Journey of Marketed Unapproved Drugs in the United States

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Abstract

Pre-market approval of drugs by regulatory authorities is a crucial process. However, many manufacturers market drugs illegally without approval. The United States Food and Drug Administration (US-FDA) did not have the provision of pre-market approval for drugs before 1938 as a result of which numerous drug related disasters occurred during this period. Following these untoward incidents, the US-FDA made drug approval compulsory with the passage of Federal Food and Drugs Act in 1938 and Kefauver-Harris Amendments in 1962. These amendments stated that the 'pre-1938' drugs need not require approval and were termed as 'grandfathered' drugs. The amendments also directed National Academy of Science/National Research Council to review the drugs approved between 1938 and 1962 for efficacy. These drugs were called Drug Efficacy Study Implementation drugs. Later the US-FDA introduced Over the Counter Drug Review System (1972), Prescription Drug Wrap-up Program (1980s) and a guidance document (2006, revised in 2011) to streamline the drug approval system and discourage the marketing of unapproved drugs. Despite these efforts, many unapproved drugs are still available in the US market. The US-FDA needs to further improvise its policies to restrain the threat posed by these marketed unapproved drugs.

Keywords: Grandfathered drugs, drug efficacy study implementation, unapproved drugs, US-FDA

INTRODUCTION

Marketing of unapproved drugs has always posed a threat to the health of people in every nation. Before 1938, the United States Food and Drug Administration (US-FDA) had no provision for pre-market drug approval on the basis of their safety and efficacy. Unregulated availability of drugs led to several drug induced disasters. To curb this menace, the US-FDA later formulated and amended several policies to ensure the welfare of the people. Despite stringent US-FDA regulations, thousands of unapproved drugs are still available illegally in the market. Here, we describe the journey of unapproved drugs in US market and the US-FDA policies to curtail them.
**PRE-1938 ERA**

In 1906, Federal Food and Drugs Act\(^2,3\) was passed which made it compulsory for all the manufacturers to state the presence of any dangerous ingredient with its amount on the label and also prohibited the interstate commerce of adulterated or misbranded drugs. However, this Act had many shortcomings like pre-market approval was still not required. Further cosmetics and medical devices were not covered under this Act. Also it did not restrict the false therapeutic claims of drugs like in the case of a drug named 'Banbar' which was falsely claimed to cure diabetes. Similarly 'Wilhide Exhaler' was misleadingly advertised as a cure for tuberculosis. As a result of these shortcomings, several untoward incidents were rampant like eye injuries due to 'Lash-Lure' (an eyelash dye). Despite untoward incidents, the US Congress was adamant not to amend or replace the 1906 Act. Later in 1937, over 100 people lost their lives in Elixir Sulfanilamide disaster\(^4\). This propelled the US Congress to pass Food, Drug, and Cosmetic (FD&C) Act 1938.5

**FOOD, DRUG, AND COSMETIC ACT 1938**

This Act mandated that the manufacturers need to provide evidence of drug safety before marketing it. This Act also brought the cosmetics and therapeutic devices under the ambit of the US-FDA. This also prohibited false therapeutic drug claims and directed the manufacturers to mention the adequate directions for safe drug use in the label. However, it was not mandatory for the manufacturers to prove efficacy of the drugs for approval.

**KEFAUVER-HARRIS AMENDMENTS 1962**

In 1962, after the thalidomide tragedy, US Congress introduced Kefauver-Harris Amendments\(^6\) to the FD&C Act 1938. It became mandatory for the manufacturers to prove efficacy of the drugs along with their safety as pre-requisite for the US-FDA approval. These amendments empowered the US-FDA to have stricter control over clinical drug trials. Also good manufacturing practice strategies were formulated and were made mandatory for the drug companies to follow. The pre-1962 drugs were divided into two broad categories:

**a) Grandfathered Drugs**

As per 1962 amendments, it was made compulsory to establish the efficacy for the drugs marketed since 1938. However, this was not applicable to the drugs marketed before 1938 and these drugs were referred to as “grandfathered” or “pre-38” drugs.\(^1,7\) Grandfathered drugs were exempted only if their formulation, dosage form, potency, route of administration, indication and labelling had not changed since 1962. Otherwise, filing of New Drug Application was required for approval. The drug manufacturer or distributor was made responsible to maintain documents necessary to support the grandfathered status. The US-FDA believes that there might not be any grandfathered drug still available in the market as they might have changed with regards to their formulation, dosage form, potency etc.

