

FDA CASE STUDY

FDA Drug Information Curriculum Case Study

Useful FDA Drug Information for Clinicians: Practicing clinicians seek available information on a new drug before making a treatment decision

This fictionalized case study is part of an educational series published by the U.S. Food and Drug Administration.

A Rounding Team and One Patient

If they listened closely, the patients in the cardiology wing of Sun Valley hospital could hear them. Several pairs of rubber-soled shoes slapped the ground in quick patterns as they tried to keep up with the long stride of Dr. Michael Carosel, attending physician and director of the cardiology department. In his wake, the steady and practiced steps of his chief resident, Dr. Andrea Nash, barely made a sound as she followed with ease. Behind her, the newest crop of residents and interns beginning their four-week rotation program worked hard to keep pace in what many nurses at the community hospital jokingly called “Carosel’s Running of the Interns.”

However, no one complained. Dr. Carosel was well-respected in the California medical community. A practitioner of medicine for over 20 years, he had served as the Director of Cardiology at Sun Valley for the past 11 years. In that time, he had managed to employ Andrea, one fellow, and two residents. The four were among the brightest talents in cardiology in the country.

Quick sighs of relief once the march

stopped at the central nurse’s station were the only signs from the students that they had experienced any hardship. They took some time to calm their breathing as the attending greeted the nurses on duty, then stood up straight and ready. It was time for the real work to begin.

Dr. Carosel favored the traditional model of rounding. First, his team would talk about a patient before entering a room. Then they examined the patient together. After, they left the room to debrief and Dr. Carosel walked everyone through the plan of the day. Students were expected to have reviewed any pending tests or lab values, radiology investigations, and vital signs.

Despite this traditional approach, the attending’s rounds were always well attended by pharmacy and nursing residents and students too. His engaging teaching style was part of the reason, and the other was the patient cases. To keep the students on their toes, Dr. Carosel and Dr. Nash always tried to choose a comprehensive patient case with unique circumstances that several teams in the hospital worked on together. The goal was to encourage the students to work as a team to thoroughly assess the patient case for the week and brainstorm ideas for treatment plans that they would present to the doctors each Friday. The case Dr. Carosel was currently presenting was being overseen by Dr. Nash, and the students couldn’t wait to learn about their first patient.

“Okay, everyone,” Dr. Carosel began, “our patient of the day is named Simone, a 52-year-old female who was admitted two days ago after experiencing severe chest pain. This is not her first myocardial infarction (heart attack),” he continued. “She was admitted to Sun Valley at the age of 48 after she experienced severe chest pain and fell unconscious at her oldest son’s graduation party. Since then, she has quit smoking and lost 30 pounds, but she is still considered moderately obese. We’ve managed her as an outpatient for her high cholesterol, and in addition to taking cholesterol medicine everyday, she works to keep a healthy lifestyle and limit her salt intake. When she started experiencing chest pains similar to her first heart attack, she immediately drove herself to the hospital.” He turned to his chief resident, “Is there anything I’m forgetting Dr. Nash?”

No, that about covers it,” Dr. Nash replied with a small, slightly disinterested smile. As exciting as she used to find these rounds when she started teaching at Sun Valley three years ago, she was ready to complete her education in cardiovascular medicine and explore a subspecialty in interventional cardiology. One year left before I complete my residency and move back home, she reminded herself. The thought helped her smile more brightly at the group. “Since Simone is a well-spirited patient who truly wants to succeed in managing her health care, I selected her for this week’s educational patient case. Let’s go in and say hello.”

Lizzy, Simone’s assigned nurse, joined them as they entered the room. After asking Simone how she was feeling, the group examined her and checked in with Lizzy about the

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patient's latest vitals. Then Dr. Carosel asked the group for initial treatment suggestions. David, a young pharmacy student, spoke up.

"I wonder if Simone might be a good candidate for a medication I just learned about called Drug123. It's an injectable drug used with patients who have clinical atherosclerotic cardiovascular diseases caused by plaque buildup in the arteries of the heart, such as heart attacks or strokes, who need to lower their low density lipoprotein (LDL) cholesterol."

