

Bioequivalence of Generic Drugs Commercialised on the Canadian Market

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Abstract

Several international studies have revealed that there are deficiencies and non bioequivalencies in generic drug reports. The purpose of this study is to determine if monographs were available in both of Canada's official languages for all generics introduced in the Canadian province of Quebec in 2012 and 2013, if the monographs contained all the required 90% confidence interval for the ratios test/reference of the bioequivalency parameters and if the generics were bioequivalent. From the list of solid oral form of generic drugs marketed in 2012 and 2013 in the Canadian province of Quebec, we downloaded the monographs of generics from Health Canada's website. We then proceeded to gather information on monograph availability, whether they respected Health Canada's guidelines and if they were bioequivalent. Our study revealed that in 2012, there were 254 eligible generics, 9.8% of them had no monograph available and only 47.6% were available in both of Canada's official languages. Similarly for 2013, there were 227 eligible generics, 7.0% of them had no monograph available and only 41.0% were available in both of Canada's official languages. Overall, only 57.09% of generics in 2012 and 65.20% of generics in 2013 were shown bioequivalent to their reference drug. This data indicates that health care professionals amongst others, lack crucial information to make a responsible decision on the use of generics.

Keywords: Bioequivalence; Generic drugs; Health Canada; Canadian provinces; Quebec; AUC; C_{max} ; Pharmacokinetics

Introduction

Generic drugs are increasingly being dispensed by health care professionals in hospital and community pharmacies. In fact, from the 575 million drugs prescribed in Canada in 2013, 65.3% were generics [1]. This percentage slightly increased compared to the previous year (2012), where 63.2% of the 529 million drugs prescribed were generics [2]. Of the 229 million drugs prescribed in the Canadian province of Quebec, generic drugs represented a total of 61.8% of total prescriptions in 2012, while representing only 19.3% of the total market cost (\$1.1 billion for generic vs. \$4.8 billion for innovator drugs).

The growing use of generics is primarily due to intellectual property patents that come to term for several innovator drugs. Consequently, we see the arrival of generic drugs whose price ranges from 18% to 35% of the innovator drug [1]. Furthermore, since the provincial governments are responsible for managing and financing the health care system and drugs (the federal government only ensures the respect of drug patent rights), this growth in prescribed generics is explained by the arrival of aggressive laws established by the different provincial governments in order to contain the increase in costs of the health care system [3]. The importance of generics in prescription habits will continue to increase over the next few years because of the pharmacist's empowerment for substitution, unless otherwise instructed by the physician. Moreover, pharmacists are highly compelled to exert this substitution right, often by pressure from third party payers, from patients without health insurance coverage or from patients with low income, in order to reduce or control costs [4].

Before such a substitution by health care professionals is applied, it is of utmost importance that the generic drug being substituted by the health care professional is deemed therapeutically equivalent to its innovator drug. It is assumed that generics will be therapeutically equivalent if bioequivalency is shown (defined below) [5]. In order to guaranty bioequivalence, Health Canada has put forward guidelines for manufacturers to standardize bioequivalency recognition. Health Canada also established guidelines on how bioequivalency data is to be

reported. It comes as a monograph and is composed of three sections; the health care professional section, the scientific information section and the patient section. This information is made available on Health Canada's website for health care professionals to freely consult and base their decisions to proceed or object to a drug substitution. In fact, the determination as to whether two drugs are therapeutically equivalent remains the sole responsibility of health care professionals who rely completely on the bioequivalency data found on the website.

It is a common misbelief that Health Canada is responsible for interchangeability. Health Canada is responsible for granting market access through a Notice of Compliance; a document confirming that a product has met the required Health Canada criteria and includes the application of official guidelines issued by Health Canada to evaluate and accept the bioequivalency of generic drugs. It is thus assumed that interchangeability is based on adequate bioequivalency data, the determination of which is under the responsibility of Health Canada. Health Canada is thus the official Canadian agency that requests, analyses and recognizes bioequivalency of Canadian generic drug products targeted for the Canadian market. It is also misleading to think that Health Canada bears the sole responsibility for interchangeability which in fact is part of a clinical decision process and is thus the ultimate responsibility of health care professionals. This clearly reveals that not only is substitution a health care professional activity, but that they have to take into account the expected and maintained therapeutic efficacy.

