Generic drug makers eye lucrative Zantac market

Glaxo Wellcome, the world's largest pharmaceutical company, is preparing for a new round of litigation over its most profitable anti-ulcer drug, Zantac. The German company Boehringer Ingelheim had applied to the US Food and Drug Administration (FDA) for approval to market a generic version of the drug when a key patent for Zantac was scheduled to run out this December. But certain patent changes recently mandated by the General Agreement on Tariffs and Trade (GATT) have extended the patent term until July 1997.

Boehringer Ingelheim is not the first company to lock horns with Glaxo Wellcome over Zantac. It is one of many companies waiting in the wings to market generic versions of ranitidine hydrochloride (ranitidine HCl), the active ingredient in Zantac, when the patent expires.

The expiry date of the Zantac patent is currently under legal scrutiny. Recent patent changes due to GATT provided a welcome boost for a small number of pharmaceutical companies (many of whom lack innovative new products in their drug development pipelines), including Glaxo Wellcome, and came at a time when the industry has been under pressure to limit price increases. These will now be able to squeeze more profits out of their best-selling drugs before the market is opened up to price competition from generics.

Nevertheless, the changes are a setback for many makers of generic drugs, who, like Boehringer Ingelheim, had set their sights on the earlier expiry dates as a chance to cash in by selling generic versions of some of the more lucrative brand-name drugs. The stakes are indeed high. Sales of Zantac, for example, brought in an estimated US$4 billion last year (more than half from the United States), and made up more than 40 per cent of Glaxo's (as it was called before it acquired Wellcome) total sales worldwide.

In an attempt to lessen the impact of the recent patent changes on generic drug companies, a provision was included that would allow companies to market generic versions of brand-name drugs during the extended patent term if they could show they had made a significant investment in drug development before the changes took effect in early June. In such cases, the generic drug companies would be obliged to pay the patent holder 'reasonable' royalties.

That may have been the intent, but a 1984 drug pricing law had left the FDA little legal room to manoeuvre. Makers of brand-name drugs contended, and the FDA concurred, that the law precluded the agency from approving generic versions of a drug until the patent term on a brand-name drug has expired.

The situation for most generic drug makers brightened on 7 June when the US Patent and Trademark Office decided that the new GATT extensions would not apply to most brand-name drugs, because their patent terms had already been extended under the Waxman–Hatch Act of 1984. That extension was granted to compensate inventors for the long times spent waiting for FDA approval. That same law provided generic drug makers with the right to ready their products for market, through testing, before a patent had expired.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Glaxo Wellcome

Zantac, Glaxo Wellcome's profitable anti-ulcer drug, could face fierce price competition from generics once it loses patent protection.

Glaxo Wellcome's Zantac patent, and a small number of others, were not extended under Waxman–Hatch, and they have now been permitted extensions under GATT. This has held back generic drug makers like Boehringer Ingelheim from the market by as much as two years.

But help from Congress may be in sight. Senator David H. Pryor (Democrat, Arkansas), who has long crusaded against the pricing practices of the industry, is likely to introduce a bill in the next few months that would, if passed, provide relief for those generic drug makers whose plans had been suspended by the GATT extensions.

The current dispute with Boehringer Ingelheim centres around the finer points of ranitidine chemistry. In order to be made into tablets, the free base is combined with hydrochloric acid to yield the salt, ranitidine HCl. Scientists at Glaxo discovered in the early 1980s that an effective way to purify the salt away from other components in the reaction mixture was to crystallize it. The uncrystallized salt and the crystalline form of ranitidine HCl are known as form one and two, respectively. Glaxo has only ever marketed form two as it was found to be easier to handle and can be stored for longer periods than form one.

Although the two forms of ranitidine are chemically the same and have the same biological activity when released in the body, they are covered by different patents because they have different higher order structures (form two is a crystal, form one is not). The US patent term on form one was due to expire this December but, under the GATT extension, will now run for another eighteen months. Patents on form two and on the process for making form two will expire in 2002 and 2004, respectively.

Boehringer Ingelheim filed its application with the FDA in May to market a generic version of form one. To gain approval, the manufacturer must first demonstrate that the generic version is the 'bio-equivalent' of its brand-name counterpart and must satisfy the FDA that it is not infringing any existing patents. Generic drug makers must submit production protocols to the patent holders, who then have 45 days to respond. If challenged, the application is put on hold for up to 30 months while the matter is reviewed by the courts.

Glaxo Wellcome is already suing Canadian-based Novapharm and Geneva Generics, a US subsidiary of Ciba Geigy Corporation, for infringement. Both companies applied to the FDA in 1994 for approval to sell generic versions of 'form one'. The case against Novapharm will begin later this year; no date has been set for Geneva Generics. Glaxo Wellcome also announced last month that it is suing Boehringer Ingelheim as well, claiming that the company is infringing both its form one and two patents, as well as its process patent for making form two. Company representatives remain tight-lipped about the case. But Boehringer Ingelheim contends, however, that its manufacturing process does not result in the production of any form two.

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