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Interchangeability of Generics—Experiences and Outlook Toward Pharmacokinetics Variability and Generic-Generic Substitution

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Prior to registration, new medicines have demonstrated to adequately treat or prevent diseases based on established efficacy and acceptable safety data in clinical trials. Usually, the registration file for a new medicine (i.e., brand-name drug) contains clinical efficacy and safety trials or references to such trials, both premarketing and postmarketing. Due to the presence of these efficacy and safety data in the registration file for a brand-name drug, healthcare providers sometimes tend to have more trust in the brand-name drug than in a generic drug, because the latter seems to be supported only by a limited amount of drug exposure data in healthy subjects.[1] However, the drug's efficacy and safety actually are largely the characteristics of the active substance(s) rather than that of the drug product. Therefore, if two drug products contain the same active substance(s) in a qualitatively and quantitatively manner and have comparable exposure, they are expected to reach the same efficacy and safety in treating or preventing the target disease. In light of this knowledge, a so-called generic drug containing the same active substance(s) at the same dose is allowed to be marketed without efficacy and safety clinical trials after the exclusivity of the brand-name drug expired. Instead, in most cases a bioequivalence study between the brand-name drug and the generic drug is sufficient and serves to demonstrate that there is no impact of excipients and different manufactory processes of the generic drug on the pharmacokinetics (PKs) of the active substance(s). In case demonstration of bioequivalence is complex (e.g., for drugs with controlled release or drugs with narrow therapeutic index) or not possible (e.g., for locally acting drugs), in most cases, the requested comparative studies still are less extensive than the clinical data requested by regulatory authorities for a brand-name drug. Because of this abridged regulatory requirement, generic drugs are competitive in price, and from that perspective more suitable to healthcare systems than the brand-name drugs. However, because of the lack of actual clinical efficacy and safety data for generic drugs, patients, patient's organizations, and healthcare providers sometimes have concerns about generic drugs (i.e., these may not be as effective/safe as the brand-name drugs).[2]

In practice, an adverse event (AE) reported after switching from the brand-name drug to a generic drug are often ascribed to the generic drug.[2] AEs are reported more frequently in the period when a new generic drug enters the market or, in case the sale of a generic drug is strongly increased, whereas the incidence of the reported AEs some time after switching is usually comparable with that of the brand-name drug.[3] However, the observation of an AE cannot be *a priori* considered evidence for the assumption that the generic drugs perform worse than the brand-name drugs with regard to safety. The perception of issues toward generics differs among different stakeholders; a survey published by Colgan *et al.*[4] investigated concern about generic drugs in the Netherlands. They found that patients mostly have concerns about the effectiveness of the generic drugs, pharmacists about the quality of the drugs, whereas doctors mostly have concerns about the safety of the drugs.

In response to the public concerns about generic drugs, it is considered important for regulatory authorities to verify whether the concerns bear value, also to verify whether the current requirements for generic drug approval with respect to bioequivalence are still sufficient to guarantee therapeutic equivalence between the generic drug and the brand-name drug, and to consider if any actions could be taken to resolve the concerns. For that purpose, in the past years, the Dutch regulatory authority (Medicines Evaluation Board) aims to provide explanations, supported by Regulatory Science investigations toward some generic concerns to the stakeholders. In our investigations so far, we have focused on potential explanations for differences in drug exposure, which are occasionally observed or suspected in individual patients upon switching from a brand-name drug to a generic drug. Furthermore, we also looked into concerns about generic-generic drug interchangeability. Such generic-generic switching occurs very frequently in

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Received 28 June 2018; accepted 28 September 2018; advance online publication 20 November 2018. doi:10.1002/cpt.1250

Table 1 Estimation of intrasubject variances and variance due to subject-by-formulation interaction for AUC_{0-t} and C_{max} in individuals in the investigated studies.

