HSC 335 -- Pharmaceutical Policy (Fall 2020)

Week 4 Questions

Deadline: September 17, 2020 at 2:45pm (submit via Slack DM)

Name:

Benefits and Risks of Alternative Approval Pathways

On average, it takes about 7-8 years for a drug to proceed through clinical trials and FDA approval. What happens during this time? In this video, we'll start to review issues such as whether this time can be shortened and what the FDA's role might be in reducing the clinical trial time. In particular, we will ask:

- What are the benefits of accelerating drug approval?
- What are the risks of approving drugs on an expedited pathway?

Question 1

Success in early-phase clinical trials is a reliable predictor of a drug's ability to improve patient outcomes.

☐ True

☐ False

Question 2

Indicate whether each of the following is a (A) benefit or (B) drawback of expedited drug approval:

_____ Shorter development time may be associated with lower development costs.

_____ Drugs can turn out to offer less therapeutic benefit to patients than initially perceived.

_____ Patients can access promising medicines sooner.

_____ Patients are exposed to risks that are less well-characterized.

Orphan Drugs, Fast Track, and Accelerated Approval Pathways

The "Fab Five" are special designations and pathways that are designed to accelerate drug testing or approval. First, we'll consider the FDA's special pathways that have the effect of reducing the time that a company spends on drug testing or the nature of pre-approval trials, including the orphan drug designation, and the fast track, and accelerated approval pathways. Please consider:

- What are the goals of these pathways?
- How do drugs qualify for each of these pathways?
- How are baseline clinical trials modified in these pathways?

Question 3

What is an "orphan drug"?

☐ A drug approved to treat a disease that affects fewer than 200,000 people in a year in the US.

☐ A drug for which the original manufacturer cannot be identified.

☐ A drug with highly limited marketing rights.

☐ A drug that once faced competition from multiple generic competitors but is now the only version of the drug available.

Question 4

An Orphan Drug Act designation grants manufacturers which of the following? Indicate all that apply.

☐ The opportunity to earn federal grants

☐ Tax credits to offset research costs

☐ Exemption from the requirement to demonstrate efficacy.

☐ A 7-year competition-free period after approval during which no copy of the drug can be marketed by another manufacturer

Question 5

Which of the following most accurately characterizes the "fast-track" program?

☐ It encourages development of drugs for rare diseases.

☐ It expedites approval of drugs for serious diseases that lack other treatment options.

☐ It allows FDA approval to be based on a single Phase III trial that may not be placebo-controlled.

Question 6

Which of the following is a hallmark of the "accelerated approval" pathway, but not the fast-track program?

☐ The use of surrogate measures only "reasonably likely" to predict clinical benefit

☐ The need to address serious or life-threatening conditions

☐ The use of a phase II trial as the basis for initial approval

☐ Faster FDA review of the resulting drug application

Priority Review and Breakthrough Therapy Designations

The previous three pathways were designed to reduce the amount of time spend on drug development and clinical testing. Next, we'll take a look at two designations that are designed to affect the FDA regulatory process: Priority Review and Breakthrough Therapy. Consider how these special pathways compare to those that we already discussed, and:

- How did the Prescription Drug User Fee Act affect drug review times?
- How does a drug qualify for the Breakthrough Therapy designation?
- How does the Breakthrough Therapy designation affect the drug testing and approval process?

Question 7

For each of the following characteristics, indicate which designation applies:

_____ Grew out of the HIV/AIDS epidemic in the 1980s, after calls from patient advocacy groups to allow approval of drugs for life-threatening or severely debilitating diseases on the basis of a single phase II trial.

_____ This designation is based on preliminary clinical evidence of superiority over existing therapies. Sponsors can work early with the FDA to streamline the approval process through efficient design of clinical trials. In practice, this designation has been awarded to 1/3 of all new drugs, cutting the clinical development and FDA review time.

_____ The name for the pathway that cuts FDA review time to 6 months from the usual time period of 10 months.

_____ Drugs qualifying for this pathway may be approved on the basis of a surrogate measure that is only reasonably likely to predict patient benefit.

A. Orphan Drug

B. Fast Track

C. Accelerated Approval

D. Priority Review

E. Breakthrough Pathway

Question 8

For one of the 5 pathways, describe a benefit and a risk of the pathway and discuss whether or not you think the benefit outweighs the risk below:

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 one other student response.

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

Use and Consequences of Alternative Pathways

In the next video, we'll review the phenomenon of how more and more drugs are found to qualify for the FDA's expedited designations or review pathways. Accelerating the timeline for drug development and review has both positive and negative consequences. In this video, we will ask:

- What are the benefits of expedited drug development and review pathways? What are the risks?
- How do drugs approved via one of these pathways compare to drugs that go through the standard review pathway, in terms of their innovativeness, safety, and effectiveness?
- Is the exception becoming the rule?

