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ORIGINAL ARTICLE

Changing paradigms in bioequivalence trials submitted to the EMA for evaluation – A clinical and regulatory perspective

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Abstract *Background:* The selection of a robust bioequivalence (BE) study designs for registering a generic product remains still a hard task. This task is still challenging despite the fact that generic products are much needed by health care providers in economical terms. Thus, BE study designs could be a means to allow companies to reduce costs and reach the market earlier. We therefore investigated whether different approaches in various products assessed by the European Medicines Agency during the approval phase resulted in a reduction in resources required to show bioequivalence for different medicinal products.

Methods: European Public Assessment Reports (EPARs) for off-patent medicinal products authorised within the European Union (EU) through the centralised procedure during the period 2007–2015 were retrieved and reviewed to identify the clinical studies that resulted in fewer number of subjects, the number of centres or trial duration versus the two-period crossover design.

Results: 7 studies out of 108 were considered as having benefitted from having a different design. Differences noted included having a different dose allocation scheme, having a different number of dosing periods, having a different number of treatment arms, and having one study evaluating different strengths. Benefits noted included a decrease in the number of subjects and centres required,

Abbreviations: EU, European Union; MA, marketing authorisation; BE, bioequivalence; BCS, Biopharmaceutics Classification System (BCS); CHMP, Committee for Medicinal Products for Human Use; NHS, National Health System; API, active pharmaceutical ingredient; EMA, European Medicines Agency; EPAR, European Public Assessment Report; BSA, body surface area

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decreases in study duration and a reduced number of studies required to demonstrate bioequivalence.

Conclusion: Bioequivalence studies can be designed in a specific manner to require fewer resources to carry out. Fewer resources required to register a medicinal product, could impart an advantage to companies (such as to be first on the market) or could even translate to making medicines more accessible (such as cheaper) to patients.

1. Introduction

In the European Union (EU) a medicinal product needs a marketing authorisation (MA), to be placed on the market. The EU's medicinal products' legislative framework allows for a reduced application for medicines outside their data exclusivity. Such applications include generic medicinal products.

Generic products are defined within the EU by article 10.1 of Directive 2001/83/EC (Directive 2001/83/EC, 2012) as "medicinal product[s] [having] the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies." In the EU, the Committee for Medicinal Products for Human Use (CHMP) guideline on bioequivalence (BE) requires that bioequivalence studies are carried out to show that the rate and extent of absorption of test product are equivalent to reference product. In the EU, the CHMP Guideline on the investigation of bioequivalence was first published in 1998 and subsequently updated (the last update was in 2010) (CHMP, 2010a). In the US, the FDA define BE as the absence of a significant difference in the rate and extent the active ingredient becoming available at the drug action site when administered at the same molar dose under similar conditions in an appropriately designed study. Products classified as generics require less research and development compared to originator products. The MA of a generic medicinal product is supported by bioequivalence (BE) studies instead of full clinical trials for safety and efficacy. A biowaiver may also be requested instead of the BE studies, when justified, in line with the Biopharmaceutics Classification System (BCS) as per CHMP guideline (CHMP, 2010a). As a result the resources required in bringing these products to market are hence substantially lower than those for the originator products.

The aim of a generic manufacturer's pharmaceutical development was to develop me-too medicines (i.e. copies), because if a bio-"better" medicinal product (for example, a formulation with a better bioavailability then the reference product) is developed, the applicant would not be able to register the product as a generic medicinal product. However, the drive to be the first company to reach the market with its generic product so that it benefits from a perceived 'first mover' advantage and thus subsequently a potential significant market share over subsequent generics, is driving generic companies to explore how to reduce further the resources required in bringing generics to market (Grabowski et al., 2011). This effort generally results in generic drugs having lower prices compared to the originator (King and Kanavos, 2002). By encouraging the use of such products, National Health Systems (NHSs) benefit from substantial financial savings (Duerden and Hughes, 2010). The market for generic drugs is very competitive, as several companies may market the same active pharmaceutical ingredient (API) following expiry of the originator product's market exclusivity period (Reiffen and Ward, 2005). In the EU, the standard study design expected for a generic medicine is the randomised, two-period, two-sequence, single-dose crossover design (a crossover design is a repeated measurements design where each patient receives different treatments during the different time periods; the parallel design is one where patients are randomised to a treatment and remain on that treatment throughout the duration of the trial) as per CHMP guideline on the investigation of bioequivalence (please note that the Guideline should be read in conjunction with several guidelines (such as Pharmacokinetic studies in man)) (CHMP, 2010a). However, based upon our experience (as regulators) in evaluating generic medicinal products for human use, we noticed in our assessments different approaches used for BE study designs. This intrigued us to explore further whether the design of such studies was becoming more common and whether they ultimately led to fewer resources required to bring the generic to the market. For this aim, we looked at all the studies submitted to support the MAs of generics issued by the European Commission through the centralised procedure, from September 2007 till February 2015.

