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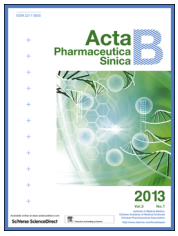

REVIEW

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.

Table 1 A delicate balance between the interests of the brand-name drug industry and the generic drug industry according to the Hatch-Waxman Act[4].

Encourage competition Generic manufacturers	Reward technical advance Brand manufacturers
• ANDA process – only bioequivalence required • Allows testing before the brand patent expires • Creates incentive 180-day marketing exclusivity for the first successful ANDA filing with patent challenge	• Defines the conditions for patent extensions – 100% approval time+50% testing time – Up to maximum extension of 5 years – Patent life cannot be extended beyond 14 years • Non-patent exclusivity – NDA data kept as proprietary by FDA – Excludes salts or esters of approved drugs – Three years exclusivity for improvements to approved brand products *via* clinical trials (*e.g.*, new uses, dosage forms, dosage regimens) • Sets forth a process for patent challenges

2. The generic drug scandal

The beginning of the modern generic drug industry was marked by fraud and other criminality on the part of some companies that almost destroyed the industry before it got started. The fraud was pervasive from 1984 to 1989 and became collectively known as the Generic Drug Scandal[17,18]. The generic drug scandal reduced consumers' perception of the quality of generic drugs[19,20]. With the passage of the Hatch-Waxman Act, the field for new generic drug products was wide open with many top selling brand-name drugs available for generic competition[21]. The Hatch-Waxman Act granted 180-day marketing exclusivity to the first filed ANDA containing a paragraph IV certification (a patent challenge). If the first filed paragraph IV applicant was sued and won in court, they would get 180 days of exclusive marketing of the generic. Generic companies knew that the first approved generic product would attract relatively high prices and take the majority of the generic market share[22], and those who entered later would reap lower margins. Therefore the race was on to develop products and file first to gain first approval for a given product. Also driving the race to file was the fact that FDA had a "first in, first reviewed" policy, although it would later become known that some FDA reviewers were bribed to manipulate this policy[23]. The stakes were high for the new industry and tens or hundreds of millions of dollars in potential profits were at stake.

Fraud began on day one of the new industry. One company, Bolar Pharmaceuticals, was reported to have driven to the FDA and filed 40 ANDAs on November 23rd 1984. It would later be found that all of these ANDAs were fraudulent, fabricated for the purpose of filing first to ensure a timely approval[24]. One generic company, Mylan Laboratories, had complained to the FDA-CDER Division of Generic Drugs (DGD) that ANDAs were not being reviewed according to the "first in, first reviewed" policy and that some applicants were receiving favored treatment[17]. By 1988, Mylan became frustrated with the lack of response to their complaints of favoritism and hired a private detective to investigate. Evidence of bribery of DGD reviewers was found and turned over to the US House of Representatives Energy and Commerce Committee's Subcommittee on Oversight and Investigations (the Subcommittee). The Subcommittee began an investigation that revealed bribery and fraud, and resulted in charges against FDA officials and generic drug companies and some of their executives, managers, and employees. The investigation continued for several years and investigators from the Department of Justice and Department of Health and Human Services discovered that not only had there been bribery, but that some companies had submitted fraudulent data, substituting brand product for generic product as samples in bioequivalence testing[25,26].

In all, thirty individuals and nine companies were either found guilty or admitted their role in FDA corruption. At one point, in the subcommittee investigation during a press briefing, it was reported that subcommittee staff stated that "of 39 generic drug companies… (investigated) … only about a half dozen appear to be free of criminal or regulatory taint"[27]. Representative John Dingell, Chairman of the Subcommittee, declared that the generic drug industry was "the most pervasively corrupt this subcommittee has ever uncovered"[28].

Clearly by late 1990 the public's faith in generic drugs and in FDA's ability to regulate the drug industry was severely shaken[29]. Among the 1009 consumers of a broad range of ages surveyed by Gallup in October 1989 to ascertain their attitudes toward generic drugs after the scandal, 51% feared that generic drugs were not manufactured to the same standards as brand medications and more than 70% indicated that the scandal had affected their confidence in generic drugs to some degree[19]. Realizing the risks of lack of trust in FDA and to the fledgling generic drug industry, FDA acted very aggressively to root out fraud. Indeed so aggressive was FDA's approach that one industry analyst reported "everybody is scared to death about the FDA because they know the FDA means business"[30]. This aggressive approach was successful in restoring public confidence in both FDA's ability to regulate the drug industry and in generic drug products, although it took many years before public confidence in generic drugs returned to pre-scandal levels.

Two major steps were taken to rectify the problems revealed by the Generic Drug Scandal and to restore public faith in generic drugs. First was the passage of the Generic Drug Enforcement Act (GDEA) which gave FDA the ability to take actions against persons or corporations abusing FDA regulations[31]. These actions included debarment, withdrawal of product approval, suspension of product distribution, and the ability to levy civil penalties[32]. Second was a large product analysis effort aimed at determining whether generic drug products obtained from the market met product specifications. By November of 1989 the FDA had analyzed over 2500 product samples representing the 30 most prescribed generic products. Less than 1% failed to meet product specifications and none was deemed a health threat[33].

The broad-scale unreliability of data submitted to support marketing approval applications, particularly fraudulent data in

records submitted in premarket approval applications during the generic drug scandal, resulted in the establishment of the application integrity policy by FDA in the early 1990s[34]. In addition to the very public actions, FDA took numerous other actions in the wake of the Scandal in an effort to prevent a recurrence in the future[6,35], including:

