

pk: 1
Instructions
Renewal for balance
Pharmacist. See
Consult your doctor
You are breastfeeding
Warning: Do not use
May cause dizziness

From concept to creation: A look at the drug discovery, development and approval processes

TERI JUNGE, CST, CFA, BS, FAST

DRUG DISCOVERY

The development of a new drug may be necessitated by an intentional quest for the treatment of a very specific need, such as the ongoing search for a drug that will treat tuberculosis more efficiently.¹ The discovery of a drug can also be totally unintentional. On occasion, the intentional quest for a specific drug can result in findings that are totally unrelated. For example, the drug now known as sildenafil citrate (Viagra®) was originally developed with the hope that it would treat hypertension. When that effort was found to be unsuccessful, the drug was evaluated for its effectiveness in treating angina, at which time an unexpected side effect was noted. Sildenafil citrate is now a popular drug for treatment of erectile dysfunction.²

LEARNING OBJECTIVES

- Examine the process of drug development
- Compare the four phases of clinical trials
- Assess the FDA's role in drug regulation
- Explain the safeguards instituted in clinical trials
- Evaluate the legal challenges faced in clinical trials

DEVELOPMENT

A drug can remain in development for as long as 12-15 years, and the cost for each drug in development is more than 800 million dollars. In addition to the time and expense, the drug must also meet rigid guidelines set forth by the US Food and Drug Administration (FDA) before clinical trials can begin.³

PRECLINICAL TESTING

The preclinical testing of a drug under development may involve research that includes hundreds or thousands of existing compounds or new chemical entities. A new chemical entity (also known as new molecular entity) is a drug



Lab technicians prepare a new drug for a clinical trial.

that contains active molecules that have never been included in any other new drug application.⁴ Each possible chemical or combination of chemicals is purified and systematically tested in the laboratory setting (including short term and long term animal trials) to determine if the chemicals produce the desired effect(s). This is called the pharmacology portion of the study. During this phase, the chemicals are also tested for purity and efficiency while being evaluated for pharmacodynamics. Pharmacodynamics is the interaction of the drug molecules with the target cells. The action of the drug substance

causes an alteration in physiological activity but is incapable of initiating a new function.⁵ Three principal concepts affect drug interaction:

1. Onset—the length of time from administration of the drug until action becomes obvious.
2. Peak effect—The length of time that the drug is most effective.
3. Duration of action—The length of time from administration of the drug until the action is no longer obvious.

The frequency of future doses of the drug is determined by applying these three concepts along with consideration of other patient factors, such as their current condition, any comorbid conditions (other diseases occurring at the same time), the type of drug, route of administration and dosage.⁵

Results of the pharmacology studies are carefully recorded and any chemical that shows promise is advanced to the next step of preclinical testing. The others are abandoned, however, they may be used in development of future drugs.⁶

Next, toxicology studies are conducted to determine the dosage and safety of the potential drug for human use. Toxicology studies are performed on animals and are useful in determining the proper starting dosage for human studies. Any short and long term toxic, side, or adverse effects are noted. The effects may be mild (*eg*, skin rash, irritation at the administration site, etc) to severe (*eg*, hair loss, cancer, reproductive harm, death, etc). Also noted during the toxicology studies are any antagonists (reversal agents) to the drug and if the drug has the potential to be addictive.⁶ Several more chemicals may be eliminated during the toxicology studies.

Pharmacokinetic studies, which encompass the entire process of the drug within the body, while not required, may also be performed during preclinical testing. The process of pharmacokinetics involves absorption, distribution, biotransformation and excretion.⁵ Pharmacokinetic studies provide information concerning the best route of administration (absorption), how the drug is transported to the target cells (distrib-

bution), how it is metabolized (biotransformation) and how the byproducts are eliminated from the body (excretion). This information may be very valuable in that it could save time and expense during the human trials by allowing for better predictions concerning the route of administration, size of the dose and timing of future doses.⁶

Only a few of the thousands of possible compounds or new chemical entities that are tested during the pharmacology and toxicology testing will be selected for clinical testing. Toward the end of the preclinical testing phase, the developers seek patent protection and submit an investigational new drug application (IND) to the FDA for those chemicals that show promise.³ The IND must be approved prior to the start of clinical testing of the drug.