2. Materials and methods

All the generic products authorised through the centralised procedure (from September 2007 till February 2015) in the EU were extracted from the European Medicines Agency (EMA) database of centrally approved medicinal products for human use, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (European Medicines Agency, 2015a). The European Public Assessment Report (EPAR) was retrieved for each different product and the relevant BE studies were reviewed to identify the following:

(1) Any studies that were not the randomised, two-period, two-sequence, single-dose crossover design.
(2) Differences in design from other studies submitted for the same API.
(3) Differences in the resources (specifically, identifying reductions in the number of subjects required, the time frame of the study and the number of centres involved for the study) between studies submitted for the same API.

Descriptive statistics for the different products and studies were carried out.

3. Results

3.1. Review of the EPARs for generic medicinal products authorised in the EU (Sep 2007-Feb 2015)

A total of 148 generic products were reviewed (includes both products authorised and 1 product refused) in the EU from September 2007 till February 2015 for 38 different active substances. BE studies were conducted for 32 out of these 38 substances (84.2%). The other 6 APIs containing atosiban, busulfan, docetaxel, methylthioninium, topotecan and zoledronic acid, were exempted from such studies, all due to being formulations intended for parenteral use, which is in line with CHMP guideline on the investigation of bioequivalence (2). Out of the 32 substances for which BE studies were carried out, there were 22 active substances (68.8%) for which more than one generic product was authorised. Medicinal Products containing these 22 substances were submitted with a total of 108 BE studies. The results are shown in Table 1.

Out of these 108 BE studies, 103 employed a crossover design (95.4%) while 5 employed a parallel design. The majority of studies, 91, had two dosing periods (84.3%), 5 had one dosing period, all due to being parallel studies (4.6%), 4 had three dosing periods (3.7%) and 8 had four dosing periods (7.4%). A two-arm comparative design was used for 102 studies (94.4%) and 6 studies (5.6%) opted for a three-arm design. A total of 107 studies (99.1%) were single-dose studies, while 1 study, C11-1612 (RIVASTIGMINE 3M HEALTHCARE LTD (Procedure EMEA/H/C/003824)) (CHMP, 2014) had both single- and multiple-dose components which is understandable since the BE study was used to support a transdermal patch. The results are shown in Tables 2–4.

Analysing the BE studies submitted for the same active substance by different marketing authorisation holders, 7 out of 108 BE studies (6.5%) were identified to be different in design from other studies submitted for the same API. Therefore, it was interesting to understand whether these differences could impact the resources required to carry out the studies compared to the two-period, two-sequence, single-dose crossover design.

3.2. Description of the studies identified

The 108 studies were then analysed and the following themes identified:

Table 1 Descriptive statistics for products and studies reviewed.

Generic products	148
Active Pharmaceutical Ingredients (APIs)	38
APIs having BE studies	32
APIs reviewed[a]	22
BE studies carried out for reviewed APIs	108
Different innovative studies identified	7
Different themes noted	4

[a] Reviewed APIs had BE studies available and were available as more than one product.

Table 2 Study designs submitted.

Study design	Studies
Crossover	103
Parallel	5

Table 3 Number of dosing periods designed.

Number of dosing periods	Studies
One	5
Two	91
Three	4
Four	9

Table 4 Number of arms designed.

