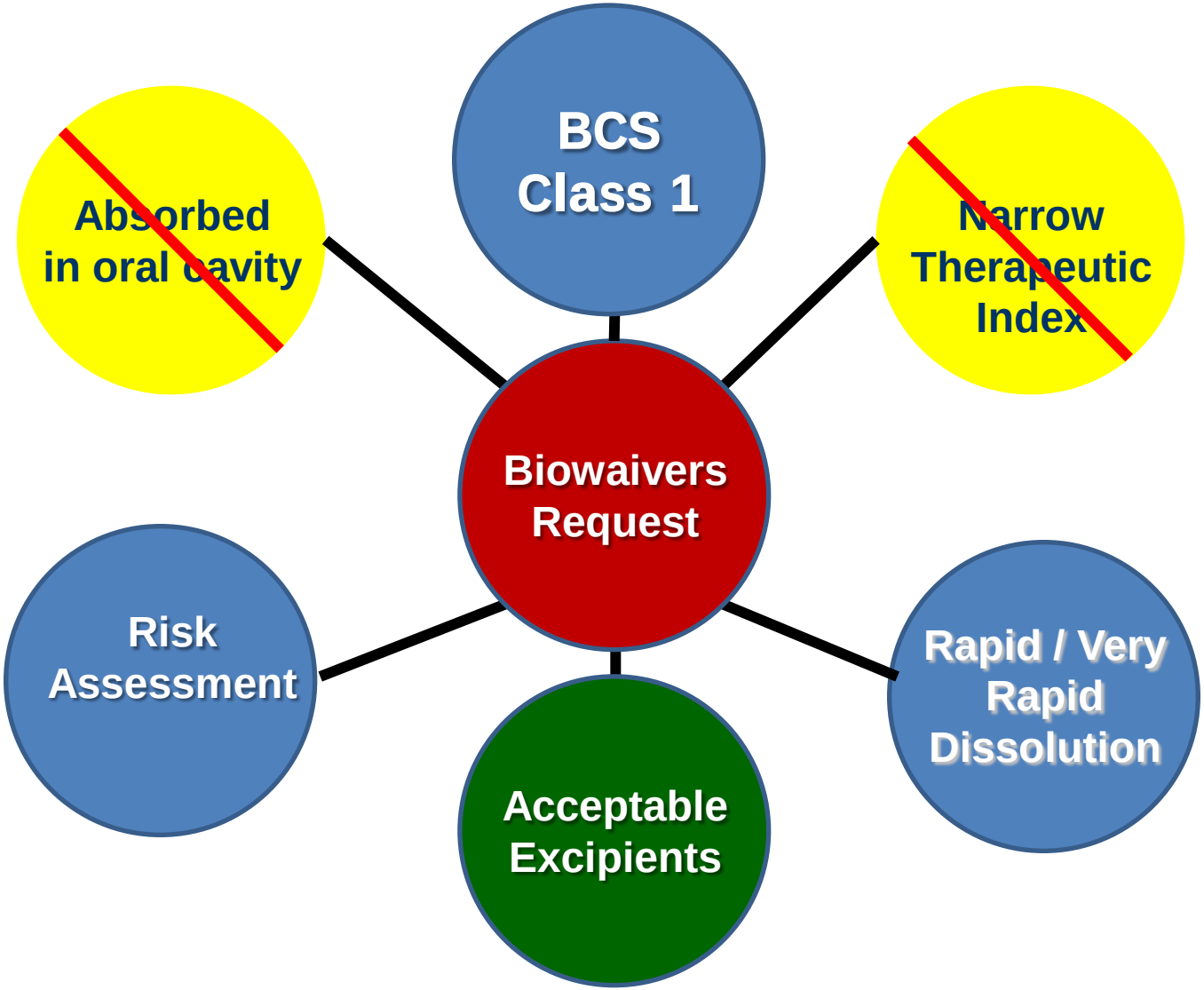
  TFDA: - USP Apparatus I, 100 rpm

  - USP Apparatus II, 50 or 75 rpm
- NLT 85% la. dissolves in 30 min
- $f_2 \geq 50$

