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**ORIGINAL ARTICLE** / ÖZGÜN ARAŞTIRMA

# Bioavailability and bioequivalence studies in Turkey: A status report from the national registry of studies between 2008-2014

## Türkiye'deki biyoyararlanım ve biyoeşdeğerlik çalışmaları: Klinik çalışmalara dair 2008-2014 yılları arasında tutulan ulusal kayıtlardan oluşturulan bir durum raporu

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**ABSTRACT**

**Objective**: To evaluate bioavailability (BA) and bioequivalence (BE) studies conducted in Turkey between January 2008 and the end of June 2014.

**Materials and Methods:** Data on BA/BE studies collected from databases for 2008-2014 studies of Turkish Medicines and Medical Devices Agency were evaluated in terms of endpoint classification (BA/BE), allocation status (randomized/non-randomized), blinding (open/single blind/double blind), dose (single/multiple dose), and interventional group (single group/ parallel/cross-over/factorial).

**Results:** All studies were open, randomized with healthy male volunteers, and the majority had a crossover design and a single dose. Overall, 670 studies were conducted in Turkey between January 2008 and June 2014, while BE (n=631, 94.2%) studies formed the major part. All studies conducted between 2008 and 2010 (n=274) were BE studies. Thirty-nine (5.8% of overall studies) BA studies were conducted from 2011 to 2014, including 13 studies in 2011 (33.3% of overall BA studies), 15 in 2012 (38.4% of overall BA studies), 6 in 2013 (15.4% of overall BA studies) and 5 in 2014 (12.8% of overall BA studies).

**Conclusions:** Our findings showed that 670 BA/BE studies were conducted in Turkey between 2008 and 2014, including 631 BE and 39 BA studies with gradual increase in the number of both types of studies throughout the years.

**Keywords:** Bioequivalence, Bioavailability, Clinical trials, Turkey

**ÖZET**

**Amaç**: Türkiye'de 2008 yılı Ocak ayından 2014 yılı Haziran ayı sonuna kadar yapılan biyoyararlanım (BY) ve biyoeşdeğerlik (BE) çalışmalarının değerlendirilmesi.

**Gereç ve Yöntem:** BY/BE çalışmalarına dair veriler Türkiye İlaç ve Tıbbi Cihaz Kurumu'nun 2008-2014 yılları klinik araştırmalar veritabanından derlenmiştir. Çalışmalar son nokta sınıflandırması (BY/BE), yerleştirme durumu (randomize/ nonrandomize), körleme (açık etiketli/tek kör/çift kör), doz (tek/ çoklu doz) ve müdahaleli grup (tek grup/paralel/çapraz/faktoryal) göz önüne alınarak değerlendirilmiştir.

**Bulgular:** Çalışmaların tamamının randomize yerleştirilen sağlıklı erkek gönüllülerle ve açık etiketli yapıldığı, çoğunluğunun da çapraz tasarımlı olduğu ve tek doz içerdiği belirlenmiştir. Türkiye'de 2008 yılı Ocak ayından 2014 Haziran ayının sonuna kadar 670 çalışma gerçekleştirilmiş, bu çalışmaların büyük bir kısmını ise BE (n=631, %94,2) çalışmaları oluşturmuştur. 2008-2010 yılları arasında yapılan 370 çalışmanın tamamı BE çalışmalarıdır. 2011-2014 yılları arasında toplam 39 (%5,8) BY çalışması yapılmış olmakla beraber 13 çalışma 2011 yılında (BY çalışmalarının toplamda % 33,3'ü), 15'i 2012 yılında (BY çalışmalarının toplamda % 38,4'ü), 6'sı 2013 yılında (BY çalışmalarının toplamda %15,4'ü), 5'i ise 2014 yılının ilk yarısında (BY çalışmalarının toplamda %12,8'si) yapılmıştır.

**Sonuç:** Bulgularımız, yapılan 670 çalışma arasında 631 BE ve 39 BY çalışması bulunduğunu ve yıllar içerisinde çalışma sayısının her iki çalışma türünde de kademeli olarak arttığını göstermiştir.

**Anahtar kelimeler:** Biyoeşdeğerlik, Biyoyararlanım, Klinik araştırmalar, Türkiye

## Introduction

Measurement of bioavailability (BA) of new drug candidates is an essential component of not only the drug development process but also the registration files submitted to the health authority. On the other hand, demonstration of bioequivalence (BE) of the generic with the innovator

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(reference) drug product via conduction of a clinical trial in healthy volunteers by measuring blood/urine concentrations of the active ingredient has been an essential part of generic drug portfolio implemented by drug manufacturers [1,2].