Number of arms	Studies
Two	102
Three	6

- Differences in dose allocation.
- Differences in the number of dosing periods.
- Differences in the number of arms.
- Different strengths studied within the same BE study.

3.2.1. Differences in dose allocation

Out of the 108 studies, 1 had a dosing scheme based upon the participants' body surface area (BSA) as compared to other trials on the same active substance. Where studies designed on BSA versus fixed dosing resulted in differences in the number of study centres and patients recruited as follows.

3.2.1.1. Capecitabine: EMA Procedure: EMEA/H/C/002050/0000. 5 generic products were authorised from September 2007 till February 2015: CAPECITABINE SUN (EMA procedure no: EMEA/H/C/002050/0000) (CHMP, 2013a); CAPECITABINE ACCORD (EMEA/H/C/002386) (CHMP, 2012a); CAPECITABINE MEDAC (EMEA/H/C/002568) (CHMP, 2012b); CAPECITABINE ECANSYA (EMEA/H/C/002605) (CHMP, 2012c); CAPECITABINE TEVA (EMEA/H/C/002362) (CHMP, 2012d). The studies used to support the MAs of these 5 generic products are listed in Table 5.

1 bioequivalence study (CPB 500T IR 3265 11(a)) was submitted to support CAPECITABINE SUN (CHMP, 2013a). CPB 500T IR 3265 11(a) employed a different dosing scheme compared to other studies submitted in support of the marketing authorisation for other capecitabine containing products. Study 438-08 submitted in support of CAPECITABINE ACCORD (CHMP, 2012a), CAPECITABINE MEDAC (CHMP, 2012b) and CAPECITABINE ECANSYA (CHMP, 2012c) and studies 130/09-06.CE and 005/10-06.CE submitted for CAPECITABINE TEVA (CHMP, 2012d) all followed a fixed dosing scheme.

Study CPB 500T IR 3265 11(a) was a randomised, open-label, two-treatment, four-period, two-sequence, replicate crossover, single dose BE study aiming to establish the

Table 5 Generic Capecitabine medicinal products authorised in the EU.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/002050/0000	CAPECITABINE SUN	CPB 500T IR 3265 11(a)	2013
EMEA/H/C/002386	CAPECITABINE ACCORD	438-08	2012
EMEA/H/C/002568	CAPECITABINE MEDAC	438-08	2012
EMEA/H/C/002605	ECANSYA (PREVIOUSLY CAPECITABINE KRKA)	438-08	2012
EMEA/H/C/002362	CAPECITABINE TEVA	130/09-06.CE and 005/10-06.CE	2012

comparative BE of CAPECITABINE SUN 500 mg film-coated tablets. The reference product used was XELODA 500 mg film-coated tablets. The formulations were administered to cancer patients under fed conditions.

Study CPB 500T IR 3265 11(a) was conducted in five different centres. The subjects were grouped and dosed based upon their BSA. Subjects having a BSA less than 1.26 m^2 received a total daily dose of 3000 mg of capecitabine, subjects with BSA between 1.53 and 1.66 m^2 received a daily dose of 4000 mg and subjects with a BSA between 1.93 and 2.06 m^2 received a daily dose of 5000 mg. The test and reference formulations were administered thirty minutes after administration of a high fat high calorie breakfast, on each of days 1–4, representing periods I–IV. All of the subjects received 2 mg intravenous granisetron thirty minutes (±10 min) prior to each dose.

Study CPB 500T IR 3265 11(a) enroled fifty (50) subjects while the other three studies, study 438-08, study 130/09-06.CE and study 005/10-06.CE, had a mean of seventy-seven subjects (n = 3, range 70–88). In addition study CPB 500T IR 3265 11(a) was conducted in five (5) different sites as opposed to the fixed dose, two-period study 438-08, used to support granting of the MA for CAPECITABINE ACCORD, CAPECITABINE MEDAC and ECANSYA, which study was conducted in thirteen (13) different centres. The duration of the clinical part of study CPB 500T IR 3265 11(a) was not specified in the CAPECITABINE SUN EPAR.

