Common Deficiencies with BE Submissions in ANDAs assessed by GCC

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3rd MENA REGULATORY CONFERENCE ON BE, BIOWAIVERS, BIOANALYSIS & DISSOLUTION

Outlines

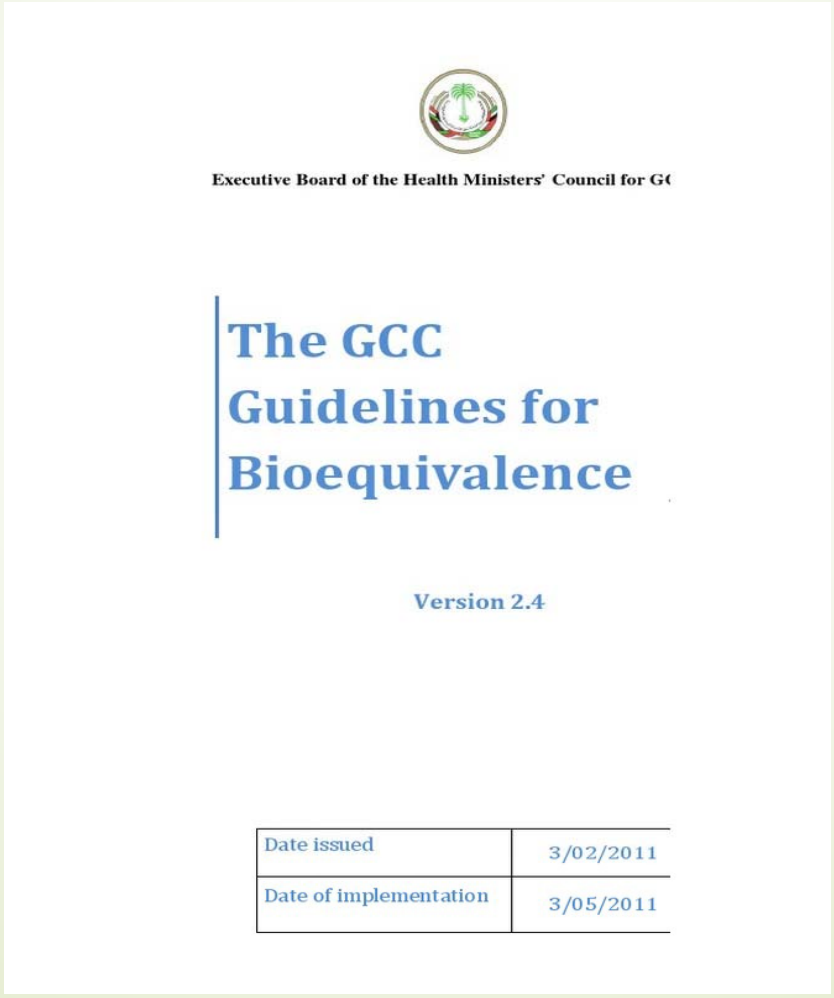
- Overview on GCC guidelines for BE

- ANDAs submissions

- Common deficiencies in BE studies

- Summary, Conclusions and Recommendation

Overview on GCC Guidelines for BE



Executive Board of the Health Ministers' Council for G(

The GCC Guidelines for Bioequivalence

Version 2.4

Date issued	3/02/2011
Date of implementation	3/05/2011

Overview on GCC Guidelines for BE

Present **Gulf Cooperation Council (GCC)** guidelines adapted from the European Medicines Agency (EMA) guideline on the investigation of bioequivalence.

These guidelines have been prepared taking into consideration the need for worldwide harmonization , at the same time specific needs for the GCC countries.