Despite her earlier feelings, Dr. Nash was intrigued. "David?" She said, guessing the student's name, and then continued after he gave her a slightly nervous nod, "I'm not sure if this drug is on Sun Valley's formulary, but it sounds interesting. Why don't all of you look into the drug further and then report what you find to Dr. Carosel and me at Friday's meeting. Work together to confirm Simone's diagnosis and LDL level. Then we can move forward with seeing if she's a candidate for this drug after hearing what you find."

David smiled and Dr. Nash looked at Dr. Carosel for confirmation of that plan. After he nodded, she turned to say goodbye to Simone, then walked out of the room for the debrief. As they left behind her, most of David's peers smiled at him or whispered "way to go!" But Charles, a second-year post graduate drug information resident in the group, kept his eyes on the backs of his attending and chief resident and didn't say a word.

The group debriefed and went over the plan for the day with the doctors before walking to the hospital's library to start working on the treatment plan they would present on Friday. When they had gone, Dr. Carosel looked at his chief resident. "Well, that was unexpected."

"I know," Dr. Nash responded. "It's rare for a student to suggest a therapy change on their first day of rounds.

And a first year pharmacy student, no less. Have you heard about this drug before?"

"I have. I received an email update about it from FDA CardioBeat, but I haven't had the chance to look into it. What I did read seemed promising, though. Let's see what our curious group turns up, shall we?" The attending smiled and rubbed his palms together like a mad scientist.

"I can hardly wait," Dr. Nash laughed as they began to walk. As eager as she was to move on from Sun Valley, she was grateful to have found an incredible mentor there whom she could also call a friend. At the end of the hallway, the two separated to attend to their individual duties.

Pharmacy Team Evaluates

Later that morning, Charles found himself sitting across from David at a wooden table in the middle of Sun Valley's medical library. The more the pharmacy student spoke, the more unimpressed with him Charles was. David's drug suggestion could be the key for solving Simone's chest pain issues, but he couldn't answer any of the questions the group needed answered to figure out if that was the case.

"Do you know if the drug therapy is available in the hospital?" Chantel, a second-year resident in the group, asked.

"No, I'm not sure," David responded.

"Can you tell us what the characteristics of an ideal candidate are?" Jess, a junior medical resident, asked.

"Well, like I said in the room, the drug is used with patients like Simone—people who have experienced diseases like heart attacks or strokes who need additional lowering of LDL cholesterol. Other than that, I'm not sure what other characteristics these candidates would need to have," David said.

Charles and the rest of the group exchanged looks. There was more to it than that. A lot more.

"Can you answer any questions about the drug?" Charles asked, annoyance creeping into his voice. "Results of pivotal trials? Side effects?" As David shook his head no at each of the questions, the defeated look on his face went from bad to worse.

Charles sighed and sat back. It was clear David was embarrassed that he didn't know anything about a drug he told his supervisors about in front of a patient. Seeing that look on David's face made Charles feel like a bully, and he quickly decided he'd rather help his teammate learn more about the proper way to research drug treatments than fight about who knew what.

"Well, it looks like we have a lot of homework to do," he smiled gently at the worried-looking student. The others nodded in support, and David returned their kindness with thanks and open relief. Quickly, the older residents divided their homework tasks. Jess would look through Simone's medical history and write up any details and diagnoses of interest. Chantel would order relevant labs and escort Simone to each test. Charles would review the lab results and evaluate any potential new therapy options, and he would work with David to research and review the newly-approved drug.

Jess and Chantel left to work on their assignments, and Charles and David walked over to a laptop set up for research in the corner of the library.

"I'm sorry I couldn't tell you guys more about Drug123," David started as Charles logged in to the computer. "I learned about it while I was watching this show about finance. I had forgotten about it until we examined Simone, and just suggested it without thinking. I probably should have waited until I had looked into it more before I said anything, huh?" Charles patted him on the shoulder and smiled, "Really, don't worry about it. It sounds like an interesting

lead, and if it isn't, you and I will work together to find a different treatment that will help Simone get her health back on track. Now," he said, turning to the computer where, after several quick keystrokes and mouse clicks, a blue and white window with the words U.S. Food and Drug Administration had appeared, "what do you know about FDA and the process for learning about new drugs?"

