HSC 335 -- Pharmaceutical Policy (Fall 2020)

Week 3 Questions

Deadline: September 10, 2020 at 2:45pm (submit via Slack DM)

Name:

Introduction to Drug Development

Question 1

Since the early 1960s, there has been an overall upward trend in the number of new drugs approved annually.

☐ True

☐ False

The Process of Developing Drugs

Where does drug innovation come from? Despite the widespread belief that innovative drugs originate in the biotechnology or pharmaceutical manufacturers that produce them, the truth is more complicated. In the following video, we review the drug development process and the relative contributions of publicly-funded research -- often based in academic institutions -- and industry-based development. Questions to consider include:

- What are the stages of drug development? In what kinds of settings does each occur?
- Why is it important to understand the nature of the various contributions to drug development?

Question 2

Place the following in the order that they typically occur during the process of drug development.

☐ Translational research, Clinical trials, Basic science research

☐ Basic science research, Translational research, Clinical trials

☐ Basic science research, Clinical trials, Translational research

Question 3

"Translational Research" is best defined as:

- [ ] Research that converts basic science insights into practical applications.
- [ ] Research that translates objectives in grant applications into basic science findings.
- [ ] Research that seeks to uncover the best practices for translating foreign language studies into English.
- [ ] Research that studies new uses for existing, FDA-approved drugs.

Question 4

Large pharmaceutical manufacturers typically spend a greater fraction of their revenues on novel drug research and development than they spend on marketing and administration.

- [ ] True
- [ ] False

Funding Drug Development

In the previous video, we reviewed the different contributors to the drug development process. Next, we'll consider how innovative scientific discoveries that lead to drug development are funded and commercialized. A key law influencing these processes is the Bayh-Dole act. As you watch, think about how well the Bayh-Dole Act appears to function on some important parameters, such as efficiency in moving important discoveries forward, equity in assigning credit, and public health needs for new treatments. Consider:

- Do the main provisions of the Act seem reasonable? Do you think that it is used appropriately?
- How do manufacturers represent the cost of drug development? Do these estimates reflect true costs?

Question 5

Under US patent law, it is easier to patent natural phenomena, such as newly discovered biochemical pathways, than specific molecules targeting those pathways.

- [ ] True
- [ ] False

Question 6

The 1980 Bayh-Dole Act did which of the following? (Select all that apply.)

- [ ] Allowed researchers at universities to maintain control of patents arising from public funding to them.
- [ ] Granted the federal government the exclusive right to control any patents arising from federally funded research.
- [ ] Gave the federal government the ability to step in and issue a new license relating to a patent when an existing licensee does not move the technology forward.
- [ ] Redefined which biological molecules and methods discovered in academic research institutes were eligible for patents.

Question 7

Fortune 500 pharmaceutical companies have similar profit margins to the Fortune 500 average.

- [ ] True
- [ ] False

An Overview of Drug Development

The drug development process begins with basic science research, which provides scientists with an understanding of how a new potential drug works, and if it might be used to treat disease. The most promising drug candidates are then tested in humans in clinical trials. In this video, we will introduce the key drug development steps before we take a more in-depth look at clinical trials and FDA review.

(No questions associated with this video)

Clinical Trials

Translational and product development research can turn basic science discoveries into drugs to treat disease. To determine that investigational drugs are safe and effective in humans, they must proceed through clinical trials. As you watch the following video, focus on the different phases of clinical trials and the characteristics of the drug that each phase tests.

- Which phase(s) of clinical trials determine if a drug is safe for use? How?
- Which phase(s) of clinical trials determine if a drug is effective? How?

Question 8

Which term best matches each description? (A - E)

_____ Clinical trials that occur after a drug has been approved	A. IND
_____ Testing of a drug's pharmacokinetics and pharmacodynamics usually in a sample of 20 or so healthy adults	B. Phase I
_____ Trials of a drug usually featuring randomization and concurrent control groups that leads to information about the drug's efficacy and safety at the dosing regimen(s) intended for widespread use	C. Phase II
_____ The application to start clinical trials for a chemical or biological compound believed to have clinical value for a particular disease or condition	D. Phase III
_____ Early studies of a drug in patients with the disease or condition intended to be treated	E. Phase IV

Question 9

If a company submits an Investigational New Drug (IND) application and receives no response from the FDA within 30 days, the company may begin clinical trials.

☐ True

☐ False

Drug Approval Standards

What happens when a drug is ready for FDA review? The drug sponsor will submit data that it has gathered relating to the drug's safety and efficacy, and FDA evaluates these data to determine whether the benefits outweigh the risks. As you watch the video, think about what you would consider if you were evaluating a drug for approval and how it might overlap with—or be different from—the FDA's approach.