Very rapidly dissolving

- NLT 85% la. dissolves in 15 min
- f_2 is not necessary

Data Supporting a Request for Biowaivers

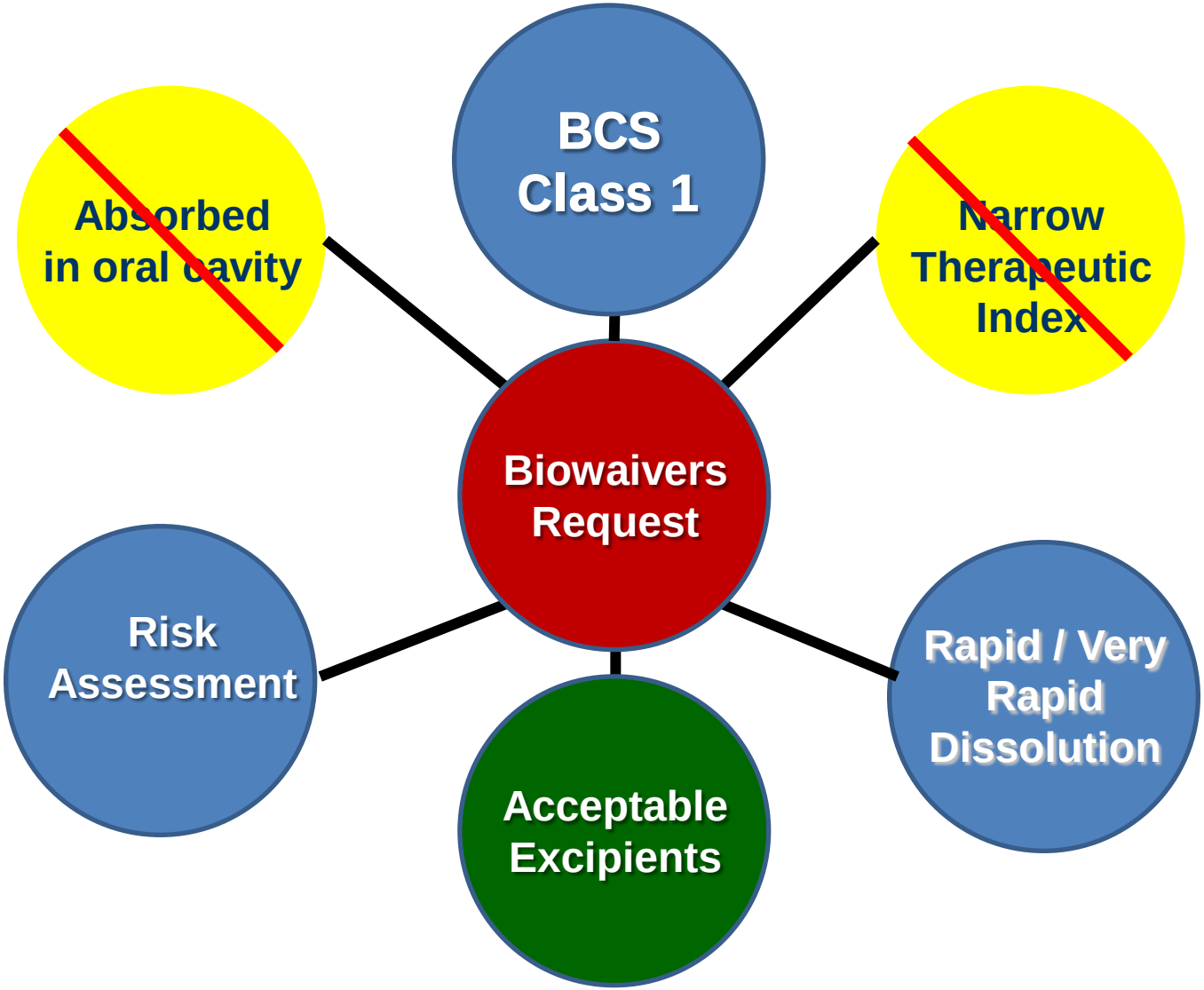


Data Supporting a Request for Biowaivers

Excipients

- Well established
- No interaction with the PK of the active substance expected
- Not affect the rate and extent of absorption
- In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted.

