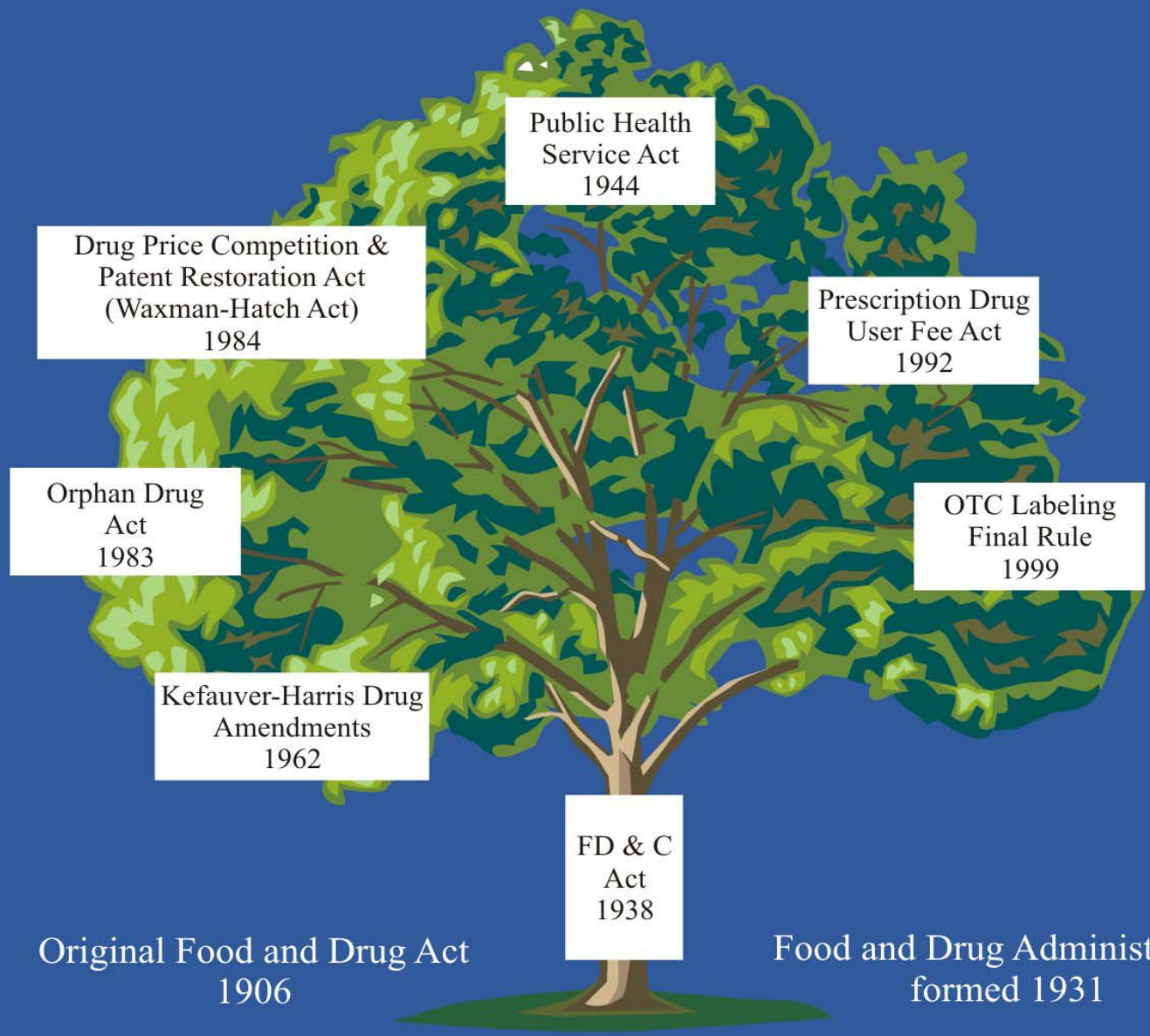
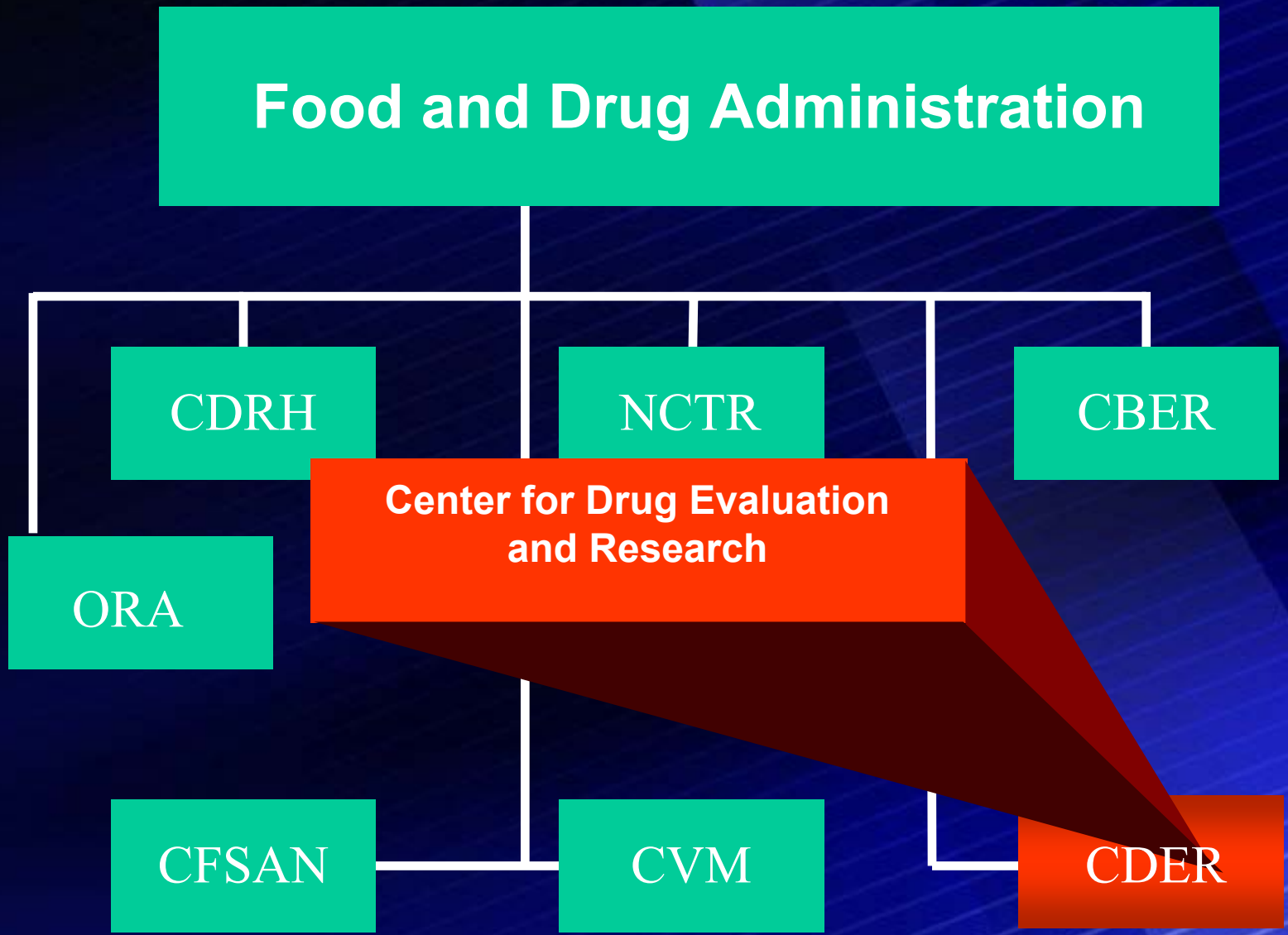
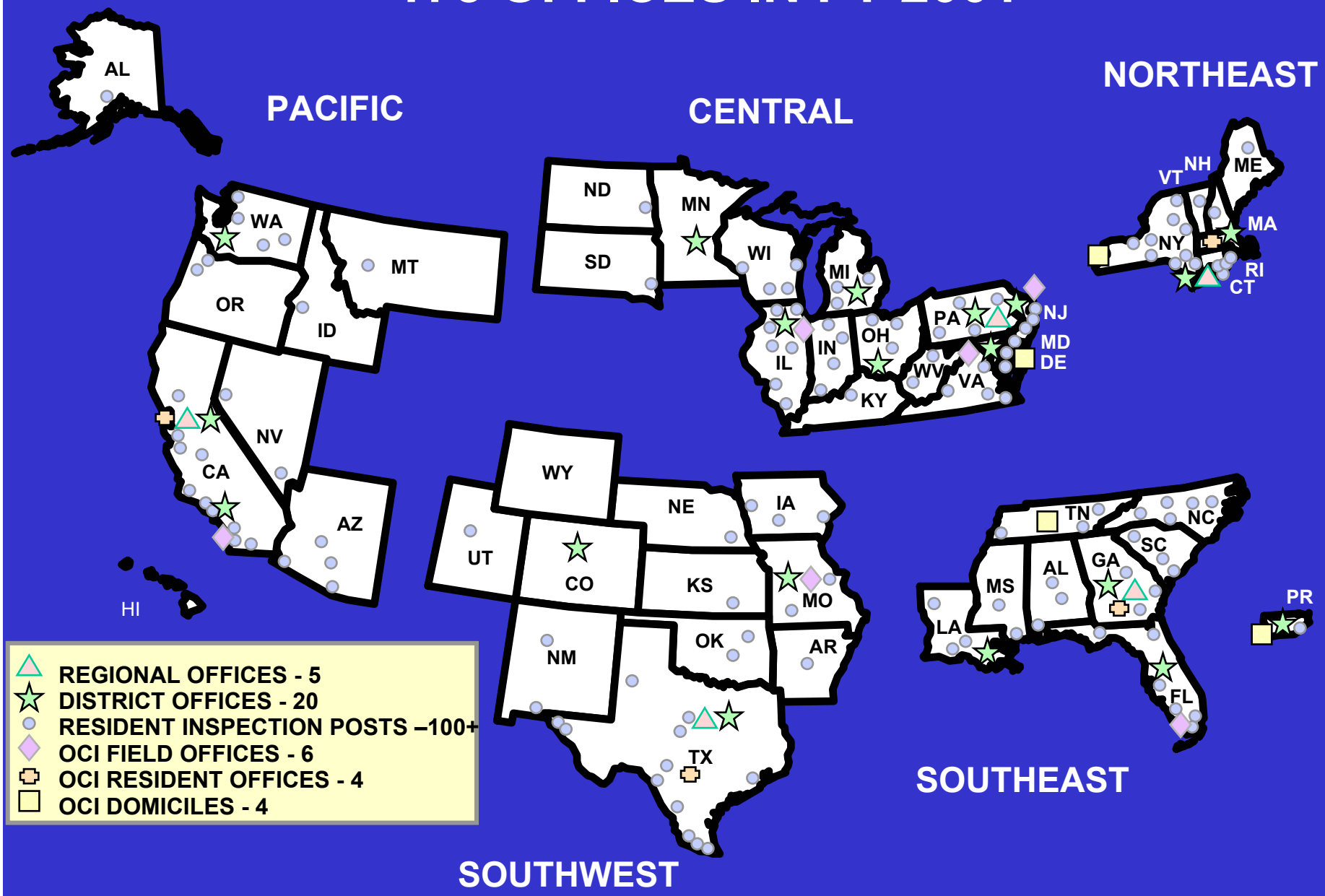
Russell Campbell Jr.
Associate Director for International Policy
Office of the Commissioner

