

Orphans

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In the past orphaned children have often suffered greatly, being abused, neglected, brought up by hand, or denied a second helping of gruel. But orphan drugs have escaped such a cruel fate, at least in recent times. Indeed since 1983 these drugs for rare diseases and with limited commercial potential have prospered. For in that year congress promoted their development by granting the manufacturers several tax incentives as well as a seven year market exclusivity.

These arrangements worked well. Even critics of government interference conceded that for once congress had done something right. About 400 new drugs were developed during that period. Some 50 were approved for marketing, notably erythropoetin, synthetic growth hormone, and inhaled pentamidine — some with annual sales exceeding \$200 million.

But lately the stellar success of these orphans has bred concern and envy. Several lobbies complained that the prices charged were too high and kept the drugs from patients, especially those with AIDS. Drug companies left out in the cold may also have experienced the green eyed passion. To help, last year Democrat Congressman Henry Waxman sponsored a bill revoking the seven year marketing exclusivity once the number of patients needing a drug exceeded 200 000. The bill would have also allowed a second company to market the drug if it could prove it had begun work on it within six months of orphan status being granted to the first company.

Supporters of the Waxman bill argued that the original bill needed fine tuning and that million dollar drugs were not orphans. Lack of competition kept prices high, they said, increasing the burden on patients and taxpayers. Others countered that congress was fixing something that wasn't broken and would stifle future drug development and that the high cost of drugs was a different issue that might be addressed across the board. But on the whole opposition to the bill was quite mild because the earlier versions had been more stringent, and the final version passed in December was viewed as a reasonable compromise. Then the bill went up to the White House where President Bush apparently surprised many by vetoing it, claiming that it would wreck the whole programme. Calling the veto a shocking thing, representative Waxman declared that the bill would have saved money and promoted competition, and promised to try again later. Meanwhile all orphan drugs, rich and poor, continue to enjoy their hard fought special privileges and status.

No stomach for such an issue

Also languishing in the orphanage we find mifepristone, the progesterone antagonist that may suppress endometriosis, has cured Cushing's syndrome, and could save 43 000 women with oestrogen dependent cancer. But no company will touch it, neither to test nor to develop, no agency will dare approve it. For mifepristone is RU-486, the French pill that causes over 85% of women to expel their fetus within 24 hours. Doctors in France prescribe it, China has approved its use, and several European countries are also considering approval. The World Health

Organisation thinks it could avoid 100 000-200 000 deaths world wide from surgical and botched up abortions. But in America antiabortion groups have made threatening noises, no company will risk a boycott, nor have regulators the stomach to face such a sensitive issue.

Instead they have looked favourably on bovine growth hormone, the genetically engineered molecule that makes cows yield more milk, could be useful in man, but has angered some activist groups. Regulators also intervened in the fierce spaghetti sauce wars, where one company spent \$20 million on advertising its ragu as "fresh". Competitors argued that heat processed tomatoes could not possibly be fresh, and the Food and Drug Administration agreed. Although the ragu maker explained that the term "fresh" applied to the whole sauce and not just to its tomatoes, the unmoved regulators ordered that the company should change the labelling or face "seizure and/or injunction".

Of perhaps greater moment is the abuse of anabolic steroids and diet pills by the young. One million people may be taking steroids, athletes in health clubs or tournaments, young Adonises wishing to build up their muscles or improve their self image. No regulator has so far been able to suppress this profitable \$100 million black market. Yet androgens will masculinize women and suppress testosterone production in men, in whom they also cause psychological dependence. But among the women the main problem is diet pills, diuretics, emetics, laxatives, and the nasal decongestant sympathomimetic phenylpropanolamine, mostly available without prescription. Last year sales to women wanting to be thin exceeded \$200 million. But several young women have died from electrolyte disturbances, dehydration, hypertensive stroke, or heart failure.

Drug wars continue

Also in danger of being orphaned last year was the generic drug industry, subject to a great public scandal. Though taught in universities and encouraged in academia, generic prescribing has long been hampered by a public perception that generic is inferior, as drug companies promote their products on pens, rulers, calendars, carrier bags, and coffee mugs. Patients and nurses often remember only the brand name, the pharmacist often prints only the brand name on the label, and the young doctor will sow untold confusion by ordering nifedipine when the whole world knows that the wonder drug is Procardia.

At bottom the issue is money. It is a \$25 billion retail and hospital market, with \$6 billion from drug patents due to expire within the next four years. At this time one third of all prescriptions written in the United States are for generic drugs, many in public hospitals and health maintenance organisations. These generics often cost two to ten times less than the brand name. They are made by hundreds of manufacturers who compete fiercely in what has been called the drug wars. The large drug houses have called their generic competitors get rich entrepreneurs, parasites, or profiteers. They emphasise supposed bioequivalence, supporting studies published in scientific journals and

encouraging doctors to report anecdotes about patients who remained deathly ill until they were switched to the proprietary drug. Problems have been said to have occurred with anticonvulsants, antibiotics, and pancreatic enzyme. According to one expert the effect of digoxin is so critical that it should always be prescribed by brand name. Last year the family physicians' organisation voted against using generics in diseases "difficult to stabilize such as depression, asthma, congestive heart failure, diabetes, cardiac problems," also for drugs with "narrow therapeutic margins," antipsychotics, loop diuretics, and in patients over 75—which leaves little else.

The large drug houses have also fought the drug wars by lobbying, frightening politicians and the public about the horrors of generic drugs, and challenging the generic drug makers in the courts. They support their cause by citing the high cost of research, of development, of obtaining market approval. The proponents of generics have countered by citing the savings to the consumer and the overall safety of the products, fighting back by lobbying and influencing administrators and politicians. They also fight among themselves, because a drug approved first yields its greatest profits before the other companies' drugs are also approved. It was indeed a generic drug house that precipitated the scandal when it hired detectives and blew the whistle on the practices of another.

Sensational exposes followed. Food and Drug Administration officials had been bribed to grant early approval. One company had submitted samples of the

corresponding brand name product to pass the bio-equivalence tests. Investigators found irregularities in record keeping, data had been suppressed and falsified, manufacturing standards had been flouted. Several companies had their approval licences revoked and pleaded guilty to criminal charges. The commissioner of the Food and Drug Administration resigned and transferred to another post in a lateral move seemingly related to the scandal. There were newspaper headlines of "Clouds over generic drug industry," "Controversy calls into question effectiveness of generic drugs," and "Patients shun generics in wake of scandal." The big drug houses got every bit of mileage out of the episode, more doctors wrote up anecdotes about worthless generic drugs, and the writers for the drug lobby had a field day.

Yet when the Food and Drug Administration concluded its investigation of over 30 companies it found that 99% of samples were within acceptable limits. Consumer groups said that they saw no reason to switch. The secretary of health declared that he had no evidence that safety had been compromised. The large American Association of Retired Persons said it would continue its extensive mail order service and the polls indicated that 75% of respondents retained confidence in generic drugs. The large public hospital and prepaid plans likewise continue to use generics. But the problem of policing the 750 companies approved to manufacture some 10,000 products remains, and considering the huge stakes involved the drug wars are not likely to end soon.