FDA CASE STUDY

Drug Approval—Bringing a New Drug to the Market

SEPT 2015

A SMALL PHARMACEUTICAL COMPANY REVIEWS THE PATH LEADING TO FDA APPROVAL TO MARKET A NEW DRUG IN THE UNITED STATES

THIS FICTIONALIZED CASE STUDY IS PART OF AN EDUCATIONAL SERIES PUBLISHED BY THE CENTER FOR DRUG EVALUATION AND RESEARCH, PROFESSIONAL AFFAIRS AND STAKEHOLDERS ENGAGEMENT, U.S. FOOD AND DRUG ADMINISTRATION.

Questions to consider as you read this fictional case study:

1. What are the objectives of the drug development and approval process?
2. What are the major activities that occur during the drug development and approval process from nonclinical testing to market approval?
3. What are the major elements and steps required to conduct a clinical trial?

Preparing to Meet a Big Need at a Small Company

9.3 percent. Dr. Abby Green circled the number and snapped the cap back in place on the dry erase marker.

Green and her new operations manager, Jon Soto, looked at the whiteboard. "That's almost 10 percent!" he exclaimed.

Green replied, "Yes, in 2012, 29.1 million Americans, or 9.3 percent of the population, had diabetes. Out of those, 90–95 percent are type 2 diabetic patients[1] and the numbers have been growing."[2]

Five years ago, Abby Green, soon after receiving her M.D. and Ph.D. degrees, started a small pharmaceutical company called Green Pharmaceuticals.

"I was able to get funding from multiple investors to start this company because of my interest in researching a disease that impacts so many people," Green remarked.

Her company had developed a drug aimed at type 2 diabetes: lowagliflozin. The drug works similarly to a class of drugs known as SGLT2 inhibitors. The SGLT2 inhibitors treat diabetes by inhibiting the sodium glucose co-transporter 2 (SGLT2) in the kidneys. This decreases the reabsorption of urinary glucose and increases excretion of the urinary glucose.

Lowagliflozin, however, is different. The drug aims to prevent the intestinal absorption of glucose in addition to blocking glucose reabsorption in the kidneys. Green envisioned lowagliflozin as a treatment for patients with type 2 diabetes unable to adequately control the disease with diet and exercise.

"But aren't there already a lot of diabetes drugs on the market?" Soto asked.

Green answered, "Yes, there are at least 10 classes of drugs that work to treat type 2 diabetes, but they all have limitations. (Appendix A) Some work better in some people, and some of the drugs have side effects that some patients cannot tolerate. I think that lowagliflozin, with its novel mechanism of action, may have much to offer patients. The drug is ready to be tested in healthy volunteers, and I am excited to see if it lowers blood glucose in people with type 2 diabetes."

[1] Centers for Disease Control and Prevention (CDC) 2014 National Diabetes Statistics Report Infographic. Diabetes in the United States: a Snapshot.

[2] CDC. Long-term Trends in Diabetes.

The company was almost done with the basic laboratory work on lowagliflozin, including the necessary animal studies to initiate Phase 1 studies in patients. Green and her colleagues now faced the task of beginning the clinical trials needed to obtain approval from the U.S. Food and Drug Administration (FDA) to market the drug in the United States.

"Can you give me a big picture overview of the drug development and approval process?" Soto asked.

"Sure, I will start at the very beginning with how the Federal Food, Drug, and Cosmetic Act defines a drug." Green said. She located the definition on the FDA's website and angled her tablet towards him:

> *The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).*[3]

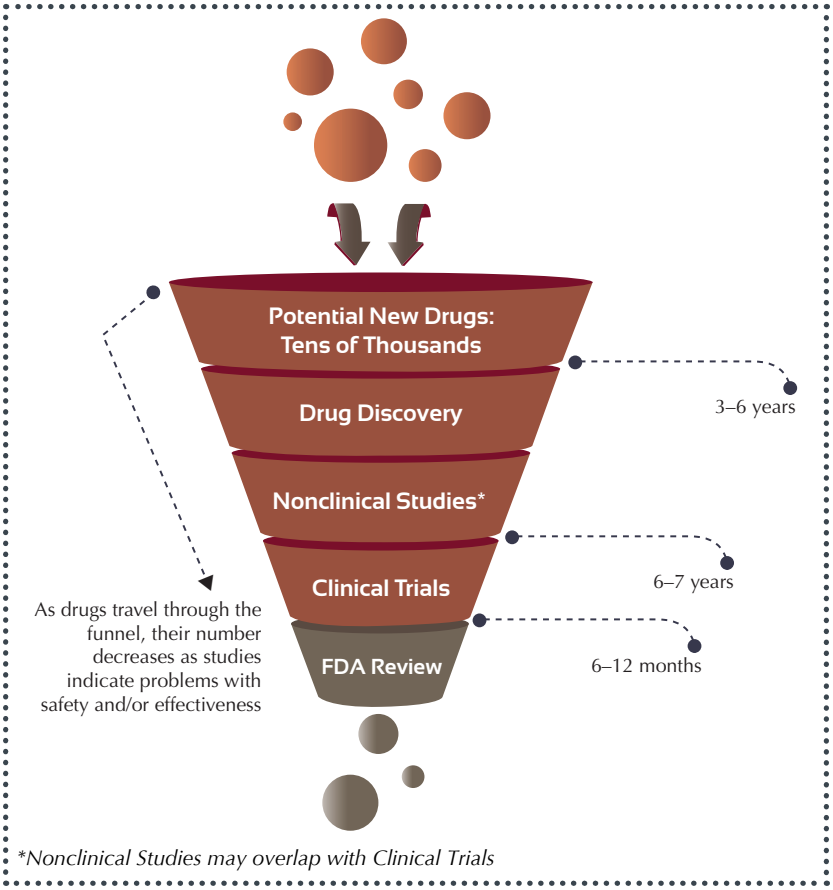
[3]Section 201 (g)(1) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 321.

"Potential drugs are first tested in the lab and later in lab animals," Green said. She explained that most drugs undergoing animal testing never make it to human testing and review by the FDA. She drew a large funnel on the board. Pointing at the wide end of the funnel she said, "At the mouth of the funnel, there are tens of thousands of potential drugs being developed in laboratories.

As the drugs begin flowing through the funnel, the number decreases as the developers discover some of the drugs do not work or they are too dangerous. The drugs that make it through the initial stages then undergo the FDA's evaluation process, which scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to how the drug is manufactured. Even fewer drugs have the safety and efficacy profile needed for approval." (Exhibit 1 and Appendix B)

Green said that, given Green Pharmaceuticals' inexperience

Exhibit 1. Drug Development Funnel



*Nonclinical Studies may overlap with Clinical Trials

http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf

interacting with the FDA, she was going to find a consultant to help the company navigate the drug approval process.

Following a Logical Path with Clear Milestones

Green hired Dr. Sheryl Roberts, a physician and regulatory affairs consultant who specialized in guiding smaller pharmaceutical companies through the drug development and approval process. Green asked Soto to join her in the initial meeting with Roberts, "You have a lot of experience developing and managing processes. I'd like to get your perspective as we make sense of what we need to do to meet FDA requirements."

Nonclinical Testing: Initial Drug Development Steps

On the day of the meeting, the three claimed the small company's one conference room. Green reported that they were concluding the initial nonclinical studies and were ready to begin testing the drug in humans. (Appendix C1)

"That's good to hear," Roberts replied. "It sounds as if you have made good progress and met the objectives of the initial nonclinical testing: To find out if the compound is reasonably safe for initial use in humans and if the compound shows pharmacological activity and effect on a disease marker that justifies the time and money needed to bring it to market." Roberts asked if the company was done with animal testing and could now focus on clinical trials.

"That is a good question, and the answer is yes and no," Green replied.

"We know we will eventually need additional nonclinical studies to support the safety of the clinical trials as the trials become larger and of longer duration. Also, there are some safety endpoints that we can only characterize sufficiently in nonclinical studies, such as the risk of cancer and teratogenicity from the drug. We need to match nonclinical studies for dose, schedule, and duration. Adequate nonclinical studies will assist in identifying parameters for clinical safety monitoring and guide patient eligibility, as well as assist in managing risk. But we do not need that information yet to support our early clinical trials."

"Then let's move on and talk about the requirements for a New Molecular Entity, known as an NME, since your drug is an NME," Roberts noted.

"What's an NME—in layman's terms?" Soto asked. Roberts shared the FDA's definition of an NME: An active ingredient that has never before been marketed in the United States in any form.

"That's us!" Green and Soto agreed.

Roberts walked to the whiteboard near the head of the table. She announced, "The drug development process is lengthy and detailed, but it is a logical path with clear milestones." She chose a marker and drew a long, horizontal line. "So where does this logical path go?" she turned and asked.

Safety and Efficacy

"The path leads to FDA approval for marketing the drug or biologic in the United States. And it is designed to demonstrate the safety and efficacy of the drug or biologic for the proposed indication," she announced. Soto scooted his chair closer to the whiteboard and added the words "safety and efficacy" at the end of the line on the board. Roberts nodded and continued, "Before your company can test a new compound in humans, it must show FDA the results of the nonclinical tests in laboratory animals and tell FDA what you propose to do during testing on humans. This brings us to your first milestone: the Investigational New Drug (IND) Submission." (Exhibit 2)

Soto leaned over and added "IND submission" to the path on the whiteboard.

Green asked, "What do we do if we have questions before we submit the IND? Can we talk to FDA at that early stage?"

