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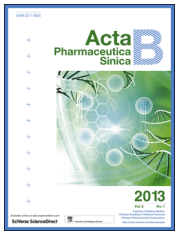

REVIEW

Development of the generic drug industry in the US after the Hatch-Waxman Act of 1984

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Abstract The key events in the development of the US generic drug industry after the Hatch-Waxman Act of 1984 are systematically reviewed, including the process of approval for generic drugs, bioequivalence issues including "switchability", bioequivalence for complicated dosage forms, patent extension, generic drug safety, generic substitution and low-cost generics. The backlog in generic review, generic drug user fees, and "quality by design" for generic drugs is also discussed. The evolution of the US generic drug industry after the Hatch-Waxman Act in 1984 has afforded several lessons of great benefit to other countries wishing to establish or re-establish a domestic generic drug industry.

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1. Introduction

The Drug Price Competition and Patent Term Restoration Act of 1984 (US Public Law 98-417), commonly known as the Hatch-Waxman Act, was signed into law on September 24th 1984 following a vote of 362-0 in favor in the House of Representatives of the 98th Congress and passage through the Senate on by voice vote[1,2]. The Hatch-Waxman Act amended the Federal Food, Drug and Cosmetic Act (FDCA) and the Patent Act, established an abbreviated new drug application (ANDA) process, provided for filing of generic drug applications 60 days later, and so created the modern US generic drug industry[3]. Although the Hatch-Waxman Act was passed with overwhelming support in the US Congress, it was, and remains, an uneasy compromise and a delicate balance between the interests of the brand-name drug industry and the generic drug industry (Table 1[4]). The legislation is complex and has given rise to many unforeseen situations as the industry has developed over the subsequent years. The history of the US generic drug industry after the enactment of the Hatch-Waxman Act has presented several lessons which are of benefit to other countries wishing to establish or re-establish a domestic generic drug industry, and especially so for countries like China, where generic drugs constitute the largest share of the pharmaceutical industry and drug consumption.

Prior to passage of the Hatch-Waxman Act, there were relatively few generic drug products in the US. The 1962 amendments to the Food, Drug and Cosmetic Act (FD&C Act) had some unintended consequences[3]. The requirements imposed by the amendments to gain approval to market a new drug had made the approval process costly and lengthy. With the exception of antibiotics, generic drugs were approved *via* a "paper NDA" process which required filing scientific literature to support the safety and efficacy of a generic drug, since the FDA regarded the safety and efficacy data filed by the innovator as proprietary. However, for the majority of branded drug products, excluding the antibiotics that were not subjected to the requirement, the innovator companies did not publish sufficient scientific literature to enable justification of safety and efficacy *via* the "paper NDA" route[3]. Hence in 1983 only 35% of top-selling branded drugs with expired patents had generic competition, and the generic market share was only 13%[5,6]. These generic drug products required that a prescription be written for the generic.

The Hatch-Waxman Act addressed the shortcomings of the post-1962 amendments to the FD&C Act situation by providing a less arduous approval route for generic products but restoring a new drug patent term lost by the post-1962 NDA process[1]. Thus, and as suggested by the name, the Hatch-Waxman Act is a compromise between the interests of the brand and generic industries[7].

Title I of the Hatch-Waxman Act amended Section 505 of the FD&C Act to create an Abbreviated New Drug Application (ANDA) which allowed approval of generics as equivalent products to an existing brand product[(1)] (called a reference listed drug, RLD) on the basis of bioequivalence. It allowed for some variance in the RLD provided this was approved *via* a petition before filing.

Title II of the Hatch-Waxman made two changes to Title 35 of the United States Code regarding patent law: it amended the statute to provide for restoration of that part of the patent term lost to the time taken for FDA required pre-market testing and review, up to a maximum of 5 years for new drug applications. It amended the statute to make using an invention solely for the purposes of generating information to file an application not an act of infringement and that filing an ANDA or paper NDA that challenges a patent could be deemed an act of infringement, albeit an artificial infringement.

The Hatch-Waxman Act grants generic manufacturers the ability to mount a validity challenge without incurring the cost of entry or risking enormous damages flowing from any possible infringement. In addition, the Hatch-Waxman Act requires that the FDA, among other things, makes publicly available a list of approved drug products with therapeutic equivalence evaluations with monthly supplements, commonly known as the Orange Book. This list also included patent and exclusivity listings for drug products where those were in force, which were provided by the drug application owner, and the FDA is obliged to list them[8]. Because the FDA-published list included drug products designated as therapeutically equivalent to an original drug product, it became possible for health care providers to substitute a generic equivalent for a brand product[3]. This allowed the creation of a substitution system where state legislation would allow or mandate the substitution of generic equivalents, where they exist, for prescriptions written for brand products. The only exceptions to this substitution are if the prescription is marked "Do Not Substitute" or the patient refuses a generic substitution. This substitution system created the generic industry marketing system where it is only necessary to get a pharmacy to stock generic products to ensure their selling to patients, and physicians need not know that a generic exists or that it will be taken by their patients. Because the US drug distribution and retail pharmacy industries are concentrated, a generic company requires relatively few people to market its product. In addition, the high prices for branded products means that pharmacy profit margins for generic products are higher as low priced generics can tolerate a higher markup by the pharmacy[9].

This substitution procedure created an extremely efficient marketing and distribution system and ensured the rapid "pull through" of new generic products into the distribution chain due to their higher profitability. Studies have shown that patients and doctors prefer brand name drugs, although pharmacy computer systems default to substitute generic for brand-name drugs. Studies also found problems with health insurance companies and poor communication with the doctors' offices, leading to patient confusion and poorer drug treatment[10].

In 2012, generics reached 84% of dispensed prescriptions, and spending in this segment grew by $8 billion[11]. The fourth annual Generic Drug Savings Study revealed remarkable reductions in health care costs over the previous 10 years (from 2002 to 2011)[12]. Clearly, despite all the attempts by the brand industry to counter generic product development and use after the enactment of the Hatch-Waxman Act, generic drugs have risen to become a significant majority of the US prescription pharmaceutical market by volume. This has been driven entirely by cost. Because the brand pharmaceutical industry has chosen to maintain very high costs for products dispensed through retail pharmacies, it has created a huge incentive for payers to switch to generics and for retail pharmacies to dispense generics[13–16].

There is no doubt that the US generic industry has been successful beyond the wildest dreams of those who formulated the Hatch-Waxman Act. Even though successful, the development of the generic drug industry has been anything but smooth and the rest of this paper will discuss some key events since its enactment.

[(1)]Also could be generic products.