David's answer was, unsurprisingly, not much. "Not a problem," Charles said. "The U.S. Food and Drug Administration, or FDA, is the regulatory Agency responsible for approving all new pharmaceutical products before they are allowed to be sold in the United States. FDA doesn't do research for developing drugs, but they do review scientific evidence from pharmaceutical companies to ensure that their products demonstrate U.S. regulatory standards and meet approval requirements for safety and effectiveness. FDA's review and evaluation of scientific evidence and the decisions reached once a product is approved are available to the public through FDA's website: www.fda.gov."

David looked at Charles a little stunned at his peer's knowledge. "What?" the older man shrugged, "I completed a rotation at the FDA during my last year of pharmacy school—that's something you might want to look into for yourself at some point. Anyway, if there is a prescription drug therapy for treatment of a disease on the market in this country, it should be approved by FDA. That's always the first place you should look for drug information before turning to secondary sources."

Charles scrolled down the page and stopped when he saw a heading called "News & Events." "New products are commonly announced on the FDA website in press releases," he said. He clicked on a button called "Newsroom" and then navigated to a page called "Press Announcements."

The men looked down the page of press releases until a heading that read "FDA approves new drug to treat cardiovascular disease and lower LDL cholesterol" caught David's eye.

"Hey, this might be it!" David pointed at the screen. Charles clicked on the link and the two quickly scanned the press release. Sure enough, it was the drug they were looking for. Charles scrolled back up so they could read the release more closely.

Drug123 was the first cholesterol-lowering treatment approved in a new class of drugs. It was approved for use with diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia—a genetic disorder characterized by very high cholesterol levels, particularly LDL

cholesterol—or patients with clinical atherosclerotic cardiovascular disease who require additional lowering of LDL cholesterol.

"Looks like the company that produces Drug123 is called Shawmitch Health," Charles said after they were done reading. He logged into hospital's formulary database and searched for the drug. "The drug is not in Sun Valley's formulary, but that's okay because we have two leads for more information. We can go directly to Shawmitch and ask them for the approved drug label, or we can search for it on Drugs@FDA." He pulled up the site on the computer and gave David a brief overview of two FDA drug resources.

When he was done explaining, Charles searched for and located the drug's label on Drugs@FDA, then opened the

Charles' Overview: Two FDA Drug Resources

Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
Drugs@FDA is a searchable database containing official information for most brand name and generic drugs and therapeutic biological products that have been approved by FDA since 1939. Labels and approval-related documents in the database, including reviews, approval letters, and current and archived labels, are available for most drug products approved since 1998.

Drugs@FDA is an important resource for health professionals responsible for drafting drug evaluation documents and offers substantial information that cannot be found using other drug information resources. Searching for a therapeutic product, either by brand name or active ingredient will display an overview of the product's regulatory status, dates of FDA's approval action, New Drug Application (NDA) number, chemical type (e.g., new molecular entity), and the review classification (e.g., orphan product designation, priority review designation).

Drug Shortages Program: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/>
FDA's Drug Shortage Program offers free online and mobile resources that provide information about drug shortages to the public. From the FDA website, users can access the Drug Shortages database, a searchable list of drugs that FDA has determined are in short supply or have been discontinued. Most of the drugs in the database are medically necessary drugs, which are products used to treat or prevent serious diseases or medical conditions for which there are no alternative drugs available in adequate supply that have been determined to be acceptable substitutes. The database provides users with easy access to information about product availability, supply, and estimated duration of shortage; resolved shortages; discontinuations of specific drug products; corresponding therapeutic categories; resource information; and relevant links.

Users can also access this information through the Drug Shortages Mobile App, which will send notifications when FDA has new or updated information about a shortage of a drug product or about a drug within selected therapeutic categories.