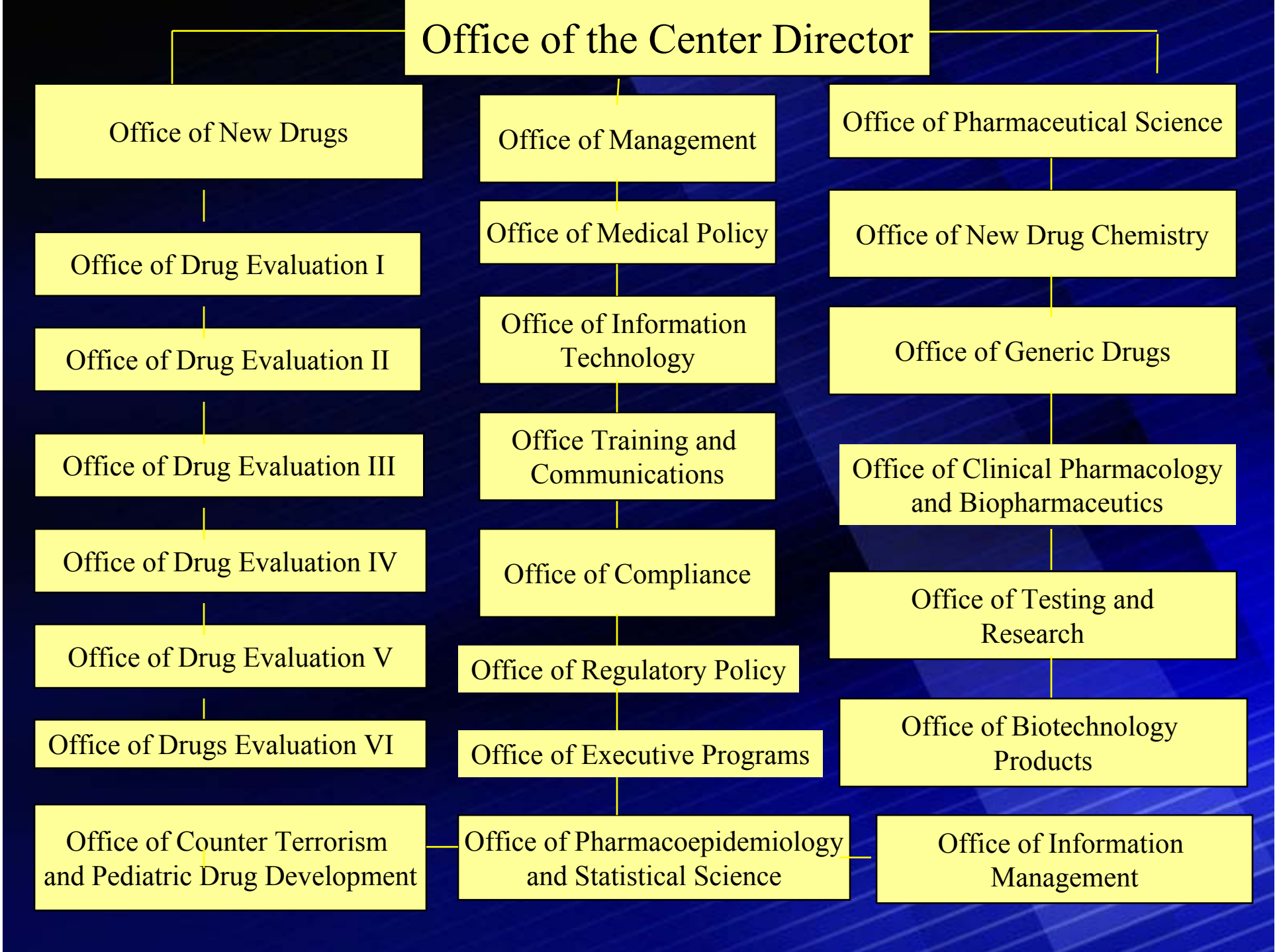
Drug Review and Related Activities in the United States