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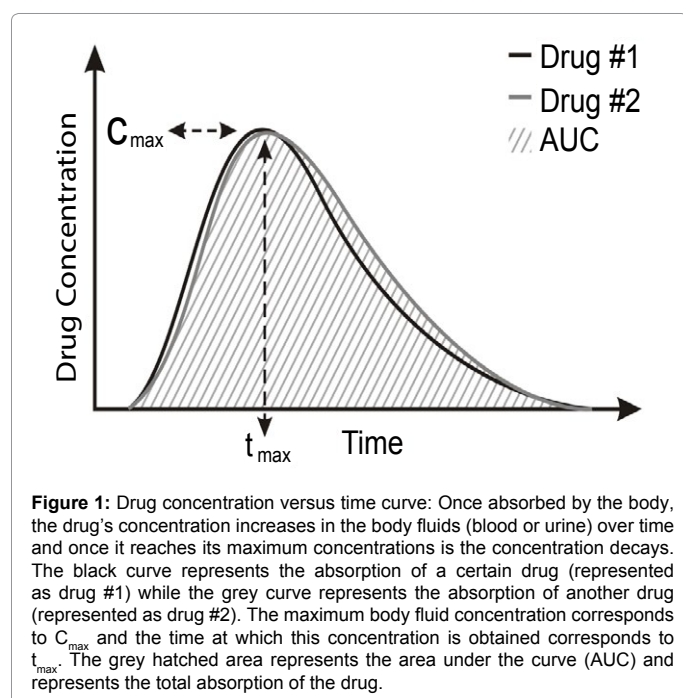
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Bioequivalence is defined as two drugs that have comparable pharmacokinetic parameters, such as the absorption rate, total absorption level and elimination. These pharmacokinetic parameters can easily be identified on a concentration vs. time curve, such as the one illustrated in Figure 1. The peak of the curve for a drug represents its maximum concentration (C_{max}), the speed to reach this peak represents the time for maximum concentration (t_{max}) and the total drug absorption is represented by the total area under the curve (AUC_{∞}). When the pharmacokinetic parameters of two drugs are comparable, such as a generic and its innovator equivalent, the curves will eclipse each other (Figure 1) and these products will be deemed bioequivalent. Health Canada's guidelines consider that two drugs are bioequivalent if the test/reference ratios for AUC_{∞} and C_{max} fall within a 90% confidence interval (90% CI) included between 80% and 125% [6]. All of these parameters are found in the product monograph through Health Canada's website. It is of utmost importance that these parameters are easily accessible, clearly outlined and written in Canada's official languages (French and English), so that health care professionals can easily decide whether two drugs are bioequivalent in order to proceed with a drug substitution.

Studies done in the United-States of America [7,8] and in Europe [9] investigated independently whether generic drugs released were bioequivalent to their brand-name counterparts. These studies revealed a fair amount of irregularities, which consisted mostly of 1- non-respect of the governing authority's guidelines (such as incomplete reports, dissolution methods used, bioanalytical methodology); 2- missing elements in the drug reports (such as missing operation procedure, missing storage information, missing analytical data, missing administration method) and 3- pharmacokinetic parameters not meeting bioequivalency requirements (C_{max} and AUC_{∞} test/reference ratio exceeding the 90% CI are not considered bioequivalent).

