

## DRUG DEVELOPMENT AND CLINICAL TRIALS 101

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# **DISCOVERY - PHASE 1**

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### DRUG DISCOVERY AND DEVELOPMENT

### Why is it important?

- Rare hormone producing tumor of the anterior pituitary gland
- Cabergoline, an ergot derivative, is a potent dopamine D2 receptor agonist that blocks pituitary production of prolactin
- Ergot is a fungus that grows on rye and related plants, and produces alkaloids that can cause ergotism in humans and animals that eat the contaminated grain
  - Painful seizures, mania, psychosis, headaches, nausea, vomiting





### PHARMACOLOGY

- Pharmacology is the science of how drugs and biologics act on biological systems and how the system responds to the drug
- Clinical Pharmacology applies the basic science and principles of pharmacology to the practice of medicine

Basic science

Translational pharmacology

Clinical practice

Doctors, pharmacists, dentists, veterinarians use the information discovered from pharmacology to select the best medications to treat patients



### **MECHANISM OF ACTION**

- Modern drug discovery is a mechanism driven field
- Nearly all new experimental therapeutics have a defined mechanism-of-action and most have companion diagnostics allowing researchers to track mechanistic engagement in complex systems like the human body
- What are the known consequences of that mechanism in a disease state? ie.
   potential efficacy
- What are the known consequences of that mechanism in healthy systems? ie.
   potential toxicity
- What mechanisms do we know can't be tolerated in healthy systems? ie. <u>known</u>
   <u>toxicity</u>

"All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison." - Paracelsus

### PHASES OF DRUG DEVELOPMENT





### HIGH-RISK/HIGH-COST BUSINESS

- The process of discovering a new drug and conducting clinical trials to ensure it is safe and effective is estimated to take **15 years** and cost **\$2.6 billion** on average!!!
- During the discovery process it takes 5,000-10,000 compounds to get just 5 that will be worthy advancing into the clinical development process (human studies)
- For the 5 compounds that make it into clinical trials, the likelihood of receiving FDA approval is about 12%

DiMasi et al. 2016 Journal of Health Economic, 47;20-33

#### Number of FDA approved drugs

2016	2017	2018	2019	2020
22	46	59	48	53

https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020FDA Drug Approvals

### DRUG DEVELOPMENT IS A TEAM SPORT



Shen et al. Clin Transl Sci (2019), 12, 6-19

### DISCOVERY

- Major aspects of early drug discovery
  - Discovery biology
  - Discovery chemistry
  - In vitro pharmacology (test tube, petri dish)
  - In silico models, often aided by artificial intelligence (AI)
  - Ex vivo studies in human tissues
  - In vivo pharmacology and efficacy assessment



### PHASE I STUDIES

- Healthy volunteers
- Double-blind, randomized, placebo controlled
- Investigate safety/tolerability and identify maximally tolerated dose (MTD)
- Consider possible drug-drug interactions (DDI)
- Food interactions and absorption
- Specific populations
  - Age, gender, pre-existing conditions



### CLINICAL PHARMACOLOGY

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### **Pharmacokinetics (PK)**

- Drug disposition or what the body does to a drug
- This is calculated using mathematical equations
- Four processes involved (LADME) (actually 5)
  - (Liberation)
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

### Pharmacodynamics (PD)

- Drug actions or what a drug does to the body
- This is assessed using a wide variety of measurement tools depending on the drugs mechanism and disease states of interest
  - Cardiovascular heart function
  - Endocrinology hormone measurement
  - Psychiatry emotional and behavioral signs

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#### **Parameters of drug bioavailability**

- Maximum concentration (Cmax)
- Time to reach maximum concentration (Tmax)
- Area Under the Curve (AUC)
- Absorption rate
- Elimination half-life
- Pharmacogenomics is a relatively new, but incredibly important aspect of drug development
  - Liver enzymes (Cytochrome P450 enzymes) can impact on drug metabolism.
    - Poor, intermediate, rapid and ultra-rapid metabolizers

#### **Routes & dosing regimens**

- Parenteral (IV, IM, SC)
- Oral (po)
- Intranasal
- Inhalation
- Topical
- Once daily (QD), twice daily (BID), three times daily (TID), four times daily (QID), as needed (PRN)

#### **Risk-Benefit Ratio**

- Some toxicities can be managed and may be acceptable while others are not
  - Treatment of aggressive cancers vs treatment of hypertension
- Pharmacogenomics: patients with certain genetic predisposition
  - eg. Patients with the HLA-B\*1502 genetic variant can lead to Stevens-Johnson syndrome (severe skin disorder) when treated with carbamazepine