3.2.2. *Differences in the number of dosing periods*

Out of the 108 studies reviewed 8 studies had four dosing periods (Refer to Table 6):

- 3 studies related to Capecitabine (studies 130/09-06.CE (CHMP, 2012d); 005/10-06.CE (CHMP, 2012d) and CPB 500T IR 3265 11(a) (CHMP, 2013a)).
- 1 study related to Clopidogrel (2009–2089) (CHMP, 2011a).
- 2 studies related to Ibandronic Acid (IAT-P9-457 (CHMP, 2010b, 2011b) and IAT-P7-289 (CHMP, 2010c)).
- 1 study related to Mycophenolate (Study 3668) (CHMP, 2010d).
- 1 study related Telmisartan/Hydrochlorothiazide (study 2335/11) (CHMP, 2013b).

3.2.2.1. Capecitabine – EMA Procedures EMEA/H/C/002362, EMEA/H/C/002050/0000. Studies, 130/09-06.CE and 005/10-06.CE (Procedure EMEA/H/C/002362) (CHMP, 2012d) and CPB 500T IR 3265 11(a) (Procedure EMEA/H/C/002050/0000) (CHMP, 2013a) followed a four-period design. While Study 438-08 submitted in support for granting of an MA for CAPECITABINE ACCORD (Procedure EMEA/H/C/002386) (CHMP, 2012a), CAPECITABINE MEDAC (Procedure EMEA/H/C/002568) (CHMP, 2012b) and ECANSYA (Procedure EMEA/H/C/002605) (CHMP, 2012c) followed a two-period design.

Study CPB 500T IR 3265 11(a) has already been described in the previous section. Study 130/09-06.CE and Study 005/10-06.CE, were both randomised, open-label, two-treatment, four-period, two-sequence, replicate crossover, single dose BE studies. The two studies aimed to evaluate the BE of CAPECITABINE TEVA 150 mg tablets and 500 mg tablets respectively, with the reference XELODA equivalent strength tablets.

Subjects in Study 130/09-06.CE, all undergoing a treatment cycle of capecitabine chemotherapy, were administered a fixed dose of 1950 mg made up of 150 mg tablets on the mornings of days 1, 2, 8 and 9, representing periods I–IV. The doses were administered following a high-fat high-calorie breakfast. The evening dose was of the product normally used during the rest of the treatment cycle. The same procedure was followed for Study 005/10-06.CE, with the exception that subjects received a fixed dose of 2000 mg made up of 500 mg tablets.

Table 6 Generic medicinal products submitted with studies having four dosing periods.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/002362	CAPECITABINE TEVA	130/09-06.CE and 005/10-06.CE	2012
EMEA/H/C/002050/0000	CAPECITABINE SUN	CPB 500T IR 3265 11(a)	2013
EMEA/H/C/001226	CLOPIDOGREL TEVA PHARMA B.V.	2009-2089	2011
EMEA/H/C/002025	IASIBON	IAT-P9-457	2010
EMEA/H/C/001195	IBANDRONIC ACID TEVA	IAT-P7-289	2010
EMEA/H/C/1218	MYCLAUSEN	Study 3668	2010
EMEA/H/C/002676/0000	ACTELSAR HCT	2335/11	2013

All four-period studies conducted for capecitabine-containing products (i.e. studies 130/09-06.CE; 005/10-06.CE and CPB 500T IR 3265 11(a)) had an average of (64) sixty-four subjects ($n = 3$, range 50–72). In contrast, the two-period Study 438-08 (Procedures EMEA/H/C/002386, EMEA/H/C/002568 and EMEA/H/C/002605) submitted to support the granting of an MA for CAPECITABINE ACCORD (CHMP, 2012a), CAPECITABINE MEDAC (CHMP, 2012b) and ECANSYA (CHMP, 2012c) had (88) eighty-eight subjects (see Table 5).

In terms of study duration, the four-period capecitabine studies were of the following lengths: 5 months (13 April to 13 September 2010) for Study 130/09-06.CE and 3 months (19 July to 26 October 2010) for Study 005/10-06.CE. In contrast the clinical portion of the two-period study (Study 438-08) lasted around six months (1 September 2009 to 25 February 2010).