Exhibit 2. Milestone 1

Roberts answered, "Yes, sometimes companies seek advice from the FDA before they submit an IND. If we have questions regarding the IND, we may request a meeting with the appropriate division within the Office of New Drugs (OND), which, in the case of a drug to treat diabetes, would be the Division of Metabolism and Endocrinology Products. Although there are instances when a pre-IND meeting would be necessary, many divisions will answer our questions in writing at this stage." (Appendix C2)

Milestone 1: Submitting an IND Application

"As you know, once your compound completes the initial nonclinical testing phase, the next step is to test it in humans," Roberts said. "At that point, the compound's legal status changes under the Federal Food, Drug, and Cosmetic Act, and it becomes a new drug subject to specific regulatory requirements. Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because the sponsor, meaning your company, will probably want to ship the investigational drug to clinical investigators in multiple states, it must seek an exemption from that legal requirement. Companies

IND Content and Submission Resources

The FDA's IND web page outlines the need for this application, the kind of information to include, and the Federal regulations that apply.

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

Resources include:

- ✓ An Investigator's Checklist for IND Application Submission

  http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/UCM368873.pdf

- ✓ A Guidance for Industry, titled "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products." This Guidance lists and explains the IND sections required by the regulations. (Appendix C3)

get this exemption by submitting an Investigational New Drug application to FDA," she reported.

What Does the IND Include?

"So what do we have to include in the IND submission, and how do we organize it?" Green asked.

"I will be mentioning some FDA Guidance documents as we talk, but don't worry about writing them all down. I have a reference list I will give to you at the end of our meeting," Roberts said. (Appendix C)

Roberts explained that, in general, the IND application must provide information about four broad topics (Appendix C3):

1. **Animal Studies (also called nonclinical data).** These studies provide the first data to support the safety of initial testing in humans. The amount and type of nonclinical data required at this stage depend on the proposed development plan. For lowagliflozin, at a minimum, the IND should include:
   - Proof-of-concept pharmacology studies
   - Safety pharmacology studies, including an assessment of the effects on the central nervous system, cardiovascular effects, liver, renal, and respiratory effects
   - Absorption, distribution, metabolism, and excretion (ADME)
   - Short-term general toxicity studies in two animal species
   - An *in vitro* gene toxicology assessment

   There is an FDA Guidance that recommends the nonclinical safety studies that would support human clinical trials, and the FDA can always answer more specific questions. (Appendix C1)
2. **Chemistry, Manufacturing, and Controls Information (CMC).** The relevant regulation[4] and Guidance documents outline the amount of CMC information required at all phases of drug development. (Appendix C4) For Phase 1, you need to describe the drug substance or active ingredient, the initial structural characterization, and the composition. You will also need to describe how it is manufactured, the results of tests to show that it is stable, and comparative impurity profiles for the toxicology batches and clinical batches. The FDA reviews this manufacturing information to ensure that you can produce adequate, consistent batches of the drug.
3. **Clinical Protocols and Investigator Information.** The FDA will review your proposed study to ensure it does not expose the subjects to unnecessary risks. FDA will review the full protocol for your Phase 1 trial and detailed information about the qualifications of the clinical investigators who will run the trial to ensure they can fulfill their duties.
4. **Informed Consent.** Sponsors often submit informed consent documents, and FDA will review them if submitted. For lowagliflozin, we cannot comment on adverse events in humans yet. However, if you observed a significant adverse event in the nonclinical studies, a statement in the informed consent should report the event, as it could be an important safety signal.

Where Do We Send the IND?

"You will submit the IND application to the appropriate review division in the Office of New Drugs (OND)[5] within the Center for Drug Evaluation and Research (CDER)[6] in FDA. CDER regulates prescription drugs and over-the-counter drugs," Roberts remarked as she shared a copy of an organizational chart from FDA. (Appendix D)

[4] 21 CFR Part 312.23(a)(7)(i).

[5] Office of New Drugs.

[6] Center for Drug Evaluation and Research.

"Remember, you submit the IND before your company tests a drug in humans," Roberts emphasized.

The Role of the Institutional Review Board

"Does anyone else review the IND?" Green asked.

"Yes, in addition to the FDA reviewing the IND, the institutional review board (IRB) also reviews the proposed studies and informed consent," Roberts answered. "IRBs are panels of scientists and non-scientists that oversee clinical research. IRBs make sure the study is well designed, participants are fully informed of the risks, participants have given informed consent, and researchers take appropriate steps to protect people from harm."

Roberts noted that the IRB reviews the proposed study and approves the following:

- Clinical trial protocols describing the type of people who may participate in the trial
- Schedule of tests and procedures
- Medications and dosages to be studied

Exhibit 3. The basic elements of an Informed Consent Form

1	State that the study involves research, explain the purposes of the research, and report how long the person is expected to participate.
2	Describe the study procedures and identify any experimental procedures.
3	Describe any foreseeable risks or discomforts to the subject.
4	Describe any benefits to the subject, or to other people, that may reasonably be expected from the research.
5	Identify other appropriate studies or courses of treatment, if any, that might benefit the subject.
6	Describe how much, if at all, records identifying the subject will be kept confidential. Explain that the FDA may inspect the study records.
7	Explain, for any research posing more than a small risk, if the subject will be compensated or receive medical treatment for any injuries arising from the study. If yes, describe the available compensation, treatment, and where the subjects can get more information.
8	Provide contact information for a person who can answer questions about the research and the rights of the subjects. Also identify the contact person for any research-related injuries.
9	State that participation is voluntary. If subjects choose not to participate—or want to stop participating—they will not be penalized or lose benefits that belong to them.

The required elements of the informed consent are found in the regulation at 21 CFR Part 50.25: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25

- Length or duration of the study
- Study objectives and other details

Informed Consent

"You mentioned informed consent. I'm familiar with the concept, but can you outline the basic requirements?" Soto asked.

"I'm glad you asked," Roberts answered. "It is important to understand that informed consent is an ongoing and interactive process. It is not a one-time event where a person reads and signs a form. The purpose of informed consent is to give potential research study subjects the information they need to make an educated decision to join a study or continue participating." (Exhibit 3)

Roberts explained that the study sponsor needs to provide a statement written in understandable language—not legalese. The sponsor must allow the potential subjects the opportunity to ask questions and time to think about participating in the study. The study sponsor must also continue to provide information to the subjects, as needed, during the study. She noted that FDA's informed consent requirements are found in the FDA's regulation on the Protection of Human Subjects.[7]

These regulations apply to clinical investigations regulated by FDA. The FDA also has a Guidance covering informed consent for IRBs, clinical investigators, and study sponsors. (Appendix C5)

The 30-Day Waiting Period

"Once we submit the IND, when can we start our Phase 1 trial?" Green asked.

Roberts answered, "After the IND is received by FDA, you must wait 30 calendar days before initiating any clinical trials. During that time, FDA reviews the IND to ensure that you will not expose your research subjects to unreasonable risks.

By the 30-day date, one of the following will occur:

1. **Safe to proceed.** FDA sometimes notifies sponsors in writing that their proposed initial trial may start. The FDA's letter, however, may contain comments and suggestions for the trial and your overall development program. The sponsor can assume that it is safe to proceed if they do not receive one of the clinical hold letters.
2. **Clinical hold.** The proposed trial is not safe to proceed. If this happens, after a call between the sponsor and FDA, the FDA's letter will explicitly state why it's not safe to proceed and what you need to do to reverse the clinical hold.
3. **Partial clinical hold.** The proposed trial may proceed only with restrictions that FDA will describe in their letter to the sponsor.

If FDA places your IND on a clinical hold, we will work with FDA to resolve the deficiencies. We would prepare and submit a response to the critical issues that led to the clinical hold. You may need to submit additional nonclinical data, explain existing data, or modify the protocol to ensure patient safety. The FDA then has 30 days from receipt of the information to review the new data and decide whether the deficiencies have been adequately addressed. When FDA considers the initial trial safe to proceed and communicates that decision to you, you have reached another milestone: You may initiate the Phase 1 trial." (Exhibit 4)

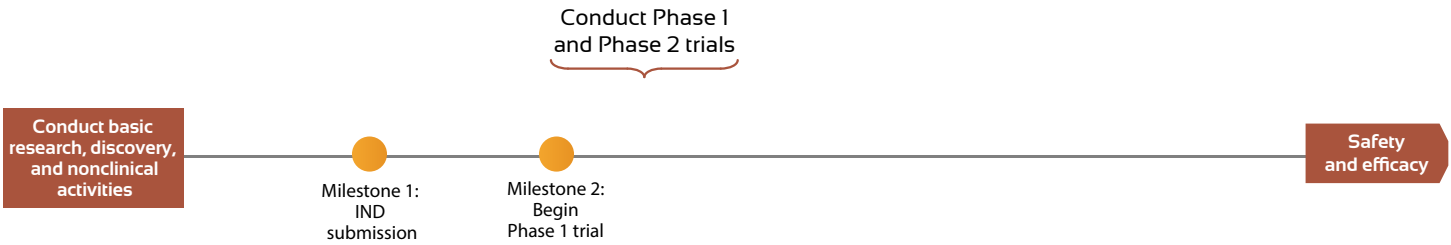
Milestone 2: Initiate the Phase 1 Trial

"While we are conducting our Phase 1 trial, I imagine there are some reporting obligations to the FDA. Can you tell us about them?" Green asked.

"Yes, as you are conducting the initial trial under the IND, there are specific obligations. FDA will detail the reporting requirements in the letter you will receive at the end of the 30-day IND review period," Roberts replied.

