OFF-LABEL TRAINING HANDBOOK FOR

Pharmaceutical Sales Reps

An Introduction to

Off-Label Prescription Drug Issues

hcPro

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Saul Ewing LLP: An overview

Saul Ewing LLP was founded in 1921 in Philadelphia by a small group of enterprising attorneys. Most of these young lawyers had been trained by the late John G. Johnson, Philadelphia's premier lawyer of the late 19th and early 20th century. They understood that if they served their clients with skill and diligence, both they and their clients would prosper.

Saul Ewing LLP continues to have a proud heritage that is both a source of confidence and a continuing ethical guide. We have earned and maintained our superb reputation for more than eight decades by keeping more than one step ahead in areas of developing and emerging law. Saul Ewing LLP attorneys are dedicated to the key values of excellence, energy, and enthusiasm: excellence in our legal services, the energy to succeed, and an enthusiasm for understanding and being responsive to our clients' needs.

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Off-Label Training Handbook for Pharmaceutical Sales Reps

Introduction

Pharmaceutical companies stand to make a lot of money from off-label drug use. However, the government has strict rules that pharmaceutical companies must follow when marketing prescription drugs off label—and the stakes are high for companies that violate these regulations. One manufacturer recently paid $430 million to resolve criminal charges and civil liabilities in connection with the promotion of unapproved uses for one of its drugs.

Pharmaceutical companies must ensure that their sales representatives—whether employees or independent contractors—understand the requirements regarding promotions of their products and what they can and cannot tell healthcare providers and other customers about off-label drug use.

This handbook offers an overview of the statutory and regulatory issues governing the Food and Drug Administration's (FDA)

oversight of prescription drugs, assesses the effect of the long-running litigation between the Washington Legal Foundation and the FDA, lists tips that sales representatives can use when promoting prescription drugs, and uses case scenarios to help sales representatives understand the challenges they face when marketing to providers and other customers. This handbook ends with a 10-question quiz.

Note: This handbook is intended for general information purposes. It does not constitute, and should not be construed as, legal advice or legal opinion on any specific facts or circumstances. This handbook is the product of its authors and does not represent the views of their respective employers.

What does 'off label' mean?

A pharmaceutical company must identify all planned uses of a prescription drug in its new drug applications to the FDA. The drug's label—also known as the package insert, or PI—includes all the information necessary for physicians to prescribe the drug safely and effectively for the approved indication(s).

Off-label uses are those that are not included in the drug's FDA-approved label. This could include using the drug for an indication, dosage form, dose schedule, population, or other parameter not listed on the drug's approved labeling. These uses are also referred to as unlabeled, unapproved, or out-of-label. In this handbook, off-label refers to all of these practices.

There are three general categories of off-label activities:

- Off-label use by individuals
- Off-label prescribing by healthcare providers
- Off-label marketing and promotion by a pharmaceutical company

As a pharmaceutical sales representative, you must understand all three aspects. However, this handbook focuses on pharmaceutical company marketing and promotion and the appropriate role of the pharmaceutical sales representative.

Regulations for off-label prescription drug use

The FDA regulates the manufacturing, labeling, and promotion of prescription drugs. Until 1997, the Federal Food, Drug and Cosmetic Act (FDCA) prohibited pharmaceutical companies from promoting their drugs for any off-label use. The FDA could consider a pharmaceutical company that violated this provision as misbranding their product in violation of the FDCA.

The FDA justified this blanket prohibition with the following rationale:

- If a pharmaceutical company could distribute information regarding the off-label use of its drug, it could be a disincentive for the company to perform the necessary clinical studies to prove that a drug is safe and effective for the off-label use

- Information given out by a pharmaceutical company could be biased because the company has a direct interest in ensuring the commercial success of its products

However, the Food and Drug Administration Modernization Act of 1997 (FDAMA) allows pharmaceutical companies to distribute information about off-label uses if they comply with certain statutory and regulatory requirements. The relevant statutory off-label protections can be found at 21 USCA. § 360aaa et seq., and the relevant regulations are located at 21 *CFR* 99.1 et seq. Your company's inhouse counsel or compliance officer has copies of these documents.

Does the FDA regulate physician-prescribing practices?