**b) Drug Efficacy Study Implementation (DESI)**\(^1\)

Under DESI review, the US-FDA gave
According to the information provided by the US-FDA to Energy and Commerce Committee, in March 2016, most of the DESI proceedings had been completed and there were only 12 DESI proceedings which were pending. However, the US-FDA had not tracked the number of applications approved for DESI drugs.

### OVER THE COUNTER (OTC) DRUG REVIEW

In 1960s, the US-FDA received many drug applications for their approval as OTC drugs. The US-FDA was not able to process all the applications due to lack of sufficient resources. Later, in 1972, the US-FDA formed advisory panel for each therapeutic class of drug to review data relating to claims and active ingredients. Based on their recommendations, the US-FDA prepared and published the monographs for each class of drugs. The monograph mentioned the therapeutic claims, labelling and active ingredients. If any OTC drug was manufactured as per the monograph, it was considered to be generally recognized as safe (GRAS) and effective (GRAE). These drugs need not take approval for marketing.

The US-FDA has still not published monographs for some therapeutic classes of drugs. It also published a number of negative monographs which mentioned the therapeutic classes in which no OTC drugs can be marketed. The US-FDA also listed active ingredients not to be used in OTC drugs as there was inadequate data to consider them GRAS/GRAE.

### PRESCRIPTION DRUG WRAP-UP

Despite the efforts of the US-FDA to curb the menace of unapproved drugs in the market, large number of prescription drugs
were still illegally available. These were neither DESI/IRS nor grandfathered drugs, but manufacturers claimed them to be so. Later in 1983 the US-FDA noticed that a high potency Vitamin E injection (E-Ferol), an IRS drug to a pre-1962 drug, caused death of 40 premature infants. In response to this tragedy, US-FDA directed the Centre for Drug Evaluation and Research to assess the severity of situation and launched Prescription Drug Wrap-Up program to address marketed unapproved drugs. Under this program, a drug was considered to be marketed illegally, unless the manufacturer of the drug could establish that a drug is either grandfathered, DESI drug or is as per OTC monograph, but not a new drug.

UNAPPROVED DRUG INITIATIVE

In June 2006, the US-FDA released “Marketed Unapproved Drugs—Compliance Policy Guide” (CPG). It outlined the US-FDA policies to efficiently and rationally bring unapproved drugs into the ambit of approval process. Further, a risk-based enforcement program was designed in which drugs posing highest threat prioritized for action to prevent undue burden on consumers and unnecessary disruption of the market. The CPG gives highest enforcement priority to the following:

- Drugs with potential safety risks.
- Drugs that lack proof of effectiveness.
- Health fraud drugs—The US-FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article".
- Drugs that challenge the new drug approval and OTC drug monograph systems.
- Unapproved new drugs which violate the Act in other ways.
- Drugs that are reformulated to escape any enforcement action by the US-FDA.

CPG issued official notice to the manufacturers that illegally marketed drug product would be subject to enforcement action which can be including requesting voluntary compliance; providing notice of action in Federal Register; issuing an untitled letter or a warning letter; and/or initiating a seizure, injunction, or other proceeding. Since the release of CPG, many unapproved drugs have been withdrawn from the market. In September 2011, US-FDA revised the guidance document which clarified that any unapproved new drug introduced onto the market after September 19, 2011 would be subject to immediate enforcement action without prior notice.

CONCLUSION

The US-FDA has developed one of the world’s most inflexible process for drug approval in the world. It also efficiently and rationally identifies and prioritizes the illegally marketed unapproved drugs and accordingly take enforcement action. Despite this thousands of unapproved
drugs are being marketed illegally in the US. This warrants further improvement in drug regulatory policies to curtail this public health issue.

REFERENCES


