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Consideration of international generic distribution policies on patient outcomes in the United States and Germany

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Received August 1, 2013, accepted September 9, 2013

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Pharmazie 69: 238–240 (2014) *doi: 10.1691/ph.2014.3786*

Generic substitution of narrow therapeutic index drugs can have unintended consequences. Generic switching is often driven by cost incentives, regulations and supply, but may raise concerns about equal bioavailability, therapeutic equivalence and about possible confusion for the patient. Integrated systems of care with active management of patient behaviors, including adherence, may minimize the impact of switching. This article is intended to present policy drivers and potential consequences of generic switching and the role of pharmacist education in minimizing patient risk using warfarin and the pharmaceutical distribution systems of the United States and Germany as examples.

1. Background

Recent estimates indicate over 70 % of the prescriptions dispensed in the U.S. and in the German statutory health insurance system are generic medications (Kaiser Family Foundation 2010; Schwabe and Paffrath 2012). Financial incentives for payers, patients, and pharmacies; improved consumer knowledge and confidence in generics; increased generic availability; and regulations encouraging generic substitution have all likely contributed to the rise in generic medication use (Assistant Secretary for Planning and Evaluation Staff 2010), including the use of generic warfarin, a narrow therapeutic index (NTI) medication. Historically, there has been some reluctance in switching patients from innovator or brand-name warfarin (Coumadin®) to U.S. Food and Drug Administration (FDA) A-rated generics. This hesitancy stems in part from the definition of a NTI and how the FDA establishes therapeutic equivalence. Narrow therapeutic index drugs are those defined by the FDA as having less than a 2-fold difference in the ratio between the median toxic concentration and the minimum effective blood concentration and necessitating dose titration and patient monitoring for their safe and effective use (US Department of Health and Human Services 2013). This article is intended to present the possible policy drivers and consequences of generic switching and the role of the pharmacist in minimizing patient risk, using warfarin and the pharmaceutical distribution systems of the United States and Germany as examples.

2. U.S. and European Bioavailability Guidelines

Approval of a generic by the FDA or the European Medicines Agency (EMA) requires demonstration that the 90 % confidence interval associated with the rate and extent of absorption of the generic is entirely contained within 80–125 % of the log transformed data compared to the reference product, i.e. the originator (Committee for Medicinal Products for Human Use 2010; Food and Drug Administration Center for Drug Evaluation Research 2011). This definition allows for some variability in the bioavailability between the brand and generic. The substitution of one manufacturer's generic for another generic formulation is common practice and highlights a concern with the FDA's and EMA's bioequivalence standards with respect to NTI drugs: for market approval, the registration authority compares the bioavailability of the generic to the brand innovator product, but not with other approved generic formulations in the marketplace, posing potential for greater variability in drug bioavailability between generic to generic substitutions versus brand to generic substitutions. Hence, when substituting one generic for another generic, pharmacists are faced with a lack of data on this matter, and the substitution of a product must be made on the basis of assumed (but not proven!) bioavailability.

3. The warfarin controversy

An observational study with subsequent commentary regarding the impact of warfarin substitution was published in 2011. A commentary by Haines indicated no difference in patient response with generic substitution when measured in a prospective, controlled, randomized clinical trial setting (Haines 2011). In contrast, results of a retrospective real world analysis in a national health insurance claims research database highlighted safety concerns of multiple switching between NTI drugs of different manufacturers (Ghate et al. 2011). Patients with atrial fibrillation that were switched from one generic warfarin product to another manufacturer's generic warfarin had the highest likelihood of thrombotic and hemorrhagic events relative to those staying on the branded drug for the study duration. Compared with continued use of Coumadin®, switching from the originator product to the generic formulation was associated with significantly higher risk of thrombotic events (hazard ratio (HR) = 1.81; 95 % CI 1.42 to 2.31) and hemorrhage events (HR = 1.51; 95 % CI 1.17 to 1.93). Similar findings concerning thrombotic and hemorrhage events were observed for switch-

ing from generic warfarin to Coumadin® (HR = 1.76; 95 % CI 1.35 to 2.30; HR = 1.60; 95 % CI 1.23 to 2.1), and from one generic to another generic product (HR = 1.89; 95 % CI 1.57 to 2.29; HR = 1.74; 95 % CI 1.45 to 2.11).