- Institution of a new system to control new drug sponsors' access to application reviewers. The new system required formal requests for meetings and those meetings, which are now usually held by telephone, had to be held with a Project Manager and the Reviewer's Supervisor. Uncontrolled and unsupervised access to reviewers had facilitated the bribery that had occurred as part of the scandal.
- Establishment of a strict application queue system to assign applications to "the next available reviewer" on a first-come basis. Although such a system had existed previously, this was a much more robust system that had better visibility within the Office of Generic Drugs (OGD).
- All ANDAs had to be complete when filed. A "received for filing" procedure was instituted to ensure that each ANDA received for filing by OGD was complete. Previously applications could be filed incomplete and amended with additional data, such as additional strengths test batches, stability test results, bioequivalence studies, etc. This created situations where fraudulent information could be filed to get a position in the review queue. If subsequent to initial filing failures occurred, there was a temptation for the sponsor to overlook or manipulate failing data to keep the review moving forward. In addition, post filing failures wasted review resources.
- Establishment of the Office of Generic Drugs for ANDA review. Previously this function resided in the Division of Generic Drugs which was not a separate office within the Office of Pharmaceutical Sciences. This action raised the status and management visibility of generic drugs within the Center for Drug Evaluation and Research (CDER). Previously generic drug review had been seen as a sub-branch of the review divisions and this lack of visibility may have been a contributing factor to the failure to recognize the problems for so long.
- Establishment of the pre-approval inspection (PAI) system. This system was put into place to verify the accuracy of data filed in an application. A number of firms filed in their ANDAs fraudulent data which were made to appear genuine on the surface. The PAI system sent FDA compliance investigators into firms to verify the accuracy of filed data.
- Institution of measures to address bioequivalence studies including the establishment of the retention sample requirements, financial interest disclosure requirements, and increased inspection of contract research organizations conducting generic drug bioequivalence studies. During investigations that followed the initial disclosure of fraud and bribery, it was discovered that some firms had substituted brand-name product samples for generic product samples in bioequivalence studies[26]. These measures were meant to prevent bioequivalence fraud.
- Establishment of the FDA Office of Ombudsman reporting directly to the Commissioner. The Ombudsman receives and investigates complaints from both within and outside the FDA and provides remedies where necessary. Mylan Laboratories had complained repeatedly to DGD that they believed there were irregularities in the review queue order and the order of approvals, and claimed these complaints were ignored by those responsible for DGD management[17,22]. Had the early complaints been properly investigated, the outcome in the public view would have been much more favorable for FDA.

The root cause of the generic drug scandal was the large number of generic product opportunities suddenly presented by the Hatch-Waxman Act and the profits that could be made by companies securing competitive FDA application approvals for these new generic drug products. Some companies engaged in criminal activities in order to gain an advantage in being first to market and to reap large profits[32]. The fact that this was not isolated to one or two companies but was apparently widespread in the fledgling generic drug industry brought the whole industry into disrepute and severely shook confidence in generic drug products[26]. It is apparent that FDA was too trusting of the new generic drug industry and of its own staff. In retrospect, the filing of such a large number of ANDAs in the months following passage of the Hatch-Waxman Act should have been a warning sign that all was not as it seemed with these applications[36]. The lesson from the scandal is that when you do not have a history of an industry, such as the largely new generic drug industry, and there are potentially large "windfall" profits to be made, you need to put in place robust systems to prevent bribery and fraud.

3. "First-in, first reviewed" and the "bundling" of approvals

According to FDA procedures for the review of generic drug applications, applications should be reviewed in the order in which they are received[23]. There are several common situations with regard to possible time-of-approval scenarios for multiple ANDAs for the same RLD[37,38].

3.1. Approval limited by a patent expiry where patent life post-RLD-approval is >5 years

In this situation, applications can be filed over a fairly long period of time and reviewed in the normal course of OGD ANDA review. Several applications can be reviewed and ready for approval on the day of patent expiry, so multiple generic approvals can be expected regardless of the initial quality of the ANDA filings because there are several years in which to address and correct deficiencies. This situation provides a low competitive scenario and little incentive to file high quality applications. Provided the filing is made several years ahead of patent expiry even poor quality applications should be approved at market formation.

3.2. Approval is limited by new chemical entity (NCE) exclusivity, no listed patents

In this situation, the time between filing and NCE expiry is limited and so only better quality applications, if reviewed in the normal course of OGD ANDA review, would be expected to receive approval at the expiry of NCE exclusivity. In this situation it is possible to "bundle" approvals to ensure multiple approvals at NCE expiry. Although one may expect that multiple approvals will ensure low prices and remove the temptation of a windfall profit, it also removes the incentive to produce a high quality filing since filings of lower quality are "pushed through" to ensure multiple day 1 approvals.

3.3. *Approval is sought by patent challenge, the so-called "Paragraph IV" filings*

In this situation, one or more Orange Book listed patents is challenged as not infringed, invalid, or unenforceable. The law provides that the first person to file an application containing a Paragraph IV certification is entitled to 6 months of marketing exclusivity if the applicant is sued for patent infringement and successful in winning that suit[21]. Obviously the prospect of 6 months of exclusive marketing is a potentially large windfall profit and an enormous incentive to achieve the first filed position. This situation strongly encourages filing quickly rather than after good product development; the reward is for being first, not for being good.

Clearly what is occurring here in the first two situations is that FDA is attempting to remove the windfall profit incentive through ensuring competition in as many situations as possible as a way of eliminating the commercial incentive that was the cause of the fraudulent applications during the first 5 years after the enactment of the Hatch-Waxman Act. Unfortunately, this also largely removes the incentive for doing good development and filing complete, high quality applications, since that approach costs more and provides no advantage. Policy makers should consider the use of commercial advantage through more timely approvals to encourage the behavior they want to see, high quality filings and good development of robust products. High quality development is more expensive and takes longer so the best way to ensure it occurs is to make it more profitable[39].

In the third situation, the first-to-file Paragraph IV, the legislation potentially rewards the first filer, and in doing so effectively punishes other filers. This is perhaps the ultimate encouragement to do bad product development as speed to file is the sole determinant of success. It is virtually impossible in this situation to do good product development and succeed in filing first. The current state is that many ANDA filings contain Paragraph IV patent certifications rather than the few in the first decade of the Hatch-Waxman Act[21]. The incentive to challenge patents should be the possibility of obtaining a competitive approval if both your product development and your legal basis are of high quality.

If a regulatory authority wants to encourage good product development and high quality filings, they should align these aims with the commercial success gained from high quality product development. If approvals are bundled together regardless of filing quality, or if filing first rather than filing best is rewarded, the senior corporate managers will not spend the time and money required for a high quality development.

4. Bioequivalence and switchability

The system of marketing generic drugs in the United States is one of "switching" from a brand product to a generic equivalent (usually an AB-rated generic in the Orange Book). This substitution is performed by the pharmacist, the prescription is most often written as a brand name product. One consequence of this system of substitution is that patients have their medication "switched" either from brand to generic or from one generic to another generic without input from or knowledge of the physician or the patient[40,41].

The system of determining equivalents depends on the product type[42,43]. The most frequent types are:

- Bioequivalence determined by single dose blood level studies, with the test and reference products determined to be bioequivalent if C_{max} and AUC meet confidence interval requirements of 80%–125% at the 90% level. AUC measures the extent of drug absorption (or exposure), and C_{max} is a surrogate measure of rate of absorption (that is over what time period the drug is absorbed).
- Bioequivalence determined by clinical equivalence studies either with or without blood level studies. This system typically is used when the action of the drug in the drug product is not a result of systemic absorption of the drug. For example topically applied drug products or inhaled drug products generally fall into this category.
- Bioequivalence determined by the rate of *in vitro* drug dissolution from the drug product. This is generally applied to situations where the drug is highly soluble and no *in vivo* nonequivalence issues are expected.
- Bioequivalence is determined because the drug products are true solutions of the drug substance. Generally, if the true solution is not a solution for oral administration, then the formulation of the product must also be the same as the RLD (with certain limited exceptions). Some drug products in this class also require equivalent systems of administration (*e.g.*, nasal spray, inhaled nebulizer, ophthalmic dropper).