[7]The Protection of Human Subjects is found in the regulation at 21 CFR Part 50.

Exhibit 4. Milestone 2



Phase 1 Reports

Roberts described the IND safety reporting[8] obligations:

- Report any suspected fatal or life-threatening adverse reactions to the FDA no later than 7 calendar days after your initial receipt of the information.
- Report other serious or significant issues: (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or *in vitro* studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction. Report to FDA and all investigators no later than 15 calendar days after you determine you need to report the information.

"In addition, you will submit annual progress reports within 60 days of the anniversary of the date your IND went into effect (the date clinical studies were permitted to begin)," she noted.

Green responded, "Those requirements seem reasonable. The FDA wants to know about any concerning safety signals and also wants general annual updates about the status of the application."

Phase 2 Protocols and Reports

"After you finish your Phase 1 trials, you will submit a study report summarizing the results of the trial," Roberts noted. "Assuming nonclinical studies and the Phase 1 trials are completed with no concerning safety issues observed, you will submit your Phase 2 protocol, or protocols, to the FDA's Review Division. The Division may or may not have comments about the protocols. Once the Phase 2 trials begin, the general reporting requirements are similar to what we discussed for the Phase 1 trials. However, before we proceed, I would like to mention one very good opportunity to obtain input from the FDA for your drug development program: the End-of-Phase 2A (EOP2A) meeting."

Roberts continued, "This meeting precedes the big End-of-Phase 2 meeting, but it is no less important. Usually the EOP2A meeting occurs after the completion of Phase 1 trials and the first set of exposure-response trials in patients, but before beginning Phase 2B (i.e., patient dose-ranging trial) and Phase 3 clinical efficacy-safety trials.

An EOP2A meeting would occur after the completion of clinical trials that provide data on the relationship of dosing and response for the particular intended use, including trials on the impact of dose ranging on safety, biomarkers, and proof of concept. This helps sponsors to find the optimal dose and save money, while maximizing the success rate in late-stage clinical trials."

Preparing for a Major Milestone Meeting: End-of-Phase 2

"Let's assume our Phase 1 and Phase 2 trials run smoothly. Once Phase 2 ends, how soon can we move on to the important Phase 3 trials?" Green asked.

[8]The IND Safety Reporting regulation is found at 21 CFR Part 312.32.

Roberts responded, "This is a major point in the development program. Up to this time, you hopefully will have shown that your drug has biological activity, have begun to establish a safety profile, and documented some preliminary efficacy. Proper planning of Phase 3 is vitally important because it is the Phase 3 trial or trials that will be used to support your eventual drug approval application. The FDA understands the importance of this step in the drug development process. And the FDA strongly encourages companies to request an End-of-Phase 2 (EOP2) meeting before the start of the Phase 3 program." Roberts said.

She described what the company and FDA would do during the EOP2 meeting:

- Examine whether the pharmacology and toxicology profile (i.e., nonclinical program) is supportive of Phase 3 studies.
- Examine the clinical pharmacology and clinical data that support Phase 3 dose selection.
- Examine the dosing and administration strategy. Clinical Pharmacology data will guide administration concurrent with other medications, administration conditions (fasted/fed), and dosing in specific populations if necessary.
- Examine sampling plans for population pharmacokinetics and exposure/response determination.
- Discuss the primary efficacy endpoint—the main outcome used to evaluate the effectiveness of treatment in the clinical trial.
- Examine key aspects of trial design for the Phase 3 program. Review the adequacy of the safety data that will be collected in Phase 3.
- Discuss whether the Phase 3 population will adequately represent the population who will use the drug, e.g., securing racial and/or gender diversity and addressing pediatric needs.
- Review development activities to ensure they satisfy relevant regulatory requirements.
- Determine whether the CMC information supports Phase 3 studies, as discussed in FDA's published guidelines. (Appendix C4)

"And, within 60 days of the EOP2 meeting, we are required to submit the pediatric study plan," Roberts remarked. (Appendix C6)

"It sounds like we will discuss just about everything about the Phase 3 trial. How do we prepare for this meeting?" Green asked.

"To maximize your interaction with FDA, about a month prior, or earlier, to the meeting, you will submit a meeting package that includes your plan for Phase 3. If you do not submit this package, FDA may cancel the meeting. This package will include the Phase 3 protocols, summaries of the Phase 1 and 2 investigations, and plans for pediatric studies," Roberts answered.

Special Protocol Assessments

"One more thing, once a drug company and the FDA agree to a specific Phase 3 protocol for a drug, it is considered a binding agreement."

"Can you explain how this works? I thought the point of the EOP2 meeting was to reach an agreement," Green asked.

"That is a great point," Roberts said. "You are referring to a special protocol assessment, also known as an SPA. For diabetes drugs, existing Guidance documents and the Package Inserts of recently approved products already characterize the types of clinical trials that form the basis for approval, so an SPA is usually not necessary. SPAs are also submitted for review of carcinogenicity protocols. There is an FDA Guidance document with more information about the SPAs if you want to find out more about these agreements." (Appendix C7)

Green rose, "I suggest we all take a break before we continue."

Milestone 3: Conducting the Pivotal Phase 3 Trials

"Are you ready to talk about Phase 3, our next milestone?" Roberts asked as she returned to the conference room.

Soto said, "Let me update our path. It may be my process-engineering mind, but I find it helpful to display the steps and activities. I'll update it as we go and transfer the information to a permanent document later." (Exhibit 5)

"See? That's why I asked you to join the meeting," Green replied.

"Only 9 percent of the drugs make it to Phase 3," Roberts continued as they settled around the conference table. "You will then use the Phase 3 trials to gather more information about efficacy and safety. This information is vital for evaluating the overall benefit-risk relationship of the drug and providing the information needed to label the drug for the physicians who will prescribe it. In addition, because your drug is intended for the long-term treatment of a non-life-threatening condition, you will also want to consider the International Conference on Harmonisation (ICH) guidelines for assessing its clinical safety." (Appendix C8)

The Role of the Pivotal Trial: Phase 3

"Phase 3 is often a pivotal trial, a term you'll hear often in the drug development and approval process. Pivotal trials are the clinical trials that serve as the basis of FDA approval," Roberts emphasized.

She went on to explain that the Federal Food, Drug, and Cosmetic Act guides the FDA's review of new drug applications. This law requires "adequate and well-controlled investigations" to determine the efficacy of a drug. She noted that the FDA Guidance on this topic suggests that drug manufacturers submit at least two controlled trials providing independent evidence of efficacy. (Appendix C9)

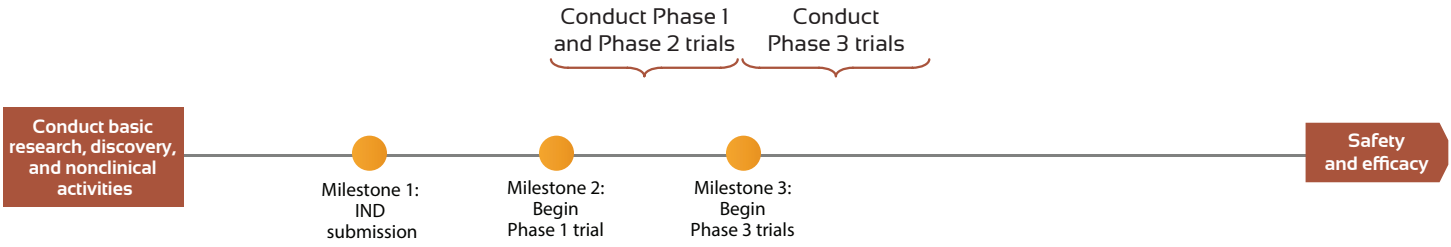
Roberts reviewed why FDA prefers at least two adequate and well-controlled trials:

- Protects against the possibility that an occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.
- Reduces the false positive rate. Ensures the consistency of clinical trial findings, providing some confidence when generalizing the results to a larger population.

"Would the FDA ever consider approving a drug based on a single efficacy trial?" Green asked. (Appendix C9)

"Only in certain instances, such as for a drug intended to treat a rare disease," Roberts replied. "This would typically not be the case for drugs intended for the treatment of type 2 diabetes, and most Phase 3 programs for drugs that treat type

Exhibit 5. Milestone 3



2 diabetes have multiple trials. You will discuss the specific number of trials required for lowagliflozin during your EOP2 meeting with FDA," she said.

How Will it Help Patients? A Meaningful Primary Efficacy Endpoint

"I mentioned the importance of the primary efficacy endpoint in our earlier discussion of the EOP2 meeting. To obtain marketing approval, the primary efficacy endpoint in the Phase 3 trials should measure something that matters to a patient," Roberts stated.

"In essence, the primary endpoint of a clinical trial is the endpoint for which subjects are randomized and for which the trial is powered. It is the outcome used to evaluate the effectiveness of treatments in a clinical trial. Secondary endpoints are endpoints that can be used to explore other important aspects of an intervention for which the trial may not be powered nor randomized."

She noted, "The established primary efficacy endpoint for type 2 diabetes mellitus is the change from baseline in hemoglobin A1c (HbA1c). HbA1c is a lab test that reports the average level of blood sugar (glucose) over the previous 3 months. The test shows how well patients are controlling their diabetes and, more recently, is also used to diagnose type 2 diabetes. A protocol for a type 2 diabetes drug will also include several secondary endpoints, such as changes in fasting plasma glucose, that support the indication."