3.2.2.2. Clopidogrel–EMA Procedure EMEA/H/C/001226. For generic products containing clopidogrel ($n = 24$), 1 study was submitted which followed a four-period design while 9 studies were submitted following a two-period design. In total 10 studies were used to support the MAs of 24 clopidogrel medicinal products (this is possible as parallel procedures are acceptable upon regulatory filing; see Table 6). The four-period study 2009–2089 conducted for CLOPIDOGREL TEVA PHARMA B.V (Procedure EMEA/H/C/001226) (CHMP, 2011a) enroled 96 subjects. From a total of 9 two-period studies, 8 specified the number of subjects which had a mean of 70 subjects (range 23–117). Thus it seems that a four-period design did not have a reduction in the number of subjects required for the study.

3.2.2.3. Ibandronic acid – EMA procedures EMEA/H/C/2025, EMEA/H/C/002367, EMEA/H/C/001195. There were only 2 studies submitted for products containing ibandronic acid, which both followed a four-period design: Study IAT-P9-457 submitted for both IASIBON (Procedure EMEA/H/C/2025; Finalised Regulatory Evaluation Year 2010) (CHMP, 2010b) and IBANDRONIC ACID SANDOZ (Procedure EMEA/H/C/002367; Finalised Regulatory Evaluation Year 2011) (CHMP, 2011b) and study IAT-P7-289 submitted for IBANDRONIC ACID TEVA (Procedure EMEA/H/C/001195; Finalised Regulatory Evaluation Year 2010) (CHMP, 2010c). Therefore, since no studies have been submitted with a two period design to support a marketing authorisation with ibandronic acid it was not possible to compare these studies with the four-period studies for ibandronic acid.

3.2.2.4. Mycophenolate – EMA procedure EMEA/H/C/001218. Study 3668, submitted as support for the granting of an MA for MYCLAUSEN (Procedure: EMEA/H/C/001218) (CHMP, 2010d) was conducted to verify the BE of the test product, after a previous two-period study on the same product, and Study 411-87-06-02-0001 (Procedure: EMEA/H/C/001218) (CHMP, 2010d), had been inconclusive. As a result, study 3668 could not be considered as having been designed in order to prove the product's BE on its own. Comparison with other studies is therefore not suitable.

3.2.2.5. Telmisartan/Hydrochlorothiazide – EMEA/H/C/002676/0000. Out of two studies submitted for telmisartan/hydrochlorothiazide combination products one, Study 2335/11 (Procedure EMEA/H/C/002676/0000) (CHMP, 2013b) submitted to support the granting of an MA for ACTELSAR HCT, was a four-period study (see Table 7). The other study, Study 10-302, submitted as support for granting of an MA for TOLUCOMBI (Procedure EMEA/H/C/002549) (CHMP, 2013c), was a two-period study.

Study 2335/11, was a randomised, open-label, two-treatment, four-period, two-sequence, replicate crossover, single dose BE study evaluating the BE of ACTELSAR HCT 80 mg/25 mg tablets with MICARDIS PLUS 80 mg/25 mg tablets under fasting conditions.

The number of subjects enroled differed between the studies, where Study 2335/11 had 48 subjects, while Study 10-302 enroled 70 subjects. Duration of the studies was not specified in the EPARs.

3.2.3. Different number of arms

Out of the 108 studies reviewed, 6 had three arms, as opposed to two arms (see Table 8).

- 1 study related to Desloratadine (Study 90044) (CHMP, 2012e).
- 1 study related to Imatinib (Study IAI-P1-453) (CHMP, 2013d).
- 1 study related to Temozolomide (Study PKD-08-054) (CHMP, 2011c).
- 1 study related to Irbesartan (Study 1056) (CHMP, 2009a).
- 2 studies related to Olanzapine (Study 60679 and study A37552) (CHMP, 2012f, 2009b–e).

3.2.3.1. Desloratadine – EMA Procedure EMEA/H/C/002404. Study 90044 submitted as support for the granting of an MA for DESLORATADINE RATIOPHARM (Procedure EMEA/H/C/002404) (CHMP, 2012e) was designed to compare the test product with both the EU and the Canadian reference products. However, only results for comparison with the EU product are presented in the EPAR for the product, and therefore, comparison with other three-armed studies is not possible. One possible reason why the results for comparison with the Canadian reference product were not reported in the EPAR could be due to the reference product being sourced from outside the EU and the relevant results were used to register the generic product in a different regulatory region.

