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Evaluation of the Bioequivalence Documentation Required For Registration of Generic Drug Products in Burkina Faso: Methodology of Implementation and Impact

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Abstract

With a view to better warranty quality, efficacy and security of generic medicines, the national medicine regulatory authority (NMRA) of Burkina Faso has firstly evaluated in 2009, the country marketing authorization legal provisions and procedures. Then, a new procedure intended to enforce the technical evaluation of the registration applications has been adopted and progressively implemented during 2010 and 2011. This evaluation included the compliance of generic drugs to the quality and bioequivalence requirements. The results of the evaluations of the bioequivalence documentations provided in 2009, 2010 and 2011 for the registration of generic drugs were collected, analyzed and compared. Only the capsule and tablet oral dosage forms were considered in this study.

The implementation of the new procedure did not discourage the applicants since the number of the drug registration applications has progressively increased from 2009 to 2011. More than 72% and 54% of the applications respectively concerned generic drugs and generic oral solid forms (tablets and capsules). These included various therapeutic groups and were mainly manufactured in Asia, Europe and Africa. The adjournment rates of the registration applications, whatever the reasons, were 11.1%, 32.5% and 51.9% in 2009, 2010 to 2011, respectively. Those for absence or non compliance of bioequivalence documentation were also dramatic and progressively increased from 0%, 26.4% and 51.4% in 2009, 2010 and 2011, respectively.

This work shows that implementation of a more rigorous bioequivalence evaluation for registration of generic drugs is not only benefic and necessary in term of public health but also, performable in the sub-Saharan African developing countries.

Keywords: Generic drug; Marketing authorization; Bioequivalence documentation; National medicine regulatory authority (NMRA); African countries

Introduction

To ensure quality, efficacy and safety of medicines, one of the most important activities of any national medicine regulatory authority (NMRA) is to approve the pharmaceutical products, also known as registration or marketing authorization of drugs [1].

To increase the financial accessibility of people to the medicines, the pharmaceutical politics of the developing countries like Burkina Faso encourage the use of generic drug products, which are pharmaceutical equivalents to the innovator brand-name drugs. The two types of drugs contain the same active pharmaceutical ingredients (API) or drug substance in the same strength, the same dosage form and the same route of administration. However, they may differ in certain aspects like shape, configuration, packaging, excipients and manufacturing process [2,3].

The therapeutic equivalence, that to say the similarity of therapeutic effects (efficacy and safety) between generic and original brand-name (innovator's) formulations is essential for interchangeability purposes. The documentation of the interchangeability is currently provided by *in vivo* bioequivalence studies and rarely, by *in vivo* therapeutic response trials [4]. However, *in vitro* alternative methods like comparative dissolution tests can be used in some conditions [5,6]. The bioequivalence documentation has also to be claimed and adequately evaluated by the pharmaceutical regulatory authorities [1].

In this respect, the NMRA of Burkina Faso has engaged since 2009, a process intended to implement the evaluation of bioequivalence data provided by the manufacturers for registration of their generic drugs. This engagement has become necessary because prescribers and patients are more and more exigent for the efficacy and safety of the drugs available in the country regulated market.

This paper firstly describes the method of the implementation of bioequivalence requirements for registration of generic drugs in Burkina Faso, a West African developing country. It secondly analyses and discusses the impact of this implementation on the rates of marketing approvals of the generic solid oral dosage forms such as capsule and tablet recorded in 2009, 2010 and 2011.

Materials and Methods

This study, which focuses on the methodology of implementation of the bioequivalence evaluation during the registration process and its impact, is retrospective, descriptive and analytical.

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Study of the implementation methodology for bioequivalence requirements

The legal provisions, plans and operating procedures available and used from 2009 to 2011 by Burkina Faso NMRA for reviewing the drug registration applications have been collected and analyzed. This analysis was focused on the aspects related to the generic medicines and their bioequivalence requirement and evaluation. The evaluation reports of the various applications have also been examined with a view to verify the respect of the national legal provisions and procedures. Finally, the modes of information and communications established with the public (applicants) were analyzed by visiting the NMRA web site (www.dgpml.sante.gov.bf), letters and administrative notes.

Measurement of the impact of the bioequivalence evaluation implementation

To measure the impact of the provision described above, information and data were collected from the different evaluation reports and notifications concerning the drug registration applications submitted to the NMRA in 2009, 2010 and 2011.

The variable of studies were the year of the application submissions, the characteristics of the drugs (generic or brand-name drugs, dosage form, route of administration, therapeutic class, origin), the rate of the application adjournments and the characteristics of the bioequivalence information (presence, type, design and methodology, compliance).