Question 9

Use of the various expedited pathways offered by the FDA for faster development or approval of new drugs has increased over time.

☐ True

☐ False

Question 10

In recent years, the percent of new drugs qualifying for at least 1 expedited program is approximately:

- [ ] 10%
- [ ] 20%
- [ ] 30%
- [ ] 60%

Question 11

Disadvantages of expedited development and approval include (**indicate all that apply**):

- [ ] New safety risks that may have emerged in pre-approval testing are now more likely to be uncovered after approval
- [ ] Drugs may not turn out to be as effective as initially perceived
- [ ] Expanded access requests for the qualifying drugs may be less common
- [ ] Clinical trials may be less expensive

Question 12

Which of the following is true of post-approval studies?

- [ ] FDA often penalizes manufacturers that fail to complete post-approval commitments.
- [ ] Some post-approval studies have not been completed in a timely fashion.
- [ ] When new safety issues arise, FDA can quickly and easily remove the drug from the market if need be.
- [ ] Companies that do not complete post-approval studies in the prespecified time window have had their drugs removed from the market until those studies are completed.

Mini-Advisory Committee

In the final activity for this module, you will put yourself into the shoes of a member of the FDA advisory committee tasked with reviewing an application to market a new drug – a new nasal spray formulation of desmopressin. This drug would be used to treat patients with nocturia, the need to wake at night to urinate. You will compare your evaluation of the clinical trials and their results to the evaluations of your peers, as well as a mini advisory committee composed of faculty members from Harvard Medical School. This is a great opportunity for you to apply your understanding of the drug development and approval processes to a sample drug.

To summarize, here are some of the key characteristics of the clinical trials that were submitted to the FDA for approval. Most of this information is mentioned in the video, though the list of exclusion criteria here is more extensive.

Number of Trials	**Information from two trials was submitted to the FDA in the Noctiva NDA**
Basic design	Patients were randomized to receive placebo or Noctiva (high dose or low dose)
Primary endpoint	Two different endpoints were used to determine the efficacy of the drug: (1) # of episodes of nocturia after 12 wks compared to baseline (2) % of patients with a ≥50% reduction in the number of times that they woke per night to void their bladders
Inclusion Criteria	Age > 50 with 2 or more episodes of nocturia per night
Exclusion Criteria	Uncontrolled diabetes mellitus, congestive heart failure, polydipsia, uncontrolled hypertension, nephrotic syndrome, peripheral edema, history of urinary retention, neurogenic detrusor overactivity, obstructive sleep apnea, loop diuretics, glucocorticoids, and severe lower urinary tract symptoms due to benign prostatic hypertrophy, overactive bladder, or severe stress urinary incontinence
Exclusion Criteria	1707 patients with nocturia due to nocturnal polyuria (waking 2+ times per night to void their bladders)
Demographics of participants	Mean age 66, 57% male 78% Caucasian 60% had one or more causes identified for their nocturia

Question 9

Was desmopressin studied in the appropriate patient population?

☐ Yes

☐ No

Explain why you chose this answer:

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 one other student response.

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

Experts Comment on the Patient Population

Now, let's see how your reasoning compares to that of the experts. In the video below, the members of our advisory committee will share their thoughts about the patient population that was used in these clinical trials, and some concerns that they have about the drug.

(No questions associated with this video.)

Reviewing the Results

Next, it's time to review the results of the clinical trials. Let's find out what happened when patients in the trial took this new formulation of desmopressin. Was it effective in treating their nocturia?

Benefits	
Number of episodes per night	With the higher dose of desmopressin, the number of episodes of nocturia prior to treatment was 3.3 per night. This dropped to 2.1 episodes with placebo and 1.8 episodes with high-dose desmopressin. The lower dose of desmopressin showed similar results.
% of patients with a ≥50% reduction in number of episodes per night	With the higher dose desmopressin, 49% of patients achieved a reduction of at least 50% in number of nocturic episodes per night. 30% of patients in the placebo group achieved a reduction of at least 50%. With the lower dose desmopressin, the results were similar to placebo.
Time before first episode	With the higher dose desmopressin, patients went an average of 108 minutes prior to their first nocturic episode. With placebo, the first nocturic episode occurred after an average of 72 minutes.
Quality of Life	Quality of life was assessed in one trial using a questionnaire (scored from 0 to 100). This score improved by approximately 14 points in the group receiving high-dose desmopressin and approximately 12 points in the placebo group. No difference was seen between placebo and the low-dose desmopressin groups.
Risks	
Safety overall	Between the two trials, 4% patients receiving placebo had mild hyponatremia (4.6%), 10% of patients receiving the lower dose of desmopressin had hyponatremia (mild, moderate, or severe), and 14% patients receiving the higher dose of desmopressin had hyponatremia (mild, moderate, or severe).
Severe hyponatremia	5 patients receiving the higher dose of desmopressin had severe hyponatremia ($Na+ \leq 125$ mmol/L) compared to 0 patients in the lower dose and 1 patient in the placebo group
Death	5 patients receiving the higher dose of desmopressin died during the trials; three of these deaths were determined to be unrelated to the drug, while for the other two it was unclear whether or not they were related to the drug. No deaths were observed in the placebo group.