In short, no. The FDA does not have the statutory authority to regulate the practice of medicine. This FDA policy is known as the "practice of medicine exemption." Physicians can use FDA-approved drugs in any way they feel will best serve their patients without interference from the FDA, even if the FDA has not approved the drug for treating that condition.

Off-label prescription drug use is an important part of many physicians' prescribing patterns for several specialties, particularly oncology. Medical textbooks, research institutes, and professional organizations recommend many off-label uses.

The American Medical Association (AMA), the largest physician organization in the country, believes that physicians may prescribe drugs for off-label uses based on sound scientific evidence and medical opinion. The AMA asserts that the physician is responsible for deciding which drug and which regimen is best for the patient's condition.

There is a statutory and regulatory disconnect between the FDA's regulation of off-label drug promotion and the FDA's long-standing practice of medicine exemption that largely leaves physician's prescribing practices out of the FDA's regulatory realm. This separation in FDA authority is one potential reason for the dramatic escalation in physicians' off-label drug prescribing practices and the resulting use of off-label prescription drugs by the public.

Marketing guidelines for sales representatives

Although the FDA does not generally interfere with physician-patient relationships, it does regulate how drug companies can communicate with healthcare providers. Understand the following statutory and regulatory requirements that your company must meet regarding off-label promotions.

Who can receive off-label information?

According to FDAMA, pharmaceutical companies may distribute written information about the safety, effectiveness, and benefits of uses not described in a prescription drug's approved label to the following parties under certain circumstances:

- Healthcare practitioners
- Pharmacy benefit managers
- Health insurance issuers
- Group health plans
- Federal or state government agencies

Format for off-label information

The information that pharmaceutical companies can distribute to those entities listed above must be in one of the following forms:

- Reprint or copy of an article published in a peer-reviewed scientific or medical journal.

- A reference publication that has not been written, edited, excerpted, or published for or at the request of a pharmaceutical company. This should be available in bookstores or other places that sell medical textbooks—not solely distributed by the pharmaceutical company.

Information distributed may not be false or misleading or pose a danger to public health.

Disclaimers to include with off-label information

All information distributed by a pharmaceutical company must include a prominently displayed statement that lists

- a note that the information concerns a drug use that is not approved or cleared by the FDA
- the official drug label and all updates to that label
- the identification of any person who has provided funding to support a study of the new drug use for which the company is distributing information
- a note that the information is being distributed at the manufacturer's expense, if applicable
- the name of any authors of the distributed information who are employed by, consultants to, have received compensation from, or who have significant financial interests in the pharmaceutical company

Pharmaceutical companies must also include a list of articles published in scientific reference books or scientific/medical journals about the drug or device that is the subject of the information being distributed.

Note: If the off-label information you want to distribute comes from another pharmaceutical manufacturer's research, your company must get that manufacturer's permission before you share it.

What manufacturers must provide to the FDA

Under FDAMA, before distributing information on off-label uses, your company must submit a supplemental application to the FDA for approval of the new use.

With limited exceptions, the pharmaceutical company must have completed studies to support the new use, or the company must submit a protocol and schedule for completing the studies within 36 months of first distributing off-label information.

When companies can disclose off-label information

Under FDAMA, drug companies must also meet the following requirements:

Before giving out off-label information

Sixty days before distributing off-label information, your company must give the FDA a copy of the off-label information that will be

distributed, any clinical trial information related to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information.

After giving out off-label information

Every six months, your company must prepare and submit to the FDA a list of the articles and reference publications related to the new use of the drug distributed by the manufacturer during that period. It must also list the categories of providers that received the articles and reference publications.

When the FDA can stop distribution of off-label information

If the FDA determines that data indicate that the new use of the drug is ineffective or poses a significant risk to public health, after consulting the pharmaceutical manufacturer, the FDA may take any action it deems necessary to protect public health. This could include ordering the pharmaceutical company to stop distributing information on off-label uses.

Pharmaceutical companies' First Amendment rights

One of the FDA's primary missions is to ensure that a pharmaceutical company's prescription drugs are safe and effective for the patients for whom they are prescribed. The FDA believes that prescription drug promotion must be truthful and not misleading.