Question 10

For which of the following reasons can the FDA deny approval of a New Drug Application (NDA) for a drug treating diabetes? Indicate all that apply.

☐ The NDA fails to present substantial evidence of effectiveness.

☐ The NDA demonstrates that the drug is unsafe.

☐ The NDA fails to specify a reasonable price in light of the drug's therapeutic value.

☐ A similar product has already been approved by a different manufacturer for the same indication.

Question 11

FDA approval of a new drug for a certain condition means which of the following? Indicate all that apply.

- [ ] The drug has therapeutic benefit over the current standard of care for that condition.
- [ ] The drug sponsor can sell the drug for use in patients.
- [ ] The FDA has determined that the drug's benefits outweigh its risks for that condition.
- [ ] The drug has undergone Phase III testing with a placebo control.

Question 12

Manufacturers are **required** to have a minimum of two Phase III trials to receive FDA approval.

- [ ] True
- [ ] False

Criteria for Evaluation

What sources generate the data that the FDA uses to evaluate drugs? The FDA reviews data submitted by a drug sponsor and labels the most critical studies as "pivotal trials," but the characteristics of pivotal trials can vary greatly among different drugs. As you watch the following video, consider how clinical trials are performed, and how they can be designed to be optimally useful by the FDA. In particular, ask yourselves:

- What are the key pieces of information that emerge from a pivotal trial?
- Why are randomized controlled trials considered to be the gold standard? What are the alternatives?

Question 13

Which of the following, by itself, could qualify as a pivotal trial for an investigational drug, leading to FDA approval?

- [ ] A case series.
- [ ] A phase 2 trial that is neither randomized nor blinded.
- [ ] A phase 3 trial that is randomized, controlled, and blinded but that does not demonstrate benefits outweighing the risks of treatment with the drug.

Question 14

For purposes of FDA review, surrogate measures can be used to establish sufficient drug efficacy instead of clinical endpoints.

☐ True

☐ False

Question 15

Indicate which of the following would be considered a clinical endpoint (A) and which would be considered a surrogate measure (B). (Enter A or B)

_____ Reduction in cholesterol level, for a drug to treat heart disease

_____ A diagnosis of AIDS, for a drug to treat HIV

_____ Tumor size after 30 and 90 days of treatment, for a drug to treat liver cancer

_____ Survival, for a drug to treat prostate cancer

_____ The amount of time it takes for an infection to clear, for a new antibiotic

Timeline for Drug Development and Review

The FDA's speed is a frequent point of public debate. In the modern era, the FDA is one of the fastest drug regulatory agencies in the world. Still, drug development requires years of pre-clinical research and clinical trials prior to submission of a new drug application to the FDA. By contrast, unnecessarily truncating pre-approval clinical testing or shortening the FDA review time also has its risks. As you watch the following video, consider:

- Why have FDA review times been shortening in recent years?
- What are the benefits of approving drugs quickly? What are the risks?

Question 16

On average, the modern FDA approves small molecule drugs more slowly than the European Medicines Agency.

☐ True

☐ False

Question 17

The average time from the beginning of clinical trials to drug approval is:

- [ ] about 7 months
- [ ] about 17 months
- [ ] about 7 years
- [ ] about 27 years

Question 18

Of drugs that enter clinical trials, about ___% are eventually approved.

- [ ] 10
- [ ] 50
- [ ] 75
- [ ] 90

Question 19

In recent years, what percent of new drug applications that are approved earn their approval after their first FDA review (as opposed to needing multiple cycles of review)?

- [ ] 5%
- [ ] 10%
- [ ] 25%
- [ ] 95%

Clinical Trial Design

Now that we have provided an overview of the drug development and approval processes, the next step is to take a closer look at the characteristics of clinical trials. Joining us to lead this discussion is Dr. Jerry Avorn, the Chief Emeritus of the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham and Women's Hospital, an internist, and a professor of medicine at Harvard Medical School. Dr. Avorn address such questions as:

- In the context of clinical trials, what do "randomization," "control," and "double-blind" mean?
- What are the placebo and nocebo effects?