CLINICAL TESTING (TRIALS)

Clinical testing on humans cannot begin until all of the pharmacology and toxicology testing is complete and the FDA has approved the IND. Once those requirements are met, the human trial must be designed, protocols established and safeguards put into effect in order for the value of the new drug to be compared to the current standard treatment for the same problem.

TRIAL DESIGNS

Several methods are available to researchers when designing a trial. The most common method, and the one considered to be the “gold standard,” is the randomized control trial (RCT). The word randomized means that the subject or subjects are chosen or placed in groups completely by chance. The word control means that one group of subjects does not receive treatment (or receives a placebo) so that the result of doing nothing can be compared to doing something. And of course the word trial is exactly that—an attempt. When participating in a RCT, the sub-

jects, and sometimes even the administrators of the trial, do not know which group they have been placed in to eliminate biases in reporting the findings. The term “single blind” is applied when the subjects participating in the trial do not

know if they are in the treatment group or the control group. The term “double blind” is applied when both the administrators and the subjects are unaware of the grouping status. Stratification, which is described as separation of the subjects into sub-

groups based on individual differences such as risk factors or severity of the disease/treatment under study, may also be applied.⁷

PROTOCOLS

A protocol is a written plan of action that follows the scientific process. Each trial will have several elements or protocols that must be established to clarify the goals of the trial and to ensure that the results of the trial are valid. There are also

A drug can remain in development for as long as 12–15 years, and the cost for each drug in development is more than 800 million dollars.

Table 1. Overview of the Drug Discovery, Development, and Approval Processes.

Step	Action
1.	Preclinical testing (pharmacology, toxicology, and pharmacokinetic testing—includes short and long term animal studies)
2.	An Investigational New Drug Application (IND) is submitted to the FDA and must be approved before human trials can begin
3.	A patent is obtained typically at the same time as the IND is submitted
4.	Clinical trials begin on humans (Phases 1, 2, and 3)
5.	Treatment use of an investigational new drug may be granted in urgent situations
6.	New Drug Application (NDA) is filed, reviewed, and approved
7.	Labeling of the new drug is approved
8.	Trademark is obtained
9.	Facilities that will manufacture the drug are inspected by the FDA
10.	Drug is manufactured, marketed, and sold (Phase 4 trials may be implemented)

clauses in the protocol that address withdrawal of a subject from the trial or stopping the trial altogether.⁸

The following list is a summary of the main protocol elements set forth by the FDA:

- General background information about the trial is provided including the statement of purpose.
- Specific objectives are listed.
- The design of the trial is specified.
- The number of subjects is identified.
- Eligibility rules are established.
- Subject selection criteria along with the rationale are set forth.
- The treatment plan (schedule) and duration of the trial is outlined and the subject is informed of the known benefits as well as any known or potential risks, including toxic, side or adverse effects of the trial drug.
- Methods for assessment of efficacy (including follow up visits, number of visits and necessary diagnostic studies) and safety are described.
- Data collection, storage, access and publication methods are defined.
- Any ethical, quality control, or quality assurance concerns are disclosed.
- The endpoint of the trial and rules for withdrawal from the trial are announced.
- Sources and methods of funding the trial and related expenses are made known.⁸

Human trials are conducted in the clinical setting in four phases. Each phase has a specific purpose with the overarching goal to achieve the desired therapeutic effect.

All those involved with the trial, including the subjects, are given a copy of the protocol as part of the process of providing informed consent.

SAFEGUARDS

Numerous safeguards are in place to protect the subjects participating in a trial from human rights abuses that have been noted in the past. Some of the safeguards are listed below:

- The Health Insurance Portability and



Accountability Act (HIPAA) of 1996 Privacy Rule—The privacy rule protects health information of the subjects of a trial. The subject may be asked to sign a release that would allow certain individuals (eg, doctors, nurses, researchers) or groups (eg, insurance providers including Medicaid and Medicare) related to the trial to share protected information about the subject, such as vital statistics

including the subject's name, contact information, social security number, medical diagnosis, treatment, results of diagnostic studies, etc. However, if the results of the clinical trial were to be published, the subject's personal information

would be withheld from the document. The full HIPAA privacy rule, as it applies to participation in clinical trials and other research efforts, is available online at <http://privacyruleandresearch.nih.gov>.⁹

