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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.