As you review the results, consider: do the benefits outweigh the risks and support approval of this drug?

Question 10

Do the benefits of desmopressin outweigh the risks and support approval?

☐ No

☐ Yes, without restrictions

☐ Yes, with restrictions

Explain why you chose this answer:

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 one other student response.

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

The Committee's Decision

Now, let's see how your reasoning compares to that of the experts. In the video below, the members of our advisory committee will discuss the results of the trials, and what they think the FDA should do. Then we'll hear about the FDA's final decision regarding this drug.

(No questions associated with this video.)

What is Hyponatremia?

Learn more about the most serious side effect identified in the clinical trials for desmopressin.

(No questions associated with this video.)

Development of Drugs to Treat Alzheimer's Disease

Alzheimer's disease is a type of dementia that affects millions of people across the globe and is the sixth leading cause of death in the US. Symptoms most often appear in those who are 60 or more years of age and include difficulty remembering new information as well as changes in thinking and behavior that are caused by damage and death of neurons in the brain. A patient's disease status can be evaluated using a set of clinical criteria known as the cognitive subscale of the Alzheimer's Disease Assessment Scale (or ADAS-cog), which is used to measure cognitive function and assess cognitive impairment. Despite the prevalence of Alzheimer's disease, limited treatments are available.

Decades of research into the causes of Alzheimer's disease have implicated the buildup of two proteins—beta-amyloid and tau—in the damage and death of neurons associated with the disease. Processing of an amyloid precursor protein produces beta-amyloid, which accumulates outside of cells to form plaques in the brain, the presence of which is associated with the disease. Reducing plaque formation has long been a focus of Alzheimer's drug development efforts, and numerous drugs to prevent buildup of beta-amyloid have been developed, tested in animals, and used in clinical trials.

Question 11

Indicate if each of the following is most likely to qualify as a surrogate measure or a clinical endpoint in a trial to test a drug to treat Alzheimer's disease.

_____ Number and size of brain plaques as visualized using positron emission tomography (PET)	A. Surrogate Measure
_____ Years of survival after diagnosis of Alzheimer's disease	B. Clinical Endpoint
_____ Change in beta-amyloid or tau levels as measured in the cerebral spinal fluid	
_____ Change in timeline of disease progression (i.e., delayed progression from mild to moderate disease)	

Question 12

Of the following, which represent desirable characteristics that help to minimize bias in the conduct of a clinical trial? Indicate **all that apply**.

☐ The principal investigator selects which patients enroll in each arm to ensure that a given clinical trial has an equal likelihood of success or failure (equipoise).

☐ Double-blinding to ensure that neither participants nor investigators know whether a given study participant is receiving the study drug or not.

☐ Concurrent control arms in clinical trials allow researchers to directly compare the effects of the study drug to a placebo or a current standard of care.

☐ A study that is as short as possible, since the longer the trial, the more likely extraneous variables will be introduced that obscure product benefit.

Question 13

In this activity, the descriptions are of four different trials that were recently completed for different hypothetical drugs intended to treat Alzheimer's disease. Each trial represents a different stage of the drug development process (preclinical research and phase 1, phase 2, and phase 3 clinical trials). Which stage of development is represented by each trial?

_____ A randomized, double-blind, placebo-controlled trial in 84 subjects with mild-moderate Alzheimer's disease to evaluate the safety and efficacy of ABC654, a monoclonal antibody that targets beta-amyloid. Subjects receive one of three doses of the drug (10mg, 20mg, or 40mg) or placebo. The primary outcome measure is change from baseline in the ADAS-cog after 12 weeks of treatment.

_____ A trial testing the effect of 1,943 different small molecule drugs on processing of amyloid precursor protein in Chinese hamster ovary cells. Lab-grown cells were treated with each drug at a concentration of 10 uM for 48 hours and the processing of amyloid precursor protein was measured using a biochemical assay.