Public Health Service Act 1944
Drug Price Competition & Patent Restoration Act (Waxman-Hatch Act) 1984
Prescription Drug User Fee Act 1992
Orphan Drug Act 1983
OTC Labeling Final Rule 1999
Kefauver-Harris Drug Amendments 1962
FD & C Act 1938
Original Food and Drug Act 1906
Food and Drug Administration formed 1931


Food and Drug Administration
CDRH
NCTR
CBER
Center for Drug Evaluation and Research
ORA
CFSAN
CVM
CDER

OFFICE OF REGULATORY AFFAIRS
175 OFFICES IN FY 2001




Office of the Center Director
Office of New Drugs
Office of Drug Evaluation I
Office of Drug Evaluation II
Office of Drug Evaluation III
Office of Drug Evaluation IV
Office of Drug Evaluation V
Office of Drugs Evaluation VI
Office of Counter Terrorism and Pediatric Drug Development
Office of Management
Office of Medical Policy
Office of Information Technology
Office Training and Communications
Office of Compliance
Office of Regulatory Policy
Office of Executive Programs
Office of Pharmacoepidemiology and Statistical Science
Office of Pharmaceutical Science
Office of New Drug Chemistry
Office of Generic Drugs
Office of Clinical Pharmacology and Biopharmaceutics
Office of Testing and Research
Office of Biotechnology Products
Office of Information Management

A drug is defined as:

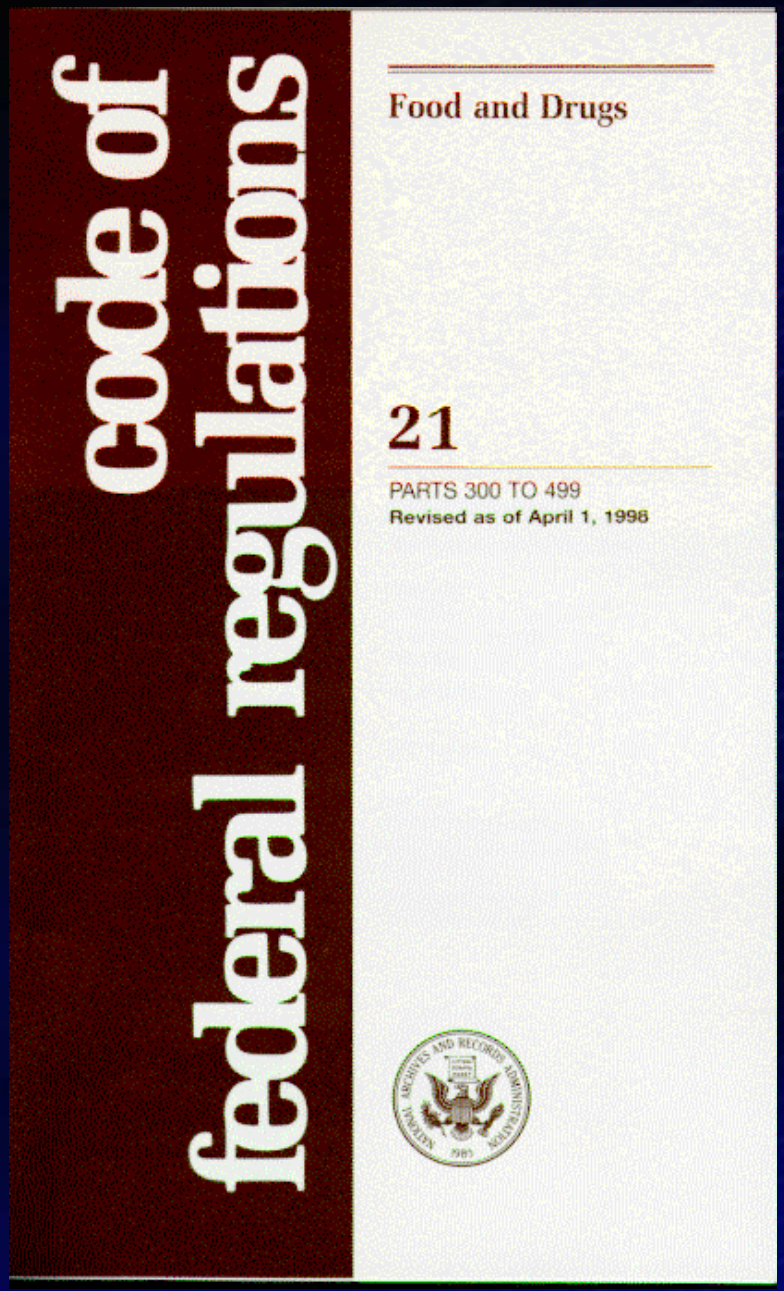
(A)articles recognized in the official USP, HPUS or NF or any supplement to any of them,

(B)articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals,

(C)articles (other than food) intended to affect the structure or any function of the body of man or other function of the body of man or other animals…..