Before FDAMA was enacted in 1997, the FDA was concerned that some pharmaceutical companies were using indirect tactics to distribute information about unapproved prescription drug uses to providers, including continuing medical education materials featuring discussions about unapproved uses for prescription drugs and distributing information discussing these unapproved uses. The FDA attempted to stop these practices by issuing a series of guidance documents to the industry.

In response to these guidance documents, the Washington Legal Foundation, a nonprofit organization based in Washington, DC, filed suit against the FDA claiming that the documents violated physicians' First Amendment rights to receive information about off-label uses from pharmaceutical companies. In court, after the enactment of FDAMA, the FDA clarified its position on FDAMA's requirements for distributing off-label information.

The FDA explained that these sections in FDAMA present a "safe harbor" that ensures that the FDA cannot use the distribution of off-label information that follows the statutory requirements

under FDAMA against manufacturers. It also clarified that these FDAMA provisions do not provide an independent basis for FDA enforcement.

In an ironic twist, one of the principal attorneys for the Washington Legal Foundation in its litigation against the FDA is now a lead attorney for the FDA.

Although it may be argued that after years of litigation the Washington Legal Foundation prevailed, the federal courts never conclusively ruled on the First Amendment issues at the heart of this dispute. These issues could be the subject of future litigation.

Off-label prescriptions in the news

Many prescription drugs are helpful for treating patients with conditions for which the drugs have not been approved by the FDA. One of the most publicized and dangerous situations resulting from the off-label prescription of drugs involved the so-called Fen-Phen combination. Fenfluromine and Phentermine were each approved individually for single-drug, short-term obesity therapy.

However, off-label promotions of the use of these prescription drugs simultaneously by the diet industry and physicians—not the manufacturers of these two drugs—resulted in patient injuries and death.

Even though the pharmaceutical companies did not promote the Fen-Phen combination, attorneys for the plaintiffs argued that the pharmaceutical manufacturers knew about the use and could have prevented patient harm.

The growth of off-label prescriptions

The FDA-approved labeling for a product only includes indications for which the product has been approved. However, pharmaceutical companies have a significant financial interest in off-label prescribing of their drugs because it can increase sales and profitability.

A 2003 report by Knight-Ridder Newspapers found that the three best-selling drugs in 15 of the top drug classes saw off-label prescriptions increase by over 96% to more than 115 million between July 1998 and July 2003. The report found that the off-label sales of the top selling drugs totaled $12.9 billion in the 12-month period ending August 31, 2003.

The Knight-Ridder Newspapers reported that antiseizure medications were prescribed off-label in 18.6 million prescriptions, or 74% of the time in the 12-month period ending July 31, 2003. In contrast, diabetes medications were only prescribed off-label about 400,000 times, or 3% of the time.

The newspaper noted that sales of Neurontin, the focus of a recent $430 million Pfizer settlement, had off-label sales of $1.8 billion in the 12-month period ending August 31, 2003. Ninety percent of Neurontin sales during this time were for off-label prescriptions, and the drug had the highest percentage of off-label prescriptions of all drugs analyzed by Knight-Ridder Newspapers.

The Pfizer Neurontin settlement

The complaint against Pfizer was for alleged off-label promotional activities prior to and after the enactment of FDAMA by Warner-Lambert's Parke-Davis division, which Pfizer later acquired. All pharmaceutical sales representatives can learn from this settlement.

The FDA approved Neurontin to treat partial seizures with and without secondary generalization in adults with epilepsy. Sales representatives promoting Neurontin, however, told physicians they could also use the drug to treat pain and several other off-label uses. The government's sentencing memorandum includes details of the scope of Warner-Lambert's regional and national efforts to promote Neurontin for off-label uses. The government described these six key tactics of the company's plans to increase off-label use of Neurontin:

- Encouraging sales representatives to provide one-on-one details to physicians about off-label uses of Neurontin
- Using medical liaisons who represented themselves—often falsely—as neutral scientific experts on a particular drug to promote off-label uses for Neurontin
- Paying physicians to allow sales representatives to see patients with the physician and participate in discussing the treatment plans
- Paying physicians to attend consultant, advisory, or speaker bureau meetings during which physicians listened to presentations about off-label uses of Neurontin
- Conducting teleconferences in which physicians were paid to speak about Neurontin off-label uses to other physicians
- Sponsoring "independent" medical education events on off-label Neurontin uses, for which the company provided extensive input regarding speakers, content, and participants

Pharmaceutical promotions: The legal way

Remember these 10 tips when selling your company's prescription drugs:

1. Closely follow your company's legal/compliance staff's directions for interacting with healthcare providers. These guidelines should be the cornerstone of your interactions with healthcare providers.