_____ Drugs can be delivered to specific cells using monoclonal antibodies via a technique known as antibody conjugation – the antibody "targets" the drug to specific cells. IC735 is one such antibody-conjugated drug that was studied in a trial of 6 subjects with mild-moderate Alzheimer's disease to learn how much conjugated antibody is found in the blood following intravenous administration, and to determine if there are any side-effects of taking a 10 mg dose twice daily for one week. The primary outcome measure was a correlation between drug intake and plasma levels of the drug, and the secondary outcome measure was safety as indicated by changes in weight, blood count, electrolytes, liver function, and kidney function in study subjects.

_____ A randomized, double-blinded, placebo-controlled trial in 692 subjects with mild-moderate Alzheimer's disease to evaluate the efficacy and safety of NO-AD, a tree-derived carbohydrate that targets beta-amyloid, neuroinflammation, and other manifestations of the disease. Subjects received either 250 mg of the study drug or a placebo twice per day. The primary outcome measure was improvement on the ADAS-cog after 36 weeks.

A. Preclinical Research

B. Phase I Clinical Trial

C. Phase II Clinical Trial

D. Phase III Clinical Trial

In the NO-AD trial (introduced in question 3), 692 participants were randomized to receive either placebo or 250 mg of a tree-derived carbohydrate that targets beta-amyloid twice per day. Some of the inclusion and exclusion criteria are listed below:

Inclusion Criteria:

- Aged 50-85 years
- Meet diagnostic criteria of mild-to-moderate Alzheimer's disease
- Subjects should have stable, reliable caregivers, or at least have frequent contact with caregivers (at least 4 days every week, at least 2 h every day).

Exclusion Criteria:

- Dementia due to other causes
- Other nervous system disorders (including stroke, optic neuromyelitis, Parkinson's disease, epilepsy)
- Laboratory values indicative of abnormal liver function, kidney function, sugar levels, clotting, or blood cell counts
- Unstable or severe cardiac, pulmonary, hepatic, renal or hematopoietic disease

At 36 weeks, subjects taking the investigational drug showed an average improvement of 2.63 relative to placebo on the ADAS-cog scale, which measures patients' cognitive impairment on a range from 0 to 70. This difference was statistically significant. The drug was found to be safe and well-tolerated with respect to major adverse events versus placebo.

Question 14

Which of the following are ways that the results of this clinical trial may not generalize to patients who could take the drug after it is approved? **Indicate all that apply.**

☐ Most patients who would take the drug as part of routine clinical care are likely to be older than the age range of patients enrolled in the clinical trial.

☐ Most patients who would take the drug as part of routine clinical care would likely not take it for as long as 36 weeks.

☐ Patients who would take the drug as part of routine clinical care are more likely to have other coexisting illnesses than participants in the clinical trial.

☐ This placebo-controlled trial does not provide information about how well this new drug performs compared to existing drugs used in mild-moderate Alzheimer's disease patients.

Question 15

For which special pathway or pathways could this drug be eligible? **Indicate all that could apply.**

- ☐ Accelerated Approval
- ☐ Priority Review
- ☐ Breakthrough Therapy
- ☐ Orphan Drug
- ☐ Fast-Track

Question 16

Over 59% of cancer drugs approved between 2014 and 2017 received the Breakthrough Therapy designation. Which of the following, if true, would be consistent with the goals of the Breakthrough Therapy designation? **Indicate all that apply.**

- ☐ Many FDA-approved products granted a Breakthrough Therapy designation had similar mechanisms of action to previously-approved drugs.
- ☐ Breakthrough therapy-designated cancer therapies were approved nearly two years earlier than other cancer drugs.
- ☐ Breakthrough-designated cancer drugs were approved on the basis of flexibly-designed pivotal trials, such as those involving only a single arm or utilizing a short-term change in tumor size as the primary endpoint.
- ☐ Surveys have found that many physicians believe that drugs designated as Breakthrough Therapies offer substantial clinical improvements.

Question 17

Alzheimer's drug development has a high failure rate: to date, no drugs have been able to change the course of this disease in patients. Some researchers suggest that the reason for this failure is that the beta-amyloid plaques targeted by previous drugs are not actually responsible for the disease – that they are a symptom, not a cause, of an underlying problem. Other hypotheses to explain the neuronal damage that occurs in Alzheimer's patients include metabolic stresses and infections. A significant investment in basic and translational research will be needed to test these hypotheses. Which of the following is likely to provide most of the investment in this research in the US?

- ☐ Philanthropists
- ☐ The National Institutes of Health
- ☐ Pharmaceutical manufacturers
- ☐ Venture capitalists