What is a Biologic?

Any virus, therapeutic serum, toxic, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives, applicable to the prevention treatment or cure of diseases or injuries of man.



Industry Guidance

http://www.access.gpo.gov/nara/cfr/

PRE-CLINICAL RESEARCH

DISCOVERY/SCREENING

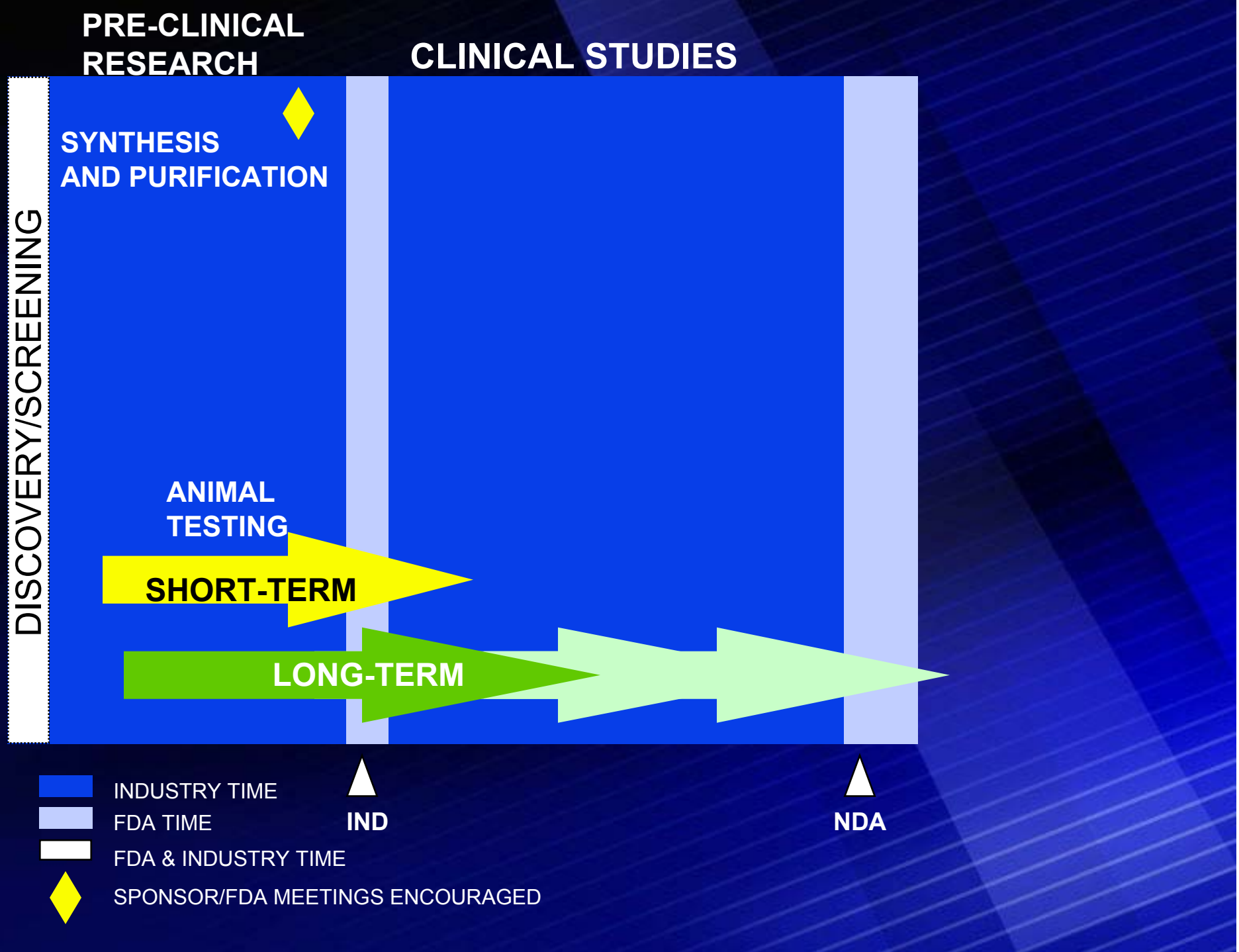
SYNTHESIS AND PURIFICATION

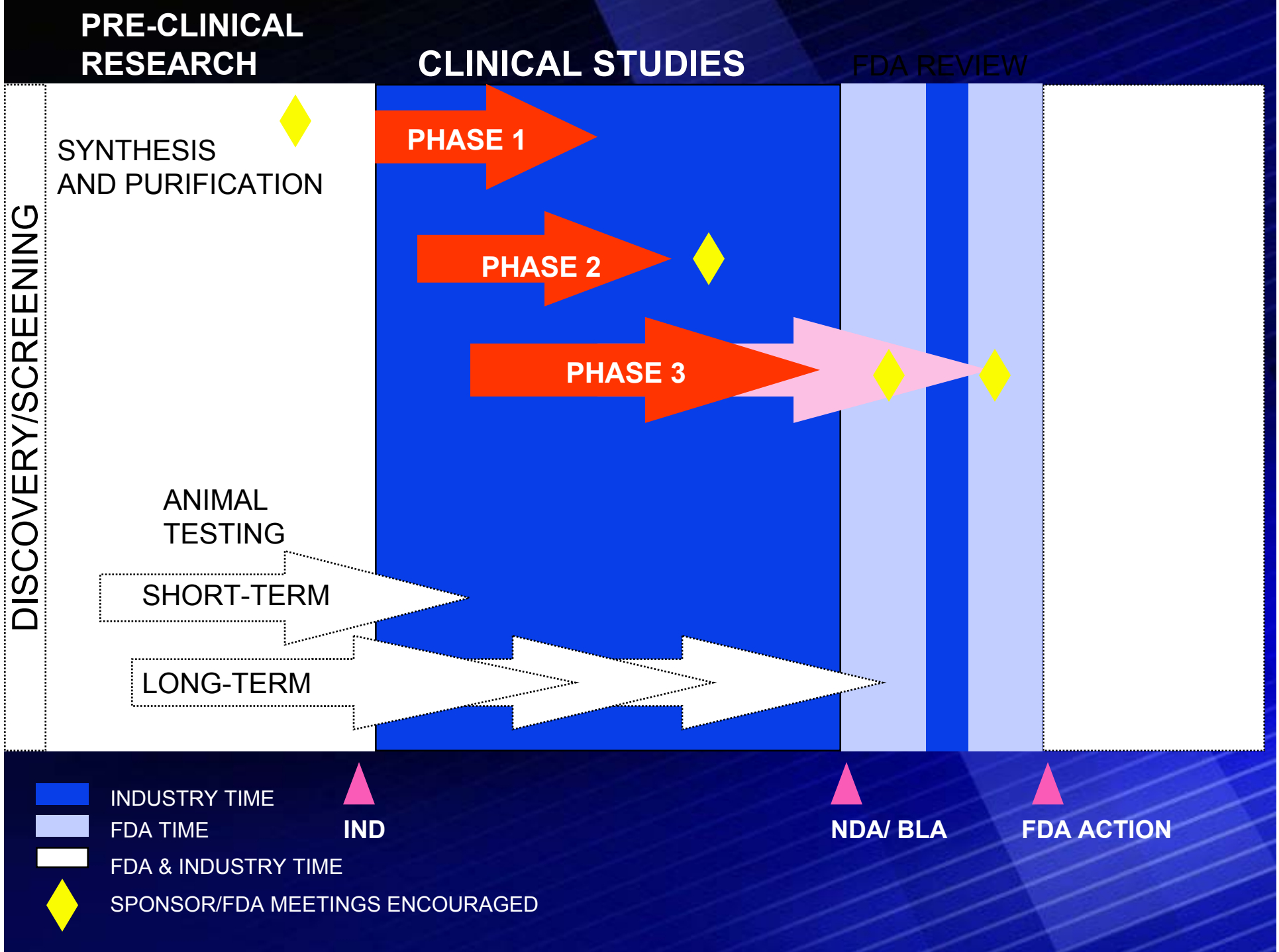
INDUSTRY TIME

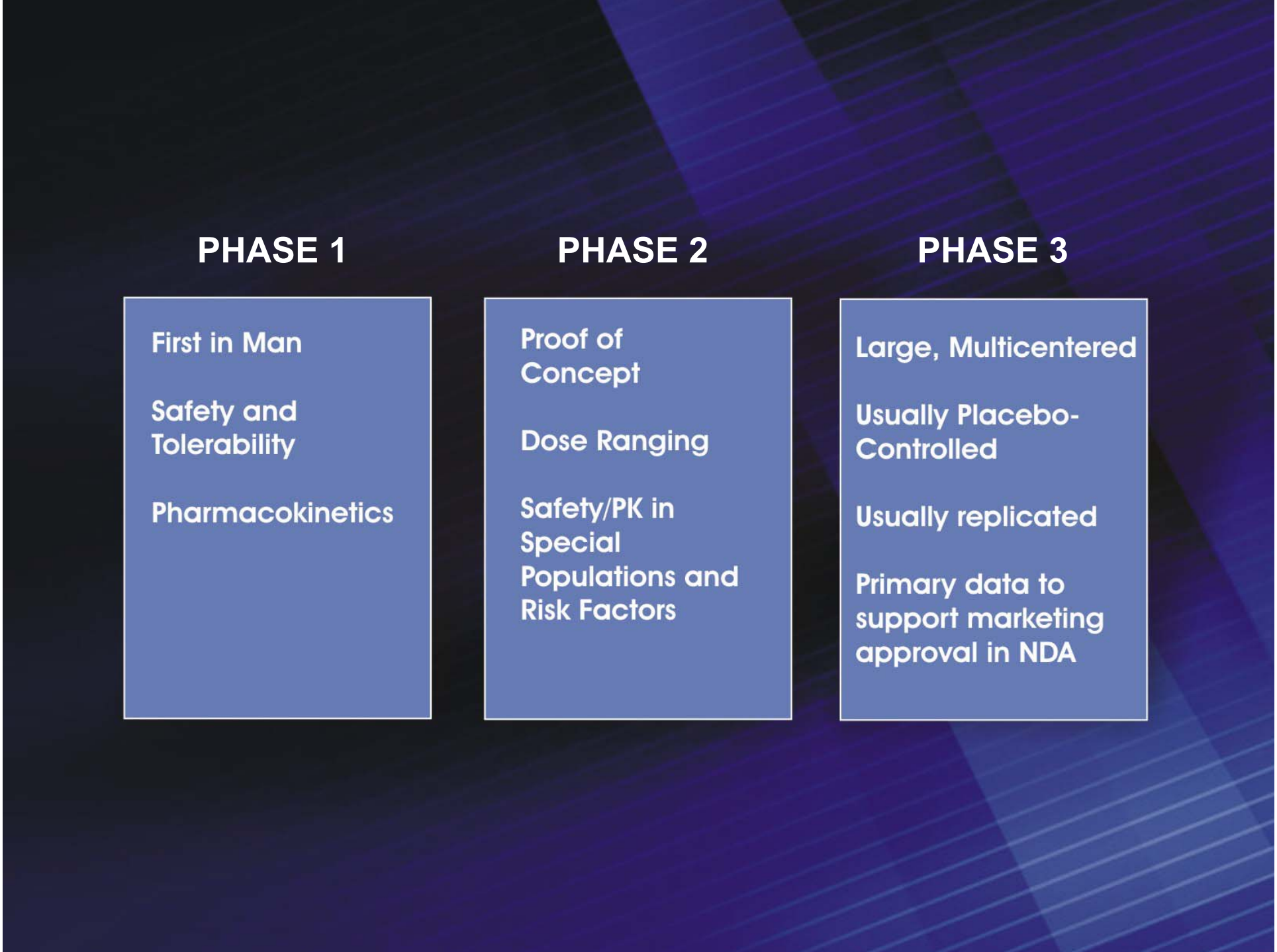
FDA TIME

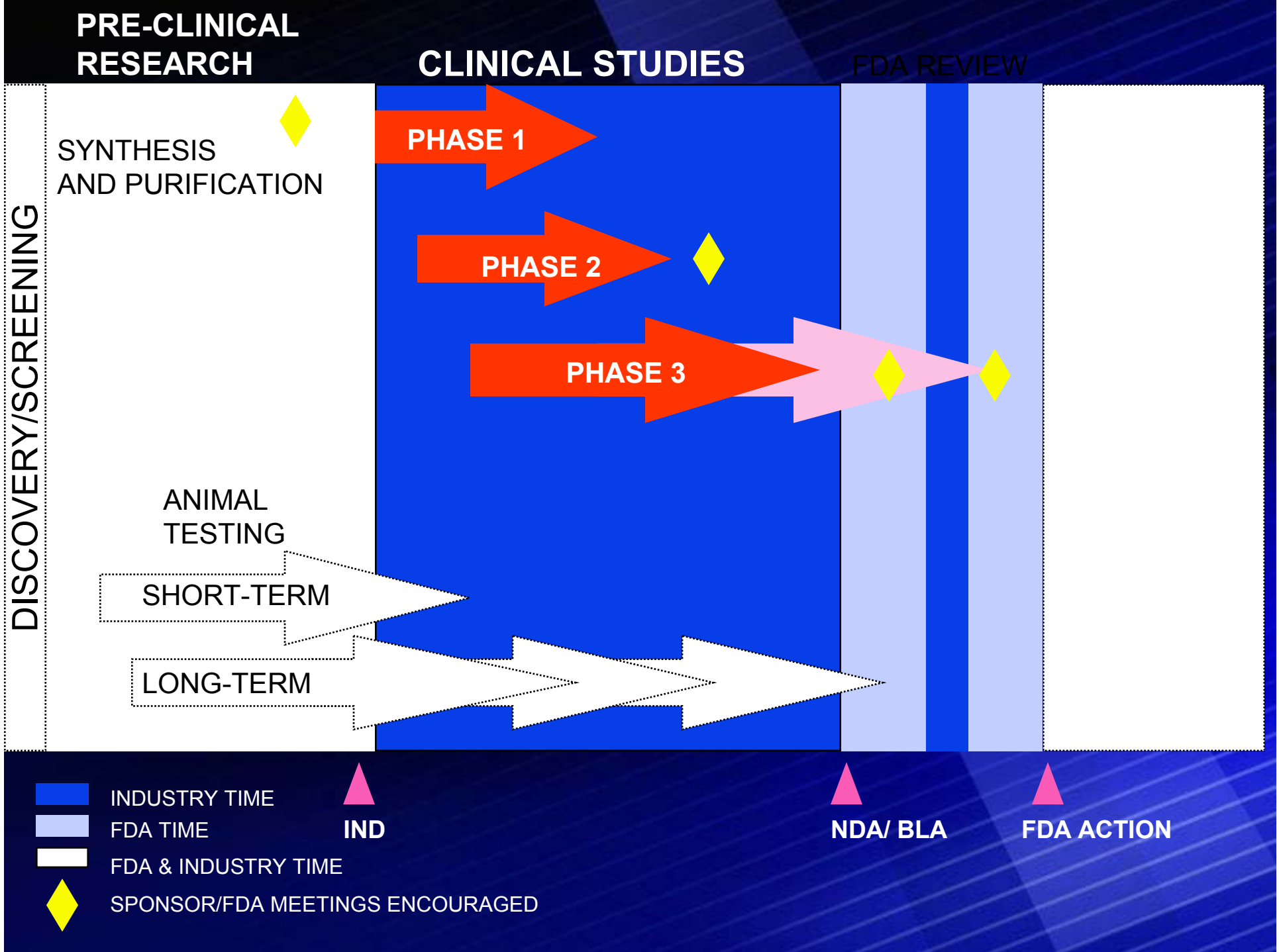
FDA & INDUSTRY TIME

SPONSOR/FDA MEETINGS ENCOURAGED


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
DISCOVERY/SCREENING
SYNTHESIS AND PURIFICATION
ANIMAL TESTING
SHORT-TERM
LONG-TERM
IND
NDA
INDUSTRY TIME
FDA TIME
FDA & INDUSTRY TIME
SPONSOR/FDA MEETINGS ENCOURAGED


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
FDA REVIEW
DISCOVERY/SCREENING
SYNTHESIS AND PURIFICATION
PHASE 1
PHASE 2
PHASE 3
ANIMAL TESTING
SHORT-TERM
LONG-TERM
INDUSTRY TIME
FDA TIME
FDA & INDUSTRY TIME
SPONSOR/FDA MEETINGS ENCOURAGED
IND
NDA/ BLA
FDA ACTION


PHASE 1
First in Man
Safety and Tolerability
Pharmacokinetics
PHASE 2
Proof of Concept
Dose Ranging
Safety/PK in Special Populations and Risk Factors
PHASE 3
Large, Multicentered
Usually Placebo-Controlled
Usually replicated
Primary data to support marketing approval in NDA