The often stated standard is that equivalent generic products have the same safety and efficacy profile as the RLD to which they are compared. This is probably true in virtually all cases[44]. However, when considering how generics products are dispensed in the USA, the standard is that they must be "switchable", essentially identical. Patients can be switched from the brand to a generic or from one generic to another by the dispensing pharmacist with no input beyond that the switched products are rated as interchangeable in the Orange Book[20]. Switchability is a higher standard than "same safety and efficacy profile". Even from the beginning there have been complaints that some generic products are not switchable[41,45,46]. In the early years, there was a strong campaign by some brand drug companies to discredit generics and complaints concerning switchability were dismissed as just part of the campaign to discredit[41,42,47]. However, while the brand-name company anti-generic tactics have largely subsided, the complaints concerning switchability of some classes of drugs, and of some specific drug products have continued and gained more credence in recent years[45,46]. Some groups believe that antiepileptic drugs (AEDs) have switchability issues and claim that break-through seizures occur following switching and are resolved upon switching back to the original medication[48,49]. One physician group advises switching with caution when patients are stabilized on a particular AED drug therapy[48].

In the last few years there have been issues with some specific generic products in switchability[40,50]. One product that generated a lot of debate concerning switchability was generic Bupropion ER[51]. Many patients claimed that when switched from Wellbutrin XL to a generic there was a lack of efficacy for the generic product. There do appear to be differences in the blood level profiles between the generic and the branded product, although the generic meets C_{max} and AUC confidence interval standards. It has been reported that Teva, the generic marketer, undertook a clinical study to test whether the brand and generic are equivalent in a double blinded study[52]. FDA reviewed new data that indicate Budeprion XL 300 mg (bupropion hydrochloride extended-release tablets) manufactured by Impax Laboratories, Inc. and marketed by Teva Pharmaceuticals USA, Inc. is not therapeutically equivalent to Wellbutrin XL 300 mg. FDA has changed the therapeutic

equivalence rating for this product in the Orange Book from AB to BX, signifying that Budeprion XL 300 mg fails to demonstrate therapeutic equivalence to Wellbutrin XL 300 mg. Impax has requested the Agency withdraw approval of Budeprion XL 300 mg extended-release tablets. The announcement does not affect the Impax/Teva Budeprion 150 mg product or generic bupropion products made by other manufacturers[53].

The types of products most susceptible to switching issues are those with patient perceived feedback and/or generally complex drug release profiles. Examples of drug classes with patient perceived feedback include analgesics, antidepressants, hypnotics, anticonvulsants, etc.[44,54]. These are drug classes where the patient can relatively easily perceive the effect of the medication. Types of dosage forms most likely to give rise to switchability issues are those where the dosage form exerts significant control on the pattern of drug release or where inactive ingredients influence the action of the drug, for example affect penetration of the drug into the target tissue. Products currently being examined are mostly modified-release oral products with complex drug release profiles[54]. Some of these products have patents protecting the formulation that gives rise to the drug profile, and so generic product sponsors are trying to circumvent the patented formulation but still meet the C_{max} and AUC bioequivalence confidence intervals. Some examples of this type of product are:

Bupropion XL 150 mg – The RLD has an initial delay in drug release due to a delayed-release coating; some generic products did not employ the delayed-release component[51–54].

Ambien CR – The RLD is 50% immediate-release and 50% controlled release. Some generics altered that ratio to avoid the patent[55–58].

Concerta – The RLD has an immediate-release outer layer and an osmotic pump extended-release core. The blood level profile is largely independent of food effect. Some generics are attempting to use a hydrophilic matrix extended-release core or not to have the immediate-release component[55–58].

Adderall XR – The RLD is a mixture of immediate-release pellets and delayed-release pellets. Some generics are using a short extended-release or a pH-independent pulsatile release[59].

Cardizem CD – The RLD has a ratio 40:60 of fast releasing drug and slow releasing drug which gives rise to a double peak in blood level. Some generics used a single type of drug release to yield a single blood level peak[60].

There are several possible issues that might relate to switchability. FDA states switchability or "interchangeability" as "the risk of alternating or switching between use of the product and the reference product is not greater than the risk of maintaining the patient on the reference product"[61]. This recognizes that there may be dose-to-dose or lot-to-lot variation in the reference product. A switchable generic should fall within the variability envelope of the reference product, which may range from essentially zero variability for an immediate-release BCS Class I product to significant variability for some complex products such as some modified-release products[62–64].

Much effort in this area has been focused on potential bioavailability differences between generic and reference products or theoretically even wider differences between generics. The US standard for generic bioequivalence is that the "true" mean of the generic product C_{max} and AUC must be between 80% and 125% (log-transformed data) at the 90% confidence level as measured by two one-sided *t*-tests. Critics have pointed to this standard as potentially allowing a generic to differ from a reference by as much as 20% and two generics by as much as 40%. This is somewhat of an exaggeration; however the difference for a very well behaved drug and dosage form could be 15% from reference and still pass confidence interval[65]. The corresponding worst case for two generics would then be a 30% difference in "true" geometric means. FDA recently (April 13th and 14th, 2010) asked the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) whether the acceptance criteria should be tightened such that the calculated ratio of the means for bioequivalence (the so-called point estimate) should be constrained to fall within 90%–111% (log-transformed data)[66]. As part of FDA's presentation to the ACPS-CP, data was presented from 2070 bioequivalence studies for solid oral products. These studies were from approved ANDAs from the period 1996–2007. The test/reference ratios are shown in the table below (Table 2)[65].

Analysis of these studies shows that the great majority of generic products already fall within the proposed 90%–111% range for the geometric mean ratio and the grand means for C_{max} and for AUC are very close to 1 (Fig. 1). Frequency histograms presented at the April 14, 2010 meeting of the ACPS-CP showed that while C_{max} is slightly more variable than AUC_t, the great majority of bioequivalence studies over the 12 year period analyzed fell within the proposed 90%–111% point estimate range. It was stated that based on C_{max}, only about 6% of studies fell outside these limits[64]. The ACPS-CP voted 12 to 2 against adopting the 90%–111% limits for geometric mean ratio for C_{max} and AUC. The committee felt that this is primarily a public perception issue and that imposing a further limitation was not justified, that increased efforts in public education were better than additional and possibly unnecessary regulations[66].