- Informed Consent—The subject will be asked to sign a consent form. Informed consent means that the subject has been provided with information that is typically contained in the protocols that have been established



to accompany the planned study, including the subject's diagnosis, the risks and benefits of the proposed treatment, alternative treatments and of abstaining from treatment. The subject should have the opportunity to ask any questions that may arise.¹⁰

- Establishment of Institutional Review Boards—An institutional review board of at least five members, who meet certain requirements, is established to oversee most clinical trials. The board reviews all protocols, consent forms, advertising, etc. related to the trial and decides whether the materials are approved, need modification or are declined and if the trial can proceed. Once underway, the institutional review board meets to review the progress of the trial at least once a year—more often if necessary. Responsibilities of the review board include minimizing risks to the participants, ensuring that the risk to benefit ratio is appropriate, that selection of the subjects is carried out fairly, that the data produced from the trial is monitored, protecting confidential information, and regulating other safeguards that may be deemed necessary. The institutional review board may discontinue a trial earlier than planned due to unforeseen risks or severe toxic, side or adverse effects.⁸
- Reporting of Adverse Events—Researchers are required to report adverse events to the

institutional review board, the sponsoring organization (holder of the approved IND) and the FDA.⁸

- Audits—An audit of the clinical trial may occur at any phase. Audits are typically conducted by the institutional review board, but may also be accomplished by an outside entity such as the National Institutes of Health.⁸

HUMAN TRIALS

Human trials are conducted in the clinical setting in four phases. Each phase has a specific purpose with the overarching goal to achieve the desired therapeutic effect. Keep in mind that any of the safeguards can be activated during any phase, causing the trial to be delayed, suspended (put on hold) or terminated for a variety of reasons. Each of the four phases is described below:

1. Phase 1—The first phase of a trial is the first human contact with the drug and is conducted on a small group of people (20-80) who qualify. The subjects for phase one trials may be healthy or have the problem that the manufacturers of the proposed drug hope to treat. The protocols for phase one of the human trials are based on the knowledge learned from the pre-clinical trials. The purposes of phase one of the trial include identification of the ideal dosage, determination of the best route of administration, observation of the therapeutic effects

on the body, and notation of any toxic, side or adverse effects. The ideal dosage is considered to be the highest dose with acceptable toxicity. The drug is given via several different routes of administration (eg, oral, intravenous (IV), intramuscular (IM), etc) to determine which is the most effective. The subject is observed or is instructed to note the positive and negative effects of the drug. It may be necessary for the subject to undergo various diagnostic tests during the trial to gain information about the efficacy of the drug. This phase typically lasts one to two years.

2. Phase 2—The second phase of the trial is the second human contact with the drug and is conducted on a larger group of people (several hundred) who qualify. The subjects for phase two trials are selected because they have the problem that the manufacturers of the proposed drug hope to treat. The protocols for phase two of the human trials are based on the knowledge learned from the preclinical trials as well as the results of phase one of the trial. The purposes of phase two of the trial include deter-

Any of the safeguards can be activated during any phase, causing the trial to be delayed, suspended (put on hold) or terminated for a variety of reasons.

mining the effectiveness of the drug and identification of any short term risks (toxic, side or adverse effects) associated with the drug. The study design for phase two trials is usually a double blind randomized control trial.

3. Phase 3—The third phase of the trial is the third human contact with the drug and is conducted on a much larger group of people (several hundred to several thousand) who

qualify. The subjects for phase three trials are selected because they have the problem that the manufacturers of the proposed drug hope to treat. The protocols for phase three of the human trials are based on the knowledge learned from the pre-

clinical trials as well as the results of phases one and two of the trial. The purposes of phase three of the trial include determining the effectiveness of the drug in a larger population and identification of any long term risks (toxic, side or adverse effects) associated with the drug. The study design for phase three trials is also a double blind randomized control trial. Drugs in phase three may be approved for treatment use as an investigational new

Table 2. Summary of the Phases of a Clinical Trial

Phase	Goal(s)	Estimated Time	Number of Subjects
1	<ul style="list-style-type: none"> — Identify the ideal dosage — Determine the route of administration — Observe the therapeutic effects on the human body — Note any toxic, side, or adverse effects 	1-2 Years	20-80
2	<ul style="list-style-type: none"> — Determine effectiveness of the drug in subjects with the disease or condition that the drug is designed to treat — Identify short term risks associated with the drug 	1-3 Years	Several hundred
3	<ul style="list-style-type: none"> — Determine effectiveness of the drug in subjects with the disease or condition that the drug is designed to treat — Identify long term risks associated with the drug 	Several Years	Several hundred to several thousand
4	<ul style="list-style-type: none"> — Further evaluation of effectiveness of the drug — Identify long term safety of the drug 	Varies	Varies

drug. Toward the end of phase three, the New Drug Application is filed with the FDA.

