Jordan Food and Drug Administration

JFDA Bioequivalence Regulations

1st Bioequivalence symposium In Morocco

6 -7 Dec 2012

Pharmacist Wesal Alhaqaish

Head of Drug Registration Dept./JFDA

Presentation outline

- Overview : Jordan Food & Drug Administration
- Laws and guidance .
- Bioequivalence guidance .
- Common deficiencies in the B.E studies .
- Statistics for BE studies submitted.

JFDA OVERVIEW

As of April, 2003, the Jordan Food and Drug Administration (JFDA) was created by law.

JFDA enjoys financial and administrative independence .

It is entitled to exercise all legal actions that are deemed necessary to achieve its goals :-

(a) The safety of food stuffs, their quality and their suitability for human consumption through out their use.

(b) The safety of Drugs (medications) and their quality control.

(c) The safety of other stuffs specified in the Drug and Pharmacy law which is in effect.

JFDA OVERVIEW

JFDA is deemed to carry out all necessary actions to fulfill its mission through:-

1. Setting & Implementing Legislations.
2. Monitoring & Surveillance.
3. Raising the public awareness.

JFDA OVERVIEW

The following directorates & departments became under JFDA Jurisdictions:

1. Drug Directorate .
2. Food Directorate .
3. Quality Control Laboratory .
4. Food Laboratories .
5. Medical Devices Directorates (New).

JFDA MAIN POINT OF STRENGTH

- A major strength in managing JFDA is the scientific expertise available to us from several technical committees assigned by the Drug & Pharmacy law and composed of highly qualified technical scientists from both, public and private sectors.

- Another important strength is contributed to the spontaneous correspondence & meetings with our JFDA counterparts both in the region & internationally through which we exchange information & develop our knowledge & capabilities.

JFDA MAIN POINT OF STRENGTH

TRANSPERANCY & ACCOUNTABILITY

- Refers to the ability of citizens, public officials and civil society to obtain the material information that they need in order to make informed decisions and hold public sector agents accountable.

Active web site (www.jfda.jo) presents:

- JFDA News, Laws & regulations, Activities, Contacts, Forms, Consumer Page, Recalls & Alerts, CROs , Barcode Project (pricing data base), Other Inquiries (Circulars & Public statements).

Publishing all drug applications submitted to JFDA, all new chemical entities registered with their Reg.date.

JFDA LAWS

- Public Health Law.
- Food & Drug Administration Law.
- Drug & Pharmacy law #80 for the year 2001 & its relevant amendment law No.30 for the year 2003.
- Clinical Studies Law.
- Narcotic Drugs & Psychotropic substances Law.
- Drug Testing Bylaw.
- Guidelines stemming from the Laws.

DRUG & PHARMACY LAW STEMMING CRITERIA

1. Drug Registration Criteria/2004 **(under development)**.
   - Monitoring of Raw material Criteria/2007.
2. Manufacturing Sites accreditation Criteria /2008**(under development)**..
3. Herbal Medicine Registration Criteria/2007.
4. Vitamins & Minerals Registration Criteria/2008.
5. Radiopharmaceuticals Registration Criteria/2008.