At the same two day meeting the question of whether to use partial AUC (pAUC) bioequivalence in assessing the bioequivalence of complex release profile modified-release drug products should be recommended. The committee expressed concern with the large number of subjects that would be required to obtain sufficient power for bioequivalence assessment based on pAUC. The committee felt that evaluating time of onset was important but could not suggest methodology at this time[55,66].

Table 2 Average of generic/innovator (test/reference) bioequivalence parameter geometric mean ratios* (point estimates).

BE parameter	Number of studies	Geometric mean ratio	Range
AUC_t	2070	1.00 ± 0.04	0.86–1.16
AUC_∞	1939	1.00 ± 0.04	0.86–1.16
C_{max}	2070	1.00 ± 0.06	0.83–1.18

AUC: area under the concentration-time curve; BE: bioequivalence; and C_{max}: peak drug plasma concentration.
*Mean ± standard deviation (SD).

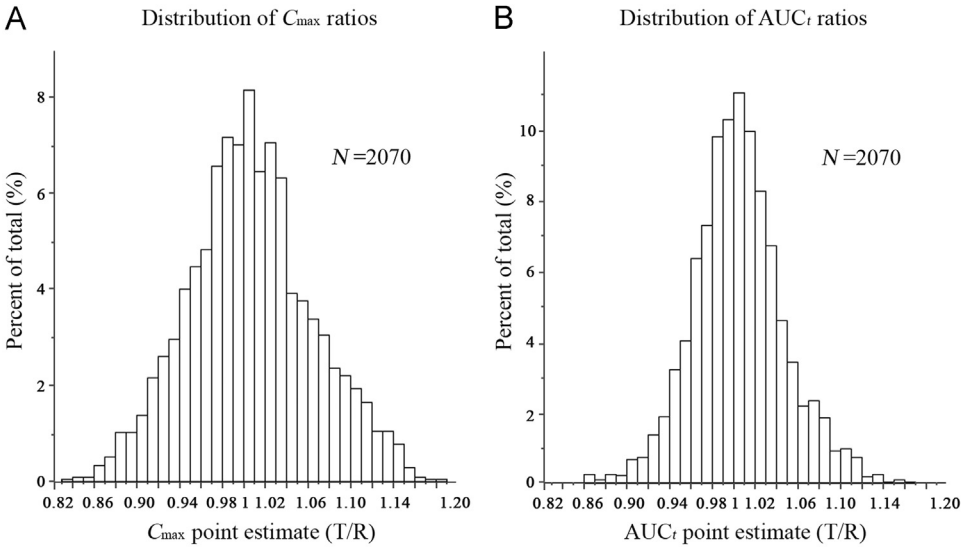

Figure 1 Distribution of C_{max} ratios and AUC$_t$ ratios shows that the great majority of generic products already fall within the proposed 90%–111% range for the geometric mean ratio and the grand means for C_{max} and for AUC are very close to 1[65].

The issue of switchability remains unresolved. It is clear that FDA and its Advisory Committee feel that much of the switching complaints are "placebo" effect and not grounded in any real differences between bioequivalent products[67]. There is a lack of well controlled studies in this area and the question of switchability is likely to remain unanswered until such studies are performed. From a public health perspective this is an important question regarding the approval and use of generic drug products. Given the complexity of disease states and the diversity of the patient population, it would seem improbable that all generic drug products would be switchable based solely on the bioequivalence criteria. While it may be considered expedient to continue to maintain that all bioequivalent generic drug products are switchable, it would seem from a scientific view to be an unlikely situation.

The debate on switchability has focused on possible differences between brand drugs and generic drugs that might occur within the constraints of the bioequivalence statistical range, however that involves an assumption that commercial batches of generic products perform exactly as the exhibit batch(es) subjected to bioequivalence studies. Many of these generic products are scaled up for commercial manufacture and changes might occur as a result of the scale-up, for example changes in drug substance particle size or changes in dosage form properties. If this kind of product change does occur at some level, then individual generic drug products might have an altered bioavailability profile and so possibly present switchability issues.

One study of a calcium channel blocker published in 1993 showed differences between bioequivalence in young healthy volunteers when compared to older patients[68]. Both generic products were bioequivalent to the reference product in young healthy volunteers, but only one of the two was bioequivalent in older patients. Another publication in 1997 showed differences in bioequivalence in older patients with yet another generic product of this reference product; however, the authors concluded these differences were not clinically significant[69].

5. Bioequivalence methodology for complex dosage forms

Methodology for bioequivalence determination for some complex dosage forms remains to be defined. The Hatch-Waxman Act defined single dose blood level studies as the method of establishing bioequivalence for systemically acting drug products. The FDA was to define methodology for dosage forms where systemic blood levels, if present, are not related to or relevant to the pharmacological action of the drug product. There are many dosage forms where systemic blood levels cannot be used to determine bioequivalence as the product is not intended to be systemically active. Examples include:

Topicals – creams, lotions, solutions, shampoos, nail varnish, etc.

Ophthalmic and otic drops – solutions and suspensions.

Dosage forms intended to act within the gastrointestinal tract lumen – orally administered, suppositories, rectal solutions, etc.

One way to determine that a non-systemically active generic product was "bioequivalent" was to formulate the generic in an identical way to the RLD, qualitatively and quantitatively the same, the so-called "Q1/Q2" approach. While this approach is attractive, it will only work where the RLD formulation can be determined with the necessary accuracy (within $\pm 5\%$ *w/w* for all inactive ingredients) and where the form of the drug substance is known; almost always implying the drug substance is in solution within the dosage form. While Q1/Q2 is required for some dosage forms[(2)], for example, parenterals, otic and ophthalmic drops or semi-solids, being Q1/Q2 does not necessarily imply being "bioequivalent". For example, if the drug substance is a solid present in the dosage form as a dispersion, then being Q1/Q2 does not imply that the drug will act in an identical way to the RLD. That will depend on the drug substance having the identical particle size distribution, polymorphic form, and for some complex dosage forms, being present in the same phase of the dosage form. Since it is currently virtually impossible to define and then achieve the exact form of the RLD drug substance solid form, clinical equivalence studies are required in addition to Q1/Q2. Additionally formulation patents may prevent taking the Q1/Q2 approach.

[(2)]Note that some variations are allowed from Q1/Q2 for some dosage forms. These are defined in 21CFR.