EpiInfo version 7.1 Software was used for the collection of the data. The variables being qualitative, the data were summarized as numbers and/or percentages.

Results and Discussion

Methodology of the implementation of the bioequivalence requirements

The review of the marketing authorization process has been firstly done at 2009 by the NMRA of Burkina Faso, using the guidelines proposed by World Health Organization (WHO) [7]. It showed that the national legal provisions [8] and those of the Economic and Monetary Union of West Africa (EMUWA) [9] adapted from the WHO recommendations [1], clearly describe the approval process of the pharmaceuticals products (registration, re-registration and renewal). The demonstration of quality and bioequivalence is therefore required for registration of generic drugs. However, evaluations of the registration applications by the NMRA were very weak, and the bioequivalence compliance was not verified.

The NMRA has then proposed, at the end of the year 2009, a progressive scheme to implement evaluation of the applications, including that of the bioequivalence data for generic drugs. In this respect, it has established clear and detailed procedures involved the recording of the application evaluation results and information. It has also trained the evaluators and implemented since 2010, the EMUWA drug registration guidelines. In these guidelines, the registration applications have to be firstly evaluated by a restraint and specialized expert comity and secondly, by a national large technical committee [9].

The guidelines of EMUWA regarding drug interchangeability, similar to the international ones [10-12], were applied to the generic solid oral dosage forms (tablets and capsules) during the years 2010 and 2011. For the first year of implementation (2010) and in order to avoid an abrupt change, the NMRA had also decided to approve applications if the dissolution test results were provided and compliant with the specifications of the United States, British, European or International pharmacopeias, even though bioequivalence was not correctly documented.

Appropriate communications with the applicants, that is necessary for the success of implementation of changes in the marketing authorization procedure [1], have been also enforced as follows:

- Diffusion to the public by displays or via the NMRA web site of the applicable policies, procedures, specifications, lists of approved products, administrative notes and plans of implementation, synthesis of the NMRA decisions ;
- Notifications by letters addressed to the applicants of the NMRA decisions (approval, adjournment or rebus), queries and delay of responses.

Impact of the bioequivalence evaluation implementation

Table 1 shows general information about the pharmaceutical products for which applications are been submitted for registration in Burkina Faso in 2009, 2010 and 2011. It can be observed that the number of applications progressively increased from 2009 to 2011, whatever the type of the drug product. The implementation of a more rigorous, clear and transparent system of evaluation of the drug applications for registration by African countries does not discourage the applicants.

More than 70% of the registration applications received by the NDRN concerned generic drugs, under special denominations or International Nonproprietary Names (INN). Contrary to the more expensive innovative brand-name drugs (new principle (API), new associations of existing API or new formulations), generic drugs are more affordable. According to Bamako initiatives [13], the use of generic drug products is strongly promoted by the African countries with a view to significantly increase the financial accessibility of the people to the healthcare.

Oral solid dosage forms (capsules and tablets), the most common formulations, represent more than the half of the generic drugs

Categories of products	2009		2010		2011	
	N	%	N	%	N	%
Total of products (Brand-name and generic products)	**221**	**100 %**	**361**	**100%**	**433**	**100%**
Brand-name drugs	28	12.7%	99	27.4%	54	12.5%
Generic drugs	193	87.3%	262	72.6%	379	87.5%
Generic drugs in oral capsule and tablet dosage forms *	126	65.3%	163	62.2%	206	54.4%

*The percentages were calculated in relation with the numbers of generic drugs; N=Number of applications submitted

Table 1: Distribution of the registration applications submitted in 2009, 2010 and 2011, in function of the type of pharmaceutical products.

submitted for registration. They came from all the continents, mainly from Asia (55.8 to 73.3%) and particularly from India (52.4 to 59.5 %) which appears to be the big supplier of generic drugs to the African countries. All the therapeutic classes are concerned but, according to the epidemiologic profile of Burkina Faso (about 73% of transmissible diseases in 2008) [14], the most important group such as anti-infectious drugs like antibiotics, anti-mycosis, antiviral and anti-malarial drugs (45.1% to 77.7%). Applications for registration of antihypertensive drugs were also important, particularly in 2011, indicating that hypertension has probably become a common non-communicable disease in sub-Saharan Africa, as predicted by Sagui [15].