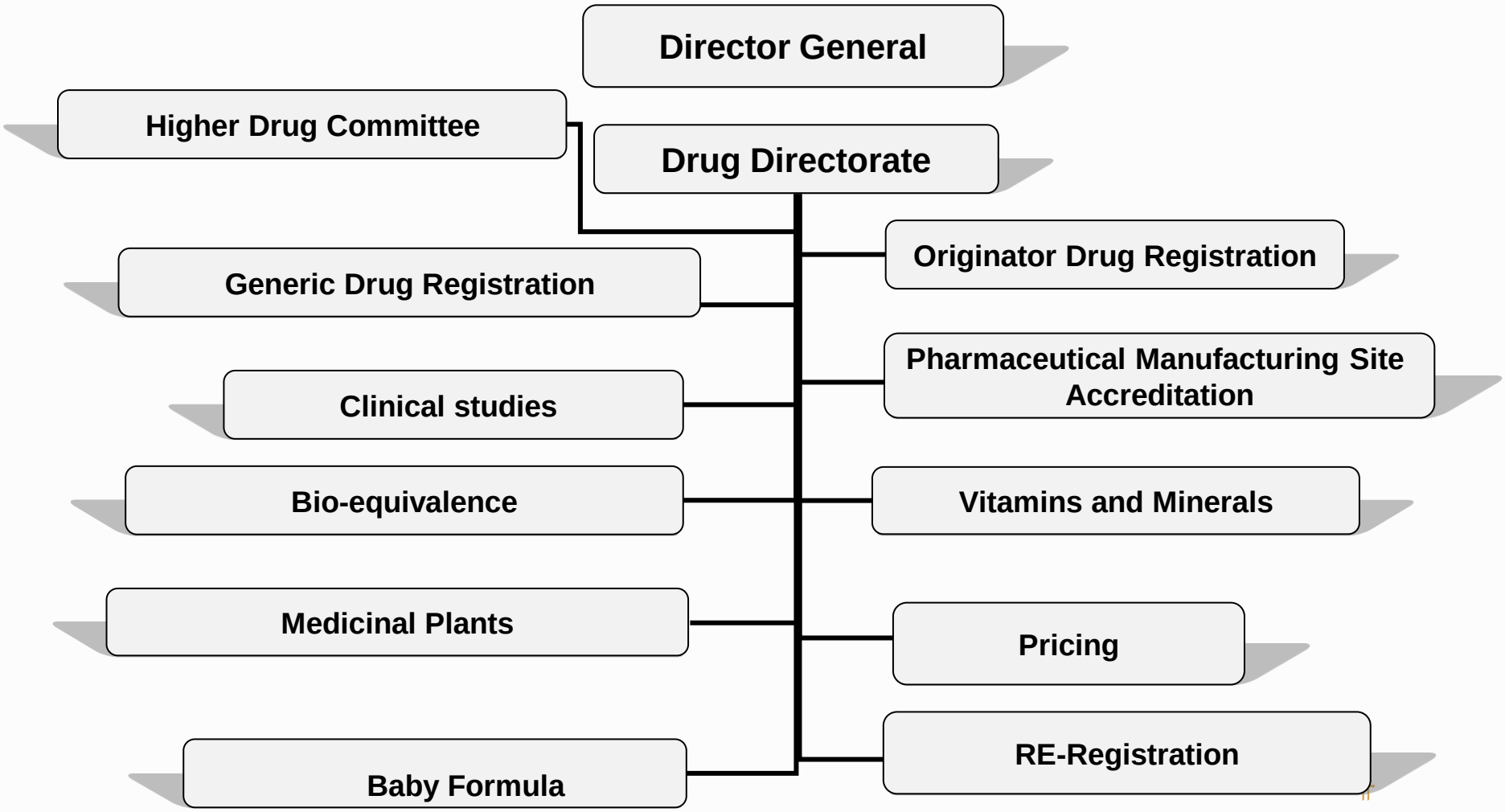
DRUG & PHARMACY LAW STEMMING CRITERIA

6. Infants Milk Formula & their Special Formula /2004.
7. Drug Promotion Guidelines/2008.
8. Medical samples specifications & distribution/2008.
9. Issuing Recommended Daily Allowance List/2009

NEW DRUG&PHARMACY LAW STEMMING CRITERIA:-

1. Clinical Studies Participants' Insurance instructions/2010
2. Technology Transfer Guidelines/2010.
3. Bioequivalence Guidelines/2010.
4. Updating Pharmacovigilance Guidelines/2010.
5. Post Approval Changes /2010.
6. Manufacturing Sites accreditation for (Intermediate products. Soft gelatin caps) 2011.
7. Herbal Product Registration Criteria/2011.
8. VIT D3 Conc. above 1200 IU /2011.

Standing Committees



BIOEQUIVALENCE REGULATIONS :

History :

- 1985 …..BE studies were submitted for NTI drugs only .
- Starting from 2000 … BE studies required for generic drugs registration .
- New Guideline released in 30/9/2010.

BIOEQUIVALENCE GUIDANCE :

- Provide assistance to industry on how to comply with regulations.

- Setting the roles for authority evaluation.

- Have been prepared taking into consideration the need for worldwide harmonization, and at the same time our specific needs .