BA/BE studies are included within the drug licensing process in Turkey and these studies sponsored by local or international companies have been conducted in certain accredited centers following the approval by the ethics committee and the institutional permission.

Conduction of clinical and analytical phases of BA/BE studies in Turkey is based on definitions included in the "Regulation for the Evaluation of Bioavailability and Bioequivalence of Pharmaceutical Products" (27 May 1994/21942) [3] and "Regulation for the Clinical Trials on Pharmaceutical and Biological Products" (13 Apr 2013/28617) [4] promulgated in the Official Gazette of the Republic of Turkey.

According to these regulations, BA is defined as "the rate and extent to which the active ingredient or active moiety is absorbed from a pharmaceutical form and becomes available in the general circulation and thereby at the site of action or reflecting biological fluids, generally serum or plasma", BE is defined as "the state of two products' being pharmaceutically equivalent and their bioavailabilities' after administration in the same molar dose being similar to such degree that their effects, with respect to both efficacy and safety, are essentially the same".

The present study was designed to evaluate characteristics of BA/BE studies conducted in Turkey in 2008-2014 based on data from database of authority in Turkey.

## Materials and Methods

Data on BA/BE studies in 2008-2014 were collected from database of Turkish Medicines and Medical Devices Agency. BA/BE studies were conducted in four centers accredited for clinical (Erciyes University Hakan Cetinsaya Center for Good Clinical Practice, Kayseri; Gaziantep University FARMAGEN Center for Good Clinical Practice, Gaziantep and Ege University Drug Development and Pharmacokinetic Research - Application Center (ARGEFAR), Izmir) and analytical (Ege University Drug Development and Pharmacokinetic Research - Application Center (ARGEFAR), Izmir and Novagenix Bioanalytical Drug R&D Center, Ankara) phases of BA/BE studies in Turkey. Blood/urine drug concentration measurements (analytical phase) in the BA/BE studies of which the clinical phases are conducted in the above centers might have performed in or out of the country.

Studies conducted within 2008-2014 were evaluated in terms of endpoint classification (BA/BE), allocation status (randomized/non-randomized), blinding (open/single blind/double blind), dose (single/multiple dose), and interventional group (single group/parallel/cross-over/factorial).

The present study was exempt from the requirement of ethical approval in relation to its retrospective design.

*Statistical Analysis*

Descriptive statistics were used to characterize the bioequivalence and bioavailability studies identified in the national registry. Data are expressed as "mean (standard deviation; SD)", minimum-maximum and percent (%) where appropriate.

## Results

*Sponsors*

According to data of BA/BE studies in 2008-2014, sponsors were generally local companies but also foreign companies conducted BA/BE studies in accredited centers in Turkey.

*Volunteers*

Volunteers registered in BA/BE studies are all healthy male and female volunteers. All volunteers were also documented to be healthy adults (generally age 18-55 years). According to data from four accredited clinical centers in 2013 totally 14800 healthy volunteers were registered to their volunteer pool.

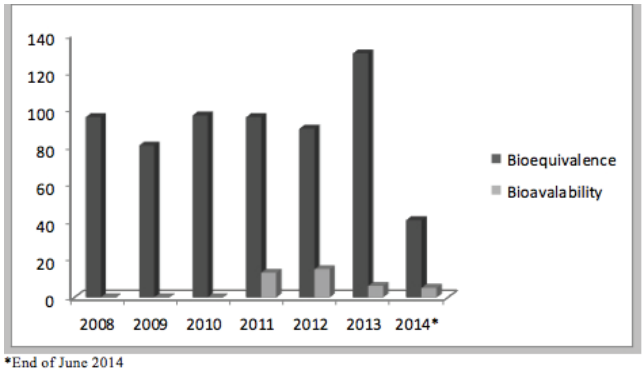
*Study design*

Generally, the BE studies were single dose, open label, randomized, crossover studies with healthy volunteers. Also parallel design studies and multiple dose studies have been conducted but the number of that study designs were very few. The number of multiple dose studies was totally eight during the time period from 2008 to 2014.

According to databases generally, BA studies have been conducted one arm, single dose with healthy volunteers.

