What's in a Name?

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In the Armed Forces, drugs are usually prescribed by generic rather than by proprietary names, both as a means of containing costs and to avoid confusion in patients minds when brand substitutions are made from refill to refill. Many doctors are not convinced of the benefits of prescribing generics and often wonder if a generic drug is just as good as its brand counterpart. These fears are not entirely unfounded. India has a large number of medicine makers, with many operating as small-scale pharmaceutical units. Today an estimated 17,000 pharmaceutical companies produce over 40,000 branded formulations, many times more than the rest of the world [1]. In this issue Kanitkar et al [2] have raised concerns on brand substitutions of dialysis fluids as a possible cause of adverse effects in their patients. It is a small, observational study which has not discounted the possible adverse role of the infusion sets or connectors, but does raise a few questions on how safe are generics or brand substitutions. It is important that healthcare givers have a better understanding of generics, drug bio equivalence, drug standards and true comparative value of formula substitutions.

Pharmaceutical companies which develop an original research molecule, market the drug under brand names and its proprietary generic name. After the patent expires, copies of drugs can be made by other manufacturers and are either sold by the name of the ingredient or under another brand name which means they are still generics from the patent point of view. For example, "paracetamol" is the non-proprietary name of a drug often sold as a generic medicine without a brand name but is also marketed under various other brand names. Drugs marketed by these trade names other than those of the original manufacturer are still called generics. Normally patent protection rules under Trade-Related aspects of Intellectual Property Rights (TRIPS) would make it illegal to copy any proprietary drug that was still under a patent. The World Trade Organization Doha ministerial conference in 2001 issued a 'waiver'

that stated intellectual property should not take precedence over public health. Governments could issue licence that enables someone other than the patent holder to copy patented products, if a patent owner fails to offer his product on the market, or offers it at a price that is too high for potential buyers to afford. Competitors can then produce the product or use the process under government license without fear of prosecution. A compulsory licence could also be issued for a drug that treats any disease causing a severe health emergency in that country [3].

'Generic' firms can sell drugs at lower prices largely because they are not carrying the same baggage as multinational drug makers, which want to recoup their research, development and marketing costs, and make a generous profit for their shareholders [3]. For this reason, India's generic pharmaceutical firms are increasingly posing a major challenge for large multinational pharmaceutical firms. Not only are they expanding aggressively in the United States of America and Europe, they are also making inroads by challenging patents on some of the world's most profitable drugs so that inexpensive Indian alternatives become more widely available. The strategy is proving to be an unexpected boon to governments of developed and developing countries that are pushing to make cutting-edge drugs more affordable for their citizens.

Worldwide, companies need to demonstrate that their products contain the same active chemical ingredient, are manufactured to the same quality standards, comply with good manufacturing practices, have similar labeling, and have the same bioavailability as the brand-name drug. The same holds true for our country as well and every formulation in India should meet the pharmacopoeia standards and their manufacture/imports are governed by the rules in 'The Drug and Cosmetic Act 1945 as amended up to 25 June 2005.

Then why this fuss about prescribing a generic drug? According to pharmacopoeia standards, a generic copy

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of a reference drug must contain identical amounts of the same active ingredient. However inactive ingredients such as binders and fillers are allowed to differ as it is assumed that these “inactive ingredients” will not alter the performance of the product. But, these ingredients may contain lactose or gluten products, which could change gut motility or drug absorption in sensitive patients or have inferior packing which would alter the composition of the drug in tropical climates.

Approval of a generic version of a proprietary drug requires demonstration of not only chemical equivalence but also bio equivalence. The latter is defined by absorption parameters generally falling between 80% and 125% of those obtained by the proprietary agent under the same testing condition. If a patient is being treated for a non-life threatening disorder with an agent that has a wide therapeutic window, clinical equivalence may not be critical. Despite the wide window on either side of ideal, the drug continues to be effective and safe [4]. The greatest concern for many physicians is, if this $-20\% + 25\%$ rule would be safe for drugs with narrow therapeutic index, where a small change in systemic concentration can lead to marked change in pharmacodynamic response [4]. The National Kidney Foundation published a white paper in 1999 [5] raised inequivalence concerns for transplant organ immunosuppressants and introduced the term “Critical Dose Drugs” to define drugs that have a narrow therapeutic range, require blood level monitoring, whose doses are individualised as per body weight and have serious clinical consequences if overdosing or under dosing is done. Some clinicians have questioned if therapeutic equivalence under clinical conditions in large number of patients can be actually determined from single dose studies in small number of fasting healthy volunteers often homogenous in character such as age and gender, using surrogate end points determined from assays with less than maximal sensitivity [4].

Pharmaceutical companies promoting generics report non-inferiority or equivalence trials to demonstrate that the drug in question is not chemically worse than the comparator by more than a pre specified small amount known as non inferiority or bio equivalence margins. Henanff et al [6] analysed 162 reports of non-inferiority and equivalence randomised trials and found important deficiencies. The justification for defining the margins of equivalence was described in less than a quarter of the reports, less than half of reports described the sample size and only intention to treat was reported. Moreover, even for trials fulfilling all statistical requirements,

conclusions were sometimes misleading.

Finally, there is always a lingering doubt that there may be a gap between what is theoretically ideal and what the ground realities are. If monitoring mechanisms were not robust enough to ensure implementation of pharmaceutical standards then a lot would depend upon each individual firm's internal quality assurance mechanisms. It is possible that these factors account for the general apprehensions harboured by health professionals on generic formulations in India.

So what should be the recommendation for health care professionals? Is it fair to view all generic formulations with suspicion, their significant cost advantage notwithstanding? Or should we evaluate each such formulation individually, on a case-to case basis? The recommendation by Peter K Kowey makes good prescribing sense. For conditions in which insufficient or excess drug effect may have serious risk; avoid repeated changes from proprietary to generic and back and redetermine the efficacy of the drug with each switch, use an alternative product only if it is widely available and there is a known and consistent relation between the generic and the proprietary compound. This analogy could be extended to brand substitutions. All health care professionals should get involved in the post marketing surveillance systems to verify both the new molecules and generic agents, so that any changes occurring in the product due to potential alterations in the manufacturing process such as may occur with bulk supplies, would be detected and made known to health care givers[4]. Fortunately we have such a reporting mechanism existing at the National level and in the Armed Forces Medical Services.

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