The work from Van Der Meersch et al. [9] relies on published data that was used to obtain commercialisation authorization, while the work presented by Davit et al. [7] and Liu et al. [8] refers to information contained in monographs appearing on websites of government organisations once the generic has been approved for



commercialisation. Thus, the data by Van Der Meersch et al. [9] could include some errors that should be eventually detected by each country's regulatory agencies and may prohibit market access authorisation. Therefore, the latter two studies contain data that has already been reviewed by these regulatory agencies and are thus more appropriate for evaluation and interpretation. Theoretically, the information held in the published regulatory agency databases should be more reliable, since the mandate of these agencies is to assess these parameters and approve market access if bioequivalency is recognised. These agencies also instruct companies to draft drug monographs in terms of specific structural guidelines.

A review of the available literature has not revealed any study investigating the generic bioequivalency data and its diffusion across Canada. As Canadian professionals are liable for their decision of the choice of a therapeutic product, it is of utmost importance to determine if the required information is available and reliable. As neither the federal nor the provincial governments have regulatory agents that verify drug interchangeability [5], the determination of whether two drugs are therapeutically equivalent remains the sole responsibility of health care professionals. Taking into consideration that there are professional liability issue if substitution for a generic is undertaken, there is a risk that pharmacists put their professional responsibility and the patient's health on the line when substituting drugs because of missing or incomplete monograph information. The purpose of this study is: 1) to assess availability of drug monographs in both official languages (French and English on Health Canada's website; 2) to search drug monographs for bioequivalency data, and 3) to determine whether bioequivalency data meet the requirements for recognition of bioequivalency.

Methods

In order to verify that Health Canada's guidelines were respected in terms of monograph availability in Canada's official languages, we used the list of generics made available for health care professionals in the province of Quebec, where French is the official provincial language. To obtain the list of generic drugs marketed in 2012 and 2013 in the province of Quebec, we consulted the Notices to the Minister on generic drugs available on the INESSS (Institut National d'Excellence en Santé et en Services Sociaux) website [10]. This list may not be complete as it includes only generic drugs considered for addition to the public drug coverage program (Assurance Médicaments du Québec), which represents most of the products. These lists were consulted for our research between the months of February and May 2014. From these lists, we considered only generic drugs that were available in solid oral form, since they represent the majority of drugs and their pharmacokinetic parameters can be easily measured in the systemic circulation. Solid oral forms include oral tablets, oral capsules, extended release oral capsules, extended release oral tablets, enteric coated oral tablets and orally disintegrating tablets. Products considered as "natural products" (i.e., without Drug Identification number or D.I.N. or with NPN number) were excluded as report of bioequivalency is not mandatory in Canada. The names and companies of these generic drugs were reported in spreadsheet softwares (Microsoft Excel and File maker Inc.). The monographs of each of these generic drugs were obtained and downloaded from Health Canada's Drug Product Database Online Query in English [11] and in French [12] when available. These monographs were consulted for our research between the months of February and May 2014.

We carefully scrutinised the list of generic drugs identified and assured that each of the listed molecules had: 1) an available monograph on Health Canada's website, 2- respected Health Canada's guidelines

(monographs in both of Canada's official languages, presence of the required bioequivalency parameters) and 3- whether the data respected bioequivalency criteria (90% CI on test/reference ratio for C_{max} and AUC_{∞}).

From these monographs, we extracted the following parameters for fasting subjects: monograph languages available, the C_{max} and AUC_{∞} test/reference ratios and the 90% CI for C_{max} and AUC_{∞} . AUC_{0-t} was used as the variable of interest for bioequivalency assessment when this variable is reported as it is considered acceptable when the area under the curve of AUC_{0-t} should correspond to at least 80% of AUC_{∞} [6]. The t_{max} parameter wasn't retained for the purposes of this study since its value is not required for establishing bioequivalency [6] and C_{max} is an indirect measure of the absorption rate.

Data and statistics (counting the number of drugs, means) were reported and calculated in the spreadsheet software, Microsoft Excel. Values were reported as Mean \pm Standard Deviation with the help of the statistics software Sigma Plot 12.3.

Results

Monograph availability

The portion of generics, eligible generics (of solid oral form) and whether they have a monograph available and their language publication is shown in Table 1. Interestingly, less than half of the monographs in 2012 and in 2013 respected Health Canada's requirement for both of the official languages.