PRE-CLINICAL RESEARCH
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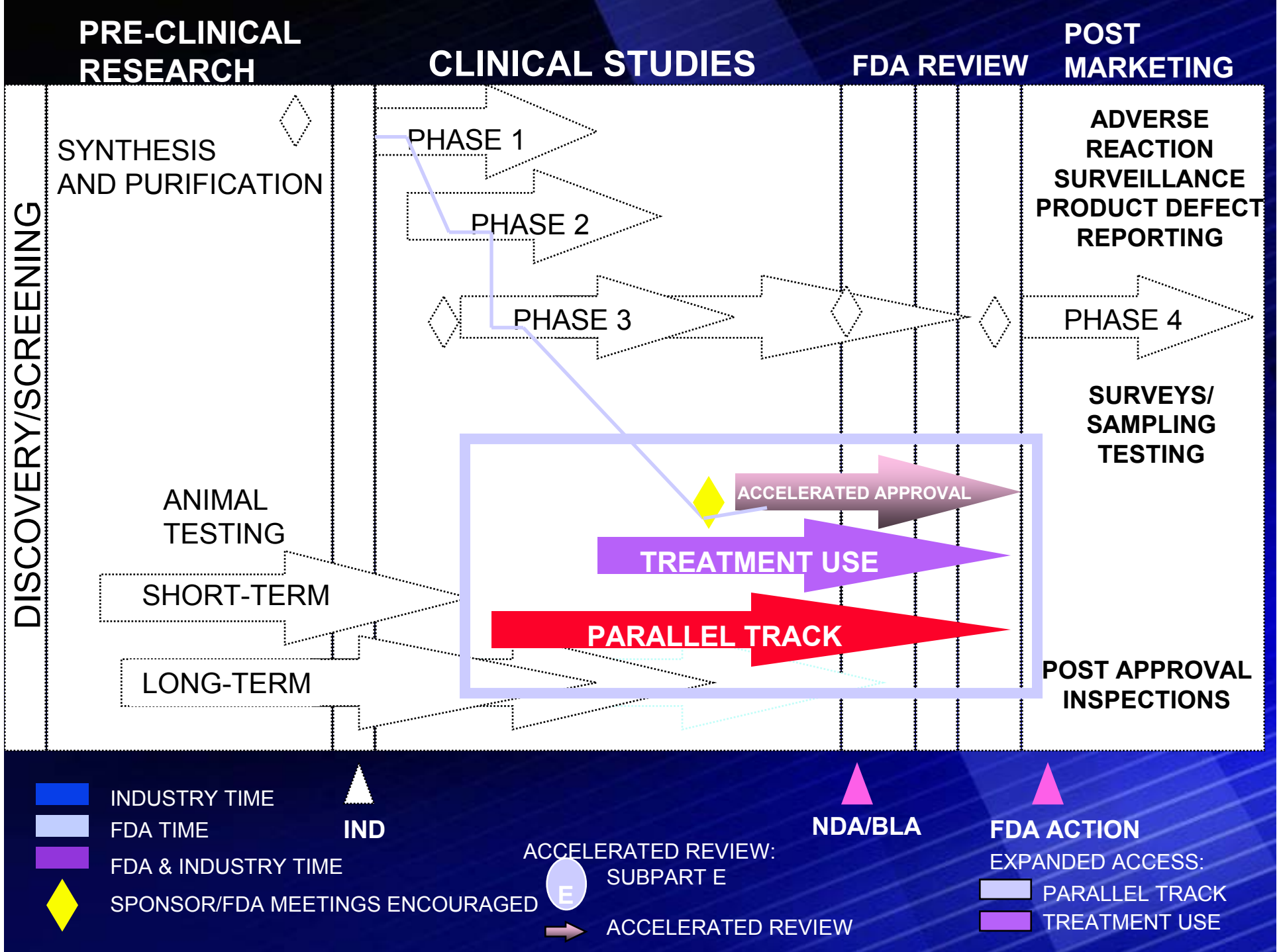

PRE-CLINICAL RESEARCH
CLINICAL STUDIES
FDA REVIEW
POST MARKETING
DISCOVERY/SCREENING
SYNTHESIS AND PURIFICATION
PHASE 1
PHASE 2
PHASE 3
PHASE 4
ADVERSE REACTION SURVEILLANCE PRODUCT DEFECT REPORTING
SURVEYS/ SAMPLING TESTING
POST APPROVAL INSPECTIONS
ANIMAL TESTING
SHORT-TERM
LONG-TERM
ACCELERATED APPROVAL
TREATMENT USE
PARALLEL TRACK
INDUSTRY TIME
FDA TIME
FDA & INDUSTRY TIME
SPONSOR/FDA MEETINGS ENCOURAGED
IND
NDA/BLA
FDA ACTION
ACCELERATED REVIEW: SUBPART E
E
ACCELERATED REVIEW
EXPANDED ACCESS:
PARALLEL TRACK
TREATMENT USE

New Drug Application (NDA) or Biologic License Application (BLA) contains the following:

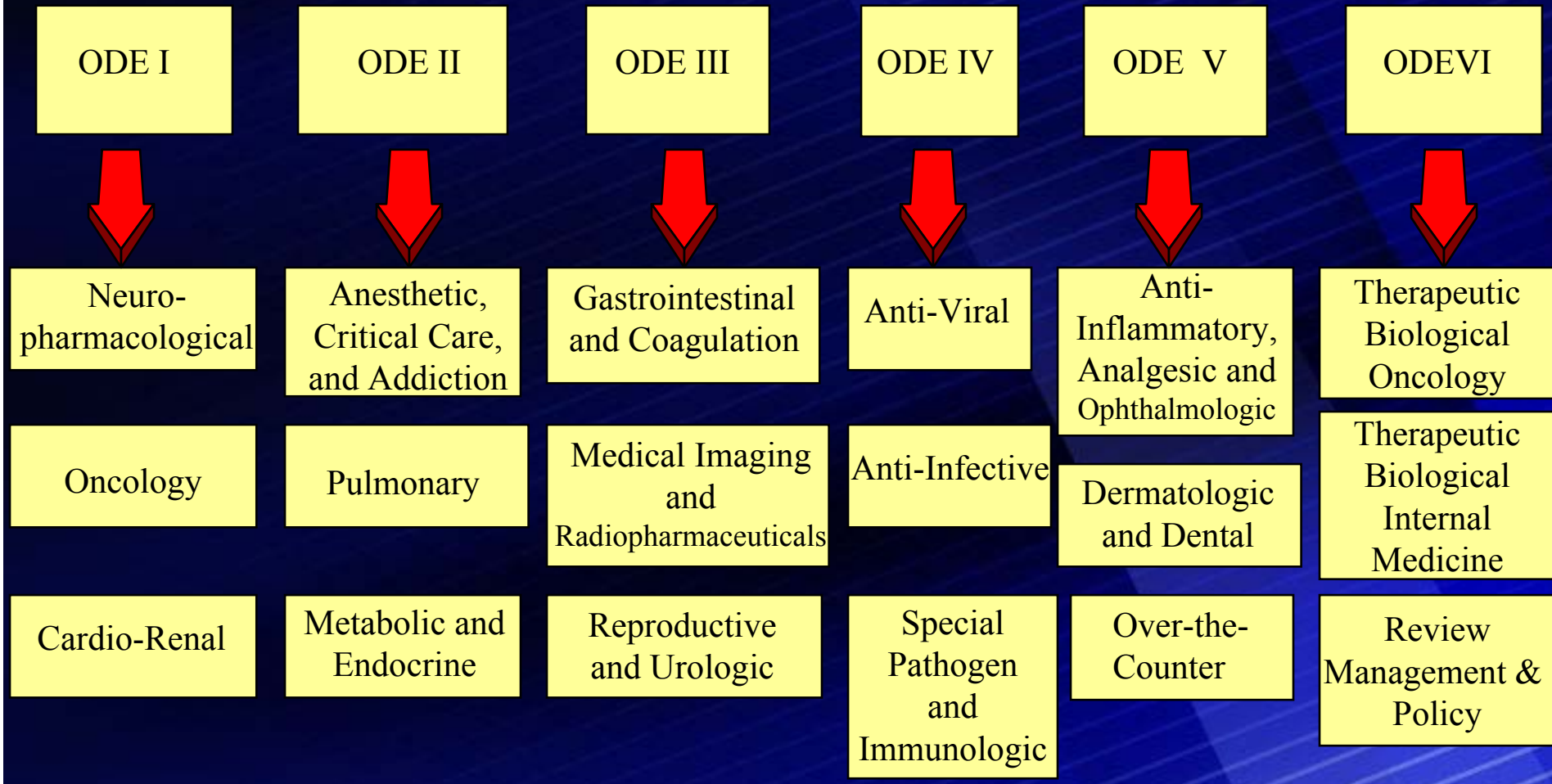
- Pre-clinical studies
- Human clinical studies
- Manufacturing details
- Labeling
- Additional information