#### Thalidomide

- Approved in many countries for sedation and used in pregnant women
- Prenatal drug exposure resulted in devastating birth defects





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#### **Cost and Time Savings**

- Considerably cuts R&D costs
- Reduces the development timeline, as various existing compounds have already demonstrated safety in humans, it does not require Phase 1 clinical trials
- Potential for reuse despite evidence of adverse effects and failed efficacy in some indications



#### Thalidomide

- Complication of leprosy (Erythema Nodosum Leprosum)
  - Clinical observation of benefit
- Multiple Myeloma
  - Targeted development
- Special Restricted Distribution Program
- Other examples of repurposed drugs: apomorphine (Parkinson's disease), sildenafil (pulmonary hypertension), taxotere (prostate cancer), lamotrigine (Bipolar Disorder), hydroxyurea (Sickle Cell Disease), minoxidil (hair re-growth)

#### 15

### FREE RESOURCES

- NIH Understanding Clinical Trials, Vaccine Development: <u>https://covid19community.nih.gov/resources/understanding-clinical-trials</u>
- Shen et al. Design and Conduct Considerations for First-in-Human Trials, Clin Transl Sci (2019), 12, 6-19: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342261/</u>
- FDA Clinical Pharmacology 1: <u>https://www.fda.gov/media/84920/download</u>
- www.clinicaltrials.gov
- NIH Principles of Clinical Pharmacology course: <u>https://ocr.od.nih.gov/courses/principles-clinical-pharmacology.html</u>
  - Provides an in-depth look at drug absorption, distribution, metabolism, and excretion
  - Describe the impact of age, pregnancy, and disease on pharmacokinetics
  - Describe the basic principles in the assessment of drug effects
  - Describe the process of drug discovery and development
  - Provide an overview of clinical pharmacotherapy including pharmacogenomics and medication safety



# **PHASE 2 – 3**

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## WHAT IS A CLINICAL TRIAL?

- Research studies that involve volunteers to test specific intervention(s) such as a drug, device, procedure or changes in participant's behavior such as diet
  - Interventional (studying a potential new treatment)
  - Observational (gathering data)
- Studies can be funded by pharmaceutical companies, academic institutions, voluntary groups, federal agencies (e.g., NIH) and can be run by Investigators or Industry
- Trials progress through a series of steps, called Phases
- If a potential treatment is successful in one phase, it may be able to move to the next phase of research
- Goal is to gather information on safety and efficacy



### PHASES OF CLINICAL RESEARCH



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## INVESTIGATIONAL NEW DRUG APPLICATION (IND)

- FDA works to protect participants in clinical trials
- Extensive application submitted to the FDA before beginning research in humans (21 CFR Part 312)
- Provides data on the animal studies and any signals of toxicity (side effects that may cause great harm)
- Details on how the drug is made, what is in it, and more
- Includes the plan for the studies to be conducted in humans
- "Living application"



### PHASE 2 BASICS



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### PHASE 2 GOALS



- Further assess safety of the drug in a larger group of patients
- Gather preliminary information on safety and potential efficacy for the dose(s) being studied, to know if it is appropriate for a larger Phase 3 clinical trial
- To accurately compare safety and effectiveness while on and off the drug, includes a comparison group such as placebo (no drug) or active comparators (already approved drug)
- Does it relieve, reverse or stop the progression of the condition?

### Approximately 33% of drugs move to the next phase

### PHASE 3 BASICS



### PHASE 3 GOALS





- Demonstrate whether or not a product offers benefit to a specific population of people (for example with Prader-Willi Syndrome)
- Known as pivotal studies
- Compare product to other treatments (or placebo) to see if it is more effective, less effective or the same
- Provide more safety information in a larger group of patients
- Treatment is longer in duration to monitor maintenance of efficacy and show any longer-term or rare side effects

#### Approximately 25-30% of drugs move to the next phase



### CLINICAL TRIAL DESIGN TERMS

#### Randomized

 Each study participant is randomly assigned to receive either the study treatment or the comparator (placebo, or other approved drug)

#### Placebo or Active controlled

 The use of placebo (fake treatment) or another treatment allows the researchers to accurately measure the effect of the study treatment

#### Blinded

- Single blind the participant involved in the study do not know which study treatment they receive
- Double blind the researchers also do not know which treatment is being given to any participant

Endpoint

- Decided before the start of the study
- An event or outcome that can be measured to determine whether the intervention being studied is beneficial

### RARE DISEASE

- A condition that affects less than 200,000 people in the United States (as defined by the FDA)
- A drug used to treat a rare disease is called an **Orphan Drug**
- Recognizing the difficulty of clinical trials in rare patient populations, the US Congress passed the Orphan Drug Act to facilitate development of treatments for rare disorders
- Most estimates indicate that PWS may affect between 1 in 10,000 to 1 in 30,000 individuals
- This would be considered very rare (likely fewer than 30,000 people in the US)



### WHO IS INVOLVED IN THE RESEARCH?

#### Sponsor

• The organization or person who initiates the study and who has authority to control the study.