Safety Issues Related to Diabetes Drugs

"I also want to alert you to a special requirement. The development of diabetes drugs raises specific safety concerns, which led FDA in 2008 to require additional data from sponsors. Because diabetes is associated with increased cardiovascular risk, sponsors must demonstrate that their drugs do not result in an unacceptable increase in cardiovascular risk," Roberts reported.

"How do we demonstrate it?" Green asked.

"The FDA outlined the requirements in a Guidance document. (Appendix C10) One of the major points in the Guidance is that sponsors should establish an independent cardiovascular endpoints committee. This committee will prospectively adjudicate, in a blinded fashion, cardiovascular events during all Phase 2 and Phase 3 trials," Roberts replied.

"Layman's clarification, please," Soto said waving his hand, "What does *prospectively adjudicate in a blinded fashion mean*?"

Roberts answered, "The phrase means the committee members will review any cardiovascular events that arise, while any information that might cause a member to be biased in favor of a specific outcome will be hidden. The purpose of the committee is to provide an independent assessment of the causes of any cardiovascular events during the trials."

Phase 3 Reporting

"What kinds of reports should we plan to submit to FDA during Phase 3?" Green asked.

"During Phase 3, while you are conducting the trials, you will continue to submit safety reports and annual reports. Remember, Phase 3 can last several years. With some exceptions, the next face-to-face interaction you will have with the FDA will be the pre-NDA meeting," Roberts said.

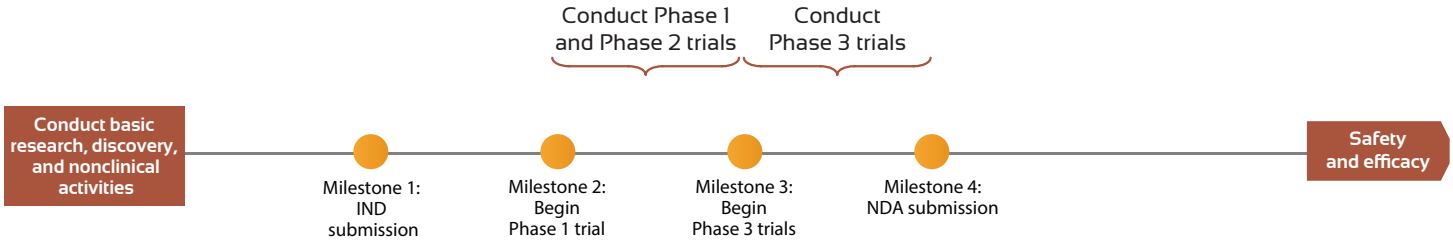
Milestone 4: Submission of the New Drug Application

"We have reached another milestone: the submission of the New Drug Application, or NDA," Roberts announced. (Exhibit 6)

"Once your Phase 3 trials are done, you should have all the data, from your animal studies to the pivotal trials, you need for your NDA. The NDA is the major submission you will use to request marketing approval."

"There are three approval pathways for a new drug. (Appendix E) We will focus on the standard NDA

Exhibit 6. Milestone 4



pathway because lowagliflozin is not a generic drug, and you are relying on your own investigations to complete your application," Roberts said.

The Pre-NDA Meeting

"The FDA encourages you to request what is called a pre-NDA meeting. The FDA has found that meeting before you submit the NDA helps resolve problems early, reducing delays associated with the FDA's initial review of your application."

Roberts described the objectives of the pre-NDA meeting:

- Uncover any major unresolved problems.
- Determine the adequacy of the sponsor's dossier for the submission of an NDA.
- Review the status of ongoing studies to assess pediatric safety and effectiveness.
- Acquaint FDA reviewers with the general and technical information that will be submitted in the marketing application.
- Discuss the content, structure, and format of the application, including the presentation of the integrated analyses of safety and efficacy.
- Determine whether the type and amount of CMC information to be included in the NDA will be sufficient to demonstrate a thorough understanding of the product and manufacturing process.

NDA User Fees

Roberts continued, "Many researchers and young companies are surprised to hear that they may need to pay a user fee with the NDA. The Prescription Drug User Fee Act of 1992 (PDUFA) authorizes FDA to charge user fees for certain drugs and biological product applications. (Table 1) These user fees support timely reviews for drugs, and we will talk about the timelines when we discuss the FDA's review of your application. There are exceptions to the user fee requirement, such as drugs for designated orphan diseases. And there is an FDA Guidance that discusses the user fee waivers, reductions, and refunds for drugs and biological products," she noted. (Appendix C11)

"One of the situations in which FDA will grant a fee waiver is when the applicant is a small business submitting its first human drug application for review. I believe we would fit into this situation, and

Table 1. PDUFA Categories and Costs Associated with the NDA Application

Fee Category for Applications	Fee Rates for Fiscal Year 2015
Requiring clinical data	$2,335,200
Not requiring clinical data	$1,167,600
Supplements requiring clinical data	$1,167,600

this would be a huge advantage for your small, but growing, company," Roberts said.

NDA Content and Format

Roberts continued, "Let's discuss your NDA preparation. I think it is helpful to think of the NDA as a story. And this story will tell FDA reviewers what happened during the clinical tests, the ingredients of the drug, the results of the animal studies, how the drug behaves in the body, and how the drug is manufactured, processed, and packaged."

She advised them to provide FDA reviewers with enough information to answer some key questions:

- Is the drug safe and effective for its proposed use?
- Do the benefits of the drug outweigh the risks?
- Is the drug's proposed labeling (the Prescribing Information) appropriate and complete?
- Are the methods used to manufacture the drug—and the process controls used to maintain the drug's quality—adequate to preserve the drug's identity, strength, quality, and purity?

"Are there resources we can use to develop our NDA?" asked Green.

"Yes, the FDA has multiple resources for drug development information, including more than 20 Guidance documents.[9] These resources outline the NDA content, format, and classification, plus the NDA review process. And there are links to the relevant laws, regulations, policies, and procedures," Roberts replied.

"But don't get overwhelmed looking at all of the information," she cautioned. "We will have several meetings focused just on your NDA preparation when we reach that step."

"It's a lot to think about," Green agreed. "Let me propose a break before we continue."

Assessing the Need for a Risk Evaluation and Mitigation Strategy

After returning to the conference room, Roberts scanned her notes. Looking up, she remarked, "Before we submit the NDA for lowagliflozin, we will need to discuss whether there may be a need for a REMS, or a risk evaluation and mitigation strategy. For most approved drugs, the product labeling and routine reporting requirements are enough to mitigate risks and preserve benefits. However, some drugs pose more serious risks."

She identified the factors FDA considers when determining the need for a REMS:

- Size of the population likely to use the drug
- Seriousness of the disease
- Expected benefit of the drug
- Duration of the treatment
- Seriousness of known or potential adverse events
- Status of the drug, e.g., is it a New Molecular Entity?

Roberts described the potential elements of a REMS: a Medication Guide or Patient Package Insert, a communication plan, elements to assure safe use or ETASU (e.g., health care provider certification, pharmacy certification, restrictions of dispensing to certain health care settings, restriction of dispensing only to patients with documentation of a safe-use condition, such as laboratory test results), an implementation system, and a timetable for submission of REMS assessments.

"Is there a way to find REMS information for the three SGLT2 drugs already on the market?" Green inquired.

"Yes, you can review a list of approved REMS on the FDA's website to see if this class of drugs requires REMS.[10] From what I recall, none of the SGLT2 Inhibitors have a REMS at this time, but there are REMS in place for other type 2 diabetes therapies," Roberts replied.

"When do we determine if we need a REMS?" Green asked.

[9]FDA drug development information.

[10]The list of currently approved individual REMS.

"At the time of the NDA application, we can propose a REMS. Alternatively, FDA may inform you of the need for a REMS during the review process. We will finalize the REMS before the end of the review cycle. FDA will tell us the required elements, but it will be our responsibility to submit the REMS in the form of a detailed plan," Roberts answered. "And, if we submit a REMS proposal, it must include a timetable for submitting our assessments."

"We are now ready to talk about an important phase: FDA's review of your NDA," Roberts announced.

FDA Review Process

Standard Review and Priority Review

Roberts continued, "When you submit your NDA, either a S**tandard Review** or a **Priority Review** timeline will be applied to your application. You may discuss the review timeline designation options with FDA at the pre-NDA meeting, but FDA's review division makes the formal decision when you submit the NDA. In 2012, when Congress renewed the Prescription Drug User Fee Act (i.e., PDUFA V), the review timelines for NME NDAs and original Biologics License Applications BLAs submitted under the Program for Enhanced Review Transparency and Communication ('the Program') were changed. The changes were intended to improve the efficiency and effectiveness of the first cycle review process, decrease the number of review cycles needed to obtain approval (without changing the standards for approval), and ensure patients have timely access to safe, effective, and high-quality drugs."

She summarized the two review timelines for NME NDAs and Original BLAs reviewed under the Program:

- **Standard Review:** This review lasts for 12 months total. It ends 10 months after the filing date, which is 60 days after you submit the application.
- **Priority Review:** This review lasts for 8 months total. A Priority Review is one of several available expedited programs. The FDA grants a Priority Review if you demonstrate that a drug (or biologic) has the potential to provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening condition.

The total time for a non-Program application review is 10 months and 6 months respectively.

"What does FDA do during the review period?" Soto asked.

"Let me use a regulatory term of art: A lot!" Roberts said with a grin.