These publications raise the question as to what drives the poor outcomes in patients switching between medicines from different manufacturers. The Haines commentary implies that differences in bioavailability of different warfarin drug products do not impact outcomes in the RCT setting. This hypothesis is supported by pharmacokinetic parameters of warfarin drug products, which are immediate-release products, and the drug itself exhibits a high bioavailability and long half-life (Coumadin® package insert 2011). However, the work published by Ghate et al. suggests that in a real world setting, multiple switching among drug formulations occurs, which is associated with an increase in risk of adverse events to the patient.

With the evidence on bioequivalence of different warfarin products from RCTs, Haines suggested looking at alternative explanations, such as our "system of care", for the observed results in the study by Ghate et al. (Haines 2011). For example, psychological factors, such as confusion or decreased compliance following a drug switch, are not typically observed in a double-blind crossover RCT, where patients and investigators are not aware of product switches. However, these factors may play an important role for the effects seen in clinical practice and observational studies. If switching between products is associated with potential errors and misunderstandings, as Haines suggests, why does switching happen so often? In the Ghate study, approximately 34 % (12,996) of the subjects were switched between formulations of warfarin during the one-year follow-up period, the majority of whom (66%) substituted one generic formulation for another (Ghate et al. 2011).

4. U.S. Drivers of generic switching

Within the U.S. health care system, many factors contribute to which manufacturer's product the patient will ultimately receive. Cost factors aside, the issue of maintaining dispensing consistency with a brand name product can usually be readily achieved if the prescriber notates 'Dispense As Written' (DAW) or similar language on the prescription (Epilepsy Therapy Project 2007). This notation obligates the pharmacist to fill the prescription with the product written on the prescription; substitutions are not permitted. A study of prescription claims from a large pharmacy benefits manager in the U.S. found that nearly 3% of all prescriptions were designated as 'DAW' by prescribers (Shrank et al. 2011). In addition, patients may request a certain manufacturer's product and in most states, the pharmacist is obligated to honor this request (Epilepsy Therapy Project 2007). If the intended medication is available generically and neither the prescriber nor patient has requested the brand name product, some states mandate generic substitution by pharmacists whereas others permit generic substitution by a pharmacist (Epilepsy Therapy Project 2007). When pharmacists may dispense generics, it is generally left to the discretion of the pharmacist as to which manufacturer's generic formulation to dispense, unless state laws governing generic substitution indicate otherwise. For example, in North Carolina, NTA drugs must be refilled using only the same manufacturer's product that was last dispensed unless the prescriber is notified and both the patient and prescriber give consent prior to dispensing (Epilepsy Therapy Project 2007).

Although it is usually in the best interest of a patient to be maintained on a single manufacturer's formulation of a NTI medication, a number of features of the drug distribution and procurement process provide challenges to this goal. For example, in order for some pharmacies to receive the lowest price from their drug wholesalers, the pharmacies participate in programs that require them to accept the wholesaler's choice of drug manufacturer for fulfilling an order (Kolassa 2009). Manufacturer supply issues can be another source of product substitution. Customers choosing to switch pharmacies may also serve as a potential source of product substitution if the pharmacies carry different manufacturer's products. Other cost-related factors, such as third-party copayments, rebates, and benefit structures, price sensitive customers, and pharmacy reimbursement levels can all play a role in which manufacturer's product the patient ultimately receives.

5. German drivers of generic switching

In the German healthcare system, 90 % of the population is covered by the statutory health insurance (SHI) organized in 134 competing insurance funds as of 4th March 2013 (Bundesministerium für Gesundheit 2013). Within the SHI system, generic substitution has become highly relevant in recent years in order to minimize costs (VFA 2010). Over the past twelve years, Germany has evolved into the world's most generics-friendly country. Currently, approximately 76 % of German SHI prescriptions in the generics-eligible market are for products available generically (Schwabe and Paffrath 2012). While corresponding legislation in Germany initially only allowed substitution with cheaper-priced drugs in the pharmacies, since 2007 it became mandatory for pharmacists to substitute the prescribed product for one where a rebate contract between a health insurance fund and a pharmaceutical manufacturer has been negotiated (GKV-WSG 2007). Product substitution can, however, be prevented by the prescriber via crossing out the 'aut idem' (allowing for substitutions) box on the prescription form, which was used in approximately 19 % of prescriptions in 2008 (Hoffmann et al. 2009). Moreover, since 2008, pharmacists are allowed to deny substitution due to pharmaceutical concerns on an individual basis, i.e. in cases where – in spite of additional counseling of the patient – therapeutic efficacy or drug safety is expected to be compromised, e.g. due to suspected adherence problems with the substituted product (Griese et al. 2010). The German pharmaceutical society has issued guidance on good substitution practice, recommending not to switch patients frequently between different products, especially in critical indications or when drugs with a narrow therapeutic index are prescribed (Blume et al. 2002).