For non-systemically acting drug products where there is a clear clinical effect, such as, for example, cure of an infection or resolution of a dermatological condition such as a rash, a clinical equivalence study can be designed and conducted to show clinical equivalence. Depending on the dosage form, some bioequivalence guidelines that recommend clinical equivalence studies also require systemic blood level studies. Although clinical equivalence studies can be lengthy and costly, they do provide a mechanism for demonstrating bioequivalence to achieve an AB rating for a successful generic applicant. Clinical equivalence studies can be expensive and risky; however with the very significant increase in brand product prices over the last several years, the financial risk is much more appealing than it was 10 years ago.

Although the FDA has made significant progress in defining bioequivalence methodology for many of these non-systemically active drug products, particularly in the last decade or so, a number of products remain without determined methodology. Perhaps the largest group of products in this category is the inhaled drug products. While FDA was directed to determine bioequivalence methodology, the necessary resources were not specifically provided to undertake the research work necessary. As a result, lack of resources in this area has hampered the research work necessary to establish bioequivalence methodology for some complex dosage forms. In recognition of the current lack of resources, the Generic Drug User Fee Amendments of 2012 (GDUFA) allocates some of the fee income to research programs to establish bioequivalence methodology, including bioequivalence of local acting orally inhaled drug products, pharmacokinetic studies and evaluation of anti-epileptic drugs, and evaluation of drug product physical attributes on patient acceptability (*e.g.*, tablet size, shape, coating, and scoring configuration).

6. Products for which a bioequivalence determination is not possible

There is a small group of products for which it is not possible to develop AB-rated generics equivalents. These fall into two broad categories.

6.1. *Ill-defined active product ingredients*

Some products have an active ingredient (or ingredients) that are not sufficiently defined or specified to enable a generic equivalent to be developed. The most notable of these is PREMARIN® (conjugated estrogens tablets). The active ingredients are a mixture of conjugated estrogens extracted from the urine of pregnant mares. The mixture is not completely defined and the relative importance of the various components to the safety and efficacy of this product is not known. In the absence of this information it is not possible to define the content or the concentration ranges of conjugated estrogens required to match the RLD. Since the active product ingredient (API) cannot be specified, it is not possible to have an AB-rated generic equivalent.

If an active ingredient is not sufficiently defined to allow development of a generic equivalent, it raises the question of how you know that the active ingredient is still the same as that used for the safety and efficiency studies that formed the basis of the original approval.

6.2. *"Bad" dosage forms*

Some dosage forms, most notably solid orals, have excessive unit-to-unit and/or batch-to-batch variability and/or the drug release changes over shelf life due to poor design of the dosage form. In extreme circumstances this can prevent the development of an AB-rated generic equivalent since it is not possible to pass bioequivalence studies due to the "moving target" nature of the RLD. Examples include:

- Diazide (Dyazide) – a powder filled capsule of a potassium-sparing diuretic (triamterene) and a thiazide diuretic (hydrochlorothiazide) that was apparently manufactured by an unstable dry blending process using an excessive amount of magnesium stearate to control the release of drug. The variable nature of the RLD dosage form made it impossible to develop a generic to this poorly developed RLD.
- Paxil CR – an extended-release tablet of paroxetine HCl which claims to be based on Geomatrix™ tablet technology. This product showed excessive variability to the point where the NDA sponsor could not pass a single dose bioequivalence study performed as part of a manufacturing site transfer. Although patent protection for Paxil CR was relatively weak, it took over 12 years before a single generic was approved.

For both of these products it is an inappropriate dosage form design and/or manufacturing process which leads to the variability and "moving target" aspect of the RLD and makes it extremely difficult if not impossible to develop an AB-rated generic equivalent. There would seem to be no rationale for dosage forms that exhibit such instability in manufacture and regulatory authorities should consider the feasibility of developing a generic equivalent when approving new products.

7. Patent "evergreening"

The Hatch-Waxman Act made provisions for encouraging generic sponsors to challenge innovator-listed patents in order to prevent "evergreening", the strategy of obtaining serial patent protection for a drug product[70]. During the drafting of the Hatch-Waxman Act, there was discussion of evergreening. The provisions included in the law for patent challenges, for first-to-file marketing exclusivity, and for modification of the patent statute to allow patent suits to be brought following filing of an ANDA were all aimed at making patent challenges attractive to generic companies[37,71]. In addition, the Hatch-Waxman Act included a provision to "carve out" newly patented indications as they were potentially seen as a way of maintaining patent protection for prolonged periods following expiry of the original patent(s).

There were some follow-on patents at the time of passage of the Hatch-Waxman Act but patent challenges were relatively uncommon in the early years of the generic industry. In later years, the majority of drug products have used a patent "evergreening" strategy[72]. The evergreening strategies used most commonly include obtaining additional patents on specific features of a pharmaceutical product, such as isomers, polymorphs, metabolites, intermediates, process patents, or double patenting, product hopping to extend the exclusivity of a drug product after the patents listed in the Orange Book have expired. In fact, it could be argued that it is almost negligent on the part of brand company senior managers not to attempt this market protection strategy on behalf of their shareholders. Brand loyalty that a new product-line

extension introduced for an original brand helps the original price stand rigid despite the entry of generic drugs facilitated by the Hatch-Waxman Act[73]. Beyond the goal of the Hatch-Waxman, one of the impacts of the patent evergreening is generic innovation by obtaining design-around patents, to invent an alternative to a patented invention that does not infringe the patent claim, or a more efficient manufacturing process, new formulations, or a new form of the active ingredient. Thus with more ANDAs filed than ever, there are an increased number of "me-too" ANDAs and ANDAs for products that already have generic versions. While in the early years the success rate for generics challenging listed patents was about 75%, this has dropped considerably in recent years as the number of challenges has increased and in the race to be first-to-file, much riskier patent challenge positions are being pursued[74,75].

In the first decade of this century, the overall success rate for the generic drug industry was 48% for cases that have gone to trial. However, the success rate increases to 76% when settlements are included. Over half of all cases are settled or dropped[76].

Many types of "evergreening" have been tried (Table 3), some being more successful than others[70,71]. One aspect not foreseen in the original legislative framework was the use of pay-for-delay settlements between innovators of a drug product and later generic filers[6,38]. In these settlements the generic company typically acknowledges the validity of the brand company's patent(s) in exchange for the right to go to market ahead of brand patent expiry[77]. This prevents a judgment in a patent suit which might affect the brand company's future patent position and guarantees the generic company the right to exclusive or semi-exclusive marketing for a period of time. While the parties to such settlements say they are good for the public because they guarantee generic entry ahead of patent expiry, the Federal Trade Commission (FTC) believes these settlements actually delay generic entry and are therefore anti-competitive[38]. According to the FTC's annual report Overview of Agreements Filed in FY (fiscal year) 2010, the FTC "received 113 final resolutions of patent disputes between a brand and a generic "during the year, 31 of which" contain both compensation to the generic manufacturer and a restriction on the generic manufacturer's ability to market its product[78]. "These so-called pay-for-delay agreements have significantly postponed substantial consumer savings from lower generic drug prices. The FTC has recommended that Congress should pass legislation to protect consumers from such anticompetitive agreements[78]. FTC has pressed Congress and the courts to make certain pay-for-delay settlements presumptively illegal.