4. Phase 4—The final phase of the clinical trial is not a required element, but may be an extension of the third phase in order to evaluate the drug for a longer period of time for safety and effectiveness. Phase four occurs after the New Drug Application (standard use of the drug) has been approved and may be useful in determining alternate (off label) or extended usages of the drug.⁴

DRUG APPROVAL PROCESS

The United States Food and Drug Administration (FDA) is responsible for the approval process of new drugs.

INVESTIGATIONAL NEW DRUG APPLICATION

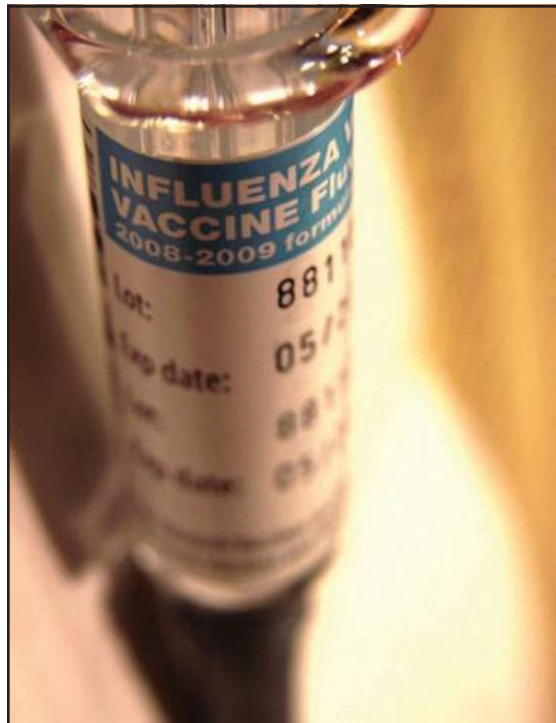
Before clinical testing on humans can occur, an investigational new drug application (IND) is submitted to the FDA. The application calls for reports of all preclinical testing and protocols for the clinical phases of the study of the drug. Additionally, an institutional review board must be set up to oversee the investigational phases of the trial. The FDA retains considerable control over the drug and the trials during the investigational phases.¹¹

TREATMENT USE OF AN INVESTIGATIONAL NEW DRUG

Occasionally, treatment use of an investigational new drug may be approved during the third phase of clinical trials (before the drug is approved for normal use) if the drug shows promise in treating a specific disease or condition. Permission may be granted for the drug to be used for treatment in life-threatening cases (called compassionate exceptions) if other treatments are not available or effective.¹²

NEW DRUG APPLICATION

A new drug application (NDA) is filed with the Center for Drug Evaluation and Research (CDER), which is a branch of the FDA, late in the third phase of the clinical trial. The NDA will contain all information known about the drug, including



Vaccines are also subject to FDA approval.

all test results (laboratory, animal and human), toxicology reports, all that is known about the pharmacodynamics and pharmacokinetics of the drug, and any negative side effects or adverse reactions. Review of the application by the CDER can take up to two years, however, in priority cases, the time can be shortened to approximately six months. Once the CDER review is complete, the information is presented via an advisory committee to the FDA for final approval. Following approval, the final steps involve inspection of the manufacturing site for the drug and the wording for the label of the drug. Upon approval of the label information, the drug is marketable.¹¹

PATENT PROTECTION

Patent protection is typically obtained from the US Patent and Trademark Office (USPTO) during the preclinical testing period. Utility patents are granted to protect the rights of the individual or group of individuals who discover a new use of an existing compound or a new chemical entity that may become a marketable drug. Specifically,

The right conferred by the patent grant is, in the language of the statute and of the grant

itself, "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States or "importing" the invention into the United States. What is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention. Once a patent is issued, the patentee must enforce the patent without aid of the USPTO.¹³

A patent is valid for 20 years from the original date of application.¹³ Because of the length of time that a drug is in development, it is important not to file for the patent too soon because the patent may expire shortly after the drug becomes marketable, providing the developer a small window in which to recover their development costs. A drug patent prevents another manufacturer from producing the drug in generic form for the length of the patent.