Overview on GCC Guidelines for BE

-The GCC guidelines were published on **FEB/2011**

-Updated in
- **2013**
- **2014**

- Last update was on **March 2016**

- There is a updated draft proposal and will be discussed in the near future

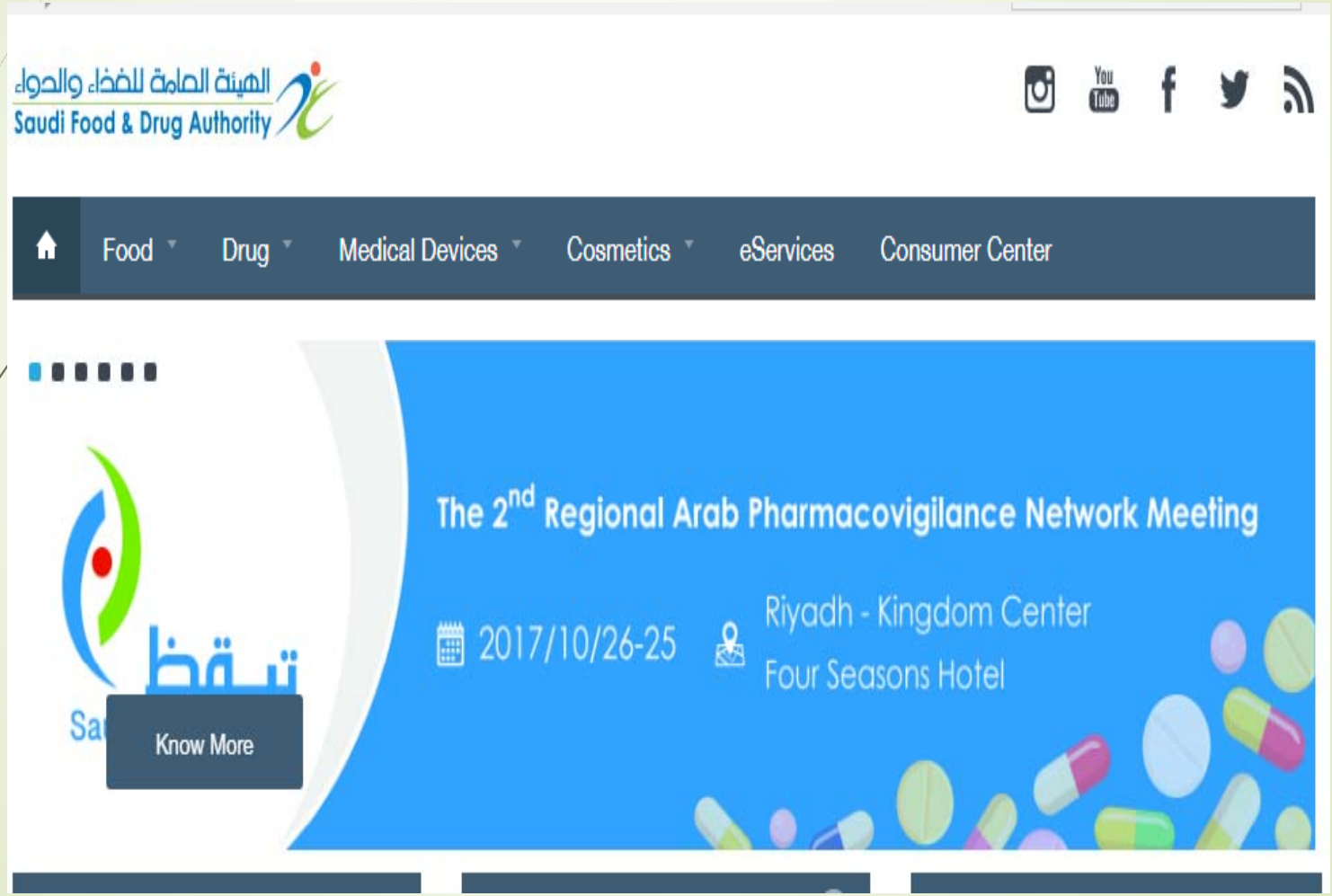
ANDAs Submissions

All applications should be submitted to the GCC central drug registration in the **electronic common technical dossier (eCTD)** format, otherwise **the dossier will not be accepted.**