SECTIONS OF THE BE GUIDANCE :

Defined different Approaches to Determining BE (compared with the reference product for the purposes of registration).

- In vivo BE studies.

- PD studies , Clinical studies, or In vitro method.

It Depends on the characteristics of the active substance , dosage forms .

SECTIONS OF THE BE GUIDANCE :

Deals with:

- Setting general roles for submitting BE studies.
- Format and contents of bioequivalence reports.
  (Check List in appendix n# 1).
- Requirement of comparative dissolution for waiver request .
- Format & content for comparative dissolution
- Clinical study report acceptable (other cases than BE).

GENERAL ROLES FOR SUBMITTING BE STUDY:

- **Accreditation of the centers & laboratory units conducting the BE studies:**

  insurance that they have GCP ,GLP (certification by drug regulatory agencies , or inspection report);

  Or they can be the subject for inspection.

GENERAL ROLES FOR SUBMITTING BE .STUDY

- Bioequivalence studies on generic products are usually conducted on the highest approved strength, unless:

1- there are safety concerns preventing the use of this strength.

2- if non-linear kinetic, then BE should be conducted on the strength(s) that are most sensitive to detect a potential difference between products(conc.).

GENERAL ROLES FOR SUBMITTING BE .STUDY

Study should be conducted on Bio batches :

(Pilot batches may be used provided that they are not smaller than 1/10 of the expected full production batch).

Same manufacturer , same composition for product intended to be marketed (if different the post approval changes or technology transfer guidance should be applied).

BIOEQUIVALENCE – FAST/FED

– For Immediate release: Single dose BE study in fasting state is adequate.

• If food enhances or interferes with drug absorption, a bioequivalence study in fed state should be performed .

– For modified release(including pellets & Beads) : BE study in fasting & under fed conditions should be performed (to ensure absence of dose dumping).

BIOEQUIVALENCE – FAST/FED

Development of Innovator product with immediate release formulation to a Generic with modified release formulation……

BE study in fasting state for all Conc. , with

Fed & Steady state for higher Conc.

THE BE REQUIREMENT FOR THE LOWER STRENGTHS CAN BE WAIVED PROVIDED:

For immediate & modified release drug Products:

(a) In vivo bioequivalence is demonstrated on the highest strengths;

(b) Qualitative composition of the different strengths is the same;

(c) Products are manufactured by the same process& manufacturer;

(d) The composition of the strengths are quantitatively proportional; (acceptable cases of Deviation from Proportionality).

(e) Linear PK profile over the therapeutic dose range.

(f) The in-vitro dissolution profiles of the test products are similar

WHEN BE STUDIES ARE NOT REQUIRED

- An aqueous solution for parenteral use containing same active substance in the same concentration & excipients do not affect the Pharmacokinetics within the biological system.
- Products in aqueous solution and contain active substance in the same concentration as an oral solution currently approved and the excipients in the product do not affect GI transit, absorption of drug substance.
- Gas for inhalation.
- Otic or ophthalmic products prepared as aqueous solutions with topical effect & contain the same active substance(s) in the same concentration & excipients do not affect the Pharmacokinetics within the biological system,

WHEN BE STUDIES ARE NOT REQUIRED

- powders for reconstitution as a solution contain the active substance in the same concentration;

- the BE committee has right to take the appropriate decision in any waiver request does not apply to the above, in the case of a prove on the safety of the use of the active substance in the preparation , & known as there is no problems in the equivalence (non problematic) after assessing supporting documents , for example, applies to grand father products , OTC monograph .

ACCEPTABLE BIOWAIVERS :

Acceptance for replacing an in vivo BE study with in vitro dissolution testing for Immediate release dosage forms:

Class I (BCS) drug substance : Provided that its
- Not 'narrow therapeutic index'
- Linear PK .

Should submit solubility study & and evidence of high permeability of the active substance according to the scientific literature.

Evidence that excipients used do not affect the bioavailability of drug.

ACCEPTABLE BIOWAIVERS :

Class III (BCS) drug substance

(Highly solubility …Low permeability).

are eligible for biowaivers provided all the general criteria are met and the risk-benefit is additionally addressed in terms of extent, site and mechanism of absorption.