For more information, see the FDA Drug Shortages Infographic at <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM441583.pdf>

tab in the browser that contained the press release again. He pointed to a line of text on the screen, “The press release states that Drug123 is the first of a new class of drugs to be approved. It’s a first-in-class therapy, also known as new molecular entity (NME). NMEs are drugs that include an active ingredient that has not previously been approved for marketing in the U.S. in any form. And that,” Charles continued, looking excited now, “means there is a chance an FDA Advisory Committee reviewed the drug. If a committee did review it, FDA would have given them background materials covering clinical study information about the drug, and there is a chance that those materials and a public record of their discussion about the drug’s safety and effectiveness would exist on the FDA website! Yes!” He turned to David, hand raised for a high-five.

David left him hanging. “Please, slow down. What exactly is an Advisory Committee, and why is any of this a good thing?”

Unbothered, Charles turned back to the computer and started typing quickly. “I’ll show you.”

Public FDA Advisory Committee Materials

On the laptop screen, a webpage called “Advisory Committees” had appeared.

“You remember how I said that drugs marketed in the United States need to be approved by FDA first?” David nodded. Pharmaceutical companies have to go through many steps to before selling their drugs to the public, and FDA reviews all of those steps. If you’re interested in learning more about the drug approval process, there is a case study available on the FDA website you can check out.

“Now, once a company has completed pivotal clinical trials for a drug, FDA might ask advisors outside of the agency for their independent opinions

on complex scientific, technical, and medical issues about the drug before approving it. FDA has formed several drug advisory committees with expertise in specific areas for this purpose,” Charles indicated the column on the left side of the page that listed the names of the different drug advisory committees.

“Oh, I see. Do these committees review all pharmaceutical products presented to FDA for approval?” David asked.

“No, not all,” Charles responded. “But novel products or products that have a potentially challenging benefit-risk profile are often reviewed. In these cases, a committee will consider the available evidence and provide scientific and medical advice on safety, effectiveness, and appropriate use of the product. Committees might also advise FDA on broader regulatory and scientific issues. FDA generally follows an advisory committee’s recommendation, but they aren’t required to do so.”

Charles turned back to the laptop screen and clicked the dropdown arrow icon next to the first committee listed in the left column of the page, the Anesthetic and Analgesic Drug Products Advisory Committee. A smaller menu appeared underneath with links to the committees’ meeting materials organized by year. “Advisory committee recommendations are recorded during formal advisory committee meeting that are generally open to the public so that people can observe and contribute their opinions about the questions FDA is asking. Before the meeting, briefing materials providing relevant clinical data about the drug in question are made available to committee members,” Charles clicked on the link “2015 Meeting Materials, Anesthetic and Analgesic Drug Products Advisory Committee.”

“These materials, along with any webinars, transcripts, and agendas, and meeting minutes containing the Committee’s final recommendations, FDA’s perspectives, and the public’s opinions are posted online after

The screenshot shows the FDA website's "Advisory Committees" page. At the top, there is a navigation bar with the FDA logo and the text "U.S. FOOD & DRUG ADMINISTRATION". Below this is a search bar and a menu with categories: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The main heading is "Advisory Committees". Below this is a breadcrumb trail: Home > Advisory Committees > Committees & Meeting Materials > Drugs. On the left, there is a list of advisory committees under the heading "Drugs": Anesthetic and Analgesic Drug Products Advisory Committee, Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee), Antiviral Drugs Advisory Committee, Arthritis Advisory Committee, Bone, Reproductive and Urologic Drugs Advisory Committee, Cardiovascular and Renal Drugs Advisory Committee, Dermatologic and Ophthalmic Drugs Advisory Committee, and Drug Safety and Risk Management Advisory Committee. The main content area is titled "Human Drug Advisory Committees" and includes a text block explaining the role of advisory committees. To the right of this text is a "Spotlight" section with links for "Applying for Membership" and "Advisory Committee Calendar".

the meeting,” Charles continued. “This information is very helpful for managed care pharmacists to consider when evaluating a therapeutic product for use in their health care system. Hospitals also have committees that assess similar issues, you know. I’m a member of the Pharmacy and Therapeutics (P&T) Committee at Sun Valley. We evaluate all drugs that are proposed for inclusion in the hospital’s formulary. If the information we find out about the Drug123 is positive and Dr. Nash and Dr. Carosel like what we have to say on Friday, the P&T committee will discuss the drug and decide if the doctors here can start prescribing it to Simone and other patients in the hospital.”