Data Supporting a Request for Biowaivers

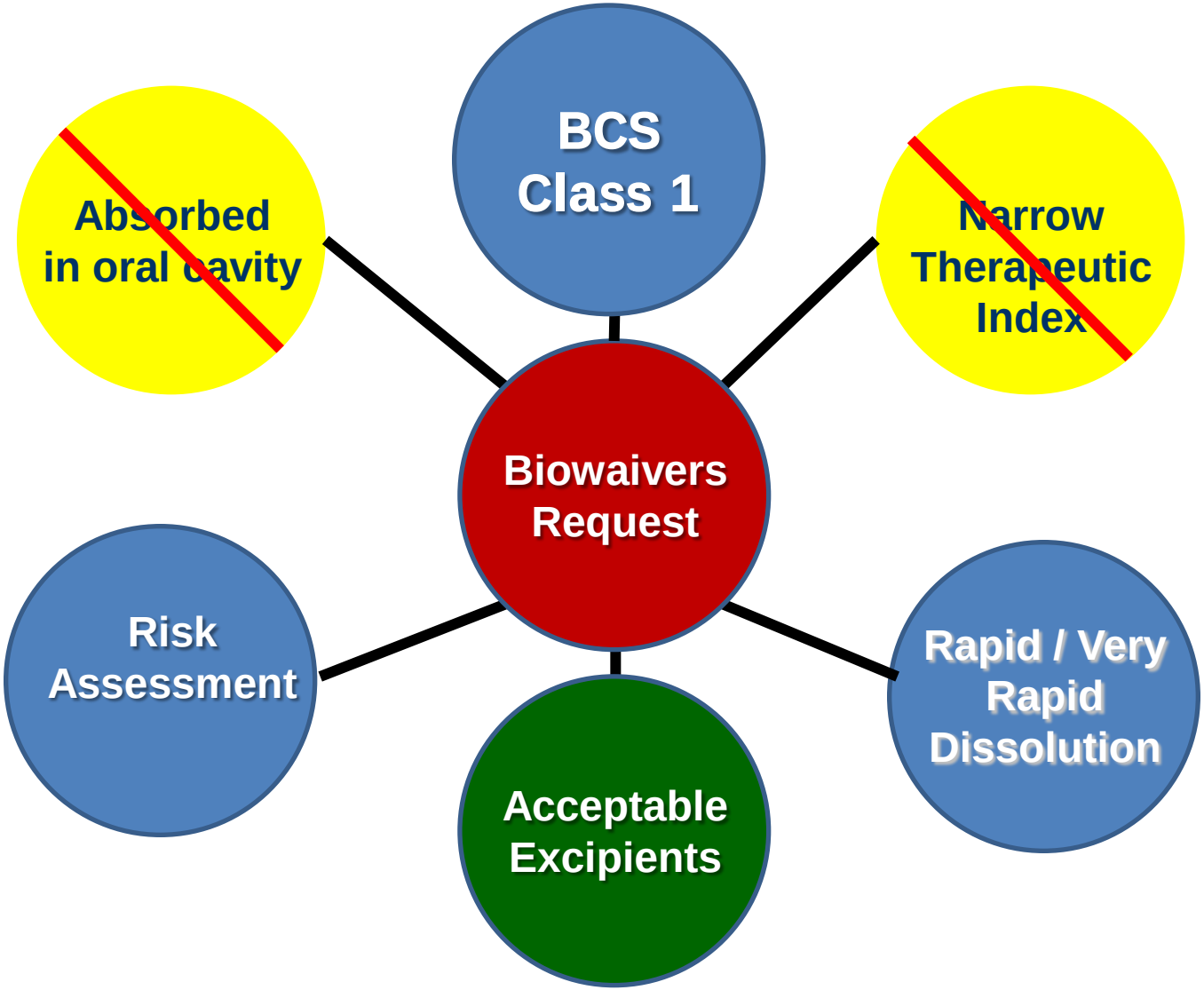


Data Supporting a Request for Biowaivers

Risk Assessment

- To minimize the risks of an incorrect biowaiver decision in terms of public health, therapeutic indications of the API should be evaluated.

Data Supporting a Request for Biowaivers



BE Recommendations for Specific Products

- www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- **Available information:**

  - Active ingredient
  - Form / Route
  - Recommended studies
  - Analytes to measure
  - BE based on (90% CI)
  - Waiver request of in-vivo testing
  - Dissolution test method and sampling times
  - Date finalized

Bioequivalence Recommendations for Specific Products

- Guidance for Industry: Bioequivalence Recommendations for Specific Products (PDF - 81KB) (Issued June 2010)
- Dissolutions Methods Database

"Please submit comments for any of the guidances posted in the Bioequivalence Recommendations for Specific Products website to the Division of Dockets Management (DDM) under Docket FDA-2007-D-0369-0015. For electronic comments refer to the website http://www.regulations.gov OR you can mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Please contact the Regulations.gov HelpDesk at 1-800-378-5457 (toll free) for assistance regarding submissions."

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 839]

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Newly Added Recommendations - April 2011 (12 New; 2 Revision) updated 4/26/2011

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended

Bioequivalence Recommendations for Specific Products: Active Ingredients starting with 'G'

- Drug-Related Guidances Main Page
- Bioequivalence Recommendations for Specific Products Main Page