3.2.3.2. Imatinib – EMA Procedure EMEA/H/C/002594. Study IAI-P1-453, submitted as support for the granting of an MA for IMATINIB ACTAVIS (Procedure EMEA/H/C/002594) (CHMP, 2013d) was designed to compare the test product with both the EU and the United States (US) reference products. As with DESLORATADINE RATIOPHARM, only results for comparison with the EU product are presented in the EPAR for the product, and therefore, comparison with other three-armed studies is not possible. The same reason as before could explain why this occurred, that possibly, the results for comparison of the generic product with the US reference product, were used to register the generic product in a different regulatory region.

3.2.3.3. Temozolomide – EMA procedure EMEA/H/C/002198. Study PKD-08-054, submitted as support for the granting of an MA for TEMOZOLOMIDE SUN (Procedure EMEA/H/

Table 7 Generic Telmisartan/Hydrochlorothiazide medicinal products authorised in the EU.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/002549	TOLUCOMBI	10-302	2013
EMEA/H/C/002676/0000	ACTELSAR HCT	2335/11	2013

Table 8 Generic medicinal products submitted with studies having three arms.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/002404	DESLORATADINE RATIOPHARM	90044	2012
EMEA/H/C/002594	IMATINIB ACTAVIS	IAI-P1-453	2013
EMEA/H/C/001093	IRBESARTAN TEVA	1056	2011
EMEA/H/C/000810	OLANZAPINE TEVA	A37552	2009
EMEA/H/C/001085	OLANZAPINE GLENMARK	60679	2009
EMEA/H/C/001086	OLANZAPINE GLENMARK EUROPE	60679	2009
EMEA/H/C/001087	OLAZAX	60679	2009
EMEA/H/C/001088	OLAZAX DISPERZI	60679	2009
EMEA/H/C/002198	TEMOZOLOMIDE SUN	PKD-08-054	2009

C/002198) (CHMP, 2011c), was designed to compare the test product with both the EU and the US reference product. However, as with DESLORATADINE RATIOPHARM and IMATINIB ACTAVIS only the results for comparison with the EU product are presented in the EPAR for TEMOZOLOMIDE SUN, and therefore, comparison with other three-armed studies is not possible. As before, it is possible that the results for comparison with the US reference product were used to support the registration of the generic product in a different regulatory region.

3.2.3.4. Irbesartan – EMA procedure EMEA/H/C/001093. A total of 3 studies were submitted for 3 generic products containing irbesartan. Study 1056 submitted as support for the granting of an MA for IRBESARTAN TEVA (Procedure EMEA/H/C/001093) (CHMP, 2009a) was designed to compare two batches of the test product with the reference product; thus, it had 3 arms. Study GE03IRB/1/06 submitted in support for granting of an MA for SABERVEL (Procedure EMEA/H/C/002510) (CHMP, 2012g) and Study IBA-P7-064 submitted in support for granting of an MA for IFIRMASTA (Procedure EMEA/H/C/000962) (CHMP, 2008a) followed a two-arm design.

The three-armed study, 1056, enroled 24 subjects, while the two-arm studies GE03IRB/1/06 enroled 29 subjects and IBA-P7-064 enroled 24 subjects. Therefore the number of arms does not seem to influence the number of subjects required for irbesartan-containing products (see Table 9).

3.2.3.5. Olanzapine – EMEA/H/C/001085, EMEA/H/C/001088, EMEA/H/C/001086, EMEA/H/C/001087, EMEA/H/C/000810. Out of the 11 studies submitted for 9 olanzapine-containing products (see Table 10), the following two studies had a three-arm design: Study A37552, submitted for the granting of an MA for OLANZAPINE TEVA (Procedure EMEA/H/C/000810) (CHMP, 2012f) and Study 60679, for OLANZAPINE GLENMARK (Procedure EMEA/H/C/001085) (CHMP, 2009b), OLANZAPINE GLENMARK EUROPE (Procedure EMEA/H/C/001086) (CHMP, 2010g), OLAZAX (Procedure EMEA/H/C/001087) (CHMP, 2009d) and OLAZAX DISPERZI (Procedure EMEA/H/C/001088) (CHMP, 2009e).