2. Use only the promotional materials that your company's legal/compliance staff have approved in advance. Do not leave these materials with a provider unless your company has told you it is appropriate to do so.

3. Do not alter any approved promotional materials.

4. Understand that your company may have different rules for some drugs. If you are detailing multiple drugs to a provider during the same visit, know how you should interact with the provider for each drug.

5. Do not bring with you or show providers promotional material intended only for sales representatives.

6. Promote only the approved uses of your company's product(s).

7. Refer any questions you receive about off-label prescription drug use to the appropriate individual (e.g., your company's medical information or medical affairs department), or have that individual contact the provider directly.

8. If a provider mentions an off-label use of your company's prescription drug during a visit, tell them that it is not an approved use of the drug. Follow the directions in #7 if the provider wants additional information. Your company should have specific policies for handling these situations.

9. If you don't know an answer, don't guess. Tell the provider you will get him or her the correct answer or have the appropriate person follow up directly.

10. Always leave a package insert for each product you discussed with the provider.

Pharmaceutical promotions: What not to do

Avoid the following practices when selling prescription drugs:

- Don't ignore, disregard, or be uninformed regarding your company's policies and procedures for interacting with providers

- Don't create your own promotional materials or use materials you find in other sources, such as newspapers

or the Internet, that have not been approved in advance by your company's legal/compliance staff

- Don't start a discussion about off-label use to encourage the provider to ask for more information from your company's medical professionals

- Don't discuss off-label information, even in response to an unsolicited question, unless your company has policies and procedures for responding to these questions and you understand these protocols

- Don't target promotions of your company's drug to specialists who would not likely prescribe the drug for an approved use unless your company has policies for doing so and you understand its protocols

Case studies

You enter a physician's office to detail your drug, which is approved to treat depression. Although your drug is not approved to treat post-traumatic stress disorder (PTSD), you know that many physicians, including the physician with whom you are about to speak, have used the drug to treat this condition. The physician soon asks whether there are any new studies on your product and PTSD. You know there are, but your company's policy does not allow you to give information about

off-label uses. You say you'll ask your company's medical affairs department to provide this information. The doctor becomes angry and says if you cannot give her this information, then you should not bother returning to her office. What should you do?

This type of situation is common. The customer becomes frustrated with the rules you and your company must follow. However, you cannot violate your company's policies even when threatened with losing a customer. Try to explain, politely but firmly, that FDA regulations and your company policy prevent you from disclosing that information to her directly, but that your medical information/affairs department will quickly get her the information. Most companies are able to fax or e-mail this kind of information within hours. If that does not satisfy your customer, seek further guidance from your manager.

As a sales representative for your company's diabetes drugs, you read medical journals to keep up with diabetes research and treatment. While reading a peer-reviewed journal, you see an interesting piece about new diabetes treatments that highlight the product you sell. It's exciting because the article positions your drug very favorably in a treatment algorithm for diabetes. You would like to show this article to your customers. Can you?

Not yet. Never use a journal reprint or another source with a customer until your legal/compliance staff approves it. Even if the article is completely about

approved uses of your drug, your company policies likely prohibit you from using these materials before they are approved. If you would like to use this article, submit it to your company's marketing team and let them take it through the approval process. If it is approved, all representatives will be able to benefit from the article.

You arrange a dinner program where one of your company's contracted speakers will discuss the use of your company's product to treat heart failure with 10 physicians. Your company has a set of approved slides that its speakers are required to use. When you attend the program, you find that not only did the speaker not use the approved slides, he used his own slides, which contained a significant amount of off-label information. Is this okay?

