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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

FDA: Addressing Concerns About Marketing Unapproved Drugs

WHAT MEASURES HAS THE FDA UNDERTAKEN TO ADDRESS CONCERNS ABOUT MARKETING UNAPPROVED DRUGS

You are listening to ReachMD XM-157, The Channel for Medical Professionals. Welcome to The FDA Voice, a program discussing the US Food and Drug Administration and its role in protecting and promoting your health. Your host is Dr. Charles Turck, Clinical Instructor at the Massachusetts College of Pharmacy and Health Sciences.

The Federal Food, Drug, & Cosmetic Act generally requires drugs to be both safe and effective prior to marketing and widespread use, but despite that fact not all marketed drugs have undergone FDA approval. What measures has the FDA undertaken to address concerns about marketing unapproved drugs? Welcome to the FDA Voice. I am your host, Dr. Charles Turck and with today is Dr. Jason Woo. Dr. Woo is the Associate Director for Scientific and Medical Affairs in the Office of Compliance for the Center for Drug Evaluation and Research of the FDA. We are talking today about the marketing of unapproved drugs and how the FDA is addressing this key issue.

DR. CHARLES TURCK:

Dr. Woo do we have any estimates on how many unapproved drugs there are on the market today.

DR. JASON WOO:

Sure, Dr. Turck thanks again for this opportunity. We estimate that about 2% of the types of prescribed drug products that are in the market are unapproved.

DR. CHARLES TURCK:

And it's a small percentage, but nonetheless, it's still a percentage. How is that these unapproved drugs made it onto the market in the first place?

DR. JASON WOO:

Well a lot of these have been around for sometime and were being marketed in some form before Congress made changes to the law

that required drugs be approved by the FDA and we have worked over, over the years to address most of these changes and most drug products available to consumers meet the approval requirements of the law. However, there are some manufacturers who have not gone through the submission process of providing a required information of their drug products, the safety information, the efficacy and manufacturing specifications that are needed to get FDA approval. It is not that FDA doesn't allow these drugs to be marketed illegally. We simply don't have the sufficient resources to identify and pursue them all at once. As in most circumstances we focus our limited resources where they will do the most good, giving the highest priority to drugs with known safety risks, drugs that lack evidence of the effectiveness. In some cases, FDA action on drug products requiring approval has to be gradual to avoid creating shortages of products that are medically necessary.

DR. CHARLES TURCK:

Now just to be clear, we are not just talking about using FDA approved prescription meds for off-label uses. We are talking about the actual presence of unapproved products on the market.

DR. JASON WOO:

Correct, the off-label use of approved drugs is something which falls under the practice of medicine, providers if they feel that an approved product is warranted for another use may use choose to treat their patients that way. We are talking about drugs that have actually never gone through the approval process, where information has not been submitted to the agency that verifies, you know, that the drug has been tested in the appropriate populations and shown to be safe and efficacious and also just as importantly have not where the manufacturer has not provided the information that they can manufacture the drugs, so that the drug is manufactured to the level of purity and potency that is expected of the consumer. In addition, there are labeling concerns to make sure that the drug has the appropriate information that is necessary for the prescriber and the patient to use the drug safely.

DR. CHARLES TURCK:

I was wondering if you could provide a little history of background behind the legislative changes that led to the current presence of unapproved meds.

DR. JASON WOO:

Okay, well the original Pure Food & Drug Act was passed in 1906 as a result of a lot of problems in the market place with many different types of foods and medicinal products. It was essentially the Wild West of medicine at that time, but after a number of good articles including, the book, The Jungle by Upton Sinclair, and a series of articles outlining the way many of the medicinal products were sold, the government decided to enact the Pure Food & Drug and Cosmetic Act. At that time, it basically required that drugs be not painted with any type of putrid material. It wasn't until 1938 that the safety of drugs became required. In 1937, there was the elixir of sulfanilamide episode where a company was marketing an antibiotic treatment and decided to change the formulation into a liquid product. While doing so, they mixed with a chemical called diethylene glycol, which is nowadays basically known as antifreeze, but that subsequently led to over 100 deaths across the country, many in children which subsequently led to the enactment of the Food, Drug, and Cosmetic Act in 1938. After that in 1962, there was another episode with the drug thalidomide which had been approved in Europe, but thanks to the work of an FDA official, a medical officer, was not approved for use in the United States. After the use in Europe, they discovered that there were a number of congenital abnormalities or birth defects that were associated with that drug. The Congress enacted a modern Food, Drug, & Cosmetic Act which now required drugs to be not just safe, but also efficacious.

DR. CHARLES TURCK:

And some of the unapproved medications that are currently on the market are they holdovers from the period before 1962 then?

DR. JASON WOO:

Well the way the law is written, it emphasizes that drugs, not only should the drug ingredient itself be shown to have been safe and efficacious, but the manufacturing also needs to be modernized as well as the labeling. So many of these drugs have been around for many years. For example, morphine is an example of a drug that has been around for 100s of years. However, the way that morphine was manufactured has changed over time and certainly the way the drug is labeled has changed. So you have some manufacturers out there who continue to make the drug without having submitted the information again of safety and efficacy to the agency and again with the information that demonstrates that they can manufacture the drug safely and with the appropriate labeling information that will allow consumers and prescribers to use that drug safely.

DR. CHARLES TURCK:

So it is then possible to say have an active ingredient like morphine, have 1 formulation by 1 manufacturer be approved by the FDA and then another formulation not be approved by the FDA?

DR. JASON WOO:

That is correct.

If you are just joining us, you are listening to The FDA Voice on ReachMD XM-157, the Channel for Medical Professionals. I am Dr. Charles Turck, and I am speaking with Dr. Jason Woo, Associate Director for Scientific and Medical Affairs in the office of Compliance at the Center for Drug Evaluation and Research of the FDA. We are talking about the marketing of unapproved drugs and how the FDA is responding to the issue.

DR. CHARLES TURCK:

Dr. Woo could you give us some examples of previously unapproved drugs that proved unsafe or ineffective.

DR. JASON WOO:

Sure, 1 example was in 1983 when it was discovered that a very high potency intravenous injection drug named E-Ferol was associated with adverse reactions in about 100 premature infants and that resulted in over 40 deaths, quinine is another good example. As an approved drug, it was a lot widely used for the treatment of leg cramps, though the agency had many reports of patients who died because of cardiac side effects of this drug. The recent approval of 1 manufacturer's application for the use of the drug as a treatment for malaria though specifically warns against its use for leg cramps because it is shown to be ineffective and unsafe for this condition. Another recent example was the use of hydrocodone products as cough suppressants for pediatric patients. No hydrocodone has been established as safe and effective for cough suppression in children under 6 years of age, but some of these unapproved drugs carry labels with dosing instructions for children as young as 2 years of age. In addition, we had received reports of medication errors associated with formulation and name changes in unapproved hydrocodone products and reports of confusion over the similarity of a number of the names of the unapproved products with the approved drug products. As part of the drug approval process, the agency

considers the possibility of medication errors, the name confusion; so that potential safety issue associated with these factors can be minimized by having all the drug products go through with the approval process. So in September 2007, the FDA took action to stop the marketing of unapproved hydrocodone products and these are just some of the examples of the safety problems that unapproved drugs present.

DR. CHARLES TURCK:

What are some other concerns that the FDA has about the safety and efficacy of unapproved drugs?