8. Authorized generics

The increasing prevalence of 'authorized' generics, that is the brand company selling a version of the brand product as a generic equivalent either itself or through a third party, appears designed to defeat the intent of the Hatch-Waxman Act 6-month marketing exclusivity for first-to-file Paragraph IV generic sponsors[79–83]. Some see this as a deliberate attempt by the brand industry to deprive a successful patent challenger of the profits from the 6-month exclusive marketing period[80–82,84]. Generic companies have complained that authorized generics have taken the market price for the generic lower than a second generic entrant would have, and some brand company senior managers have stated that authorized generics are in part a strategy to deprive generic companies of profits from patent challenges[80–82]. Authorized generics do not require approval as they are the brand product and so they are already approved[80]. If authorized generics are, in fact, being marketed during the period of marketing exclusivity for a successful generic patent challenger to deprive the generic challenger of marketing exclusivity period profits, then that is clearly an attempt to defeat the intent of the Hatch-Waxman Act[77,81,82,85–87]. Generic firms complain that authorized generics undermine the incentives the Hatch-Waxman created to encourage generic companies to challenge and invent around brand patents and so bring generic products to market ahead of brand patent expriy. They also complained that the authorized generics are anticompetitive and undermine the incentive for bringing affordable generic medicines to market, and the authorized generics give brand-name companies the unilateral right to masquerade the branded drug as generic drug. If this is the case, a legislative remedy may be needed, suggesting that the whole first-to-file system should be overhauled to remedy the incentive to make poor quality filings.

9. The generic marketplace, a generic "oligopoly", and drug shortages

A large proportion of the generic drug supply can be in the hands of only a few large generic companies[87]. In calendar year 2009, nearly 50% of the generic drug supply was produced by the top 4 generic companies. This can create a fragile drug supply situation where production problems at one generic company can rapidly lead to critical drug shortages that can take weeks or months to resolve. This is most often an issue for mature generic products where the major market share has been ceded to one manufacturer and the other manufacturers, including the brand company, reduce manufacturing capacity for the product or even cease manufacture altogether. The table shows the total prescription share and the generic prescription share of the top 4 generic companies (Table 4). Note that this is a slight overestimate because the Sandoz prescriptions are not broken out of the Novartis number[87]. The figures are from IMS data. The prescription total for 2009 was 3922 million.

This oligopoly situation is largely the result of major purchasers preferring to deal with only a few well known and well established generic manufacturers. Since these major customers control so much of the prescription drug market, they are essentially acting as de facto "kingmakers" in the generic manufacturing marketplace[87].

Table 3 Increasing trend of final settlements, potential pay-for-delay settlement, and potential pay-for-delay involving first filers[78].

Type	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010
Final settlements	14	11	28	33	66	68	113
Potential pay-for-delay	0	3	14	14	16	19	31
Potential pay-for-delay involving first filers	0	2	9	11	13	15	26

Table 4 Total prescription share and the generic prescription share of the top 4 generic companies.

Company	Prescription share (total Rx in millions)	Percentage total (%)	Percentage generic (%)
Teva	629.5	16.1	21.5
Mylan	343.1	8.7	11.6
Novartis (Sandoz)	238.8	6.1	8.1
Watson	234.7	6.0	8.0
Total	1446.1	36.9	49.2

A recent review of FDA's drug shortages list shows that there are a number of shortages attributable to "manufacturing issues" in generic drug companies[88]. Many of these "issues" are themselves attributable to FDA compliance problems faced by some of the companies. The point, however, is that over time following the introduction of generics, much of the drug product supply comes from a single generic manufacturer, most often from a single manufacturing plant. If problems occur, other suppliers cannot react quickly enough to prevent a drug shortage.

In addition, the factors leading to drug shortages also include:

- Market factors: the growth in demand has occurred while the capacity of manufacturing facilities remained stable, leading to a very high rate of capacity utilization.
- Supply chain issues: essential raw ingredient suppliers, active pharmaceutical ingredient manufacturers, final drug product manufacturers, wholesalers, group purchasing organizations, clinicians, and, ultimately, patients are affected[89].
- Pricing and reimbursement policies: the impact of changes to the Medicare Modernization Act (MMA) on the reimbursement rate for injectable drugs delivered in outpatient settings and the capped the growth rate in Medicare's reimbursement paid to providers for administering these drugs has been to dramatically reduce the price of older, generic drugs administered in non-hospital settings. Price ceilings (maximum prices enforced by federal or state law) represent barriers to price flexibility. Price ceilings effectively prohibit prices from adjusting to the levels where consumer demand is tempered and suppliers are encouraged to increase production[90]. As a result, supply and demand are not balanced. While large government price ceilings hold down the price, the total cost, which includes the cost of waiting time and other inefficient rationing mechanisms, actually increases[91].

According to the FDA, the primary reasons for drug shortages include quality and manufacturing issues, and other reasons include production delays at the manufacturer and delays companies experience receiving raw materials and components from suppliers. The fundamental problem identified is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments. These dynamics may have produced a market situation in which quality problems have become sufficiently common and severe to result in drug shortages.

When written in Chinese the word 'crisis' is composed of two characters. One represents danger, and the other represents opportunity[92]. Just as the reorganization after the generic drug scandal, the FDA has begun to consider taking the potential actions. A point has been reached where the FDA needs to engage the marketplace to help address the manufacturing problems rather than by the unilateral FDA actions. The buyers and payers could be supported by FDA to provide meaningful manufacturing quality metrics in their purchase and reimbursement decisions[93].

10. Review cycle time and number of applications

The Hatch-Waxman Act directed the FDA to review ANDAs within 180 days and to make a decision to approve or disapprove the application (the law did, however, allow for extensions of this time period). Before the Hatch-Waxman Act was passed the FDA was warning that it did not have enough reviewers to meet this goal. Initially FDA estimated that up to 900 ANDAs might be filed in the first 6 months and that 55–60 new reviewers would be needed. This estimate was later revised to 90–100 new reviewers. The Commissioner's prediction of a backlog was borne out when 370 new ANDAs were filed within the first week and 140 pending paper NDAs were converted to ANDAs. However, by the end of 1985 average review cycle time was down to 140 days, as a result of establishing the new DGD[1].