			AUC_{0-t} (ln-scale)			C_{max} (ln-scale)		
Active substances (strength)	Ratios	*N*	Mean	Intrasubject variances	Variance of SbyF interaction	Mean	Intrasubject variances	Variance of SbyF interaction
Alendronate (10 mg)	R2-R1	25	0.02	0.14	−0.069	−0.07	0.16	−0.042
	T2-T1	26	−0.11	0.23		−0.01	0.18	
	T-R	25	−0.04	0.12		−0.09	0.13	
Alendronate (70 mg)	R2-R1	68	−0.04	0.24	0.047	−0.14	0.29	0.021
	T2-T1	67	0.01	0.22		0.01	0.27	
	T-R	67	0.01	0.28		−0.04	0.30	
Atorvastatine (40 mg)	R2-R1	54	0.10	0.05	−0.015	−0.06	0.18	−0.091
	T2-T1	58	0.13	0.06		0.22	0.33	
	T-R	54	−0.04	0.04		0.02	0.16	
Cyclosporine (100 mg)	R2-R1	133	0.02	0.04	−0.006	−0.02	0.17	−0.026
	T2-T1	134	0.02	0.03		0.03	0.16	
	T-R	133	0.03	0.03		0.03	0.14	
Exemestane (25 mg)	R2-R1	54	−0.02	0.02	−0.008	−0.03	0.09	−0.007
	T2-T1	54	−0.00	0.02		0.07	0.08	
	T-R	54	0.04	0.01		0.01	0.08	
Mycophenolate mofetil (250 mg)	R2-R1	37	0.00	0.01	−0.003	0.05	0.14	−0.029
	T2-T1	37	−0.03	0.02		0.01	0.10	
	T-R	37	−0.01	0.01		0.01	0.09	
Mycophenolate Mofetil (500 mg)	R2-R1	41	−0.00	0.03	0.002	0.11	0.20	−0.038
	T2-T1	40	−0.04	0.01		−0.06	0.10	
	T-R	40	−0.01	0.02		−0.01	0.11	
Ropinirole (2 mg)	R2-R1	33	−0.01	0.01	0.000	0.04	0.02	0.009
	T2-T1	29	0.01	0.02		0.14	0.08	
	T-R	28	−0.07	0.02		0.14	0.06	

Adapted with permission from Yu *et al.*[5]
Variances of subject-by-formulation interaction for both AUC_{0-t} and C_{max} are relatively small (i.e., < 0.05) and most of them are negatively estimated by the Method of Moment, indicating that they are close to zero. The small variances of subject-by-formulation interaction indicate that the difference in drug exposure upon switching from brand-name to generic drug is very similar to repeated administration of the same drug for individual subjects in the investigated studies.
AUC_{0-t}, area under the drug concentration-time curve from time zero to the last sampling time point; C_{max}, peak plasma concentration; R, reference formulation; R1, reference formulation in first administration in replicate design study; R2, reference formulation in second administration in replicate design study SbyF interaction, subject-by-formulation interaction; T, generic test formulation; T1, generic test formulation in first administration in the replicate design study; T2, generic test formulation in second administration in replicate design study.

the Netherlands, and drift of the exposure upon switching between generics has been postulated.[5]

AWARENESS OF PHARMACOKINETIC VARIABILITY

In light of the sometimes reported differences in exposure after switching from a brand-name drug to a generic drug, we investigated whether such differences in drug exposure observed in individual patients may be due to either a difference between the drug formulations (i.e., generic and brand-name drugs), or to intrasubject PK variability of the active substance.[1] For that purpose, replicate design bioequivalence studies of various registered drugs (for drugs involved see **Table 1**) were reanalyzed with respect to intrasubject variability in total and peak drug exposure (i.e., area under the curve (AUC) and peak plasma concentration (C_{max})) for both generic and the brand-name drugs and also the variance related to the subject-by-formulation interaction.

Results showed that the intrasubject PK variability (in AUC from time zero to the last sampling time point (AUC_{0-t}) and C_{max}) was generally comparable for the brand-name drug and the generic drug (see **Table 1**). Differences in exposure caused by subject-by-formulation interaction were considered negligible in the investigated bioequivalence studies. This indicates that the variability in drug exposure is generally not affected by the drug formulation. Furthermore, the variability in exposure upon switching between the generic and the brand-name drug was comparable with that observed for brand-name drugs (or likewise for the generic drugs) after repeated administrations. This clearly shows that the variation in drug exposure upon switching between generic and brand-name drugs is the same as when

repeating the same drug (either generic drug or the brand-name drug) among the investigated drugs in the study. Therefore, the anecdotal differences in drug exposure (either increased or decreased) that have been reported or hypothesized in literature upon switching from the brand-name to generic drug, are likely to be caused by the intrasubject variability in exposure of the active substance, and, therefore, not a solid marker for a systematic difference in clinical pharmacology of the generic drug.