The other nine studies submitted for olanzapine-containing products were all two-arm studies: Studies BS590 and BS591 for OLANZAPINE MYLAN (Procedure EMEA/H/C/000961) (CHMP, 2008b), Study 007/05 for OLANZAPINE CIPLA (Procedure EMEA/H/C/000793) (CHMP, 2007a), Studies 2006-1152 and B0507, both submitted for OLANZAPINE TEVA as well (Procedure EMEA/H/C/000810) (CHMP, 2012f), Protocols 012645 and AA25817, both submitted for ZALASTA (Procedure EMEA/H/C/000792) (CHMP, 2007b) and Studies OL 5063 and OAN-P8-57.1, both for OLANZAPINE APOTEX (Procedure EMEA/H/C/001178) (CHMP, 2010e).

Study A37552 (CHMP, 2012f) was three-treatment, three-period, three-sequence, crossover, single dose BE study evaluating the BE of OLANZAPINE TEVA 20 mg orodispersible tablets. Two reference products were used: ZYPREXA VELOTAB 20 mg orodispersible tablets and ZYPREXA 20 mg film-coated tablets. After an overnight fast, which continued for four hours post-dosing, the subjects received one of the olanzapine formulations. The film-coated tablet, when given, was administered with water, while the orodispersible tablets were administered without water.

Study 60679, submitted to evaluate the BE of OLANZAPINE GLENMARK (Procedure EMEA/H/C/001085) (CHMP, 2009b), OLANZAPINE GLENMARK EUROPE (Procedure EMEA/H/C/001086) (CHMP, 2009c), OLAZAX (Procedure EMEA/H/C/001087) (CHMP, 2009d) and OLAZAX DISPERZI (Procedure EMEA/H/C/001088) (CHMP, 2009e). similar to Study A37552, was also a three-arm study with two reference products, one being a film-coated tablet and the other an orodispersible tablet. This time, the strength used was of 10 mg. However, study 60679, consisting of two dosing periods, differed from study A37552 which had been a three-period study. Study 60679 was hence a two-period crossover study, where participants received the test formulation in one dosing period and the other dosing period involved the administration of either the reference film-coated tablet or the reference orodispersible tablet.

Table 9 Generic Irbesartan medicinal products authorised in the EU.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/001093	IRBESARTAN TEVA	1056	2009
EMEA/H/C/002510	SABERVEL	GE03IRB/1/06	2012
EMEA/H/C/000962	IFIRMASTA	IBA-P7-064	2008

Table 10 Generic Olanzapine medicinal products authorised in the EU.

Procedure number	Product name	Study	Finalised regulatory evaluation (Year)
EMEA/H/C/000792	ZALASTA	Protocol 012645, Protocol AA25817	2007
EMEA/H/C/000793[a]	OLANZAPINE CIPLA	007/05	2007
EMEA/H/C/000810	OLANZAPINE TEVA	2006-1152, B0507, A37552	2009
EMEA/H/C/000961	OLANZAPINE MYLAN	BS590, BS591	2008
EMEA/H/C/001085	OLANZAPINE GLENMARK	60679	2009
EMEA/H/C/001086	OLANZAPINE GLENMARK EUROPE	60679	2009
EMEA/H/C/001087	OLAZAX	60679	2009
EMEA/H/C/001088	OLAZAX DISPERZI	60679	2009
EMEA/H/C/001178	OLANZAPINE APOTEX	OL 5063, OAN-P8-57.1	2010

[a] Current Licensing status: Not authorised.

The number of participants enroled in both studies, thirty for each study, was similar to the mean number enroled for the nine two-arm studies: twenty-four (n = 9, range: 21–28). Duration of the studies was not specified in the EPARs.