#### Investigator

 Every study location (hospital, clinic) is lead by a Principal Investigator (PI), usually a medical doctor. The PI may have a team of Investigators at the study location who all aid in regularly monitoring the participant's health

#### **Clinical Research or Study Coordinator**

• An individual that handles the day-to-day organization of the clinical trial at the clinical site (study center).

The Participant!



### HOW ARE SITES CHOSEN FOR A CLINICAL TRIAL?

#### Key criteria for site selection

- Patient population
- Investigator experience, expertise and interest
- Sufficient experienced staff and appropriate facilities
- Ability to perform study assessments adequately and safely
- Prior FDA (or other regulatory) audit findings

#### **Rare disease studies are challenging!**

- Limited patients
- Limited Investigators who specialize in the treatment of the rare disease
- Participants may be required to travel great distances to a recruiting site



~2-8+ months to get a clinical site up and running to enroll a patient in a clinical trial



### LEGAL FRAMEWORK / BACKGROUND

#### Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness
- Code of Federal Regulations (CFR)
  - Regulations under Section 505(i) describing FDA's authority over the conduct of clinical investigations including Sponsor responsibilities and Clinical Investigator responsibilities

#### Guidances

- FDA Guidance Documents
  - Advisory only to assist Sponsor and Clinical Investigators in complying with the regulations
- International Conference on Harmonization (ICH) E6(R2) Good Clinical Practice (GCP)
  - International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects



### **CLINICAL TRIAL PROTOCOL**

- The research plan detailing how a study is conducted
- Designed to answer specific research questions and safeguard the health of the participants. Protocols contain:
  - the reason the study is being conducted
  - who may participate in the study and how many will need to participate
  - the schedule of tests, procedures and study drug administration
  - the information that is gathered by the participant
- Investigator / study team must follow this document
- Prior to the initiation of the study,
  - the protocol is submitted to the FDA for review (30-day review clock)
  - the protocol and related study documents are submitted several groups (e.g., institutional review board, hospital committees, etc.) for review and approval



### WHO CAN PARTICIPATE?

- All clinical trials have guidelines about who can participate called eligibility criteria
  - Inclusion criteria: The factors that allow someone to participate
  - Exclusion criteria: The factors that disallow someone from participating
- Criteria are based on such factors as age, sex, type and stage of disease, previous treatment history, and other medical conditions which helps
  - keep the patients safe
  - researchers achieve accurate and meaningful results
  - reduce the variation within the study
- Participation should ALWAYS be voluntary, and the participant and family will be well
  informed by the researchers at the clinical site about the study details and commitment

# WHAT IS REQUIRED OF THE PARTICIPANT OR FAMILY?





#### Informed consent

- The process of learning the key facts about a clinical trial before deciding whether or not to participate.
- Continues throughout the study
- Explanation of benefits and risks to participating
- You should fully understand all aspects of a clinical trial before participating and have all your questions answered
- Assures the participant that personal information is seen only by those authorized to have access
- Updated as new safety information comes available (i.e., current study, other studies with same drug, preclinical research)



### HOW ARE PARTICIPANTS PROTECTED

#### US Food and Drug Administration (FDA)



- Responsible for safeguarding public health by assuring that current and new medical products are safe and effective, and that the evaluation of potential new therapies is done properly
- There are regulations that govern human subject protection and the conduct of Clinical Trials (Protection of Human Subjects 21 CFR Part 50, Financial Disclosure by Clinical Investigators 21 CFR Part 54, Institutional Review Boards 21 CFR Part 56, Investigational New Drug Application 21 CFR Part 312)

#### Institutional Review Boards

- Review clinical research to ensure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research.
- Use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures)
- Has the authority to approve, require modifications in (to secure approval), or disapprove research.