Now David understood why Charles was so excited about advisory committees. “So this means I just need to find out if a committee reviewed Drug123, and if they did, look through their meeting materials to find the information we were looking for?”

“Exactly!” said Charles. “And you should also search the Drugs@FDA database for any other information we might have missed. If you have any problems, you can click on the instructions link near the top of the page for explanations on how to find regulatory information within the database’s search results.” He looked down at his watch. They had spent over an hour talking about how to find information through FDA and Charles was late for another meeting. “Would you mind getting started on researching this and letting me know about any concerns the committee members may have had about the drug? I’m sorry, but I have to run to another meeting.”

“Sure!” David replied. After Charles left, David stretched before sitting in his colleague’s now empty seat. “Time to do some research.”

Patient Histories

While David combed through FDA

web pages, Jess, the junior medical resident, had been doing her own research. She had looked up Simone’s LDL lab history and diagnosis and noticed that the patient’s LDL had spiked in October. “I wonder what the cause could be,” she said, looking over the documents. Maybe something one of her group mates had found would shed some light on the incident.

On Thursday, the group met again to talk about their findings and work on their presentation. Jess had invited Lizzy to join them. After trading funny patient stories from the week, Jess shared what she had found in Simone’s lab history.

“Now that you mention it,” Lizzy said, “I was taking Simone’s vital signs the other day and we started talking about our children and how busy our lives have been recently. Simone has twin boys in high school on two different sports teams. If any of you have children who can’t drive, you know that getting them to and from practice is a huge time commitment. Between working, carpooling, and attending sporting events, she confessed that she’s had little to no time to prepare healthy meals. I understand because I have two young children of my own, but I stressed to her how important it is for her to eat healthy, especially since she’s had a heart attack before. I also offered to have the hospital nutritionist visit her to work on a meal plan.”

Jess nodded, “Thanks Lizzy. Those changes in her diet could be a contributing factor.”

Next, Chantel presented Simone’s lab reports.

“Based on Simone’s cardiac history and the results from the labs Chantel ordered,” said Charles. “Simone might need a change in drug therapy.”

“I agree,” said Jess. Chantel nodded as well. “I was also able to confirm that she was diagnosed with heterozygous familial hypercholesterolemia,” the

junior medical resident revealed.

Charles and David looked at one another. The older man nodded at the student and David took the lead. “Charles and I did some research on the Drug123 drug and found a lot of information through the FDA website. Interestingly enough, it’s been approved for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia.” He filled the group in on the details of the drug and also went over what Charles had taught him about Advisory Committees and what he had learned on his own.

“Though the therapy is an NME, it was not assigned a priority review designation or an accelerated approval designation. Luckily, it was reviewed by FDA’s Cardiovascular and Renal Drugs Advisory Committee.” He paused to pass photocopied documents around the table. “Here are some copies of the background materials the committee members were given as well as transcripts and notes from the Committee’s meeting. I went through them and thought that their discussion about the risks and benefits of the drug would be helpful when we present our final treatment plan to Dr. Carosel and Dr. Nash.”

Everyone took some time to read through the documents.

“Thanks David, this is really helpful!” Chantel said when she was done reading. “This drug seems like it could be a good alternative for Simone, but I’m a little worried about the potential liver safety concerns they mention were observed in the clinical development program.” Jess nodded in agreement.

“So was I, at first,” said Charles, “but the committee voted 11 to 3 for approval of the drug. David found a summary on the Drugs@FDA website from an FDA medical reviewer that was favorable in terms of the

drug's safety. FDA also required that Shawmitch submit a Risk Evaluation and Mitigation Strategy (REMS) before Drug123 could be approved." He passed around copies of the REMS. "You'll see that the strategy for ensuring safe use is thoroughly outlined."

After a bit more discussion, the team reached an agreement. They would suggest a trial of the new medication for Simone on Friday.