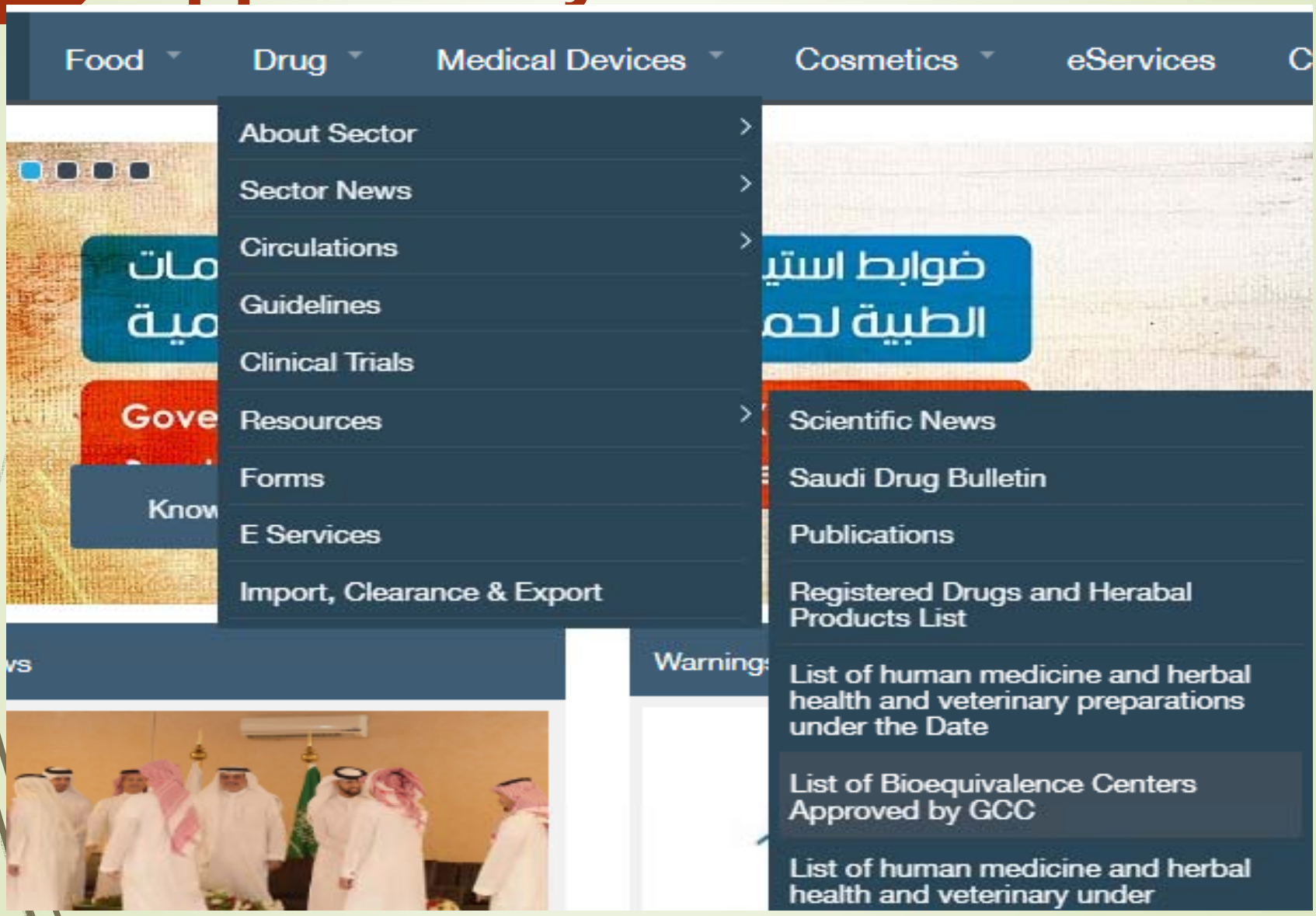
ANDAs Submissions

BE studies should be conducted in approved **Contract Research Organizations (CROs**), this approval can be guaranteed based on previous accreditation from astringent authorities such as USFDA or GCC inspection.