Before registered medicines, the drug regulatory authorities have to evaluate the applications, using national and/or international standards. For generic drugs, the evaluation mainly consists to verify the presence and the compliance of the application documents to the administrative (cost, labeling and product information), quality (actives substances and finished product) and bioequivalence requirements [1]. According to the procedures of Burkina Faso NMRA, the non compliant applications are adjourned for insufficient data or information. After the third adjournment, the registration applications are rejected [9].

The rates of the adjournments for oral generic capsule and tablet registration applications are presented in figure 1. The global rates, which take into account all the non compliant technical documentations including administrative (affordability, packaging …), quality and bioequivalence, has substantially increased: 11.1%, 32.5% and 51.9% in 2009, 2010 and 2011, respectively. Moreover, in 2010 and 2011, the majority of the applications were adjourned during the first evaluation but, a significant number of them were approved within 6 months later after the acceptable responses provided by many applicants to the NMRA queries.

These results were expected since the evaluation of the bioequivalence data were not, partially (adequate compendia dissolution tests and results were accepted) and fully carried out by the NMRA during the years 2009, 2010 and 2011, respectively. As it can be seen in table 2, absence or non compliance bioequivalence data is the major motive for the registration application adjournments, particularly in 2011. From these results, it is reasonable to believe that the majority of generic drugs distributed in the sub-Sahara African countries are not bioequivalent to their correspondent brand-name drugs, since the registration systems of the majority of these countries are very weak [16]. Consequently, the efficacy and safety of the generic drugs and so, the quality of the healthcare are deeply questioned.

As shown in table 3, the applications for generic oral capsule and tablet registration containing bioequivalence documentation were significantly and progressively increased over the three year period, in relation with the progressive implementation of the evaluation of bioequivalence documentation. Their numbers and rates respectively passed from only 11 and 8.9% in 2009 to 118 and 57.3% in 2011,

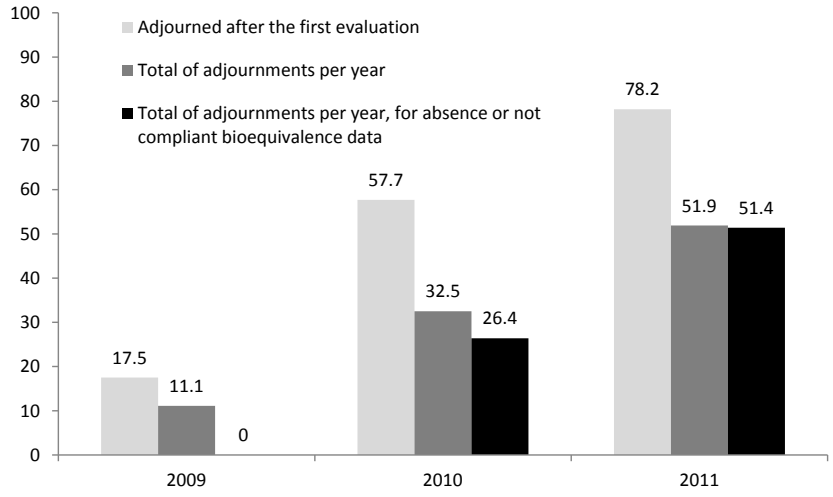

Figure 1: Rates of adjournments (in percentages) of the applications submitted in 2009, 2010 and 2011 for registration of generic oral capsule and tablet dosage forms.

	2009	2010	2011
Applications with bioequivalence information			
Number	11	62	118
Rate (% in relation with the total number of applications)	8.7 %	39.9 %	57.3 %
Types of bioequivalence documentations and rates of compliance			
In vivo comparative pharmacokinetic studies	72.7%	79.0%	37.3%
In vivo comparative clinical trial	0.0%	3.2%	0.0%
In vitro comparative dissolution tests	9.1%	19.4%	54.2%
Simple *in vitro* simple dissolution tests	18.2%	0.0%	0.0%
Total rate of compliance	**100**	**98.4***	**81.5***

*The non compliant data found in 2010 and 2011 only concerned the comparative dissolution tests.

Table 2: Rates, types and compliance of the bioequivalence documentations submitted in 2009, 2010 and 2011 for the registration of generic oral capsule and tablet dosage forms.

	2009	2010	2011
Continent of manufacturing of the product			
Africa	16.7%	4.3%	18.4%
America	0.0%	0.0%	1.0%
Asia	60.3%	73.0%	55.8%
Europe	23.0%	22.7%	24.8%
Therapeutic group of the product			
Drugs for hypertension	2.4%	14.1%	19.4%
Drugs for gastro-intestinal, respiratory and hormonal troubles	14.3%	14.7%	16.5%
Anti-infectious drugs	50.8%	46.6%	45.1%
Anti-inflammatory drugs	15.1%	16.0%	10.7%
Other therapeutic groups	17.5%	8.6%	8.3%

Table 3: Repartition (%) of the generic oral tablet and capsule applications for registration, in function to the continent of manufacturing and the therapeutic group.

indicating that a great number of manufacturers, whatever their origin, can provide the interchangeability data claimed by the African drug regulatory authorities.