FDA 60-Day Notification

"Once you submit the NDA, the FDA has 60 days to tell us if the Agency considers our application complete. Or, using FDA language, 'FDA has 60 days to determine if they file the application.' Just a quick reminder, the filing date is not the same as the submission date. An application is complete if the initial submission contains all of the information FDA needs to perform a full review and make a decision on the proposed labeling, it contains all of the required elements, it is legible, and it is easy for FDA reviewers to navigate the contents," Roberts said.

She told them that a complete application includes:

- Proposed indications
- Data required to assess the safety and efficacy of the drug, including any required long-term safety data and the pediatric plan information needed to evaluate and approve the manufacturing facilities and proposed manufacturing specifications

"If the application is not complete, FDA halts its review and takes a 'refuse to file' action. You then need to address the issues and resubmit the entire application," she emphasized.

FDA Efficiency Requirements

Congress has renewed and modified the Prescription Drug User Fee Act (PDUFA) multiple times. The last renewal, PDUFA V, was passed in 2012. This version added enhanced transparency and communication between FDA and drug sponsors during the review cycle. The law also modified the review timelines for the applications of original biologics and New Molecular Entities. This enhanced review program is referred to as the "Program."

A major objective of the Program is to improve the efficiency and effectiveness of the "first cycle" review process—the first time a company submits the NDA/BLA to FDA for review. The Program extends the PDUFA clock by 2 months. Before the Program, the goal date—the latest date FDA could take an action—was 10 months after FDA receipt of a standard review application. This change added more time at the end of the review cycle to address serious issues that commonly arise, such as issues noted during an inspection or feedback from an Advisory Committee. This opportunity to resolve serious issues during the first cycle review potentially reduces the number of drugs that have to go through a "second cycle" review.

Under the Program, FDA begins the review immediately after the submission. But the PDUFA clock starts on the filing date, which is 60 days after the date the application is submitted.

"And we want to avoid that," Green agreed.

FDA Information Requests

"By the way, once you submit your application, don't be surprised if you receive information requests from FDA. They may ask you to provide more data, conduct alternative analyses, or clarify information. Generally, FDA expects a timely response. And it's in your best interest to facilitate the FDA's review," Roberts instructed.

"What if we realize there are data we didn't submit with the original application, but we think FDA needs the data for its review?" Green wondered.

"If you believe FDA needs the data for the review, you can submit it. However, FDA will decide whether or not they will review the data during the current review cycle and if reviewed, there is a possibility that FDA will call this submission a 'Major Amendment' to the application and extend the review timeline," Roberts responded.

She continued, "During the review of Program applications, FDA will tell us through a mid-cycle communication about any important issues that have arisen.

This is a great way to find out if FDA has any major concerns, and it is an opportunity for you to respond to potential issues."

FDA Negotiation of the Drug Label/Package Insert

"Another activity that occurs during the FDA's review is the review and approval of the drug's label. I think the drug label is a misunderstood document," Roberts said. "What people typically call the label is actually the Package Insert, or PI. The Package Insert is intended for the doctors who will prescribe the drug. Your NDA will include a proposed Package Insert. This document includes your proposed indications for the drug, dosing information, warnings and precautions, results of the clinical trials, chemistry, and clinical pharmacology information, to name a few of the sections."

FDA Product Quality Review and Inspections of Manufacturing, Testing, and Packaging Sites

Form 356h of the NDA requires a complete list of all manufacturing, testing, and packaging facilities used for the commercial product (drug substance and drug product). This list includes contract facilities, contact information for each facility, and a statement that each facility is ready for the Current Good Manufacturing Practice (cGMP) inspection at the time of the NDA submission. FDA inspectors determine the cGMP compliance status of each facility based on inspection of the facility, sample analyses, and compliance history.

In addition to determining the cGMP compliance status of all of the facilities, FDA will review the Product Quality, or Chemistry, Manufacturing, and Controls (CMC), information in the NDA. This review determines whether or not the information is sufficient to demonstrate the sponsor's thorough understanding of the product and manufacturing process and to assure a consistent, high-quality production of the commercial product during its lifecycle. FDA will evaluate the analytical data to bridge the commercial product to the investigational product that had been used in clinical and nonclinical studies. FDA will also review the stability data to establish an expiration dating period and instructions for storage of the product.

Links to relevant FDA information about Product Quality, cGMP, and CMC are in Appendix C3.

She explained that the company would negotiate the label with the FDA, typically in the final half of the review cycle. "The FDA reviews the proposed PI, makes edits, and returns the PI to the company. The process may go back and forth several times before you and FDA concur on the contents of the PI. The FDA will send the final, approved version of the PI with the approval letter. The duration of the labeling negotiations depends upon the nature and volume of edits required," she reported. Roberts paused and typed on her tablet for a moment. "Here's an example of a Package Insert[11] for another SGLT2 drug," she said as she passed the tablet to Green and Soto.

[11]An example of a Package Insert.

FDA Inspections of Clinical Sites

"While FDA is reviewing your NDA, be prepared for the FDA to conduct inspections. When you submit your application, Federal law allows FDA access to your sites to confirm the accuracy of your clinical study records. Every year, FDA inspects about 700 clinical sites to support the approval of drugs, biologics, and devices," Roberts announced.

"How do we know if we will get inspected?" Soto asked.

"Because lowagliflozin is a new drug, you should expect inspections. They are conducted by a large office of inspectors throughout the U.S. and overseas, and FDA decides which clinical sites to inspect. It is also possible that FDA will inspect your company or any companies you contracted to help with the clinical trials. Because of the planning involved, especially if there are international sites, the inspections do not begin until a few months after the application is received," Roberts reported.

"Can you tell us a little more about what to expect during these inspections?" Soto asked.

Roberts explained that most inspections last about 5 days. During that time, the inspector will interview research staff, look at study records, examine patient charts, and ensure the clinical study was performed properly. At the end

of the inspection, the FDA inspector will discuss any significant findings and concerns with the research staff and document them on an official FDA form.

"The inspection findings are provided to the FDA's Office of Compliance and the Division's review team. When all of the inspections are complete, the Office of Compliance finalizes a summary report and makes a recommendation regarding the reliability of the data to the review division in the Office of New Drugs. Ideally, FDA considers the information found at the clinical sites reliable for approval of the drug. If it is not deemed reliable, the Office of Compliance works with the review division to decide how, or if, the data should be used," Roberts said.

FDA and the Potential Role of an Advisory Committee

Green finished writing her notes about the inspections and looked up. She asked, "We have seen the FDA convene Advisory Committee meetings for many drugs. How does the FDA decide which drugs are taken to these meetings? How will we know if our drug will be presented before a committee?"

Roberts answered, "Well, we won't know the FDA's preliminary thinking on the need for an advisory committee meeting until FDA has filed the application for review, which may take a long time. But FDA convenes Advisory Committees to seek input on a broad range of topics. The Committees provide FDA with independent opinions and recommendations from outside experts on drug applications. Based on the information they receive from FDA and the sponsor, the Committee may recommend approval or non-approval of a drug. Because there have been a number of other SGLT2 inhibitors approved, it is unlikely that an Advisory Committee meeting would be needed. However, if any issues arose with our drug, such as an unexpected safety signal that confounds the risk-benefit balance, an Advisory Committee meeting might be possible. It is important to understand that, although the Advisory Committees provide recommendations to FDA, FDA makes the final decisions."

FDA Review Results

"Let's look ahead to the end of FDA's review and the all-important decision," Roberts suggested.

She described the two types of letters the company could expect to receive from FDA:

- **Approval letter.** The best-case scenario is to receive an approval letter. This letter includes the final Package Insert and details about any required post-approval activities, such as a REMS or a postmarketing requirement. Once you receive this letter, you may market your drug. You can find examples of approval letters at Drugs@FDA.
- **Complete response (CR) letter (letter is not public).** The other possibility is to receive a complete response letter. This letter means that the FDA has not approved the drug during that review cycle. The letter details the reasons why FDA did not approve the application and what the company needs to do to resolve the issues that prevented approval. The deficiencies could range from an easy-to-fix manufacturing issue to a request for an additional clinical trial. When you submit data to address the issues, the application must be resubmitted and the submission initiates a new review cycle.[12]

"So even if you fail to get approval the first time, you have an opportunity to take corrective action and try again," Soto observed.

"As long as you still have funding," Green said.

"That's true," Roberts replied. "It becomes a business decision for the company and its investors."

[12]The complete response letter regulation 21 CFR Part 314.110.

Expedited Review Programs

"I have heard that the drug development process can be sped up sometimes. With our initial promising results, is there any way that could be done with lowagliflozin?" Green asked.

"FDA has four programs intended to expedite the review of new drugs to address unmet medical needs for serious or life-threatening conditions. These programs exist to get therapies for serious conditions approved and available to patients as soon as it is apparent that the benefits justify the risks," Roberts explained. "FDA makes the final designation determination."