Case Presentation

On Friday, the group and Lizzy presented their findings on the new medication and Simone's patient history to Dr. Carosel and Dr. Nash. They shared their discovery of Simone's diagnosis of heterozygous familial hypercholesterolemia (HeFH), and explained how the new drug was a great fit for her. She was already dieting and exercising, as the drug label prescribed, but the therapy would also help to address the high LDL cholesterol levels that were a result of her HeFH, something her previous treatment had not been able to do. The group also presented the materials from the Cardiovascular and Renal Drugs Advisory Committee meeting, the FDA medical reviewer's summary from Drugs@FDA, and the REMS.

"Based on Simone's diagnosis and current labs," David concluded, "We believe she would be an excellent candidate for this new medication. We also suggest cardiac rehabilitation and a nutrition strategy for the patient. After her release from Sun Valley, she should be required to come back for a follow-up assessment."

"And because the medication must be injected underneath the skin, I will counsel Simone before she is released on proper subcutaneous injection and aseptic techniques, and show her how to use the pre-filled syringes correctly," said Lizzy. "I'll also review the REMS communication plan for the product and provide an in-service

Risk Evaluation and Mitigation Strategy (REMS)

An essential part of managing a formulary system is making sure that methods for ensuring safe prescription, distribution, administration, and monitoring of medications are in place. The Food and Drug Administration Amendments Act (FDAAA) of 2007 gave FDA the authority to require a REMS to ensure that the benefits of a drug or biological product outweigh its risks. A REMS can be required for an individual drug or for a class of drugs whose members share a common set of risks. Some more restrictive REMS include elements to assure safe use (ETASU). These programs can require prescriber and pharmacy training or certification, restrictions on dispensing to certain health care settings, documentation of safe use conditions, required patient monitoring, or patient registries. These additional requirements are some considerations to be discussed at pharmacy and therapeutics committee meetings.

Resources are available to health care professionals to assist them in knowing when a new drug has a REMS or when a REMS has been required for a drug that already is on the market. The FDA's REMS@FDA website (<http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>) contains an up-to-date list of all drugs that have a REMS. Users can search for the drug name, what elements are included in the REMS, and the date the information was last updated. REMS drug information can also be sorted alphabetically or by date.

training session to the Sun Valley staff who will prescribe the drug."

Dr. Carosel and Dr. Nash looked at one another in shock, impressed with the group's excellent teamwork and the thorough presentation they had delivered. The two slowly clapped their hands, much to the delighted embarrassment of their students.

"Fantastic job!" said Dr. Nash. "You guys really did your homework. I don't think I've ever witnessed a treatment plan presentation that was this well-researched from a group in their first week. Bravo!" She was inspired. Moments like this were what had initially drawn her into teaching at Sun Valley. She had forgotten how rewarding the experience could be.

"I agree," Dr. Carosel smiled. "I didn't say so earlier, but I had heard about the Shawmitch drug through FDA CardioBeat before David mentioned it on our rounds. For those unfamiliar with this resource, you can sign up for CardioBeat to receive e-mail updates on safety and regulatory issues related to cardiovascular disease, including product approvals, safety warnings, notices of upcoming public meetings, and notices about proposed regulatory guidances. There is also a cardiovascular disease

area of the FDA site for patients to sign up for CardioBeat and read FDA news and press releases related to cardiovascular disease. Anyway, I had wondered if it might be worth looking into the drug more, but didn't get the chance to go further. Now that I have all this background material and research, Charles and I should be able to present a compelling case at the next Pharmacy and Therapeutics (P&T) Committee meeting for adding the drug to Sun Valley's formulary. Thank you all. You've really done a great job."

Conclusion

The P&T Committee decided that because the Shawmitch drug was a novel therapy and required unique administration, it made sense that the drug would be initiated in a hospital, and they wanted it to be available as an option at Sun Valley. To ensure safe use, the hospital limited the drug's prescription to "consult by the cardiology team," so not everyone with hospital privileges could prescribe it. Lizzy provided the required training to the staff on the REMS program. After the victory with the P&T Committee, Dr. Nash was excited to

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see what other learning experiences she would have with this group of students. They did not disappoint her. After a year, she left to pursue a subspecialty in interventional cardiology, but she frequently visited Sun Valley to consult with Dr. Carosel on special patient cases in the student rounds program.