List of Bioequivalence Centers Approved by GCC



List of Bioequivalence Centers Approved by GCC



List of Bioequivalence Centers Approved by GCC

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No.	Bioequivalence Centers
1.	Accutest Research Laboratories Pvt Ltd (15 - 18 May 2012), Navi Mumbai - INDIA
2.	Accutest Research Laboratories (I) Pvt Ltd (Unit-I) (26-27 September 2011), Navi Mumbai - INDIA
3.	Aizant Drug Research Solutions Pvt Ltd (20 - 21 October 2011), Hyderabad - INDIA
4.	BA Research India Ltd (18-20 October 2010), Ahmedabad - INDIA
5.	Bioserve Clinical Research (P) Ltd (19 May 2010), Hyderabad - INDIA
6.	Bombay Bioresearch Centre (BBRC) - (18-20 July 2011), Mumbai - INDIA
7.	Bombay Bioresearch Centre (BBRC) - (18-20 May 2011), Mumbai - INDIA
8.	Bombay Bioresearch Centre (BBRC) (11-15 October 2010) - INDIA
9.	Cliantha Research Ltd (19-22 March 2013), Gujarat - INDIA
10.	Cliantha (previously BA Research India Ltd) (19-22 June 2012), Ahmedabad - INDIA
11.	Lotus Pvt Ltd (25-27 April 2013 - Bangalore; 29-30 April 2013 - Chennai) - INDIA
12.	Macleods Pharmaceuticals Ltd (8-12 February 2013), Mumbai - INDIA
13.	Manipal AcuNova KH Clinical Research Centre (2-6 July 2012), Manipal - INDIA
14.	Matrix Laboratories Ltd (20-21 May 2010), Hyderabad - INDIA
15.	Piramal Clinical Research (20-24 June 2011), Ramanthapur - INDIA
16.	Sitec Labs Pvt Ltd (14-15 February 2012: bioclinical; 16-17 February 2012: bioanalytical), Mumbai - INDIA
17.	Synchron Research Services (Pvt) Ltd (17 May 2010), Ahmedabad - INDIA
18.	Veeda Clinical Research Pvt Ltd (14-18 February 2013), Ahmedabad – INDIA
19.	MDS Pharma Services, USA and Canada
20.	ACDIMA Center for Bioequivalence & Pharmaceutical Studies , Jordan.
21.	Jordan Center for Pharmaceutical Research (JCPR), Jordan.
22.	Anapharm,Canada.
23.	Algorithme pharma Inc., Canada.
24.	International Pharmaceutical Research Center (IPRC), Jordan.
25.	Triumpharma (Clinical Research Centre), Jordan
26.	Pharmaceutical Research Unit (PRU), Jordan
27.	Ranbaxy Clinical Pharmacology Unit (CPU) – Noida, India
28.	Ranbaxy Clinical Pharmacology Unit (CPU) -New Delhi, India
29.	Ranbaxy Clinical Pharmacology & Pharmacokinetics (CPP) – Gurgaon, India
30.	Ranbaxy Clinical Pharmacology and Pharmacokinetics (CPP) – Romania

Common Deficiencies in BE Studies

Reference and Test product

Selection of reference product:

- Original brand-name (i.e. manufactured in the country of origin of the original brand name)

-Original brand-name but manufactured in a different country should be marketed in GCC region, ICH region, or in any stringent regulatory authority

-Local market leader

Reference and Test product

-Selection of test drug or the bio-batch

-The test product should usually originate from a batch of at least 1/10 of production scale or
100,000 units, whichever is greater, unless otherwise justified.

- In case of a production batch smaller than 100,000 units, a full production batch will be required.

Deficiencies in Selection of the Test Product

Example: wrong bio-batch size

Submitted bio-batch size was 100.000 tablets while production batches size were 2000, 000

10% of 2000,000 = 200, 000

Example: using expired reference standard

Deficiencies Regarding Reference and Test Product

Example: missing data

- Missing type and size of the test product or bio-batch (expected production size)

- Missing manufacturing site details and expiry dates for the reference product

- *Missing COA of reference and/or test product*

- *Missing data of COA* of raw materials of the test product

Dissolution

GCC guidelines requires comparative dissolution profile between the reference product and the test product (bio-batch) on12 units in three different pH media (normally pH 1.2, 4.5 and 6.8)

Deficiencies in Comparative Dissolution Profiles

Examples:

-Missing comparative dissolution profile is not provided between the reference drug and the test drug (bio-batch)

-Competitive dissolution profile is performed but on batches different than the one used in the BE study (Bio-Batch).