TRADEMARK

A request for a trademark is filed with the USPTO near the end of the third phase of the clinical trial once the proprietary name of the drug has been determined and approval of the drug is imminent. A trademark is a word, phrase, symbol or design, or a combination of words, phrases, symbols or designs, that identifies and distinguishes the source of the goods of one party from those of others.¹⁴

CONCLUSION

The processes that result in drug discovery, development, and approval are long and expensive. The main goal is to ensure safety of the drug. "Safe," in this sense, means that the benefits of the drug appear to outweigh the risks.¹¹ The final goal is achieved when the cost of the drug has been set, the drug is being manufactured, the marketing of the drug is in process, and sales have begun.

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Ethical and legal issues in the administration of clinical trials

TOM BORAK

Before a new drug can be mass produced and distributed in the medical community, it must be thoroughly vetted. One of the most critical steps in the process is the clinical trial phase, during which the drug is administered to human patients to establish, among other things, the ideal dosage and the toxicity level of the drug. The clinical trial phase is not only filled with health implications, but legal implications as well. Over the years, several law suits have been filed against pharmaceutical companies, hospitals organizing the trials and even international organizations that are administering trials abroad.

Because of the unknown variables associated with clinical trials, there are many ethical questions involved in this phase. Consider the Hippocratic Oath, a traditional rite of passage for medical practitioners, which states, in part:

I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to anyone if asked, nor suggest any such counsel...¹

If the drug testing is in the trial phase, specifically one that is examining toxicity levels, can it honestly be said that this code is being followed?

Ethics can swing both ways. Others who favor the adage that, “the good of the many outweigh the good of the few,” may argue that the masses will ultimately benefit from the misfortune of few if the trial should go wrong.

Despite many safeguards that are instituted with the patients’ safety and dignity in mind, many clinical trials still come under fire in the legal arena for issues ranging from misrepresentation of risks in the consent form to human rights abuses. These legal threats pose a challenge to those who administer these trials because they must walk a very thin line between what is legal and what is necessary to complete a successful and medically-relevant trial.

According to CenterWatch, a clinical trials listing service in Boston, there were approximately 50,000 clinical trials underway throughout the world in 2005. Increasing at a rate of 8-10 percent per year,² the number in 2008 is likely more than 65,000. According to Alan C Milstein, JD, there hasn’t necessarily been a dramatic increase in clinical trial-related suits, only more publicity about them.²



“When you have a negative outcome,” says J Mark Waxman, JD, “questions are always raised whether [patients] understood the potential for a negative outcome and whether people properly administered the processes of the trial.”²

Waxman believes that the increasing number of clinical trials, coupled with the fact that outcomes are not always positive, is pushing up the number of suits.

The ethical line often comes into play when clinical trial subjects are exposed to a potentially harmful situation as a means by which to test a drug’s effectiveness. In 2001, for example, the Maryland Court of Appeals ruled that researchers at an affiliate of Johns Hopkins School of Medicine could be sued for exposing children to hazardous levels of lead paint during a research project aimed at determining the effectiveness of varying lead abatement procedures.^{2,3}

In another 2001 case, the families of 13 patients in a melanoma study sued the Oklahoma University School of Medicine at Tulsa, the university’s institutional review board and the company that supplied the drug used in a vaccine for fraud. The suit alleged that the defendants failed to follow federal human subject regulations, claiming therapeutic misconception and saying that the study’s principal investigator was convincing the test subjects that the procedure was therapy, as opposed to an experimental process. According to the attorney for the defense, all of the subjects were terminally ill. The doctor didn’t tell them the state of the vaccine trial was in the toxicity stage—to see if it made them sick, not if it worked.^{2,4}

According to professionals in many fields, one of the biggest hurdles in the process is the clarity of informed consent.

“I don’t think the consent forms are worth the paper they’re printed on,” says Milstein. “There’s a real disconnect between what the subjects

understand to be going on and what the consent form says.”

This situation presents a severe conflict of interests, as laid out by pharmaceutical defense attorney, Jay Mayesh, “In our current legal climate, one must err on the side of being very conservative in warnings,” he says. “But on the other hand, the problem is that the FDA doesn’t want you to be overly negative about a drug because then you’re scaring away patients who need the drug, could benefit from the drug and shouldn’t be scared away.”