COMPARATIVE IN-VITRO DISSOLUTION

For BE :

Comparative dissolution between Test & Ref. in compendial media or applicable media for batches used in BE study.

For waiver request to lower strength:

IR :

Data should demonstrate the similarity of dissolution profile between the lower strength(s)& the higher strengh of the test product

(exception for the (low soluble)with Reference product)

COMPARATIVE IN-VITRO DISSOLUTION

Modified Release :

Data should demonstrate the similarity of dissolution profile between the lower strength(s) & the higher strengh of the test product

And with same conc. of the Ref. drug as the conc. of the test drug.

WHEN OTHER STUDIES REQUIRED TO DEMONSTRATE EQUIVALENCE:

For locally applied product (nasal,, ocular, dermal, rectal vaginal etc) without systemic absorption → pharmacodynamic or clinical studies are required.

(note: if the product has systemic effects a BE study is required)

(Given grace period for 5 years from the issue date of the guidance)

WHEN OTHER STUDIES REQUIRED TO DEMONSTRATE EQUIVALENCE:

- Oral product for local use.
- Replacement therapy for endogenous substances in the body .
- Intra nasal formulations or some inhaled preparations (Inhalers).

HOW & WHAT TO EVALUATE

- **Name of product (narrow therapeutic ,or not)**
- **Dosage form (IR,MR)**
- **Certificate of analysis, Formula No.**
  - of both drugs (Batch No., EXP).
  - Assay difference (Less than 5%).
  - Type of batch Pilot, scale , Commercial.
  - Confirmation that formula did not change ,
  - formulation and full composition .
  - Comparative dissolution profile for 3 batches
- **Study design : Protocol ,Date of Study.**

HOW & WHAT TO EVALUATE

- **Subjects (selection ,number):**
  - –How many
  - –if withdrawn: Why?
  - –Outliers.
- **Study conduct :**
  - – SmPc : Fed or fast?
  - – Fast: 8hr fast before dosing, no food for 4hrs after.
- **Study Parameters PK :** – C_{MAX}
  - –AUC 0 –t at least 80% of AUC 0 –∞, NMT20% of individual has AUC 0 –t less than 80%.
  - – T_{MAX} may be important for some drugs

Critical parameters to look into when evaluating bioequivalence studies

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

DEFICIENCIES USUALLY REQUIRED BY THE B.E COMMITTEE

1- Bioequivalence study on fed condition\ justification.

2- BE study at fasting condition while SmPC of R mentions taking product with food.

3- Certificate of analysis for the reference and for the test product (Assay difference between T & R is > 5%)

4- Not including Outliers results in statistics.

5-Recalculation of AUC using the results of all the volunteers without ignoring any .

DEFICIENCIES USUALLY REQUIRED BY THE B.E COMMITTEE

6- Stability study covering the period that the samples were kept for.

7- GCP certificate for the center from the health authority or inspection report (or it does not cover study date),GLP certificate.,

8-Comparative dissolution between reference and test products in compendial media.

DEFICIENCIES USUALLY REQUIRED BY THE B.E COMMITTEE

10- IRB signatures with date.

11-Bioequivalence study for the higher concentration when a bio-waiver is required for the lower concentration.

12- Absence of study protocol.

13- Justification for the wide range of the C max results.

14- Log-transformed data and diagrams.

16-Changes happened to the composition of bio-batch (comparison of bio-batch vs. proposed production batches).

17- Labeled Chromatograms for the volunteers .

18- Validation report for method of analysis of the active ingredient.

