

Are Branded Drugs Better (Some Times)?

On a visit to my local Pharmacy some weeks ago I saw a notice to the effect that the Dispenser had the right, enshrined in Pennsylvania State Law to substitute a cheaper generic version of any prescribed brand name drug, unless specifically advised to the contrary by the Patient's Medical Practitioner.

The patient apparently has no say in the matter.

Practices like mandatory substitution and prescribing guidelines seem "unfair" to those who have spent a lifetime in programs to find new medicines and are aware of the enormous effort, expense and uncertainty associated with defining, promoting and protecting a brand, only for returns on such hard work and investment to rapidly disappear on patent expirations. Few, least of all Insurance organizations, patients and some State Legislators seem concerned about the impact of such policies and practices on the future of R&D-based medications.

However, maybe the patient ought to start worrying about generic substitution!. Insurance Organizations and Regulatory Agencies have always insisted that generic drugs are just as effective as Branded Medicines. There were few if any challenges to such paradigms by experts. Nobody consulted the patients it seems. Emboldened by such success the proponents of generic medications became increasingly emboldened, even talking of "super generics", where product formulation is more complicated.

Things may not be quite so simple. A recent report in The New York Times* states that, for several years there have been reports of "misadventures" with generic "equivalents" of the Modified Release products Wellbutrin XL 300 and Toprolol XL on a Consumer Advocacy Website. Switches from Brand to Generic dosage forms lead to side effects, or loss of efficacy or both. The volume of complaints was too great to be ignored by the hitherto self-confessed "generic enthusiast" who runs the Website.

Who raised the red flag (or several red flags)? The poor patient it seems! Some specialists, particularly cardiologists and neurologists are now and increasingly expressing concerns. Insurers and the FDA seem to beg to differ. The FDA response (if as listed in the article and reproduced *verbatim* here) is surprising if not disturbing. "*Over the 24 hours the patient ends up with the same amount of drug in the bloodstream so there should be no reasons for a variation in effectiveness*" an FDA spokesman apparently stated. This may be *regulatory speak* for "bioequivalence" viz comparable AUC, Cmax and Tmax defines product performance. One would have thought that we had all moved away from such simplistic attitudes. A biphasic profile could conceivably provide comparable conventional PK values to a relatively "smooth" profile (or other profile variants) throughout the dosage interval.

Chronotherapeutic effects, albeit as yet unknown might suggest that effects or side effects could be quite different unless plasma profiles are literally super-imposable. Yet, the Holy Trinity of Cmax, AUC and Tmax seem to be the standard by which copycat formulations are assessed and awarded "clinical equivalence" status. No wonder there may be differences that affect patient's wellbeing.

It may be time to think again as to how generic Modified Release products are characterized in the “bioequivalence” sense.

“Biosimilars” are also increasingly being touted as cheaper replacements for branded Biopharm products. Characterization possibilities for Biopharms (in the analytical sense) are leagues away from what can be done with small molecules. The Cell Line may be what defines the product. The potential for even slight differences in composition affecting safety is many times greater.

Let us hope that wise heads in regulatory, academic and the medical professions take note of what has happened with the above MR Products and resist the calls for cheap and less-than-cheerful alternatives.

And keep an eye on Patient Blogs. Maybe “patient knows best”.

Patrick Crowley

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*(http://www.nytimes.com/2009/12/19/health/19patient.html?_r=1&scp=1&sq=Not%20all%20Drugs%20are%20The%20same&st=cse)