Two Criteria: Unmet Medical Need and a Serious Condition

"While all four options are different, the common link is an effort to address an unmet medical need in the treatment of a serious condition." Roberts advised. "While the FDA encourages companies to communicate early in the process about their intention to apply for one of these programs, you should know that you have to offer strong evidence to show you meet these criteria. You can find out more about the requirements in the FDA's Guidance document. (Appendix C12)

All of my clients ask about the expedited programs, so I prepared this summary table. This information is from FDA's Guidance on Expedited Programs," Roberts said as she pulled a document from a folder. (Table 2)

Table 2: Summary Descriptions of Expedited Programs

Expedited Programs	Summary Descriptions of Drugs Eligible for Expedited Review
1. Fast Track Designation	✓ A drug intended to treat a serious condition, and clinical or nonclinical data demonstrate it has the potential to address an unmet medical need ✓ A qualified infectious disease product
2. Breakthrough Therapy Designation	✓ A drug intended to treat a serious condition, and preliminary clinical evidence shows the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies
3. Accelerated Approval Pathway	✓ A drug that treats a serious condition and generally provides a meaningful advantage over available therapies The drug demonstrates an effect on: ▪ A surrogate endpoint that is reasonably likely to predict a clinical benefit, or ▪ A clinical endpoint that can be measured before irreversible morbidity or mortality (IMM), or ▪ The drug is reasonably likely to predict an effect on IMM or on an intermediate clinical endpoint
4. Priority Review Designation	✓ An application (original or efficacy supplement) for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness ✓ Any supplement that proposes a labeling change related to pediatric studies ✓ An application for a drug that has been designated as a qualified infectious disease product ✓ Any application or supplement for a drug submitted with a priority review voucher

Recap: Meetings and Communications with FDA

As Green examined the summary table she asked, "Before we continue, can we review the various meetings and other opportunities to get feedback and advice from FDA?"

Roberts answered, "That's a good idea. There is an entire Guidance document devoted to meetings. (Appendix C2) But, in general, there are three types of meetings a company can request, depending on the urgency of the issue and the impact on the development of the drug. The meetings are classified as Type A, Type B, or Type C."

Roberts described the three major types of FDA meetings:

- **Type A meetings** are held to help restart a stalled development program. For example, you can use a Type A meeting to discuss and resolve responses to a clinical hold. The FDA will schedule a Type A meeting to occur within 30 days of receipt of a company's written request for the meeting.
- **Type B meetings** are the milestone advice meetings, including EOP2 and pre-NDA meetings. These are not urgent, so they feature a different timeline. The FDA will schedule a Type B meeting to occur within 60 days of receipt of a company's written request for the meeting.
- **Type C meetings** are any meeting other than a Type A or Type B meeting between FDA and a sponsor regarding the development and review of a product. The FDA will schedule a Type C meeting to occur within 75 days of receipt of a company's written request for the meeting.

"These meetings offer a lot of possibilities for interaction," said Green. "But we are a small company. How can we obtain FDA preliminary thoughts while our application is under review?

Roberts replied, "That's a good question and one many companies face. Let me tell you about an interesting meeting opportunity."

The Late-Cycle Meeting

"Companies may now meet with FDA in what is called a late-cycle meeting near the end of FDA's review cycle. This meeting is required for all drug applications covered by the 2012 renewal of the Prescription Drug User Fee Act Program," Roberts reported. "In addition, a mid-cycle meeting is also required. The meetings give your company the chance to discuss the status of your application with the review team, any major deficiencies in your application, the possible need for a REMS, FDA's information needs, any major issues related to the proposed labeling, and the status of any inspections."

Green said, "It sounds like we will gather valuable information in those meetings."

Summary of Meetings

Both women looked over as they noticed Soto drawing a large box on the whiteboard. "What are you creating?" Green asked.

"I want to make a reference table of these meeting opportunities," he answered.

"Great idea," Roberts agreed, "Let's recap and document it all in one place."

Soto drew the table, as Roberts and Green called out the necessary information. (Table 3)

Post-Approval Activities, Postmarketing Requirements, and Postmarketing Commitments

After Soto rejoined them at the conference table, Roberts said, "After lowagliflozin gets approved, the company will continue to file safety reports.[13] There is a

[13]Safety reporting requirements for sponsors and investigators on human drug and biological products that are being investigated under an investigational new drug application (IND) can be found in the regulations and at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm227351.pdf

Table 3: FDA and Sponsor Meeting Opportunities

Meetings	When Held
End-of-Phase 2A Meeting (EOP2A)	After the completion of clinical trials that provide data on the relationship of dosing and response for the intended use
End-of-Phase 2 Meeting (EOP2)	After Phases 1 and 2 are complete, but before the start of Phase 3 trials
Pre-NDA Meeting	After Phase 3, but before submission of the NDA
Mid-Cycle Meeting	By month 5 for PDUFA Program and standard reviews, by month 3 for priority reviews
Late-Cycle Meeting	Generally no later than 3 months prior to the review's goal date for a standard review
Type A Meetings	A company may request this meeting to help restart a stalled development program
Type B Meetings	The milestone advice meetings, including EOP2 and Pre-NDA
Type C Meetings	Any other type of meeting held between a company and FDA

continuing obligation to report any new safety information that arises after the FDA approves a drug for marketing. Postmarket studies or clinical trials may be required to assess a known serious risk, signals of a serious risk; or the potential for an unexpected serious risk related to the use of the drug; detect new uses for the product; and determine the effectiveness of the labeled indications under conditions of widespread use. But we will cross that bridge when we get there!"

"Before we wrap up, I wanted to let you know that FDA created an infographic[14] that displays many of the steps and activities we discussed today. I'll send you the link; you may find it helpful when you review your meeting notes," Roberts said.

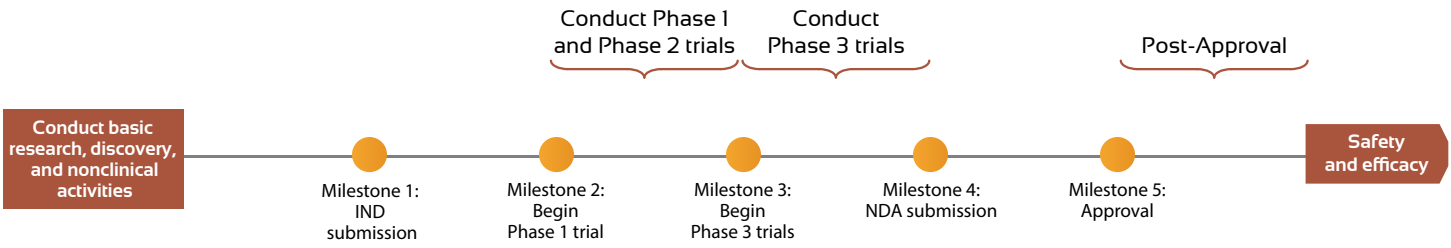
She stood, selected a marker, and finished the path they had created during their meeting. (Exhibit 7) Turning, she announced with a smile, "It's time to start the path towards approval. Let's open our calendars and choose a day to meet about your IND preparation."

Disclaimer: The information in this case study is accurate as of September 2015. Processes occasionally change. Contact FDA with any specific questions.

This case study was prepared by Francis Kalush, Ph.D.; Naomi Lowy, M.D.; and John Whyte, M.D.

[14] FDA Drug Approval Process Infographic.

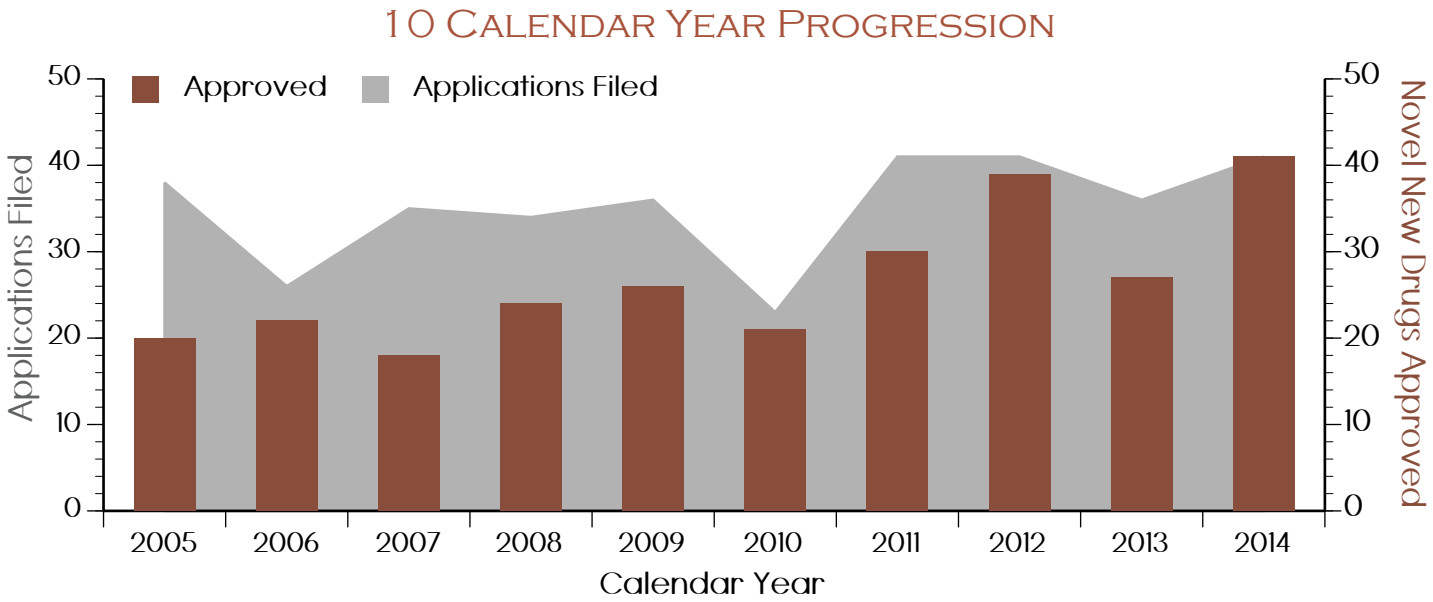
Exhibit 7. Milestone 5



APPENDIX A: AVAILABLE THERAPIES FOR TYPE 2 DIABETES

1. Sulfonylurea: Glimepiride, Glyburide, Glipizide, Chlorpropamide
2. Biguanide: Metformin
3. Meglitinide: Repaglinide, Nateglinide
4. Thiazolidinedione: Pioglitazone, Rosiglitazone
5. DPP-4 Inhibitor: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
6. Alpha-Glucosidase Inhibitor: Acarbose, Miglitol
7. Synthetic Amylin: Pramlintide
8. Insulin: NPH, Detemir, Glargine, Pre-mixed, Regular, Lispro, Aspart, Glulisine, Afrezza
9. Bile Acid Sequestrant: Colesevelam
10. GLP-1 Receptor Agonist: Exenatide, Exenatide LAR, Liraglutide, Albiglutide, Dulaglutide
11. SGLT2 Inhibitor: Canagliflozin, Dapagliflozin, Empagliflozin
12. Bromocriptine