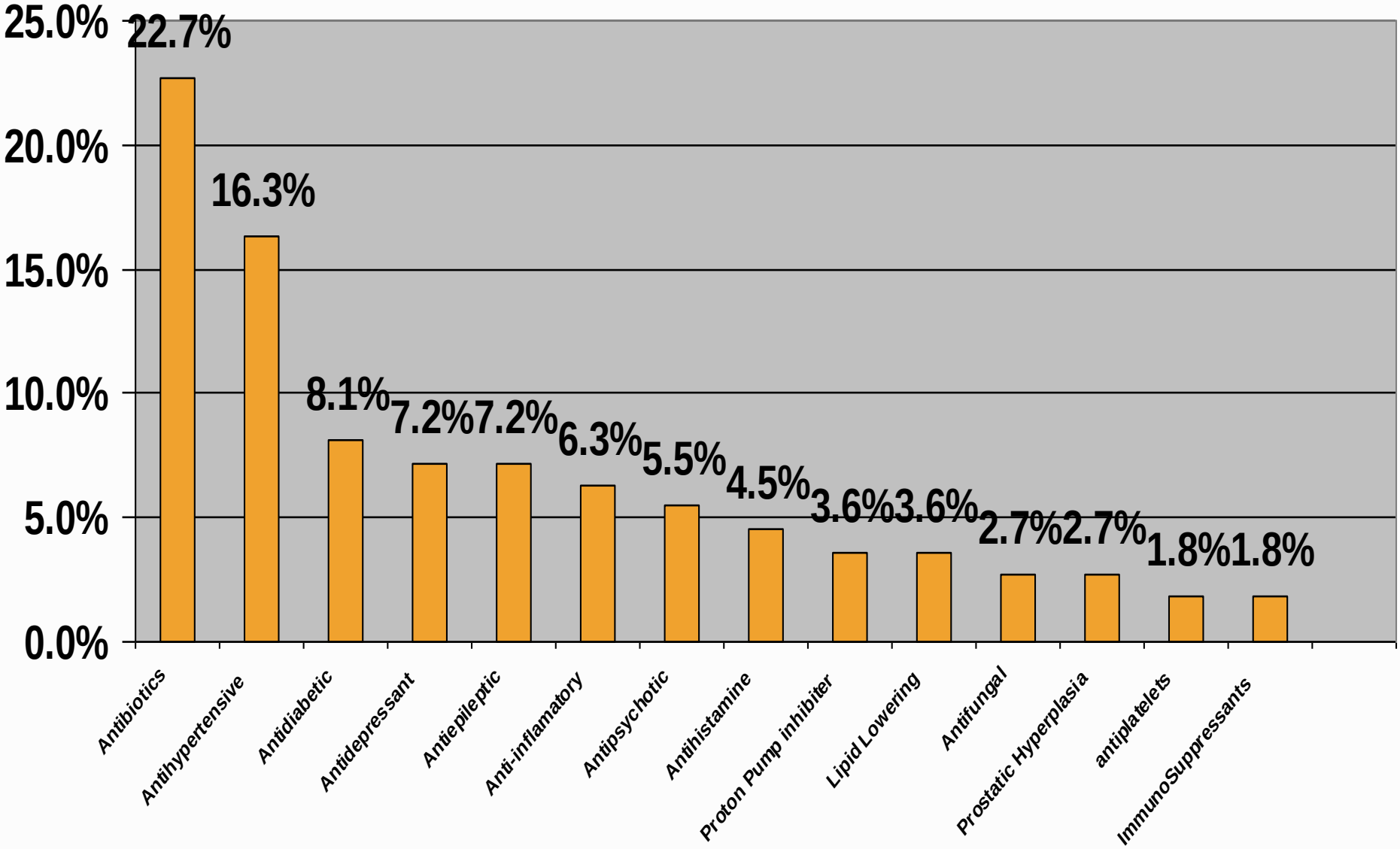
REASONS FOR REJECTING B.E STUDIES BY THE COMMITTEE :

- Absence of GLP or GCP / inspection report.
- Bioequivalence study on fed condition was not provided(in case of modified release).
- Statistical analysis was not accepted due to deletion of some outlier results.
- N# of volunteers (pilot study ,<12).
- Wide range of Cmax (not justified).
- CI of Cmax limits out of permitted one .**..*the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00%-125.00% .*
- IRB signature date was after the date of the study.
- Parent compound not analyzed .***In principle, evaluation of BE should be based upon measured concentrations of the parent compound*

Number of accepted BE & comparative dissolution studies :