- Dissolution performed on only one or two pH without any justification

-Dissolution performed on less than 12 unit

Deficiencies in Comparative Dissolution Profiles

Examples:

- Missing unit individual data

-Calculated similarity factor is not submitted

- Dissolution profile doesn't show similarity in single pH (witihout any clarification)

Deficiencies in Comparative Dissolution Profiles

Examples

-Using of surfactants even if the pharmacopeias or the USFDA recommendation for dissolution doesn't recommend it

- using surfactant above the specified limits

The need for and the amount of the surfactant should be justified

Deficiencies in Comparative Dissolution Profiles

Examples:

-Wrong calculations of similarity factor is submitted (including zero time in the calculation)

- The relative standard deviation or coefficient of variation of reference or test product is more than 20% for the first point and more than 10% from second to last time point.

Deficiencies in Dissolution for Strength Biowaiver

- Missing formula composition for the biowaiver (normally lower strength

- Missing comparative dissolution profile between the Test drug to be bio waved (normally lower strength) with the test product t

Deficiencies in Dissolution for BCS Biowaiver

- Only BCS Class I is eligible for biowaiver- BCS Class III is not eligible for biowaiver

- Missing comparative dissolution profile between the test drug and reference drug

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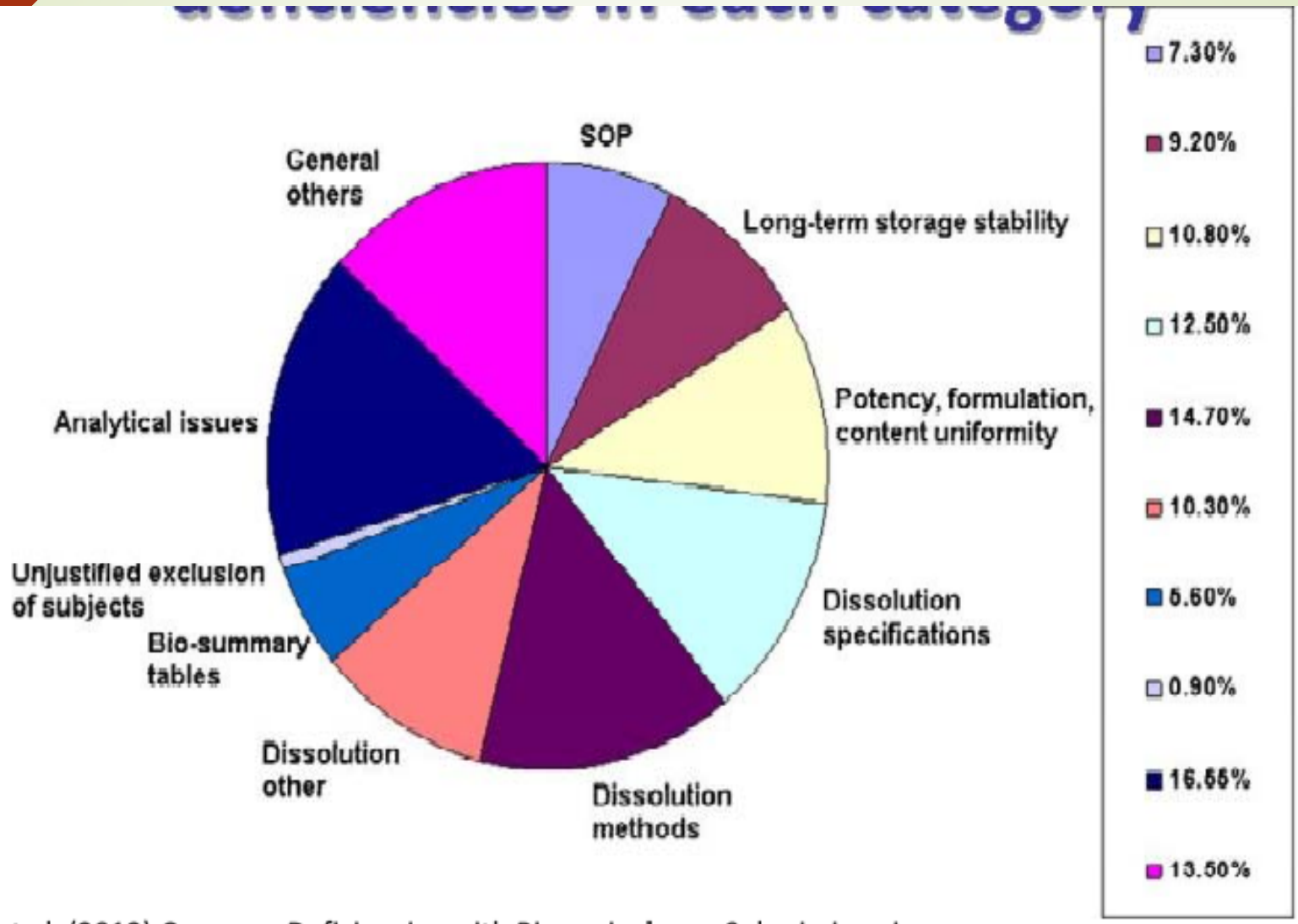
Types of BE deficiencies and % of total deficiencies in each category