APPENDIX B: NUMBER OF NOVEL NEW DRUGS APPROVED AND APPLICATIONS FILED



Notes: The 2014 filed numbers include those filed in CY 2014 plus those currently pending filing (i.e., within their 60-day filing period) in CY 2014; Receipts that received a "Refuse to File" (RTF) or "Withdrawn before Filing" (WF) identifier are excluded.

Source: 2014 Novel New Drugs Summary
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf

APPENDIX C: REFERENCE LIST OF FDA GUIDANCE DOCUMENTS MENTIONED IN CASE STUDY

1. **Nonclinical Safety Studies**

   Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)

   http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

   Also see:

   http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292340.pdf2

2. **Meetings with FDA**

   Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants

   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

3. **IND Applications**

   Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071597.pdf

Guidance for Industry: INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf

4. **Quality-Related Guidance Documents**

   A sortable list of the International Conference on Harmonisation—Quality Guidance Documents

   http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm

   A sortable table of Pharmaceutical Quality/CMC Guidances

   http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm

   A sortable listing of Pharmaceutical Quality/Manufacturing Standards (cGMP) Guidances

   http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm

   A sortable listing of Pharmaceutical Quality/Microbiology Guidances

   http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064983.htm

   Drug Applications and Current Good Manufacturing Practice (cGMP) Regulations

   http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm

5. **Informed Consent**

   (DRAFT FDA document) Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors

   http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm

6. **How to Comply with the Pediatric Research Equity Act**

   http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.Pdf

7. **Special Protocol Assessments**

   Guidance for Industry: Special Protocol Assessment

   http://www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf

8. **Assessing the Clinical Safety of Drugs for Long-Term Treatment**

   ICH E1—The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions E1

   http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

9. **Clinical Trials and Effectiveness**

   Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

   http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

10. **Cardiovascular Endpoints Committees**

    Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

    http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

11. **NDA Fees and Fee Waivers**

    Guidance for Industry: User Fee Waivers, Reductions, and Refunds for Drug and Biological Products

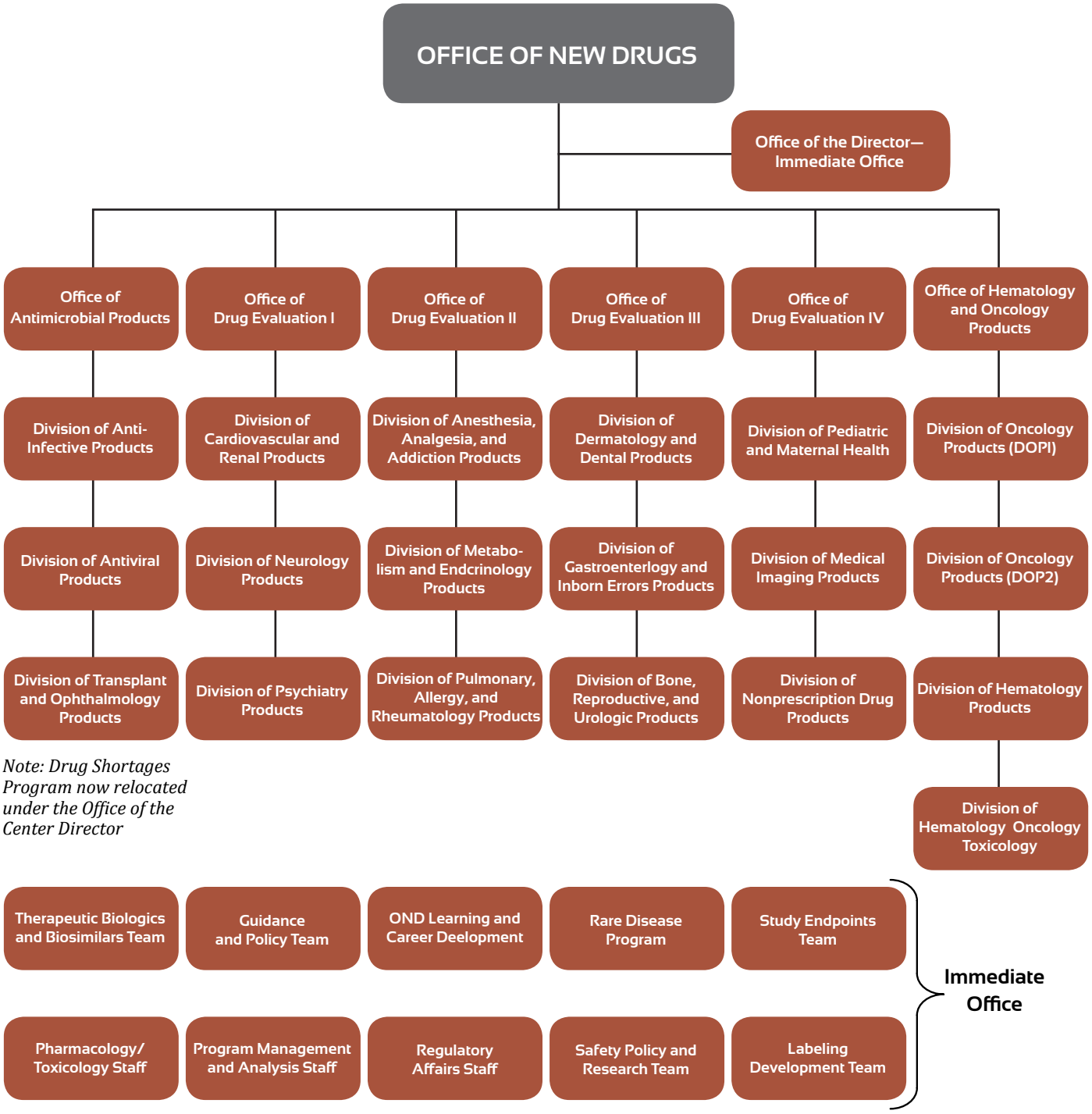
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079298.pdf

12. **Expedited Programs**

    Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics

    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

APPENDIX D: CDER'S OFFICE OF NEW DRUGS ORGANIZATIONAL CHART



Note: Drug Shortages Program now relocated under the Office of the Center Director

APPENDIX E: APPROVAL PATHWAYS FOR NEW DRUG APPLICATIONS

505(b)(1) Standard New Drug Application Approval Pathway	505(b)(2) Rapid New Drug Application Approval Pathway	505(j) Abbreviated New Drug Application (ANDA) (for generics)
An application containing full reports of investigations of safety and effectiveness conducted by the applicant.	An application containing full reports of investigations of safety and effectiveness. But some of the information required for approval is obtained from studies conducted by other entities for drugs already approved by the FDA.	An application containing information that shows the proposed product—a generic form of an existing drug— is as equally safe and effective as the existing drug.

Federal Food, Drug, and Cosmetic Act Sec. 505 (21 U.S.C. 355)

GLOSSARY

Adverse event: An unintended, harmful medical effect in a human subject, including any abnormal sign (for example, an abnormal physical exam or laboratory finding), symptom, or disease. The effect occurs while the subject participates in the research, but it may or may not be caused by the research treatment.

Approval letter: An official communication from FDA to a New Drug Application (NDA) sponsor that allows the commercial marketing of the product.

Biological products: Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources—human, animal, or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and they may be used to treat a variety of medical conditions for which no other treatments are available.

Biologics License Application (BLA): The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR Part 600–680.

Clinical investigators: Professionals, generally physicians, who oversee the administration of an experimental compound during clinical trials or studies.

Complete response letter: An official communication from FDA to the sponsor of a New Drug Application to inform the sponsor that the review period for a drug is complete, but the application is not yet ready for approval. The letter will describe specific deficiencies and, when possible, will outline recommended actions the applicant may take to gain approval.

Controlled trials or studies: Investigations that compare a test article—a drug, for example—with a treatment that has known effects. The control group may receive no treatment, active treatment, placebo, or dose comparison concurrent control.

NOTE: For further information on "adequate and well-controlled study" see regulation 21 CFR Part 314.126.

Effectiveness: The desired measure of a drug's influence on a disease or condition as demonstrated by substantial evidence from adequate and well-controlled investigations.

Efficacy: The capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness (and patient population) for which it is designed.

Guidance: Documents that represent the FDA's current thinking on a particular subject. They are not binding on FDA or users except as stated.

Indication or indications: A particular aspect of a disease/medical condition for which the drug is safe and effective.