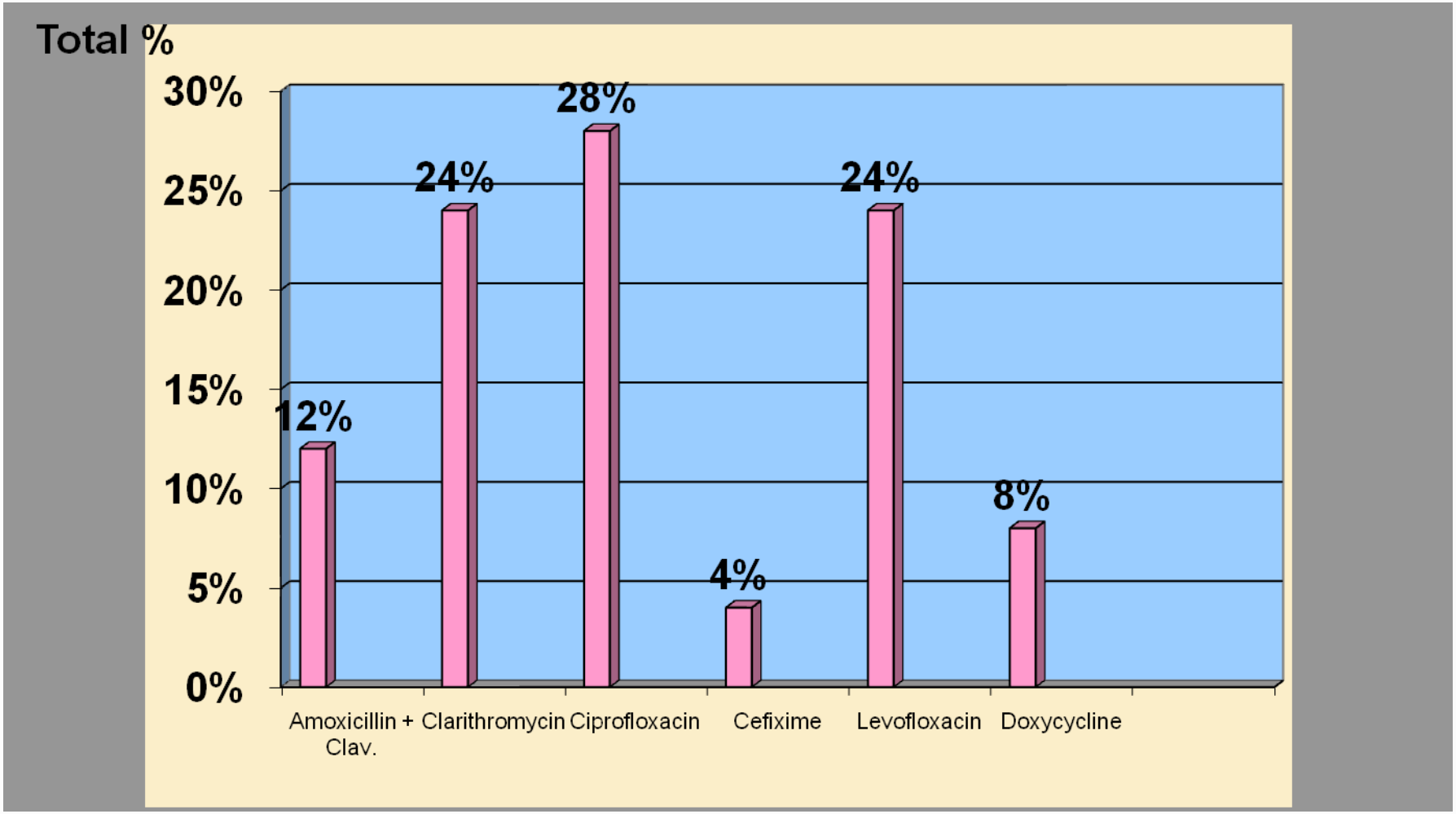
Type of study	2008	2009	2010	2011	2012
BE	63	50	30	58	39
CD	27	42	44	31	63