David was relieved that his first experience at Sun Valley, which had started off rocky, had ended on a high note. Inspired to be the best informed member of his team, David signed up for FDA's CardioBeat e-list, downloaded the FDA Drug Shortages App on his mobile phone, and continued to familiarize himself with other resources available on the FDA

website. He also took Charles' advice; after finishing the program at Sun Valley, he completed a rotation at FDA. He is now known as the go-to expert in his pharmacy program for anyone with questions about FDA's regulatory processes and drug information resources.

Glossary

Advisory Committee: A committee of experts outside of the FDA that meet to provide the agency with independent opinions and recommendations on applications to market new drugs and on FDA policies. Prior to review meetings, committees are provided with materials (e.g., briefing books of data, slides) and data that help inform their recommendations for approval or denial. Advisory meeting minutes typically include questions and voting tallies from committee members as well as public discussion details. These documents provide significant information for formulary evaluation, including the perspectives of the FDA, the manufacturer, the public, and the expert committee members. Advisory meeting agendas, rosters, and minutes are available for public viewing on FDA's website: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm>.

Accelerated Approval: Accelerated approval regulations (versus designations) allow for the approval of drugs for serious or life-threatening diseases on the basis of a surrogate endpoint; that is, the surrogate is reasonably likely to predict clinical benefit. For oncology-related therapeutics where accelerated approval has been actively used, surrogate endpoints such as progression-free survival or tumor shrinkage may be predictive of overall survival, and therefore, a clinical benefit. One requirement for drugs approved under the FDA's accelerated approval program is that the sponsor must study the drug further in postmarketing studies after approval to verify the expected clinical benefit. If confirmatory clinical trials do not demonstrate clinical benefit, FDA has the authority to remove the drug (or the accelerated approval indication) from the market. For example, in 2004, FDA determined that Iressa (gefitinib) should be withdrawn since it failed to show overall survival advantage in treating patients with lung cancer. In 2011, FDA revoked approval of the breast cancer indication for Avastin (bevacizumab); however, the drug remained on the market since it also had been approved for certain types of colon, lung, kidney, and brain cancer.

Drug: The FD&C Act defines a drug as including an "article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," and an article[] (other than food) intended to affect the structure or any function of the body of man or other animals. As part of the FDA, the Center for Drug Evaluation and Research regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. This work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, dandruff shampoos, and sunscreens are all considered "drugs."

Fast Track Designation: Fast track designation may be granted during the clinical development phase for products intended to treat a serious or life-threatening condition (e.g., include AIDS, Alzheimer's disease, cancer, epilepsy, diabetes, depression) for which there are no alternative treatments. This is called an unmet medical need. The fast track designation may be granted once proof-of-concept studies have been demonstrated. The designation facilitates frequent and interactive communication between the pharmaceutical sponsor and FDA. Therefore, the fast track designation is of greatest benefit before the initiation of adequate and well-controlled studies to establish efficacy.

Often, products deemed fast track may be suitable for a "rolling submission." In this instance, the pharmaceutical manufacturer submits the marketing application to FDA once a section of the marketing application is completed, rather than waiting for the entire application to be submitted at one time. The rolling submission practice allows for FDA's scientific review to be conducted as the pharmaceutical manufacturer completes a section and submits it. For example, the preclinical data package for the marketing application may be completed months before the final clinical studies have concluded and may be ready for submission to the FDA. However, if deemed a fast track product, it may be beneficial for the pharmaceutical manufacturer and FDA to have completed the preclinical studies and review, leaving only the clinical studies and chemistry sections outstanding.

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Orphan Product Designation: An orphan designation may be granted to pharmaceutical products intended to treat diseases and conditions affecting less than 200,000 Americans, or for which it can be shown that there is no reasonable expectation that costs of development and production will be covered by sales. If granted, the product may receive additional marketing exclusivity, waived user fees, and eligibility for drug development grants.