Liu, Qing et al. (2012) Common Deficiencies with Bioequivalence Submissions in Abbreviated New Drug Applications Assessed by FDA. *AAPS J* 14(1): 19-22

Types of BE deficiencies and % of total deficiencies in each category

Dissolution specification: 12.5% , the *in vitro* dissolution testing specifications were not proposed or not as recommended by FDA.
Dissolution method: 14.7 % the dissolution method used in the application is not optimal or not consistent as that suggested by FDA.
Dissolution other: 10.3% dissolution deficiencies that cannot be categorized into specification or method:
Failure to submit individual dissolution data for each of the 12 units of test and reference products.
Incomplete dissolution testing (for example, lacking dissolution data in multimedia for extended release products and alcohol dose dumping data for certain products).
Failure to provide information on dissolution testing date and site address High variability in dissolution data.

Dissolution deficiencies present around 37%

Conducting BE studies (Clinical aspects)

- Study design
-Number of subjects
- Selection of subjects
-Standardization
- Fed or fast condition
- Sampling times
- Wash out periods
- Subject dropout

Deficiencies in conducting BE studies

Example: Deficiencies in screening

The gap between screening and the actual study was about **six months** in anti diabetic test drug

This is unacceptable as the gap should not exceed 2 to 3 weeks

Conducting BE studies

Fast or Fed condition

For products where **the SmPC recommends** intake of the reference product on **an empty stomach or irrespective of food intake,** the BE study should be conducted **under fasting conditions.**

For products where the **SmPC recommends** intake of the reference product only **in fed state**, the BE study should generally be conducted **under fed conditions**

Deficiencies in conducting BE studies

Examples: (minor)

-Missing protocol and its amendment

- Missing protocol deviations

- Missing agreement between sponsor and CRO

- Missing subjects consent forms

- Missing vital signs records

Deficiencies in Conducting BE Studies

Examples:

-Missing subjects case report form (including ECG data)

-Missing reference and test product accountability form

- Missing dietary list

-IRB , Ethics committee (document, signed and dated , CV available)

Bio-Analytical Methodology

The bio-analytical methods used must be fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study validation should be performed using Quality control samples in each analytical run.

Common Bio-Analytical Deficiencies

- Bio-Analytical method
- Bio-Analytical method validation
- Bio-Analytical report

Common Bio-Analytical Deficiencies

Examples: Bio-Analytical Method and Method Validation

- Missing Incurred Sample Reanalysis (ISR, beyond 2013)

- Method validation performed either 10 years before or after the study

Common Bio-Analytical Deficiencies

Examples: Bio-Analytical Method and Method Validation

- Calibration and quality control (QC) values not within range of subject samples

- Inadequate long-term storage stability (From first day of period one to last day of analysis)