When the generic drug scandal hit ANDA review essentially froze as no one knew which ANDAs were fraudulent. But in the period following the scandal, review resumed and consistently met the 180-day goal. However, starting in the early 2000s the number of ANDAs being filed increased sharply. This has led to a backlog and lengthening of review times. Over the past several years the review and approval time for an ANDA has nearly doubled. It is estimated that over 2700 ANDAs are now awaiting FDA review and the average review time for an ANDA is nearing 32 months[94]. Although OGD has funds to hire more reviewers, that has happened only recently and it takes time to hire and train new reviewers. In the period before they are fully trained, new staff actually reduce overall application review productivity.

It seems clear that the US Federal Government has not staffed OGD adequately for years. Given that generic drugs are now 84% of all prescriptions filled in the US, FDA's emphasis may be on the wrong sector of the drug industry. This is perhaps a consequence of user fees, a system where government opts out of its fiscal responsibilities by getting private industry to pay for its own government oversight. This is not free money, it is simply added onto the cost of medication and so is a "tax" that hits those who buy drug products. The Generic Drug User Fee Amendments of 2012 (GDUFA) is designed to tackle the lack of resources to review and approve generic drugs is generic user fees. In any case it will take some time before adequate resources are available to again meet the 180-day review for all ANDAs.

In the performance goals in the Generic User Fee Act of 2012, the FDA agreed to expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted to avoid the possible forfeiture of 180-day exclusivity for failure to obtain timely tentative approval[95].

11. Generic drug user fee (GDUFA)

Although new drug user fees have been vigorously supported by the brand drug industry, the generic drug user fee has not, until recently, been the case with generic drugs and the generic drug industry. The first call for a generic drug user fee (GDUFA) was in 1992, twenty years ago. At that time the generic industry vigorously opposed the imposition of generic drug user fees. The industry argued that generic drugs saved the Federal Government health care programs billions of dollars and the cost of generic drug review and approval was a tiny fraction of the savings. So the argument was in essence that more and faster generic drug approvals actually saved the Federal Government vastly more money than it cost to review and approve generics. Industry remained steadfastly opposed to the imposition of generic drug user fees until 2009, when the major generic industry trade associations abruptly reversed their long held position and for the first time since the passage of the Hatch-Waxman Act, and came out in favor of user fees. The original argument that more and faster generic drug approvals saved the Federal Government (and the population at large) huge amounts of money was valid and the amount of savings was accelerating with the passage of time, so why did they change their stance on the subject? The major issue that changed the generic industry view of and policy on user fees was the same as that which encouraged the brand industry to embrace user fees – review cycle time. For most of the time since the Hatch-Waxman Act, the FDA had met or nearly met the 180-day mandate for review so little would be gained in review turnaround by paying user fees. It would, however, have provided more resources to address the issue of bioequivalence methodology for those drug products where such methodology is presently lacking. While this is a minor issue compared to review cycle time, it is becoming more important as some of the products in this category have large values and are therefore becoming more attractive targets for generic drug companies. Another issue concerns compliance inspection of foreign facilities that develop and manufacture generic drugs for import into the US. Over the years since the Hatch-Waxman Act was passed, the proportion of generic drugs being developed and manufactured in other countries has been increasing. It has long been held by US domestic manufacturers that FDA compliance inspections of foreign firms were not as thorough as those conducted for domestic firms. In addition, with the large increase in foreign facilities the FDA has been falling behind on its program for foreign facility inspections. The FDA has ascribed this situation to lack of resources and one of the important issues negotiated for GDUFA is increasing resources to provide equal inspectional intensity and timing for all facilities, domestic and foreign, so creating a "level playing field" with respect to compliance inspection of generic drug development and manufacturing facilities[96].

Prior to the 2006 fiscal year, although new ANDA filings had been steadily increasing, the ANDA review backlog had been stable at about the same level as new filings indicating that OGD review was keeping pace with the new filing rate. However from 2006 through 2009, although the new application filing rate had leveled out, the ANDA review backlog began to climb in a linear manner. OGD review staff numbers also increased over this period from about 190 in 2006 to about 260 in 2009, essentially increasing at the same rate as the backlog was increasing. From 2009 the ANDA backlog took an alarming turn upward and, although there are only two years of data to show, it appears to be increasing in an exponential fashion although new ANDA filings remain essentially flat. Although review staff numbers increased from 2009 to 2010, there is no increase between 2010 and 2011. It should be noted that this was the period when negotiations on a GDUFA were underway and so this apparent "freeze" may have been as a result of an impending GDUFA.

There are two sources of generic drug user fees: (1) facility (establishment) fees will account for 70% of annual GDUFA fees, of which 80% will be paid by finished dose manufacturers and 20% paid by active pharmaceutical ingredient manufacturers; (2) application fees – the remaining 30% of the annual GDUFA fees will come from generic drug applications[97]. The industry and FDA have agreed upon a number of additional goals, metrics, and efficiencies set forth in detail in a negotiated goals letter in return for fees, which should be reported to Congress annually.

- Application metrics: By year 5 of the program, the FDA will review and act on 90% of complete electronic ANDAs within 10 months after the date of submission.
- Backlog metrics: the FDA will review and act on 90% of all ANDAs and prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY 2017.
- cGMP inspections metrics: the FDA will conduct risk-adjusted biennial cGMP surveillance inspections of generic API and generic finished dosage form manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms by FY 2017.
- Efficiency enhancements: the FDA will implement various efficiency enhancements that impact the review of both ANDAs and DMFs, as well as inspections, upon enactment of the program (*i.e.*, use of complete review/response letters, completeness assessments for DMFs intending to be referenced by ANDA sponsors, division level deficiency review and first cycle telephonic meetings for ANDAs and DMFs).
- Regulatory science: the FDA will undertake various initiatives designed to enhance post-marketing safety, to develop guidance for industry, and mitigate regulatory science gaps in select generic regulatory pathways[98].

By focusing on equipping the FDA with additional resources to ensure safety, provide more timely access to affordable, high-quality generic drugs, and improve transparency within the agency, the generic user fee program is expected to help FDA make significant progress in addressing critical industry-wide issues, truly eliminate the disparity between foreign and domestic facility inspection rates, create a more level playing field for U.S. manufacturers, and better ensure the safety of the global supply chain. The generic user fee plan is also expected to provide resources for reviewing applications in a timely way, which will also enable FDA to complete inspections and work with companies to address issues that might otherwise lead to shortages[99].