4. Discussion

This study was carried out using information derived from EPARs available on the EMA website (www.ema.europa.eu). It is our opinion that the publication of EPARs not only helps to foster and build trust in the EU regulatory network and the manner in which risk-benefit evaluation is carried out by the EMA, but EPARs are information rich and help provide the data required to be able to carry out regulatory science research, albeit all the published information EPARs could be improved by having the same level of details across all products (European Medicines Agency, 2015b). The results of this study (although based on a limited amount of data as a low number of bioequivalence studies have been identified for this review are still of value as publicly accessible information on these studies is scarce), suggest that different clinical strategies are being implemented by sponsors/CROs to support a marketing authorisation that could result in a decreased number of resources required to carry out the scientifically robust BE studies that are required to the grant a MA in line with the CHMP's guideline on the investigation of bioequivalence (CHMP, 2010a). Our review indicates that generic manufacturers usually follow the same clinical development programme and carry out a two period-crossover design; however, there were exceptions, where changes could have been introduced due to the impact of increased scientific knowledge on the subject and due to changes in the regulatory framework (i.e. the EU guideline on BE was updated in 2010). Within the centralised marketing authorisation procedure, some generic manufacturers have used other crossover designs. For example, one generic manufacturer has used the four period crossover design for capecitabine. Reasons for such a choice could relate to the possibility to estimate a treatment effect even in the presence of a carry-over effect as this design can provide estimates of the intra-subject variability and draw inference on the carry-over effect (Reed, 2012). In fact the usual choice of a four-period design is when carryover effects are predicted. In Capecitabine's case, it is metabolised into active 5′-DFCR, 5′-DFUR, 5-FU and FBAL. For all these compounds the half-lives are short, reported at 0.85, 1.11, 0.66, 0.76 and 3.23 respectively (CHMP, 2015). Therefore no carryover effect was expected for studies with Capecitabine, yet this choice of study design by one of the generic manufactures resulted in the need to recruit few patients than the two-way crossover design and was adequate to fulfil the criteria required to register the product in the European Union. For telmisartan, although absorption is rapid, the amount absorbed varies with food resulting in a reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan of 6% (40 mg dose) to approximately 19% (160 mg dose). However, 3 h after administration, plasma concentrations are similar if telmisartan is administered with or without food. Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate (CHMP, 2013b). In this study, for telmisartan/hydrochlorothiazide combination containing products reviewed (similar to Capecitabine), no carry-over effect was expected and the four-period studies required less subjects than other designs. While for olanzapine- and temozolomide-containing products, some dossiers contained studies with 3-period studies and although this design did not result in a decrease in the number of subjects recruited into the trial or the centres required for the trial, were specifically designed to support the registration of the generic medicine in non-EU territory (as the 3rd arm was carried with non-EU product). It is clear that such a trial design provides the advantage to reduce costs required to carryout another BE study for filing in a non-EU territory (like the US). From

a pharmacokinetic point of view, no carryover effect is expected (thus the study design was shown to be appropriate) as Olanzapine is biotransformed in the liver by conjugative and oxidative pathways. The major metabolite is 10-N-glucuronide (but does not pass the blood brain barrier). Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites which are both significantly less active than the parent compound olanzapine (CHMP, 2012f, 2009b). Clopidogrel is extensively metabolised by the liver by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4 (CHMP, 2011a). In the EU, it is expected that evaluation of bioequivalence is based upon measured concentrations of the parent compound since the Cmax of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than Cmax of a metabolite. Therefore, it is expected that problems with instability create problems with detection and the use of a metabolite as a surrogate for an active parent compound in the EU is not encouraged, but can be justified by prospective applicants if they show that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration (CHMP, 2010a). Applicants should also consider if their product is a highly variable drug (HVD) whose intra-subject variability is larger than 30%. If this is the case, then in the EU, the acceptance criteria for Cmax can be widened to a maximum of 69.84–143.19%; however, this must be thoroughly justified by prospective applicants (CHMP, 2010a).

5. Conclusion

This study shows that in the generic industry, different study designs are being carried out that lead to reductions in the resources required for carrying out the study (such as the number of subjects recruited, the number of centres required and the study duration). When fewer resources are required to register a medicinal product, this could lead to an advantage to generic manufacturers (such as to be first on the market) by making medicines more accessible to patients.

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