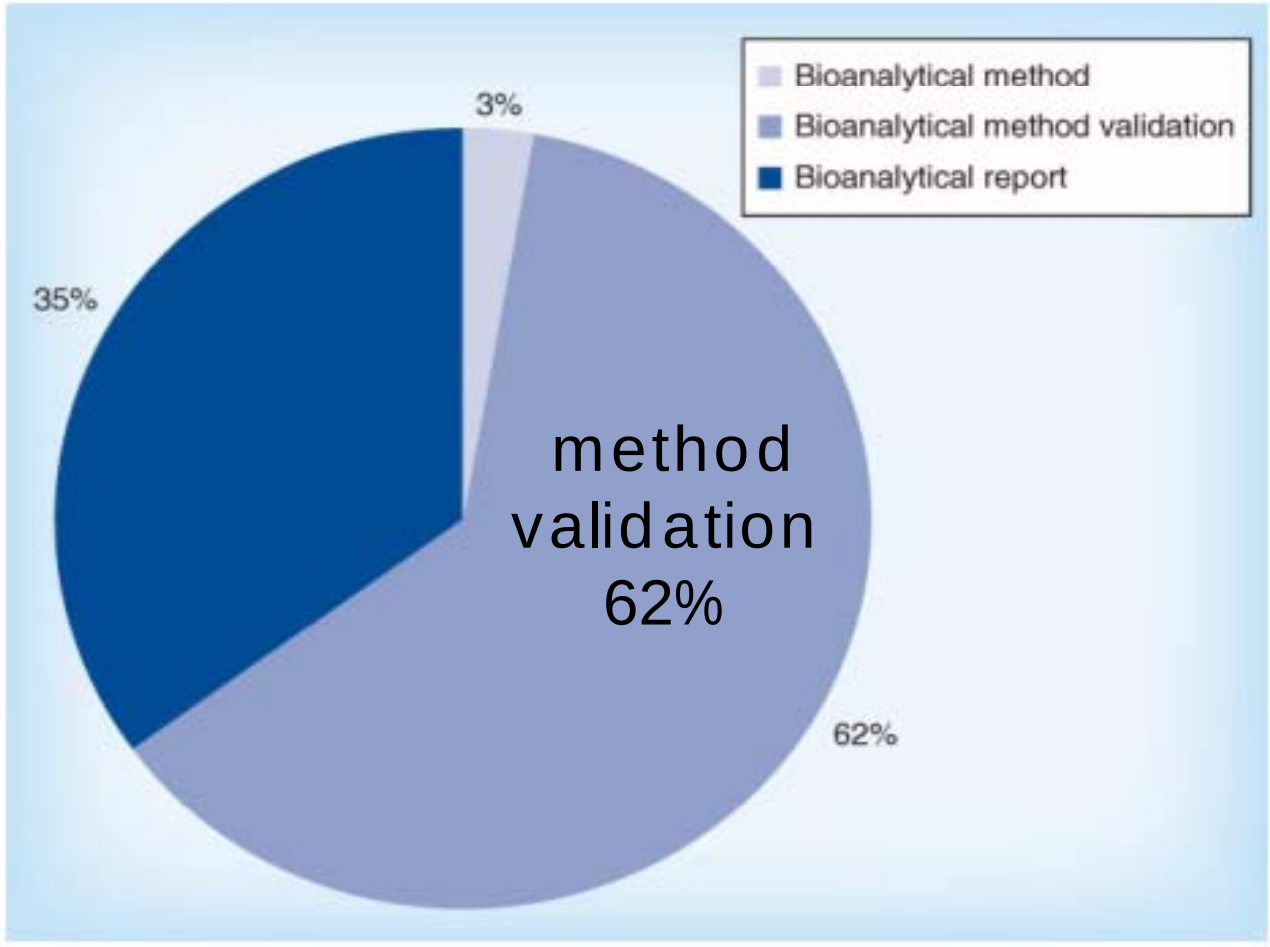
Common Bio-Analytical Deficiencies

Examples: Bio-Analytical Report

- Missing 20% of serial chromatograms

-Missing dates of analysis

Global bioanalytical deficiencies statistics



Common Deficiencies with Bioequivalence Submissions in ANDAs

GPhA Fall Technical Conference North Bethesda, MD, October 29, 2014

Summary

- Critical deficiency in any of clinical, analytical or statistical aspects will result in bioequivalence not being accepted even if 90% CI for Cmax and AUC are within the criteria

Conclusion

Avoiding common mistakes in BE submission will help expedite ANDA review

Recommendation

- Review Specific Products FDA BE Recommendations, information on BE study requirements for over 800 potential generic drug products can be found in the public domain

Contains Nonbinding Recommendations

Draft Guidance on Clindamycin Hydrochloride

This draft guidance, once finalized, will represent 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: Clindamycin Hydrochloride

Form/Route: Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 300 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 300 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Clindamycin in plasma

Bioequivalence Based on (90% CI): Clindamycin

Waiver request of in-vivo testing: 75 mg and 150 mg based on (i) acceptable bioequivalence studies on the 300 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

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.accessdata.fda.gov/scripts/cder/dissolution/. 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.