THE PERCENTAGE OF STUDIES SUBMITTED ACCORDING TO THERAPEUTIC CLASSIFICATION CALCULATED FROM THE TOTAL NO. OF STUDIES



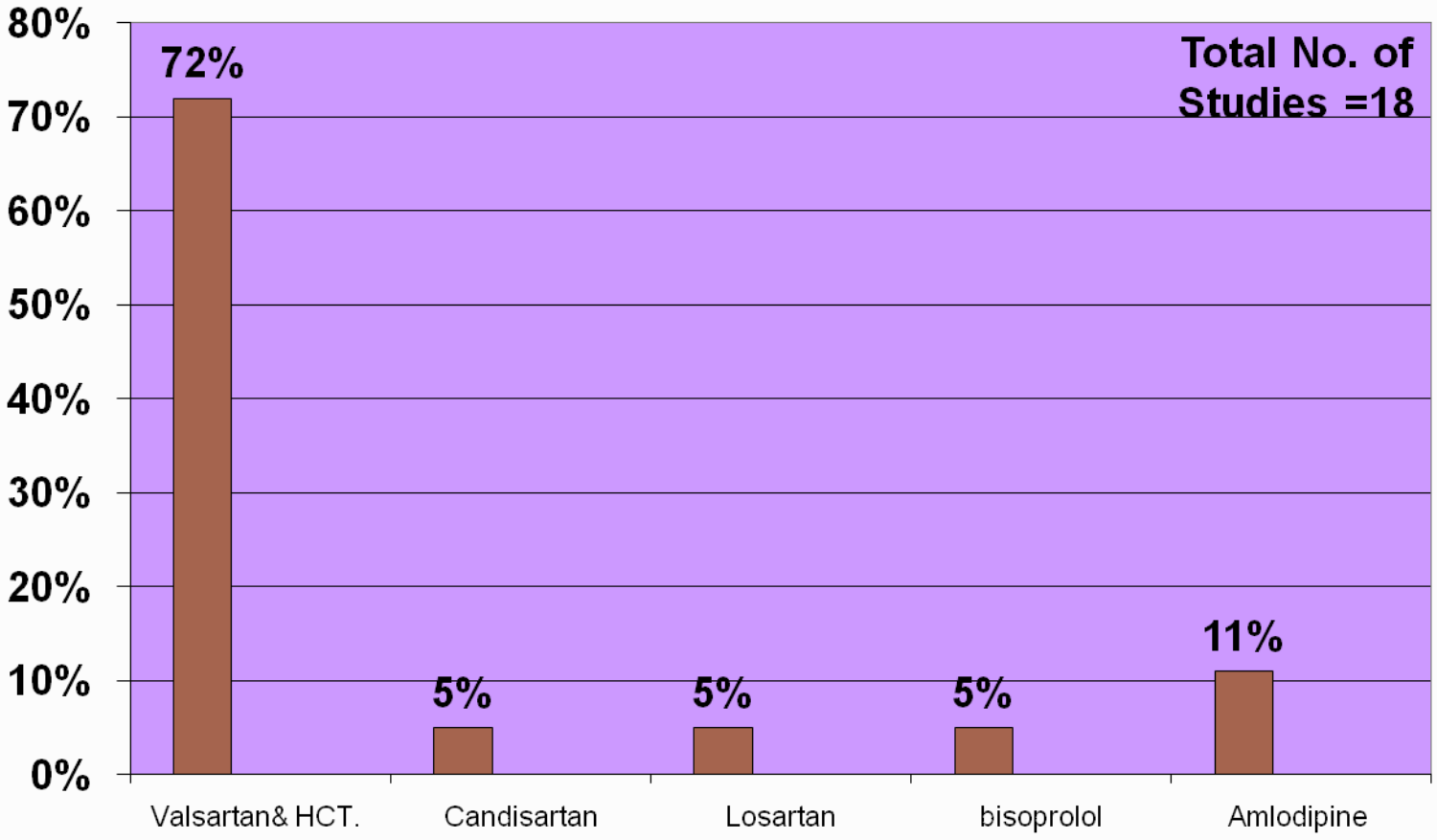
Comparison between percentage of studies for each drug within the same therapeutic classification:

- Antibiotics



COMPARISON BETWEEN PERCENTAGE OF STUDIES FOR EACH DRUG WITHIN THE SAME THERAPEUTIC CLASSIFICATION

ANTIHYPERTENSIVE DRUGS



HIGHLY PROBLEMATIC B.E STUDIES WERE

1- Cyclosporine

2- Nicotine Patches

3- Sod. Alendronate

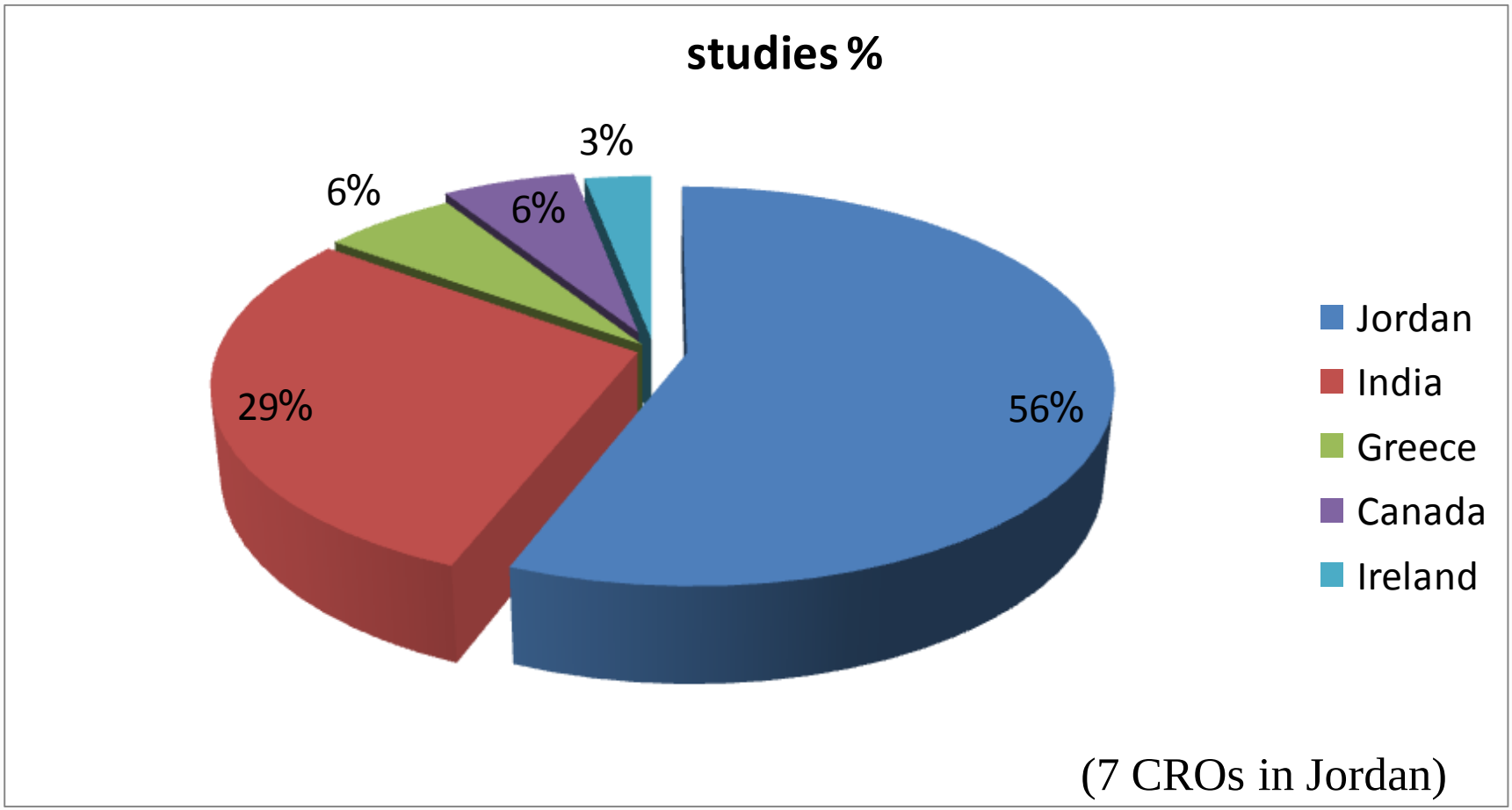
4- Meloxicam

5- Clarithromycin

6- Gliclazide

7- Iraconazole & Fluconazole

PERCENTAGE OF B.E STUDIES SUBMITTED FROM EACH COUNTRY/CENTERS.



THANKS FOR LISTENING