6. Comparison of the setting of generic substitution in the U.S. versus Germany

As stated above, generic substitution in the U.S. is subject to state-specific regulation, and substitution of drug products may be in the economic interest of the pharmacist. In contrast, generic substitution in Germany has nationwide legislation, but regional differences in rebate contracts are present between different health insurance funds. Moreover, pharmacists in Germany have no economic incentive in moving to generic substitution, because rebate contracts are negotiated between manufacturers and health insurance funds. In addition, reduced out-of-pocket costs of patients in the U.S. may be advantageous for ensuring patient adherence after generic substitution (Shrank et al. 2006), whereas in Germany, patients' out-of-pocket costs contribute only to a small financial incentive for patients. Hence, the setting of generic substitution differs based on the economic interests of healthcare providers and patients involved.

7. Other "system of care" factors

Issues other than bioequivalence may also play a key role in explaining the results observed in the Ghate study. Med-

ication adherence could have been a contributing factor for the higher observed rates of thrombotic events in those that switched between warfarin manufacturers. A study of medication adherence in patients that had one of their antihypertensive medications generically substituted reported that one-third of the patients found it more challenging to keep track of their medications following generic substitution (Hakonsen et al. 2009). These patients cited, in part, the change in appearance of the substituted product (different color/shape) as contributing to their adherence issues. The subjects in the Ghate et al. study had a mean age of around 70 years and nearly half of them (48 %) had Charlson co-morbidity index scores of at least 3, implying a strong likelihood that these patients were taking multiple medications. Generically substituted products can also have different names (e.g., warfarin, Coumadin®, Jantoven®). Although difficult to prove definitively, confusion arising from changes in product name may also contribute to medication dispensing and medication administration errors. If product substitution was poorly communicated in the Ghate et al. study, changes in tablet appearance and product name on the label could have conceivably contributed to patient confusion, decreased patient adherence, and poor outcomes.

8. Conclusion

Taking two different pharmaceutical distribution systems, the United States and Germany, as examples this article provided an overview of how current policies and financial incentives surrounding the dispensing of generic products may inadvertently undermine patient safety and health outcomes in an NTI drug such as warfarin. The controversy surrounding the substitution of bioequivalent warfarin products is not likely to subside anytime soon. More research in this area is warranted to determine if the results of Ghate et al. (2011) are replicable and to better understand the cause of the observed results. Although generics tend to be cheaper on a per unit basis than brand name products, unintended consequences associated with multiple manufacturer switches may be costly to treat. As such, this issue should not be discounted by insurers, patients, and other payers of health care.

How can healthcare providers help patients achieve the best outcomes of their warfarin therapy? In view of the limited and partly contradictory evidence regarding the effects of generic substitution on patient outcomes, we would suggest that for each individual case, the specific drug product, the indication, the patient and the setting of the substitution should be analyzed. Pharmacists should strive to maintain patients on the same manufacturer's product if possible. Patient counseling efforts should include education about the importance of remaining on the same manufacturer's product, the value of communicating a formulation switch to their provider, and emphasize the need for heightened awareness of adverse drug event symptoms and potential for additional international normalized ratio (INR) monitoring if generic substitution occurs. Furthermore, the patient should be shown the appearance of the new tablet, and product name changes on the label should be explicitly explained to the patient or patient's caregiver when the generically substituted prescription is dispensed.

Acknowledgements: This work was supported by the ONCOTYROL Center for Personalized Cancer Medicine (COMET center), which is funded by the Austrian Federal Ministries BMVIT/BMWFJ (via FFG) and the Tyrolean Future Foundation/Standortagentur Tirol (SAT). Support for this work was also provided by the Pharmacotherapy Outcomes Research Center at the University of Utah. This is a perspective piece and has not been presented previously.

Conflict of interests:
The authors have no conflicts of interest to report. MS holds an unpaid Advisory Board position of the EGA Chair, based at the University Leuven, Belgium. The European Generic medicines Association (EGA) provided an unrestricted grant to this University with regard to the EGA Chair.