GENERIC-GENERIC SUBSTITUTION

To evaluate the interchangeability between different generic drugs, we conducted a comparative exposure clinical trial using gabapentin as a test medicine.[5] The trial compared the PK of three registered generic drugs of gabapentin and the European brand-name drug Neurotin (Pfizer B.V., Capelle a/d IJssel, The Netherlands). The results showed that the three generic gabapentin drugs are bioequivalent with each other, indicating that the potential drifting effect for these generic gabapentin drugs is small, and the drugs can be considered interchangeable. This finding provided the first evidence that bioequivalence between different generic drugs occurs, despite the fact that direct demonstration of bioequivalence has not been requested upon registration. In our opinion, this result could have been expected because all registered generic drugs have been demonstrated to be bioequivalent to the brand-name drug (i.e., B = A and C = A) and the ratio of exposure between the brand-name and the generic drugs is close to 1 (100%). Therefore, the probability of generic drugs not being bioequivalent (i.e., B ≠ C) is small. In order to further substantiate this hypothesis, we have investigated bioequivalence between a broad range of generic drugs in an indirect comparison, encompassing 120 bioequivalence studies.[5] The study results indicated that in the majority of cases (within 80.5% of the generic-generic substitution cases the 90% confidence interval for both $AUC_{0\text{-}t}$ and C_{max} being within the acceptance range of 80–125%), bioequivalence was indicated. In 90.1% and 87.0% of the cases, this was the case for either $AUC_{0\text{-}t}$ or C_{max}, respectively. In case the 80–125% criterion was not met, in only 3% of the cases, the border of the 90% confidence interval was outside a wider 75–133% range.[5] Although these results cannot fully exclude the possibility of nonbioequivalence upon generic-generic drug substitution, we consider that a pronounced risk on relevant differences in exposure upon generic-generic substitution in clinical practice is unlikely.

THE FUTURE

In general, generic drugs are quite easily blamed if efficacy is not reached or an adverse event is observed. Healthcare providers tend to focus on the assumed potentially different quality of generic drugs, however, they often forget about the uncertainty in medications, brand-name as well as generic drugs, in general, and the diversity of individual patients. After the Hatch-Waxman Act in 1984, in which the regulation of generic drugs was introduced in the United States, generic drugs have now been used for > 30 years. Although discussion about effectiveness and safety of generic drugs continues, in this long period, no apparent trend or solid evidence was identified to confirm that generic drugs are not as good as claimed. Based on our investigations, as summarized above, we consider that different drug concentrations in individual subjects between generic and brand-name drugs does not necessarily indicate nonbioequivalence. Instead, the difference in concentration is likely to be mainly due to the intrasubject variability of PK of the active substance. In addition, no major issues were identified upon generic-generic substitution as compared with the branded-generic substitution.

In general, Regulatory Science activities may play a role in scrutinizing current requirements for generic drug approval with respect to bioequivalence in order to ascertain therapeutic equivalence between the generic and brand-name drugs. Besides technical regulatory aspects, also aspects like communication and education, adherence, shape, and color of the products may be considered with the aim to see at what point improvements may be obtained in the field of generic switching. For example, the principles of generic drugs may not always be sufficiently transparent to all stakeholders. Therefore, in order to improve clarity on the assumptions and extrapolations used in regulation requirements toward generics, ongoing efforts to build and maintain confidence in generic drugs by means of providing good communication, supported by sound regulatory science data, as well as a reliable and scrutinized regulatory system are essential.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

Yang Yu and Marc Maliepaard are employees at the Dutch Medicines Evaluation Board. No further conflicts of interest exist.

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