- Dissolutions Methods Database

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended
Gabapentin (PDF - 32KB)	Draft	Oral	Capsule	20235	5/2007
Gabapentin (PDF - 55KB)	**Final**	Oral	Tablet	20882	5/2008
Galantamine HBr (PDF - 36KB)	Draft	Oral	Tablet	21169	11/2010

Gatifloxacin 0.3% (PDF - 15KB)	Draft	Ophthalmic	Solution	21493	7/2008
Gemfibrozil (PDF - 16KB)	Draft	Oral	Tablet	18422	12/2009
Gemifloxacin Mesylate (PDF - 56KB)	**Final**	Oral	Tablet	21158	5/2008
Glimepiride (PDF - 56KB)	**Final**	Oral	Tablet	20496	5/2008
Glimepiride; Pioglitazone HCl (PDF - 16KB)	Draft	Oral	Tablet	21925	5/2009
Glimepiride; Rosiglitazone Maleate (PDF - 19KB)	Draft	Oral	Tablet	21700	11/2007
Glipizide (PDF - 35KB)	Draft	Oral	Tablet	17783	8/2010
Glipizide (PDF - 19KB)	Draft	Oral	Tablet, Extended-Release	20329	7/2008
Glipizide; Metformin HCl (PDF - 49KB)	**Final**	Oral	Tablet	21460	5/2008

Guidance on Glimepiride

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Glimepiride

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments: Because of the potential for hypoglycemia from using a dose of 4 mg of glimepiride tablets, you should conduct the bioequivalence studies using the 1 mg dose. Each dose in the studies should be administered with 240 mL of 20% glucose solution to minimize hypoglycemic effects. After dosing, 60 mL of 20% glucose solution should be given to each subject every 15 minutes for the following 4 hours.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments: Please comment above.

Analytes to measure: Glimepiride in plasma

Bioequivalence based on (90% CI): Glimepiride

Waiver request of in-vivo testing: 2 mg and 4 mg based on (i) acceptable bioequivalence studies on the 1 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

...Thank you...