### HOW ARE PARTICIPANTS PROTECTED

#### Data and Safety Monitoring Board (DSMB)

- Also referred to as Data Monitoring Committee (DMC) or Data and Safety Monitoring Committees (DSMCs) or Data and Safety Monitoring Board (DSMB)
- May be established by a sponsor
- Independent group of experts who assess progress of a trial
  - Safety data
  - Efficacy variables
  - May recommend modification or termination of study
- Must have a written charter and minutes
- Typically includes scientists and statisticians with appropriate knowledge
- Independence is critical to maintain integrity



### RESPONSIBILITIES

#### Sponsors are responsible for

- selecting qualified investigators
- providing investigators with the information they need to conduct clinical study properly
- ensuring proper monitoring of the investigation(s)
- ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND
- maintaining an effective IND with respect to the investigations
- ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug

Investigator

- Ensures that an investigation is conducted according to the Investigational Plan (study protocol)
- Protects the rights, safety and welfare of subjects
- Ensures that informed consent is adequately obtained
- Ensures IRB review, approve and reporting requirements are met
- Maintains control of investigational product (study drug)
- Maintains accurate records and retains these records
- Submitting progress reports / final reports to sponsor
- Report any adverse event (side effect) that is alarming (e.g., an unexpected event that is serious or life-threatening)
- Financial disclosure to sponsor

21 CRF Part 312.60; ICH E6(R2)

### **RESPONSIBILITIES (CONT.)**

#### Participant (and Caregivers)

- Be willing to come to the study visit appointments as scheduled with the study staff
- Follow all instructions of the Investigator and the study staff
- Report any side effects or any changes in the medicines that you take
- Agree to take study medication as instructed by the Investigator
- Not participate in any other clinical trials when a research drug and/or a research device is being given to you
- Understand that participation is voluntary, and, at any time, the participant may withdraw from the study without any penalty or loss of access to treatment or other benefits to which you are entitled



### WHERE CAN YOU LEARN MORE?

- Used to develop today's presentation and you can access for more information!
- Learn more about clinical trials:
  - <u>https://www.fda.gov/patients/clinical-trials-what-patients-need-know/basics-about-clinical-trials</u>
  - <u>https://clinicaltrials.gov/ct2/about-</u> <u>studies/learn</u>
  - Step 3: Clinical Research. U.S. Food & Drug Administration website: <u>https://www.fda.gov/patients/drug-development-process/step-3-clinical-research</u>
- Check what studies are recruiting
  - www.clinicaltrials.gov

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 367,057 research studies in all 50 states and in 219 countries.

See listed clinical studies related to the coronavirus disease (COVID-19)

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

**IMPORTANT**: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our <u>disclaimer</u> for details.

Before participating in a study, talk to your health care provider and learn about the <u>risks and</u> <u>potential benefits</u>.

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## NDA AND DRUG APPROVAL PROCESS

27 March 2021

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### NEW DRUG APPLICATION (NDA)

- Sponsor's formal proposal to FDA to approve a product for marketing and sale in the US
- Provides all the relevant data and information collected during years of research and development (Investigational New Drug [IND] phase)
- Includes multiple sections:
  - Administrative information, including proposed labeling (Module 1)
  - Comprehensive summaries for each discipline (Module 2)
  - Chemistry, manufacturing, and controls information (Module 3)
  - Nonclinical data (Module 4)
  - Clinical data, including tabulations of patient data, clinical study reports, patient narratives (Module 5)
- Submitted electronically in Common Technical Document (CTD) format

### **NEW DRUG APPLICATION (NDA) – CTD FORMAT**

• Agreement to assemble all the Quality, Safety and Efficacy information in a common format





- Safety and efficacy profile
- Assessment provides an acceptable risk-benefit
- Product quality adequate manufacturing methods and controls to preserve identity, strength, and purity of the product
- Countless FDA and International Council for Harmonisation (ICH) guidance documents
  - Cover all aspects of clinical development and NDAs
  - FDA website provides a wealth of information

### **NEW DRUG APPLICATION (NDA)**

- Along the way to NDA
  - Sponsor conducts milestone meetings with FDA
    - Formal meetings conducted with FDA during the IND phase
    - Allows for interaction with FDA to discuss development program, address questions, obtain agreement for specific questions or issues
    - Pre-IND, End of Phase 1, End of Phase 2, pre-NDA
  - Pre-NDA meeting
    - Addresses final questions regarding submission strategy, requirements, completeness of data, any outstanding issues
  - FDA has developed programs to expedite drug development and review
    - Fast track
    - Breakthrough therapy
    - Accelerated approval
    - Priority review



NDA SUBMISSION PROCESS

- Reviewers
- Document publishers

Write and compile NDA

Subject matter experts

- Technical experts to build the electronic submission
- Project management to track timelines, movement of documents through the process from draft to finalization
- Regulatory experts oversee all of this and ultimately guide as well as drive the process



Prescription Drug User Fee Act (PDUFA)

- Authorizes FDA to collect user fees for applications and approved products
- Fee schedule for 2020-2021:

User Fee Type	2020	2021
Application Fee – Clinical Data Required	\$2,942,965	\$2,875,842
Application Fee – No Clinical Data Required	\$1,471,483	\$1,437,921
Program Fee	\$325,424	\$336,432



- NDA review timelines (PDUFA review performance goals)
  - Review and act on 90% of new chemical entity (NCE) applications within 10 months <u>of the 60-day filing date</u> (6 months for priority review)
    - Note review timeline is set based on the 60-day filing date
    - Essentially means within 12 months of the receipt date (8 months for priority review)
  - Review and act on 90% of non-NCE applications within 10 months of receipt (6 months for priority review)
    - Note review timeline is set based on the receipt date



- FDA review teams thoroughly examine all the submitted data related to the drug and decide to approve or to not approve it
- Upon receipt at FDA, initial administrative processing
- Forwarded to the Division responsible for review
  - Assigned to a Division Project Manager
  - Screened to assess for completeness
  - Technical sections distributed to reviewers in the primary technical review disciplines
    - Medical/clinical
    - Pharmacology/toxicology
    - Chemistry/microbiology
    - Consultant reviewers (e.g., statistical, safety, device, clinical outcome assessment [COA])



- Review process divided into phases
  - Filing determination and review planning
    - By Day 60 inform the Sponsor in writing if Priority Review granted or if a Refusal to File decision is made
    - By Day 74 communicate that the application is filed, PDUFA goal date, and initial filing review issues/requests for information
  - Review
    - Communicate additional requests for information
    - Submission of major amendment during last 3 months of the review can extend the PDUFA goal date by 3 months
    - Primary review completed by end of month 8 (for standard review; end of month 5 for priority review)

- Review process phases
  - Advisory Committee meeting preparation and conduct
    - Some applications go to an Advisory Committee Meeting
      - NCE
      - Novel clinical or surrogate endpoints were used
      - Significant issues regarding safety or efficacy
      - Significant public health questions
    - Communicated early in the first cycle review process
    - Provides FDA with independent advice from outside experts
    - FDA often follows the advice of an Advisory Committee but is not required to do so
    - Open to the public
  - Requires extensive preparation and is labor intense for the Sponsor

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- Review process phases
  - Action
    - Labeling discussions occur to determine final approved labeling
    - Each review discipline writes a review summary
      - Eventually posted to FDA website as the Summary Basis of Approval
    - Goal is to complete the review and issue official regulatory action by the PDUFA goal date
    - Send official regulatory Action Letter by the PDUFA goal date
      - Approval Letter
      - Complete Response Letter
        - Describes the deficiencies identified during review of the application
        - Indicates if any amendments submitted late in the review cycle were not reviewed



- Review process phases
  - Post-action Complete Response Letter
    - Post-action teleconference or meeting to discuss the deficiencies
    - Resubmission of the application to resolve the deficiencies
      - Class I FDA goal is to review within 2 months
      - Class II FDA goal is to review within 6 months
    - Resubmission must be a complete response to all deficiencies identified
    - Class I resubmissions are for very specific situations that require minor updates to the application (e.g., final labeling, stability data, validation data)
    - Most resubmissions are Class II



### PATIENT-FOCUSED DRUG DEVELOPMENT

- Systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation
- Primary goal is to better incorporate the patient's voice in drug development and evaluation
  - Facilitate and advance use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making
  - Encourage identification and use of approaches and best practices to facilitate patient enrollment and minimize the burden of patient participation in clinical trials
  - Enhance understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes
  - Identify the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision making



### PATIENT-FOCUSED DRUG DEVELOPMENT

- Clinical trials traditionally relied on objective measures for primary and secondary endpoints
- FDA guidance issued in 2009 regarding patient-reported outcome measures
- FDA commitment to further development of patient-focused drug development guidance, as required by Section 3002 of the 21<sup>st</sup> Century Cures Act (2016) and the 6<sup>th</sup> authorization of the Prescription Drug User Fee Act (PDUFA VI) (2017)
  - Additional guidance documents issued (2019 and 2020) following two initial workshops
  - Two additional workshops held (2018 and 2019) with guidance documents to come
- Division of Clinical Outcome Assessment (DCOA) established at FDA
  - Mission: Integrating the patient voice into drug development through COA endpoints that are meaningful to patients, valid, reliable and responsive to treatment.
  - Supports CDER's mission for patient-focused drug development by providing leadership, expertise, and advice to promote the use of patient-focused outcome assessment
- Making strides but still work to be done

### FDA MISSION

- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.
- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
- FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this
  responsibility by ensuring the security of the food supply and by fostering development of medical
  products to respond to deliberate and naturally emerging public health threats.