Postmarketing Requirements: After FDA approves a product, the pharmaceutical manufacturer may conduct postmarketing studies. FDA relies on the results of these studies to gather additional information about a product's safety, efficacy, or optimal use. Agreements with sponsors to conduct postmarketing studies can be determined either before or after FDA has granted approval to a sponsor to market a product. FDA's post market requirements and commitments database (<http://www.accessdata.fda.gov/scripts/cder/pmc/>) provides details on the clinical studies that must be conducted as a condition of approval, including the study's objective, timeframe, and reason for the requirement. The information on the website, including additions and

status changes, is updated quarterly. Certain information regarding postmarketing studies and clinical trials also may be obtained from ClinicalTrials.gov.

Understanding the postmarketing study commitments for a therapeutic product and the timeframe the studies are to be conducted and completed within can be very useful when evaluating or re-evaluating formulary decisions. Additional information about postmarketing study commitments be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/default.htm>.

Priority Review Designation: FDA might give a drug a priority designation when the therapeutic product is deemed to treat a disease where no satisfactory alternative therapy exists; or where it is a significant improvement compared to marketed products, including nondrug products or therapies. For priority designations, FDA agrees to review and offer its response on a product's approval status within six months, rather than the ten-month review process for products designated standard review.

STUDENT ACTIVITIES

Before Class

- I. Review the following websites:
 1. Drugs@FDA
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>
 2. FDA Advisory Committee
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm>
 3. REMS@FDA
<http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>
 4. Drug Shortages Program
<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/>
- II. Answer the following questions before class:
 1. What is Drugs@FDA?
 2. True or False: Advisory Committee members are FDA employees. (Explain your answer.)

3. A risk evaluation and mitigation strategy (REMS) may consist of:
 - a. Medication Guide
 - b. Communication Plan
 - c. Elements to Assure Safe Use (ETASU)
 - d. Implementation Plan
 - e. Cost of the drug
 - f. All of the above
 - g. a, b, c, and d

In Class

- I. Prompts for in-class group discussion:
 1. Visit FDA's Cardiovascular Disease web page and discuss the information patients can find there.
<http://www.fda.gov/forpatients/illness/cardiovascular/default.htm>
 2. Using the REMS@FDA website, choose a drug product and discuss the different parts of the REMS.

3. Break into groups. Choose an advisory committee from the FDA Drug Committees site. Look through the materials listed for the previous year, and select a meeting to report on. Review the agenda, briefing documents, minutes, and any other available information relevant to the meeting. Report your findings on the purpose of the meeting and the committee's final recommendations to the class.
4. Pharmacy and Therapeutics Committee Meeting: For this project, you and your group members will prepare a report on a drug of interest to present to a P&T Committee at a hospital. Select a drug product listed in the Drugs@FDA database and research it using the FDA resources mentioned in the case study (also listed below). You will present your findings to the class, who will act as the P&T Committee and make the final decision on whether or not to include your selected drug in the hospital's formulary.
 - a. Using the Drugs@FDA database:
 - i. Review the product's label information
 - ii. Review the product's approval history, letter, and other review documentation available on Drugs@FDA
 - b. Using the REMS@FDA website, review any REMS documents and associated materials for the drug product (if they exist)
 - c. Visit the FDA Advisory Committee website. Check to see if your drug was reviewed by an advisory committee. If it was, review all of the relevant meeting materials available.
 - d. Check to see if the drug is listed in the FDA Drug Shortages database.

After Class

- I. Sign up to receive CardioBeat updates
<http://www.fda.gov/forpatients/illness/cardiovascular/default.htm>
- II. Identify an upcoming advisory committee meeting and view the webcast. Submit a one-page summary of the meeting to the instructor.
- III. Download the drug shortages app
<http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm>

Additional References

FDA Basics Drugs

<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192696.htm>

FDA Basics Webinar:

A Brief Overview of Risk Evaluation and Mitigation Strategies (REMS)

<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm>

Cardiovascular and Endocrine Liaison Program (CELP)

<http://www.fda.gov/ForHealthProfessionals/LiaisonActivities/ucm402222.htm>

FDA Basics Webinar : Drug Shortages

<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm422040.htm>