This is not okay. Many sales representatives think physicians who are paid to speak on behalf of the company are not subject to the same rules and regulations as they are. However, the FDA considers dinner programs, such as the one described above, as promotional, and therefore subject to the same rules and regulations as sales representatives. This is one of the reasons why many companies have developed slides that they require speakers to use. Even if your company has not developed slides, speakers' presentations should be largely on-label. Consult your company's policies for more guidance about when a speaker may provide off-label information during a company-sponsored program (e.g., in response to an unsolicited question).

You have given a third-party organization an education grant to support an independent medical education program about advances in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Your company has a product that is approved to treat asthma but not COPD. Your company's policies allow you to attend the program as long as you don't participate or ask questions. During the program, you realize that the presentation includes a lot of information about using your product to successfully treat COPD. Is this okay?

Yes. Unlike the previous scenarios of a company-sponsored dinner program, the independent medical education program for which your company has provided funding is just that—independent. That means your company only provided funding; it did not have control or influence over the content, speakers, or other aspects of the program. Accordingly, the FDA does not deem such programs to be promotional and presenting off-label information is permitted (and frequently occurs). However, remember that if the FDA determines that you or your company exercised control over the program or its content, it may deem the program to be promotional, and thus presenting off-label information would be prohibited.

Final exam

1. **When may physicians prescribe pharmaceutical products for off-label use?**

   a. Physicians are never allowed to prescribe pharmaceutical products for off-label uses.
   b. When they feel it is in a patient's best interest to do so
   c. Only for oncology patients
   d. If the patient's health insurance plan deems it appropriate

2. **On what information should pharmaceutical sales representatives educate physicians?**

   a. Efficacy information contained within the PI
   b. Safety information contained within the PI
   c. Both a and b.
   d. Neither a nor b.

3. **Which of the following best describes off-label information?**

   a. It covers a use or uses of a product that are not included on the drug's approved label.
   b. It may be detailed to a physician if it appears in a peer-reviewed journal.
   c. It is false and misleading.
   d. All of the above.

4. **Which of the following does the FDA regulate for prescription drugs?**

   a. Manufacturing
   b. Labeling
   c. Promotion
   d. All of the above

5. When can a pharmaceutical company distribute off-label information?

a. Anytime, as long as the information is unbiased and scientifically based.
b. A pharmaceutical company may never disseminate off-label information.
c. Only in response to a specific question from a physician.
d. If the manufacturer meets the requirements set forth under FDAMA.

6. What was the goal of The Washington Legal Foundation with regard to promotion of pharmaceutical products?

a. To restrict the amount of off-label information pharmaceutical manufacturers could provide to their customers.
b. To ensure that physicians' First Amendment rights to receive information about off-label uses were protected.
c. To remove all restrictions on the marketing activities of pharmaceutical manufacturers.
d. None of the above.

7. Which of the following is true for off-label uses of pharmaceutical products?

a. It may increase sales for the manufacturer of the product.
b. It has increased dramatically in the past 10 years.
c. It is never permissible, even at the discretion of the treating physician.
d. Only a and b.

8. Which of the following is true regarding Pfizer's recent settlement with the government?

a. Pfizer paid approximately $430 million.
b. The settlement related to charges that Warner-Lambert's Parke-Davis division, which Pfizer later acquired, illegally promoted Neurontin for off-label uses.
c. Both a and b.
d. Neither a nor b.

9. When can a sales representative detail a physician on information from a medical journal?

a. Anytime, as long as the journal is peer-reviewed.
b. Only if the material is unbiased and does not specifically relate to a product the sales representative sells.
c. If the information has been previously approved in accordance with the sales representative's company policies.
d. Never.

10. What should you do if a healthcare provider asks you an unsolicited question regarding an off-label use of a product you are detailing?

a. Respond that the use is off-label and refer the provider to your medical information or medical affairs department and follow your company policies.
b. Indicate that the use is off-label, then respond to the question to the best of your ability and knowledge.
c. Respond to the question to the best of your ability and knowledge.
d. Leave the office as quickly as possible.

Answer key

1. b
2. c
3. a
4. d
5. d
6. b
7. d
8. c
9. c
10. a

CERTIFICATE OF COMPLETION

This is to certify that

_____

has read and successfully passed the final exam of

Off-Label Training Handbook for Pharmaceutical Sales Reps

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Vice President/Publisher