The bioequivalence data are generally obtained from *in vivo* comparative pharmacokinetic studies and rarely, from therapeutic clinical trials. However, *in vitro* dissolution tests are largely, either to complete the pharmacokinetic studies or to support biowaiver [4,5]. The rates of *in vivo* pharmacokinetic studies and *in vitro* comparative dissolution tests found in the applications were respectively higher and lower in 2010, compared to those of 2011. The documentation of bioequivalence from *in vivo* trials is less advantage in terms of cost, time and safety and requires ethic and regulatory approbations, contrary to the *in vitro* dissolution studies that are more accessible, easier and shorter to achieve [5,17,18].

Therefore, the comparative *in vitro* dissolution studies were privileged by the majority of the applicants with some success. More than 80% of them have indeed shown $f2$ values between 50 and 100, proving the similarity of the generic and reference drug dissolution profiles [19]. Only 1.6% and 8.5% of the comparative dissolution data provided in 2010 and 2011 were respectively non compliant for many reasons: absence of the numerical values of the drug released versus time, non specification of the test conditions or the reference products used, $f2$ factor values not calculated or below to 50%.

Simple or non comparative dissolution tests have also been used in 2009 to document the bioequivalence of immediate release formulations from which the API dissolution occurred in less than 15 or 30 minutes. In these conditions, further mathematical calculations are not necessary, the complete dissolution being normally reached before the gastric emptying [11].

Among the *in vivo* studies for evidencing interchangeability, only two clinical trials were reported in 2010, the others were common pharmacokinetic studies. They were assessed on the basis of the study design, the regulatory and ethic provisions, the characteristics of the subjects and those of the generic and reference products, the description of procedures and methods, the presentation of the pharmacokinetic data (peak plasma concentrations (C_{max}), area under the plasma concentration-time curve (AUC) and their appropriate statistical logarithmically transformed interpretations [9]. All the 90% confidence intervals (CI) for the ratio of population geometric means of C_{max} and AUC between the generic oral capsule dosage forms and their reference products, reported by the applicants, were between 93 and 110%, within the international limits for the 90% CI acceptance (80–125%) [1,11,12,20].

It should be noted that the *in vivo* pharmacokinetic studies is commonly performed as the standard design (single-dose, two-period and crossover study in healthy volunteers). The number of human volunteers included was ranged from 12 to 72 and was consistent with the European Medicines Agency (EMEA) recommendations for which the minimum is 12 subjects [12]. An inclusion number of 24 subjects were reported in about 60% (59.2%) of the *in vivo* bioequivalence trials. Similar results have been reported by Van der Meersch et al. [21] in their review on the bioequivalence studies published in the scientific journals from January 2005 to December 2008.

It has been noticed that the applications for registration adjourned in 2011 for absence or non compliance of bioequivalence documentation were 36.8%, 50.0%, 52.2% and 60.8% for tablets and capsules manufactured in Africa, America, Asia and Europe, respectively. They were 57.5%, 55.9%, 48.4%, 59.1% and 35.3% for drugs of hypertension, gastro-intestinal- respiratory - hormonal troubles, infectious, inflammations and other pathologies, respectively. The rates of the non bioequivalent generic drug products detected and discarded by Burkina Faso NMRA in 2011, the second year of the implementation of the new procedure and evaluation, were therefore higher, whatever the continent of the manufacturer and the therapeutic group.

Conclusion

Since 2010, the marketing authorization of generic drugs in Burkina Faso takes into account their interchangeability to the reference brand-name drugs. This implementation, which was progressive and mainly concerned oral solid dosage forms, allowed discarding the non bioequivalent generic products without compromising the number of their applications for registration. This work proves that a methodical implementation of the bioequivalent requirements for generic drug registration is not only benefic and necessary in term of public health but also, performable by the sub-Saharan African developing countries. The challenge and perspectives of Burkina Faso NMRA in this field are to progressively consider the other important aspects like biopharmaceutical classification system criteria (solubility and permeability), therapeutic index of the drug, non solid dosage forms and routes of administration. The re-evaluation of the generic drugs registered before the implementation of the bioequivalence documentation evaluation should also be considered.

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