Recommendation

Bioequivalence study summery sheet on the SFDA website

Annex 1 Bioequivalence Study Summary Template:

Bioequivalence Study Summary Template

1. Test Product Information

Trade name	
Active ingredient(s)	
Therapeutic classification	
BCS classification	
API source(s) used in biobatch	
Particle size of API used in biobatch	
Polymorphic form of API used in biobatch	
Strength(s) to be registered	
Strength used in the study	
Dosage form	
Type of formulation *(immediate release, modified release, ...)*	
Expected production size	
Biobatch information:	
Batch type	
Batch size	
Batch number	
Manufacturing site	
Manufacturing date	
Expiry date	
Assay content in the COA	

2. Tabulation for the Composition of the Proposed Formulation(s)

Component and Quality Standard	Function	Strength (label claim)			
		xx mg		xx mg	
		Quantity/Unit	%*	Quantity/Unit	%*
Total					

**each ingredient expressed as a percentage of the total core or coating weight.*

3. Reference Product Information

Trade name	
Active ingredient(s)	
Strength	
Type of formulation *(immediate release, modified release, ...)*	
Method of administration *(with or without meals)*	
Country of purchase	
Batch number	
Expiry date	
Manufacturer/site	
Assay content in the COA	

4. Summary of *in vitro* Dissolution Studies

Testing date			
Apparatus			
Speed of Rotation			
Medium			
Volume			
Temperature			
No. of Dosage Units used			
Collection times *(minutes or hours)*			
f_2 value in the comparative *in vitro* dissolution study *(test vs. reference)*	At Buffer		
	pH 1.2	pH 4.5	pH 6.8
f_2 value in the comparative *in vitro* dissolution study *(biobatch vs. other strength(s) to be registered)*	At Buffer		
	pH 1.2	pH 4.5	pH 6.8

5. Bioequivalence Summary

No. of submitted bioequivalence studies		
Study design		
Period(s) date(s)		
Bioanalysis date		
Study site		
Number of subjects		
Parent data	☐ Yes	☐ No
Metabolite data	☐ Yes	☐ No

Parameter	Arithmetic Mean (CV%)		% Ratio of Geometric Means	Confidence Interval Stated in study protocol
	Test	Reference		
$AUC_{(0-t)}$				
$AUC_{(0-\infty)}$				
C_{max}				
T_{max}				
$T_{1/2}$				

6. Bioanalytical Method Summary

Method description		
Analyte		
Internal standard (IS)		
Average recovery of drug (%)		
Average recovery of IS (%)		
Bench-top stability (hours/°C)		
Stock stability (days/°C)		
Processed stability (hours)		
Freeze-thaw stability (cycles)		
Long-term storage stability (days/°C)		
Dilution integrity		
Selectivity		
Bench-top stability (hours)		
Stock stability (days/°C)		
Standard curve concentrations (units/mL)		
LLOQ (units/mL)		
QC concentrations (units/mL)	*List all the concentrations used*	
QC Intraday precision range (%)	*Per QC*	
QC Intraday accuracy range (%)	*Per QC*	
QC Interday precision range (%)	*Per QC*	
QC Interday accuracy range (%)	*Per QC*	
Chromatograms for bioanalytical method	☐ Yes	☐ No
20% of subjects chromatograms	☐ Yes	☐ No
Incurred sample reanalysis *(Mandatory for studies that were conducted beyond 2013)*	☐ Yes	☐ No

Annex 2 Updates:

- **What's New in The GCC Guidelines for Bioequivalence (version 2.4)?**

The following table shows the update on the previous version no. 2.3:

Section	update
3.1.2. Reference and test product • Selection of reference drug.	Reference Products must be the original brand-name (i.e. manufactured in the country of origin of the original brand name); if this is not available in the market then the brand-name regarding the same manufacturer but different country of origin is used, marketed in GCC region, ICH region, or in any stringent regulatory authority. If the original brand-name is not available in the market or no longer produced, then the product which is the local market leader may be used as a reference product.
3.1.7 Bioanalytical methodology	Refer to "Guideline on bioanalytical method validation" published by European Medicine Agency (EMA).
Bioequivalence study summary template	Table updated


THANK
YOU

Sultanate of Oman