Commentary

Comment on: Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe by Johnston *et al.* [1]

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Another view on the complex and fascinating subject of generic and therapeutic substitution [1] is welcome. The initiation of a group by Novartis adds to this topical debate [2], although for such documents the background and interests of the authors will influence the conclusions. Complete concordance within Europe should not be expected for groups as diverse as the European Federation of Pharmaceutical Industries and Associations, the European Generic Medicines Association, the European Medicines Agency, the British National Formulary, Cochrane Reviews, national regulatory agencies and health technology assessment organizations. Each group will have responsibilities to their respective constituencies, and the term 'consensus statement' fails to reflect this diversity. Here, we add another view, with comments from a regulatory perspective.

The authors suggest guidelines are needed for clinical practice and mention potential conflicts between the needs of the healthcare provider and those of individual patients. Hypertension was selected as an example and this is an excellent place to start. A key question might be – what is the first-choice monotherapy for the majority of hypertensive patients? It is difficult to disagree with the results of the ALLHAT trial, funded by the US National Institutes of Health, the largest hypertension trial at the time of completion with over 42 000 patients followed for around 5 years [3]. Chlortalidone was shown to be an effective anti-hypertensive agent, with benefit on mortality, an added bonus being the lower incidence of heart failure compared with other agents. For the majority of hypertensive patients, no drug has greater proven benefit on mortality, a better risk benefit, or be cheaper, than chlortalidone. In this case safety, efficacy, best treatment, low cost, the interest of the healthcare provider and the patient coincide. Yet, chlortalidone is rarely used in Europe (although many argue that bendroflumethiazide is a therapeutically equivalent common alternative). Perhaps, it is this discrepancy that needs to be addressed when trying to establish best practice. Why initiatives such as the ALLHAT/JNC7 dissemina-

tion project [3] had little effect on prescribing deserves an explanation. So many drugs substituted for this indication have no justification over chlortalidone.

The authors mention examples where variation exists between the originator and generic formulations. There is also variation in the manufacture of sequential batches of any innovator. Batch-to-batch variation is a recurring problem for manufacturers, particularly of biologicals. The pharmaceutical formulation of a product involves complex science, where advances in composition technology and changes in manufacturing are common during the product's life cycle. With some drugs on the market for over 100 years, adequate definition of the originator can be a challenge [4]. During development, there may be reluctance to invest heavily in large-scale manufacturing plant before marketing authorization is assured. This cost restraint has to be balanced with the need for the product used in preclinical testing, phase 1, 2 and 3, to be shown to be the same, within defined limits, as the product released onto the market.

Another common, innovator-for-innovator substitution is when medicines have more than one formulation available. There may be an immediate release capsule, orodispersible tablet, a modified release tablet, a transdermal patch or other pharmaceutical forms. Although a line extension authorizing a new formulation may be supported by clinical data, a conventional bioequivalence study may suffice, depending on the new formulation's pharmacokinetic differences. Data from a bioequivalence study comparing new and initial formulation pharmacokinetics are pivotal for these applications. The strengths and limitations of bioequivalence studies submitted for the authorization of new formulation line extensions are similar to those faced during the authorization of generics.

In this complex area, help is on hand from numerous documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [5] as well as the European Medicines Agency website [6]. For generic copies of the innovator the US Food and Drug Administration led the

way following the Hatch Waxman amendment of 1984 [7], but Europe now has up-to-date guidance on the standards expected for generic products [6], including the new Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Additional input comes from World Health Organization inspections [8].

Most bioequivalence testing involves acceptance or rejection within predefined limits of pharmacokinetic data from test and innovator immediate release formulations. A crossover design, in normal volunteers, is often adequate to detect formulation differences and the results obtained with a range of drugs confirm the suitability of the objective criteria used to define acceptance [9].

In Europe the prescriber, patient and healthcare provider continue to be informed of a product's properties by the Summary of Product Characteristics where, e.g. differences in excipients are listed. This also forms the basis of the Patient Information Leaflet. Unfortunately, the complexity of quality testing, standardization and bioequivalence are outside the interests of most prescribers and patients, although as the authors point out, increased transparency is always welcome.

Professor Atholl Johnston and colleagues have performed a valuable service in highlighting the importance of quality assurance to clinical pharmacology, even though consensus is some way off. The pioneering work of Walter A. Shewhart from 1924 onwards [10] and the influence of W. Edwards Deming in Japan [11] are reminders of how quality control is key to mass production. These statistical techniques were extended to pharmaceutical testing [12, 13]. Few products are more important than pharmaceuticals when it comes to the need for reliability. Quality control remains fundamental.

Competing Interests

There are no competing interests to declare. Although the authors work for regulatory authorities, the views expressed are their own and do not reflect those of any agency or institution.

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REFERENCES

- 1 Johnston A, Asmar R, Dahlöf B, Hill K, Jones DA, Jordan J, Karr A, Livingston M, MacGregor G, Sobanja M, Stafylas P, Rosei EA, Zamorano J. Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe. *Br J Clin Pharmacol* 2011; 72: 727–30.
- 2 Okie S. Multinational medicines – ensuring drug quality in an era of global manufacturing. *N Engl J Med* 2009; 361: 737–40.
- 3 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Available at <http://allhat.sph.uth.tmc.edu> (last accessed 14 December 2010).
- 4 Kesselheim AS, Solomon DH. Incentives for drug development – the curious case of colchicine. *N Engl J Med* 2010; 362: 2045–7.
- 5 ICH official website. Available at <http://www.ich.org> (last accessed 14 December 2010).
- 6 European Medicines Agency. Available at <http://www.ema.europa.eu/ema/index> (last accessed on 14 December 2010).
- 7 Food and Drug Administration. Available at <http://www.fda.gov/cder/guidance/index> (last accessed 14 December 2010).
- 8 World Health Organization. Information on Inspections. Good Manufacturing Practices (GMP) and inspections of manufacturing sites. Available at http://apps.who.int/prequal/info_applicants/info_for_applicants_inspections.htm (last accessed 14 December 2010).
- 9 Davit BM, Nwakama PE, Buehler GJ, Conner D, Haidar SH, Patel DT, Yang Y, Yu LX, Woodcock J. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Ann Pharmacother* 2009; 43: 1583–97.
- 10 Shewhart WA. *Economic Control of Quality of Manufactured Product*. New York: Van Nostrand, 1931.
- 11 The W. Edwards Deming Institute. Available at <http://www.deming.org> (last accessed 14 December 2010).
- 12 Westlake WJ. Use of confidence intervals in analysis of comparative bioavailability trials. *J Pharm Sci* 1972; 61: 1340–1.
- 13 Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987; 15: 657–80.

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