Bioequivalency evaluation

Bioequivalency of generics was evaluated and the results are presented in Table 2. The overall bioequivalence data allowed us to determine that 51 generic drugs in 2012 and 31 generics in 2013 had at least one value that was located outside the acceptable limit of 80% to 125%. These outliers represent 20.1% (51/254) of generics in 2012 and 13.7% (31/227) of generics in 2013 that had bioequivalence issues. Taken together and ignoring monograph languages, this represents only 57.09% (145 bioequivalent generics out of the 254 eligible) in 2012 and 65.20% (148 bioequivalent generics out of the 233 eligible) in 2013 of generics that were bioequivalent and had all the required data from Health Canada's website.

Discussion

Similar to previous studies that demonstrated deficiencies in the generic drug market in other countries [7-9], we have also highlighted several deficiencies in the Canadian generic drug market. The deficiencies found in those studies are similar to ours and they can fit in one of the following categories: unpublished monographs, non-respect of Health Canada's guidelines and non-bioequivalence. We have shown that of all solid oral generic drugs marketed, 20.1% in 2012 and 13.7% in 2013 of generic drugs with available monographs had bioequivalence deficiencies, which is the highest among published studies. As a comparison, a study done within the United-States' Food and Drug Administration (FDA) and the European Medicines Agency (EMA) demonstrated that only 89% of generics were considered bioequivalent to their innovator counterpart [9]. A notable difference exists as Van der Meersch's study relies on data obtained before market access authorisation, while the present study pertains to results obtained after approval by regulatory agencies. Furthermore, of all solid oral generic drugs marketed, 9.8% in 2012 and 7.0% in 2013 had no easily accessible monograph. Of these available monographs, only 47.6% in 2012 and 41.0% in 2013 were in both of Canada's official languages and only 57.09% in 2012 and 65.20% in 2013 of the total eligible generics were bioequivalent and had all the required data from Health Canada's website. It is quite remarkable that somehow, these generics were able to find their way on the Canadian generic market, even though they were not ideal for clinical use. Interestingly, the percentage of deficiencies and lacking drug monographs is similar between the year 2012 and 2013. This strongly excludes a delay in the publication of monographs by Health Canada since our study looks at a span of two years. One possible explanation is that bioequivalence data is not available, because the product is actually the reference product bought from the original manufacturer and sold under a generic name (Health Canada, personal communication). Although there are ways to retrieve this Information on Health Canada's website, it is not easily accessible to clinicians. Another possibility is that some of the listed products were introduced on the Canadian market before 2004 which is the reference year for Health Canada to publish monograph systematically on their website. Health Canada states that these monographs can be obtained with a written request. Although these products can be considered "old drugs", reasons why these products showed up in INESSS 2012 list remains unexplained.

Monograph availability						
Year	# of generics released in 2013	# of eligible generics	Monograph language			Generics without monograph
			English and French	English Only	French only	
2012	331	254	121 (47.6%)	107 (42.1%)	1 (0.4%)	25 (9.8%)
2013	302	227	93 (41.0%)	118 (52.0%)	0 (0%)	16 (7.0%)

Table 1: Monograph availability: This table shows the data collected concerning the availability of monographs on Health Canada's website and the language that they are available in for the years 2012 and 2013. The number of eligible generics (3rd column) represents generics that were of solid oral form.

Bioequivalency evaluation								
Year	# of generics evaluated	# of generics without available data	# of generics where C_{max} 90% CI < 0.80	# of generics where C_{max} 90% CI > 1.25	# of generics where AUC 90% CI < 0.80	# of generics where AUC 90% CI > 1.25	Total number of non-bioequivalent generics	% of total eligible bioequivalent generics
2012	254	58	24	25	2	2	51*	57.09
2013	227	48	14	14	1	3	31**	65.20

*53 bioinequivalencies in 51 generics, **32 bioinequivalencies in 31 generics, AUC: Area under the body fluid concentration vs. time Curve, CI: Confidence Interval, C_{max} : Maximal body fluid concentration

Table 2: Bioequivalency evaluation: This table assesses the bioequivalency of generics with all the proper information in their monographs for the years 2012 and 2013. Columns 4, 5, 6 and 7 give the number of generics that are outside the bioequivalency standard of 80% to 125%, while the last column gives the percentage of bioequivalent generics on the total number of eligible generics.