References

Assistant Secretary for Planning and Evaluation Staff (2010) ASPE issue brief: Expanding the use of generic drugs. Washington, DC: Congressional Budget Office; Publication No. 4043.

Blume H, Brauer KG, Dingermann T, Mutschler E, Zuendorf I (2002) DPhG-Leitlinie Gute Substitutionspraxis (GSP) [German Pharmaceutical Society (DPhG) - Guideline on Good Substitution Practice]. Pharm Ztg 147: 161–168.

Bundesministerium für Gesundheit (2013) Gesetzliche Krankenversicherung – Zahl der gesetzlichen Krankenkassen.[Cited July 31, 2013; available from: http://www.bundesgesundheitsministerium.de/fileadmin/dateien/Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM1_Januar_bis_Februar_2013.pdf]

Committee for Medicinal Products for Human Use (2010) Guideline on the investigation of bioequivalence. European Medicines Agency.[Cited July 31, 2013; available from: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf]

Coumadin® package insert (2011) Princeton, NJ: Bristol-Myers Squibb.

Epilepsy Therapy Project (2007) State laws or statues governing generic substitution by pharmacists.[Cited July 31, 2013; available from: http://professionals.epilepsy.com/page/statutes_by_pharmacists.html]

Food and Drug Administration Center for Drug Evaluation Research (2011) Approved Drug Products with Therapeutic Equivalence Evalutions. Rockville, MD: U.S. Department of Health and Human Services.[Cited July 31, 2013; available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf]

GKV-WSG Gesetz zur Stärkung des Wettbewerbs in der gesetzlichen Krankenversicherung (2007) Bundesgesetzbl 2007 Part I No. 11: 378–473.[Cited July 31, 2013; available from: http://www.bgbl.de/Xaver/start.xav?startbk=Bundesanzeiger_BGBl#__Bundesanzeiger_BGBl__%2F%2F*%5B%40attr_id%3D'bgbl107s0378.pdf'%5D__1375281505776]

Ghate SR, Biskupiak JE, Ye X, Hagan M, Kwong WJ, Fox ES, Brixner D (2011) Hemorrhagic and thrombotic events associated with generic substitution of warfarin in patients with atrial fibrillation: a retrospective analysis. Ann Pharmacother 45: 701–712.

Griese N, Goebel R, Schulz M (2010) Rabattvertraege. Pharmazeutische Bedenken bei Phenprocoumon? [Rebate contracts. Pharmaceutical concerns affecting phenprocoumon?]. Pharm Ztg 155: 1410–1411.

Haines ST (2011) Substituting warfarin products: what's the source of the problem? Ann Pharmacother 45: 807–809.

Hakonsen H, Eilertsen M, Borge H, Toverud EL (2009) Generic substitution: additional challenge for adherence in hypertensive patients? Curr Med Res Opin 25: 2515–2521.

Hoffmann F, Glaeske G, Pfannkuche MS (2009) The effect of introducing rebate contracts to promote generic drug substitution, on doctors' prescribing practices. Dtsch Arztebl Int 106: 783–788.

Kaiser Family Foundation (2010) Prescription Drug Trends (May 2010). Fact Sheet [serial on the Internet]. (3057–08):.[Cited July 31, 2013; available from: http://kaiserfamilyfoundation.files.wordpress.com/2013/01/3057-08.pdf]

Kolassa E (2009) The strategic pricing of pharmaceuticals. USA: The Pond-House Press.

Shrank WH, Hoang T, Ettner SL, Glassman PA, Nair K, DeLapp D, Dirstine J, Avorn J, Asch SM (2006) The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. Arch Intern Med 166: 332–337.

Shrank WH, Liberman JN, Fischer MA, Avorn J, Kilabuk E, Chang A, Kesselheim AS, Brennan TA, Choudhry NK (2011). The consequences of requesting "dispense as written". Am J Med 124: 309–317.

Schwabe U, Paffrath D (ed.) Arzneiverordnungs-Report (2012), Heidelberg, Germany.

US Department of Health and Human Services, US Food and Drug Administration (2013) CFR Title 21, Volume 5, Section 320.33: Criteria and evidence to assess actual or potential bioequivalence problems.[Cited July 31, 2013; available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.33]

VFA - German Association of Research-based Pharmaceutical Companies (2010) Berlin, Germany.