Informed consent: A process that provides research subjects with explanations to help them make educated decisions about starting or continuing participation in a research study or trial. Informed consent is an ongoing, interactive process. It does not waive the subject's legal rights, and it does not release the investigator or sponsor from liability for negligence.

Institutional Review Board (IRB): A group of medical, scientific, and non-scientific members formally designated to review and monitor biomedical research involving human subjects. The purpose of the IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of human subjects. Under FDA regulations, an IRB has the authority to approve, require modifications of, or disapprove research.

In vitro: Latin term meaning "in glass." An *in vitro* test is one that is done in glass or plastic vessels in the laboratory. *In vitro* is the opposite of *in vivo*.

In vivo: Latin term meaning "in a living organism." For example, an experiment that is done *in vivo* is done in the body of a living organism. *In vivo* is the opposite of *in vitro*.

Label: The official description of a drug product often found inside the drug product's packaging. The FDA-approved label includes indication(s) (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient.

Life-threatening: Any adverse drug event that places the patient or subject, in the view of the investigator, at immediate risk of death from a reaction as it occurs (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

New Drug Application (NDA): A formal request to FDA for a license to market a new drug in the United States. When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits an NDA to FDA. The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDAs are assigned an NDA number.

New safety information: Facts and data about a serious risk or unexpected serious risk associated with use of a drug since the drug was approved, since a risk evaluation and mitigation strategy (REMS) was required, or since the REMS was last assessed.

Nonclinical: A stage of research that evaluates a drug's toxic and pharmacologic effects through *in vitro* tests and *in vivo* laboratory animal testing.

Phase 1: The initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. Phase 1 studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness.

Phase 2: Clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study. They are also used to determine the common short-term side effects and risks associated with the drug.

Phase 2A: Clinical studies that occur after the completion of Phase 1 studies and the first set of exposure-response studies in patients. They are conducted before the Phase 2B (i.e., patient dose-ranging trial) and Phase 3 clinical efficacy-safety studies.

Phase 3: These studies are expanded controlled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained. Phase 3 studies are intended to demonstrate effectiveness and safety in a clinically and statistically meaningful way to confirm the drug's efficacy and evaluate the overall benefit/risk relationship of the drug. The Phase 3 findings also provide an adequate basis for the physician labeling.

Post-approval studies and trials, investigations that occur after drug approval: Studies that occur after FDA approves a drug to determine additional information about the drug's risks, benefits, manufacturing, and optimal use. These studies may be required or requested by FDA in conjunction with the marketing approval.

Prescription drug: Drug products that require a doctor's authorization to purchase.

Protocol or protocols: A written description of what researchers plan to do during a clinical study.

Risk: The probability of harm or discomfort for subjects in a clinical trial.

Safety: Risks that are acceptable in relation to the observed benefit for the indication. Relative freedom from harm. Safety may be assessed by laboratory testing of biological samples, special tests and procedures, psychiatric evaluation, and/or physical examination of the research subjects.

Sponsor: Sponsors may include physicians, foundations, medical institutions, voluntary groups, and pharmaceutical companies, as well as Federal agencies such as the National Institutes of Health, FDA, the Department of Defense, and the Department of Veterans Affairs that conduct and oversee research.

Type 2 diabetes: Type 2 diabetes mellitus is characterized by hyperglycemia and results from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion.

STUDENT ACTIVITIES

LEARNING OBJECTIVES FOR THE CASE STUDY

1. State the objectives of the drug development and approval process.
2. Identify the major activities that occur during the drug development and approval process from nonclinical tests through approval from the U.S. Food and Drug Administration (FDA).
3. Describe the major elements and steps to conduct a clinical trial.
4. Apply the drug approval process to a fictional New Molecular Entity (NME) diabetes drug.

Topics: Regulatory pathways, drug approval process, drug development, protection of human subjects

ASSUMPTIONS

- Target audience consists of medical, pharmacy, and nursing students who have no experience with drug development and approval processes.
- Students are expected to work on the case before, during, and after class.
- Users of the case study are instructors who may have some knowledge of the FDA and its website.
- Instructors have 1–2 class sessions to cover the materials involved in the case study.

SUGGESTED INSTRUCTIONAL APPROACH

- **Preparing Students:** Ask students to read the case study before class. Recommend that they scan or review the other suggested materials listed below.
- **Engaging Students:** During the session, use the discussion questions below to review and emphasize the major points of the case study.
- **Immersing Students:** Choose an application exercise for your class. There are several shorter activity options and one longer option listed below.

REVIEW THE FOLLOWING MATERIALS BEFORE THE SESSION:

1. Mandatory Reading
   a. Drug Approval Case Study
2. Optional Viewing and Reading
   a. FDA Video—JumpStarting Drug Review
      http://www.fda.gov/drugs/resourcesforyou/consumers/ucm397921.htm
   b. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
      http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm
   c. FDA Drug Approval Process Infographic
      http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf

QUESTIONS FOR CLASS DISCUSSION

1. What are the milestones in the drug development and approval process?
2. Why is informed consent required for people participating in clinical studies?
3. What is the role of an IRB?
4. What types of nonclinical and clinical tests are completed before submission of a New Drug Application?

5. How are adverse events reported to FDA?
6. What are some of the benefits of meeting with FDA during the drug development and approval process?
7. What are the two available FDA review timelines for new drugs and biologics, and what is the difference between them?
8. List the four expedited drug development and review programs. What do they share in common?
9. What is the role of an Advisory Committee in the drug approval process?
10. Apply the drug development and approval processes to a diabetes drug:
    a. What specific health risk needs to be addressed when developing a diabetes drug?

       How are sponsors supposed to mitigate this risk?
    b. What is the primary efficacy endpoint a diabetes drug must demonstrate at the end of Phase 3 trials?

       Why was this endpoint chosen?
    c. Why is it unlikely for this fictional diabetes drug to be granted an expedited review by FDA?

APPLICATION: STUDENT ACTIVITIES

Pre-Activity: Check Your Understanding (Answers are located after the activities)

1. *True or false?* The main objective of the drug approval process is to demonstrate the safety of a drug.
2. *True or false?* The majority of new drugs being developed will not be approved by FDA for marketing in the United States.
3. *True or false?* A drug intended for type 2 diabetes will likely be eligible for the FDA's expedited review.
4. *True or false?* All drugs for type 2 diabetes need a REMS.
5. *True or false?* The advisory committee provides recommendations to FDA, and FDA makes the final decision.
6. *True or false?* Secondary clinical trial endpoints are the endpoints for which subjects are randomized and for which the trial is powered.

Shorter Activity Options (For small groups or solo work)

1. STEM Presentation

   You have been asked to develop a short presentation about the drug development and approval process for high school students attending a STEM (science, technology, engineering, and mathematics) conference. You will have 15 minutes to explain the process.

   - Create a topic outline for the presentation.

2. Next Steps for Dr. Green

   Dr. Green returns to her office after the meeting with Dr. Roberts.

   - List at least four tasks she adds to her to-do list based on her meeting with Dr. Roberts.
   - Explain your choices.

3. Patient Counseling

   A patient—who has struggled to manage his type 2 diabetes—shows you an article about a promising new drug for type 2 diabetes. He asks you why the drug is not available yet. You have 10 minutes to answer him.

   - What do you tell him? List at least three main points you want to convey.

Longer Activity: Mock Company

Ask students to form small groups.

Each group will represent a company and complete these tasks:

1. Choose the company's new drug:
   - Drug A: a new drug for asthma management OR
   - Drug B: a new drug for melanoma treatment
2. Suggest the best FDA review option for your drug to your investors and justify this option.
3. Explain how your company will determine that the drug is reasonably safe and effective.
4. List your company's reporting and meeting obligations to FDA during the different phases of drug development.
5. Identify three types of information your company must include in your proposed Package Insert.
6. Share at least two lessons learned during this exercise.

Post-Activity: Check Your Understanding

1. *True or false?* The main objective of the drug approval process is to demonstrate the safety of a drug.

   False: The objective of the drug approval process is to demonstrate both the safety and efficacy of the drug.

2. *True or false?* The majority of new drugs being developed will not be approved by FDA for marketing in the United States.

   True: Most potential new drugs fail to demonstrate safety and/or efficacy at some point in the drug development process: nonclinical studies, clinical studies, or FDA review.

3. *True or false?* A drug intended for type 2 diabetes will likely be eligible for the FDA's expedited review.

   False: FDA's expedited review programs are intended for drugs that address unmet medical needs for serious or life-threatening conditions. These programs exist to get therapies for serious conditions approved and available to patients as soon as it is apparent that the benefits justify the risks. The drug developer must offer strong evidence to show the new drug meets these criteria. Because there are multiple drugs available for the treatment of type 2 diabetes, it would be difficult to establish a case for an expedited review.

4. *True or false?* All drugs for type 2 diabetes need a REMS.

   False: None of the SGLT2 inhibitors have a REMS at this time, but there are REMS in place for other type 2 diabetes therapies.

5. *True or false?* The advisory committee provides recommendations to FDA, and FDA makes the final decision.

   True: FDA always make the final decision on drug approval.

6. *True or false?* Secondary clinical trial endpoints are the endpoints for which subjects are randomized and for which the trial is powered.

   False: The primary endpoint of a clinical trial is the endpoint for which subjects are randomized and for which the trial is powered. It is the outcome to evaluate the effectiveness of treatments in a clinical trial. Secondary endpoints are endpoints that can be used to explore other important aspects of an intervention for which the trial may not be powered nor randomized.