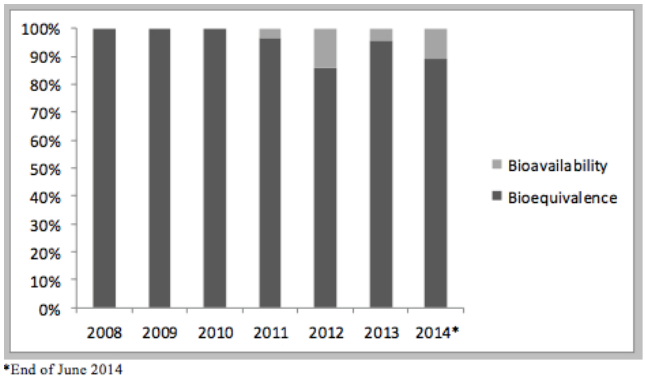
*Endpoint*

Figure 1 shows that overall 670 BA/BE studies were conducted in Turkey between 2008 and 2014, of that BE (n=631, 94.2%) studies formed the majority. From 2008-2010 all were BE studies, while a total of 39 (5.8%) BA studies were conducted in 2011, 2012, 2013, and 2014 (Figures 1 and 2). The number of BE studies per year was 96 in 2008, 81 in 2009, 97 in 2010, 96 in 2011, and 90 in 2012, 130 in 2013, and 41 in the first half of 2014 (Figure 1). There were 13 BA studies in 2011, 15 in 2012, 6 in 2013, and 5 in the first half of 2014. Most of the studies included in this study are completed.




*End of June 2014

**Figure 1.** Distribution of bioavailability/bioequivalence studies according to years.




*End of June 2014

**Figure 2.** Distribution of studies according to the study endpoint (bioavailability/bioequivalence)

## Discussion

Evaluation of the database of BA/BE studies conducted between 2008 and 2014 in Turkey revealed that a total of 670 studies (94.2% were BE studies) were conducted in Turkey in this six and a half year period. Conduction of BA studies (n=39) started in 2011 with 13(33.3%) studies and continued in 2012 with 15 (38.4%) studies, in 2013 with 6 (15.4%) studies, and in 2014 with 5(10.9%) studies in the first half of the year. The number of BE studies was around 90 per year, it raised to 130 in 2013.

In a recent analysis of all BA and BE studies registered in the United States Clinical Trials.gov registry from late 2007 through 2011 [2], it was determined that over this period, more than 2300 interventional BA/BE studies were registered. Overall, 47 of 227 (21.0%) ongoing studies and 418 of 2161 (19.0%) completed studies were BA studies, while 108 of 227 (48.0%) ongoing studies and 1270 of 2161(59.0%) completed studies were BE studies. Randomized studies composed 76% and 90% and open studies 62.0% and 81.0% of ongoing and completed studies, respectively. Studies with a crossover design composed 30.0% and 79.0% and with participants from both genders composed 82.0% and 75.0% of ongoing and completed studies, respectively [2].

According to our findings most of the studies registered in the national database 2008-2014 were open label, randomized and completed studies with a crossover design including participants from males. Selection of only healthy volunteers in BA/BE studies registered in database in Turkey is in line with the recommendation that BA/BE studies should normally be performed with healthy volunteers to minimize variability and permit detection of differences between pharmaceutical products [5].

Notably, given that most of the studies included in the present database were completed BA/BE studies, it should be noted that in US registry, ongoing BA/BE studies were reported to be more likely to have larger sample sizes, to be in later phase clinical trials, to be double-blinded and less likely to be cross-over trials, to have higher proportion of trials that primarily involved research on treatments and enrolled children, while lesser proportion of trials that exclusively recruited male participants [2].

Accordingly, to increase inpatient bed availability and the number of responsible healthcare personnel, to expand pool of healthy volunteers and to increase the number of analytical centers along with improving analysis capacity of active centers via providing new devices are amongst the targeted strategies of clinical and analytical centers accredited for conduction of BA/BE studies in Turkey.

### Conclusion

In conclusion, our findings related to evaluation of the database of BA/BE studies conducted between 2008 and 2014 in Turkey revealed conduction of 670 studies including 631 BE and 39 BA studies with increase in the number within a six and a half year period. Revealing data on the characteristics of BA/BE studies conducted from 2008 to 2014 in Turkey, our findings provide insight considering current status of BA/BE studies in Turkey and form a basis for future research in this area in relation to healthcare policy and research priorities.

### Acknowledgement

The study was presented at the First National Clinical Trials Congress held in Istanbul, Turkey on May 3-4, 2013 as a poster.

### Conflict of Interest

Authors declare they have no conflict of interest.

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