12. Generic drug safety

In calendar year 2012, generic drugs represented 84% of all prescriptions filled[11]. Over the period since the introduction of

generic product substitution there have been very few reported safety issues that can be ascribed to generic drugs "without cause". Perhaps the best known case occurred in the late 1980s and involved a company called Pharmaceutical Basics and carbamazepine tablets. This company illegally micronized the carbamazepine API used in their tablets without FDA approval of this manufacturing change. This resulted in several ADE (Adverse Drug Event) reports, including some deaths, as a result of the altered blood levels caused by the micronized API[100].

There is currently significant debate concerning switching of anti-epileptic drugs and the incidence of "break through" seizures[48,49]. However, this and other debates are issues of switchability and not issues of a more fundamental lack of safety or efficacy in anti-epileptic generic drug products. Despite the thousands of A-rated generic products approved over the years after the enactment of the Hatch-Waxman Act and the billions of prescriptions filled with these products, generic drugs have a remarkably good safety record. This strongly suggests that the system of bioequivalence is a sound system as a basis for the approval of generic drug products.

13. Generic product substitution system

The system of generic product substitution has, above all else, been the driving force behind the extraordinary success of the US generic pharmaceutical industry over the years since the passage of the Hatch-Waxman Act. Despite the shaky start and the generic drug scandal, generic drug utilization has continued to increase, driven by the ever increasing prices of branded pharmaceutical products[101].

It is difficult to imagine a more efficient system at pulling generic drug products into and through the distribution channels[85]. The system achieves the following:

- Does not require promotion of generics to physicians[102].
- Does not require generic product marketing beyond best price to distribution customers.
- Does not require physician approval to dispense generics.
- Does not require patient knowledge of generic products.
- Generics are more profitable to dispensing pharmacies than brand products.
- Generics are generally much less expensive than brand products.
- Generic profitability to the pharmacy ensures that new generic products are "pulled" into the distribution chain and that generic substitution rate is rapid.

Generic utilization rates have reached 84% of all prescriptions in the US in calendar year 2012[11].

14. $4 generics

In 2006, Walmart, the largest retailer in the US, began to offer selected generic drugs at $4 for a 30-day supply. The original list included 314 products made up of 143 compounds in 24 therapeutic categories. Although originally seen as a gimmick by some, the $4 program spread to most, if not all other chain store pharmacies. Soon after, programs of $10 for a 3-month supply were added (some $12)[103]. This is now a well entrenched prescription supply program[104]. In more recent times, some chain supermarkets have offered a number of common generic antibiotics free of charge. Not all lists offered by pharmacies are the same, so more generic drugs are available in these programs then at first appeared to be the case.

Although public perception of these programs is that they are "loss leaders" aimed at getting potential customers in the door (certainly the case for the free antibiotics), in fact these drugs are not being sold below cost. Many of these products are sold by generic manufacturers for less than $1 per 30 units[105]. At these prices virtually every patient who needs one of these generic drugs can afford the cost.

The $4 programs are perhaps the pinnacle of the aim to make prescription drugs affordable to virtually every patient who needs these drugs. However, current generic manufacturers' prices are very low because of intense competition. No manufacturer offering the prices necessary for a $4 generic program can survive on these margins, depending instead on newer, more profitable products. If there is a rationalization of the generic industry in the future that includes pricing at the level necessary for manufacturers to continue in business based on more mature products, then the $4 cost may have to rise. The vast majority of patients do not realize how low manufacturers' prices are because the retailers are generally using very high markups, so it may come as a surprise to most consumers if manufacturers' prices do rise to a sustainable level.

15. Quality by design for generic drugs

Over recent years, quality by design (QbD) has been presented by the OGD at various meetings as a necessary program to ensure high quality in generic drug development. Starting from January 1, 2013, ANDAs would not be accepted for filing without the QbD elements included in the updated ANDA checklist[106]. In other word, starting in 2013, filing requirements for generics manufacturers will be much different than in the past. The FDA had published immediate and modified release QbD examples to help the manufacturers to prepare for QbD in 2013.

QbD in pharmaceuticals is a method where quality elements are evaluated using systematic risk-based and science-based methods in development, scale-up, and the manufacturing process to ensure robust product quality.

QbD principles in the pharmaceutical development of original ANDA product submissions are strongly encouraged. A risk-based, scientifically sound submission must now include the following[107]:

- Quality target product profile (QTPP).
- Critical quality attributes (CQAs) of the drug product.
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems.
- Process design and understanding including identification of critical process parameters and in-process material attributes.
- Control strategy and justification.

Under QbD, to develop a generic product that is bioequivalent to a RLD, an applicant must understand the attributes of the formulation and manufacturing process that have the potential to change the bioavailability of a particular active ingredient. Under the current development and manufacturing path for generic drugs, product quality and performance are determined by testing of the product, whereas under the QbD system, quality is built into the final product by understanding and controlling formulation and manufacturing variables. The aim of adopting QbD is that consumers will receive quality products while manufacturers are able to improve process through the implementation of QbD.

16. Summary

The modern US generic pharmaceutical industry was created by the Hatch-Waxman Act and began accepting the first ANDAs in November 1984. The industry got off to a bad start with widespread bribery and fraud characterizing the first 5 years. The generic drug scandal damaged the reputation of the FDA and shook public confidence in the Agency and in generic drugs. However, the changes made as a result of the scandal changed the relationship of FDA with the generic drug industry and ultimately restored public confidence in generic drug products.

Generic drugs were about 13% of all prescriptions in 1984 and grew rapidly after the Hatch-Waxman Act was passed. By the late 1990s generic drugs were about 50% of prescriptions. They remained at this level until the mid-2000s when prescription growth resumed following patent expiration for a number of key "first in class" drugs. Generic prescription growth has accelerated in the last few years and in calendar 2012, reached 84% of prescriptions[11].

The growth of generic drug use in the US has been impressive, and likely beyond the most optimistic estimates at the time the law was passed. This has been driven by a number of factors, the success of the generic product substitution system with its provider profit motivation, the high cost of brand products which creates a lot of "pricing space" for cheaper generic alternatives, the gradual addition of most major therapeutic classes to the generic drug product range, the lack of productivity of the brand industry in finding new small molecule drugs, and government efforts to increase generic drug use through government entitlement programs have all helped to drive generic drug utilization. Generic drug use now stands at an all-time high. The brand industry now has a prescription share of less than 20% and is attempting to maintain profitability by increasing prices on existing products rather than on new products which have historically driven the brand industry. This situation cannot persist for more than a few more years and the future of the brand industry looks uncertain[52].

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