Question 20

Select the term that best matches each description (in the context of clinical trials):

_____The process by which each research participant gets an equal pre-specified chance of being assigned to one arm of the trial (i.e., the control vs. the experimental arm). _____ When a patient reports side effects based on the subject's belief that an intervention is causing harm, when in fact the intervention is a sugar pill that is actually doing nothing. _____ A separate group of people to which research participants receiving a study drug are compared. _____ When a patient reports clinical improvement based on the subject's belief that an intervention is helping, when in fact the intervention is a sugar pill that is actually doing nothing. _____ Neither the investigator nor the research participant is aware who gets the experimental drug.	A. Randomization B. Control C. Double-Blinding D. Placebo Effect E. Nocebo Effect

Question 21

Which of the following statements is true?

☐ Historical controls and concurrent (in-trial) controls are both acceptable for trials demonstrating efficacy to the FDA.

☐ Surrogate measures of efficacy cannot be used in pivotal trials for FDA approval.

☐ Surrogate measures of efficacy must be correlated with clinical outcomes before they can be used in pivotal trials for FDA approval.

☐ The FDA requires Phase III trials to be blinded if they are to be used to support drug approval.

Strengths and Limitations of Clinical Trials

How does the testing of drugs during clinical trials compare with the use of those drugs in routine practice after FDA approval? While clinical trials can answer important questions about a drug's efficacy and safety, there are also many reasons why a drug might have differing effects on patients during the routine practice of medicine. Consider these factors as you watch the following video:

- How are the patients in clinical trials different from those who take a drug during routine care?
- How do patient monitoring and protocol adherence in clinical trials compare to the supervision provided for a drug's use during routine care?

Question 22

Which of these is/are generally true of patients who enroll in pre-approval clinical trials of investigational drugs as compared to the population who will ultimately take the drug after it receives FDA approval? Indicate all that apply.

☐ They are often younger.

☐ They are often healthier.

☐ They tend to have more comorbidities.

☐ They are of lower socioeconomic status.

Question 23

Which of these is/are different between clinical trials and routine clinical care? Indicate all that apply.

☐ Clinical trials generally enroll volunteers.

☐ Routine clinical care is often less chaotic than the clinical trial setting.

☐ Clinical trial participants are more closely monitored than patients in routine clinical care.

☐ Clinical trial volunteers are not reminded to take medications, while patients in routine clinical care are often reminded to take their medications.

Question 24

Some drugs that are intended for lifetime use are approved on the basis of clinical trials lasting weeks to months.

☐ True

☐ False

Moving Drugs from Trial to Clinic

When a drug transitions to widespread use after FDA approval, there are many reasons to continue to actively monitor how the drug works and its safety profile. This is in part because several of the factors that we have discussed previously – the durations of clinical trials, the use of surrogate measures, etc. – may limit the effectiveness of a drug that appeared to have efficacy in a clinical trial. The following video will help answer the questions:

- Most drugs are tested for weeks or months before approval, yet many of these drugs may be prescribed in patients for years after approval. What are the implications of prolonging a patient's exposure to a drug beyond the length of the pre-approval clinical trial?
- What is important to understand about surrogate measures and their correspondence to patient outcomes?
- Why do patients with more complex medical needs respond to drugs differently?

Question 25

Match the term with its definition (A or B):

_____ Efficacy

_____ Effectiveness

A. How well a drug performs in a clinical trial.

B. How well a drug performs in a typical patient population.

Question 26

Indicate which characteristic is more closely related to placebo-controlled trials and which is more closely related to the use of surrogate measures.

_____ Placebo-controlled trials

_____ Surrogate measures

A. More rapid approval of drugs

B. Absence of comparison with current standards of care

Question 27

Would you prefer a drug that was compared to a placebo or one that was compared to existing standards of care? Discuss the reasons behind your choice.

Please also cut and paste your answer to this question into the appropriate section of the #discussion channel on Slack and comment on at least two other student responses.

☐ Click the checkbox to confirm you've posted and commented on Slack.

Addressing Challenges with Creative Solutions

In the previous video, Dr. Avorn discussed the diabetes drug rosiglitazone (Avandia), which effectively lowered patients' blood sugar levels in clinical trials, an outcome thought to help protect patients with diabetes from adverse clinical outcomes such as heart disease. However, larger testing showed that rosiglitazone actually led to an increase in heart attacks among patients who were taking it. This result revealed a significant divergence between the surrogate measure (blood sugar levels) and the real clinical result (heart disease). As you watch the next video, consider how different evaluation protocols might reveal things that standard clinical trials might miss, and ask yourselves:

- What might be the mechanisms behind such an unexpected turn of events?
- How can the FDA avoid problems like this in the future?

Question 28

Comparative effectiveness studies are required for FDA drug approval.

☐ True

☐ False

Question 29

A pragmatic clinical trial seeks to test an intervention during circumstances mirroring routine clinical care.

☐ True

☐ False