Since Health Canada is the bioequivalency granting authority, it is almost exclusively based on the data submitted by manufacturers and published in monographs available on their website, that health care professionals determine whether a generic is therapeutically suitable to meet the needs of patients. It is also from this data that health care professionals decide whether they should substitute an innovator drug for a generic. With this bioequivalency data, if they continue with a substitution, they have an idea of what the expected variations in a patient can be. This data should thus be readily available to these professionals, which is clearly not the case as shown here. It is also the responsibility of the health care professional to determine whether a prescribed innovator drug has a therapeutically equivalent generic and proceed with a substitution. Without appropriate data available for health care professionals, several problems can arise.

First, if health care professionals do not have the necessary information (available monographs or their mandatory content), they may not proceed with a substitution even though the generic might be bioequivalent. This will result in a missed opportunity to reduce the provincial authority's costs of prescribed medication and the medication costs for the patients will be higher.

Second, there is a possibility that the health care professional decides to proceed with the substitution, even though one does not have all the information or one does not understand it well because of the language barrier. There is a chance of selecting non bioequivalent products. In this latter case, the substitution might modify the therapeutic benefits, generate unwanted side effects and necessitate medical re-evaluation.

Based on the evaluation of all of these deficiencies, we hereby propose several recommendations to improve generic drug substitution in Quebec and help health care professionals to make clearer and fairer decisions. First, as soon as a new generic is made available on the Canadian market, it should be mandatory that the monograph of such generic be made readily available. For the missing monographs that we have highlighted in this study, there is no way of knowing if the company provided the monograph to Health Canada or if Health Canada has not made it available on their website.

Second, all monographs should be available in both of Canada's official languages. Although clearly stated in Health Canada's guidelines, many monographs fail to meet this criterion [13].

Third, to evaluate the bioequivalency, the monographs of generics should contain all the necessary information, including the pharmacokinetic parameters and the data of the 90% CI for AUC_{∞} and C_{max} . These three aspects should not be problematic since generic manufacturers are obliged by Health Canada to present the appropriate information in their monographs, such as indications, allegations, properties, dosage instructions and any other relevant elements [13]. Of particular interest for this research is the detailed clinical pharmacology data which has to be included in monographs. Health Canada even takes a step further by giving a clear example of a complete monograph and the table for presenting the pharmacokinetic parameters [14].

Fourth, before being accepted on the Canadian generic market, generics should be deemed bioequivalent to their corresponding innovator drug. It is surprising that a significant number of monographs include data that do not meet bioequivalency standards, even though the product being documented is commercially available. Finally, Health Canada should find a fail proof way of verifying that the previous recommendations are followed in order for their guidelines to be respected by generic companies.

Conclusion

To our knowledge, this is the first study describing the availability of monographs and their bioequivalency parameters in Canada. The data outlined here is of utmost importance for health care professionals who may safely want to substitute an innovator drug by a generic. It is alarming that, of the 254 generics in 2012 and the 233 generics in 2013, only 57.09% in 2012 and 65.20% in 2013 had available monographs with appropriate pharmacokinetic parameters and bioequivalence results. Moreover, less than half of the generics respected the monograph bilingual language criteria. Without these monographs and bioequivalence information, substitution could be risky, and as a consequence, professionals may be reluctant to proceed with such substitution, putting pressure on the financial resources allocated for provincial drug programs. The work presented here highlights important concerns for health care professionals and revealed issues that should be rapidly addressed to remedy the situation. The recommendations we provided should help to improve drug information availability and substitution.

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