DR. JASON WOO:

Well we've got several concerns. First as we discussed earlier, unapproved drugs have not been submitted to the rigorous scientific evaluation that occurs during the drug approval process. Therefore they may not meet the modern evidence standards and expectations for safety and effectiveness. Secondly, the FDA drug approval process provides a review of product specific information that is critical to ensuring safety and efficacy of the finished drug product. By this I mean that there is manufacturing processes and information that demonstrates that the manufacturer or sponsor can reliably produce the drug products to the expected level of identity, strength, quality, and purity. In addition, FDA's review and approval of the applicant's labeling ensures that healthcare professionals and patients have the information necessary to understand a drug products risks and its safe and effective use. So all three of these factors including

(1). The lack of evidence supporting safety and effectiveness.

(2). The lack of review of the manufacturer's drug-specific production capability.

(3). The lack of review of the information on the drug product label essential to the safe and effective use of that drug. These all raise significant safety concerns for the FDA about these unapproved drug products.

DR. CHARLES TURCK:

So we have established the problem of the presence of unapproved drugs in the US market. Now what is the FDA doing about it?

DR. JASON WOO:

Well the agency understands the need to provide assistance to firms unfamiliar with the drug approval process to help them secure approval for unapproved drugs that they are currently marketing and we are committed to a proactive action to facilitate voluntary compliance by these companies. As part of our commitment, we appointed an Unapproved Drugs Coordinator in the office of New Drugs to assist firms in obtaining information on the application process. In addition in January 2007, we held workshop to educate companies about the drug application and over-the-counter monograph processes and to give them some direction on how to bring their products into compliance. We have also assured companies that just approaching the agency to seek ways to bring their products into compliance will not on its own result in the agency initiating and enforcing an action against them. We, in fact, continue to work with a number of these firms who have approached the agency seeking ways to bring their products into compliance through the approval process.

DR. CHARLES TURCK:

Now the workshops that you mentioned, has the attendance been good. Have they been successful?

DR. JASON WOO:

We had a sellout for the workshop that we held back in 2007 and, in fact, we had to open up 2 additional rooms to allow for all of the attendees.

DR. CHARLES TURCK:

Changing tracks here just a moment, many of our listeners hear about or apply anecdotal experience in writing for prescription drugs that have been approved, but using them to treat unapproved indications. What is the FDA's stance on this?

DR. JASON WOO:

Well for an unapproved drug product, a patient or prescriber may believe that a drug is safe or effective because of that individual experience, but FDA has found that the subjective experiences can be misleading and/or really insufficient to establish a drug safety and effectiveness. In fact, when first FDA first reviewed the clinical information available after the 1962 law change, that required drugs to be proven, to be both safe and effective, only 12% of the drugs reviewed were found to be effective despite the widespread use of many of the drugs by physicians based on their anecdotal experience. So FDA relies really on carefully designed clinical trials that weigh the risks and benefits of taking a drug, compared with taking a placebo or another accepted therapy and in many cases, FDA finds that the original hypothesis that a drug is safe and effective isn't correct. Carefully designed clinical trials have repeatedly demonstrated that the safety and effectiveness of drugs can't be adequately established from anecdotal evidence or consumer or prescriber preferences. Another concern with anecdotal experiences is that even if there is no affirmative evidence of a safety problem with a specific drug that is not proof of the absence of a problem. We know safety and efficacy problems can be difficult or impossible to detect without well-controlled studies in larger populations and drug failures or its adverse effects may be masked by an individual patient's disease or wrongly attributed to another cause. So indeed history has shown that reliance on physician's anecdotal clinical experience is insufficient to establish a drug safety and efficacy. That is not to say that the off-label use of a drug should be prohibited. If, in fact, that is clearly the way some drugs are developed for new uses. However, that is different from an unapproved drug because at least with an approved drug being used for an off-label use, the manufacturer has submitted the information to show that the prescriber knows what the safe dosage levels may be for that drug, also what the spectrum of side effects are to be expected from that drug product. The same cannot be said for the unapproved drugs because we don’t have any of that information available.

DR. CHARLES TURCK:

Dr. Jason Woo has been our guest on The FDA Voice. I am Dr. Charles Turck and we have been discussing unapproved drugs and the FDA's response to this critical issue.

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