In short, the language in the consent form must be written both thoroughly and in language

that people can understand—outlining the methods, risks and purpose of the trial—while still generating interest and willing volunteers.

The ongoing battle over informed consent and the overall patient protection in clinical safeguards is a double-edged sword.

The increasing threat of potential legal action can also lead to a decline in the quality of the research. As more investigators and institutions grow less willing to subject themselves to the risk of lawsuits, the protective precautions they take may dilute the quality of the research.

The methodology behind clinical drug trials is still very murky. While regulations and processes are constantly being scrutinized for reform, it remains a difficult and ethically-challenging path to walk.

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3. *Grimes vs Kennedy Krieger Institute*, 782 A.2d 807 (Md Ct App)
4. *Robertson vs McGee*, No. 4:01CV60 (D Okla)

“When you have a negative outcome, questions are always raised whether [patients] understood the potential for a negative outcome and whether people properly administered the processes of the trial.” —J Mark Waxman, JD

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- The drug sildenafil citrate (Viagra®) was originally developed to treat ____.
 - Angina
 - Erectile dysfunction
 - Hypertension
 - Glaucoma
- A drug containing active molecules that have never been included in another new drug application is called _____.
 - A new molecular entity
 - An original compound
 - A unique chemical compound
 - A prototype
- Which is not a principal concept affecting drug interaction?
 - Onset
 - Peak effect
 - Duration of action
 - Frequency of future doses
- _____ studies encompass the entire process of the drug within the body.
 - Toxicology
 - Pharmacokinetic
 - Post-clinical
 - Biotransformation
- _____ studies determine the dosage and safety of the drug for human use.
 - Toxicology
 - Pharmacokinetic
 - Post-clinical
 - Biotransformation
- Toxicology studies are used to determine:
 - Toxic, side and adverse effects
 - Reversal agents
 - Addictive properties
 - All of the above
- _____ denotes a study when subjects and administrators are unaware of grouping status.
 - Single blind
 - Double blind
 - Placebo
 - None of the above
- A written plan of action that follows the scientific process is a _____.
 - Theory
 - Hypothesis
 - Protocol
 - Trial
- Examples of clinical safeguard trials include:
 - Informed Consent
 - Audits
 - Institutional review boards
 - All of the above
- Human trials have _____ phases.
 - 2
 - 3
 - 4
 - 5

301 JANUARY 2009 2 CE CREDITS PART 1 OF 2

Drug discovery, development and approval processes

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My address has changed. The address below is the new address.

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	a	b	c	d		a	b	c	d
1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Mark one box next to each number. Only one correct or best answer can be selected for each question.

11. The _____ contains all information known about a new drug.
- New drug application (NDA)
 - Food and drug administration (FDA)
 - Center for drug evaluation and research (CDER)
 - Center for disease control (CDC)
12. A patent is valid for _____ years from the original date of application.
- 10
 - 15
 - 20
 - 25
13. A _____ distinguishes the source of goods of one party from those of another.
- Phrase
 - Symbol
 - Design
 - Trademark
14. A new drug application is filed with the FDA at the end of _____.
- Phase 1
 - Phase 2
 - Phase 3
 - Phase 4
15. _____ is conducted on a small group of people (20-80).
- Phase 1
 - Phase 2
 - Phase 3
 - Phase 4
16. Determining effectiveness and identifying long-term risks are purposes of _____.
- Phase 1
 - Phase 2
 - Phase 3
 - Phase 4
17. The study design for _____ trials is usually a double blind, randomized control trial.
- Phase 1
 - Phase 2
 - Phase 3
 - Phase 4
18. Approximately how many clinical trials are currently underway worldwide?
- 50-55,000
 - 55-60,000
 - 60-65,000
 - 65-70,000
19. One of the biggest legal challenges in clinical trials is _____.
- Luring qualified volunteers
 - Misrepresentation/fraud
 - Clarity of informed consent
 - FDA regulations and safeguards
20. Increasing legal threats may lead to a decline in _____.
- Quality of medical research
 - Willing volunteers
 - Clinical trials
 - Marketable drugs

301 JANUARY 2009 PART 2 OF 2

Drug discovery, development and approval processes

	a	b	c	d		a	b	c	d
11	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	18	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	19	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	20	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Mark one box next to each number. Only one correct or best answer can be selected for each question.