FINAL
FINAL

A Better Way

The equivalent of 50,000 paper pages of data..

DRUG PRODUCT DIVISIONS



Review Team

Project Manager
Medical Officer
Chemist
Microbiologist
Statistician
Pharmacologist
Establishment/Facility Reviewer
Support Personnel

ADVISORY COMMITTEE

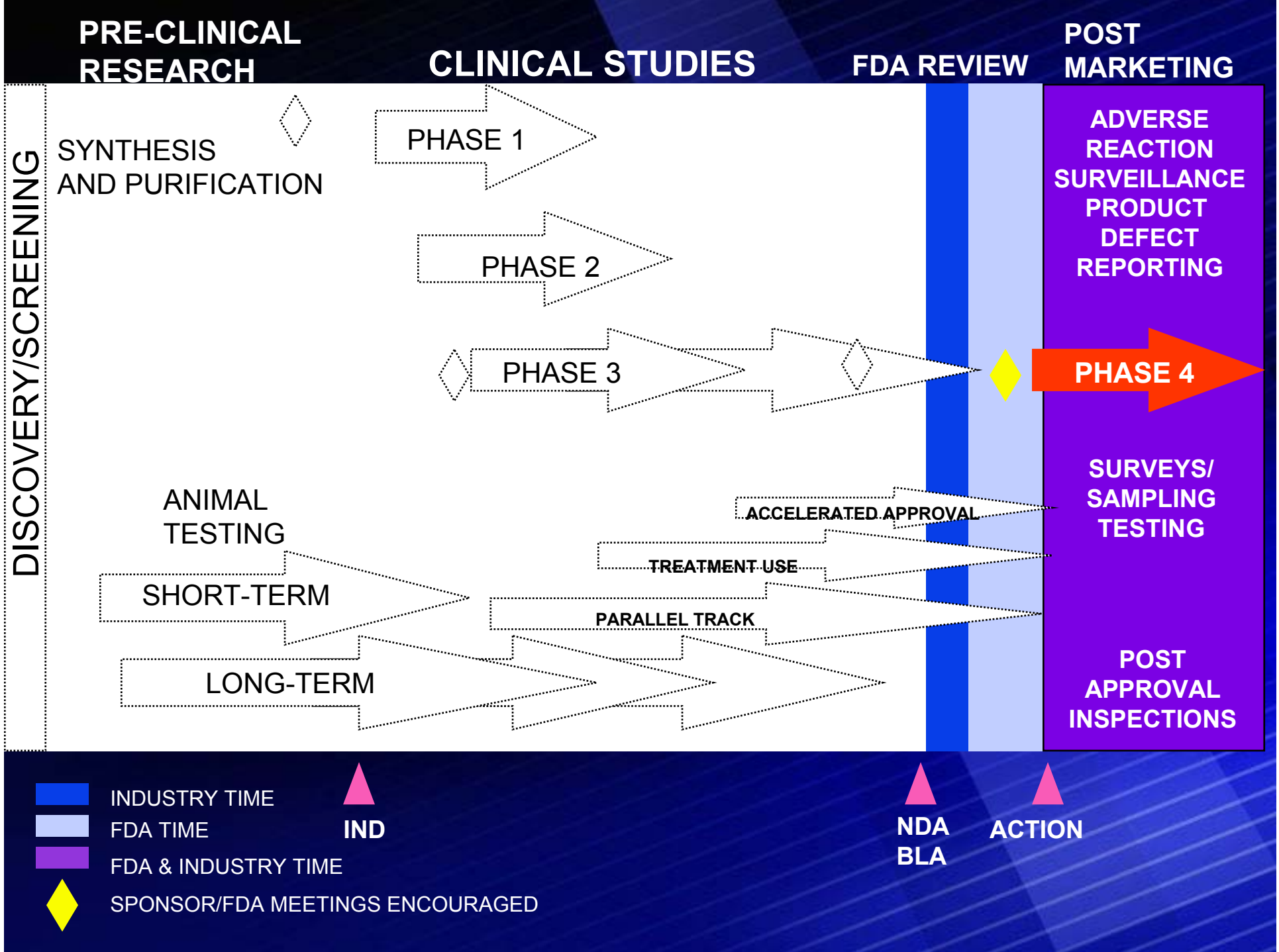
http://www.fda.gov/oc/advisory/default

- Panel of OUTSIDE experts
- Provide advice and opinions to the FDA drug review team
- FDA advisory committee information, 1-800-741-8138 or 301-443-0572

Prescription Drug User Fee Act (PDUFA)

http://www.fda.gov/oc/pdufa/default.htm

- Permits CDER/CBER to charge pharmaceutical manufacturers a fee to review drug applications
- These fees provide appropriate resources to accelerate the review of applications
- Not the only source of funds for CDER/CBER
- Funds go directly to CDER/CBER, not individuals


PRE-CLINICAL RESEARCH
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IND
NDA BLA
ACTION

Registration & Listing

Registration & Listing

All foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the U.S. are required to:

- **Register their name & place of business** (additional requirements- under the PHS & BT Preparedness Act (2002) Section 321
- **List all drug products imported or offered for import into the U.S.**
- **Designate a U.S. Agent**

(FD&C Act Section 510 & 21 CFR 207.40)

Registration & Listing
PHS & BT Preparedness Act (2002)

- Yearly electronic registration of foreign establishments- (electronic registration delayed-Medical Device User Fee and Modernization Act of 2002)
- Name of each importer of each drug in the U.S. known to the manufacturer
- Name of each person who imports or offers for import each drug to the U.S. for purpose of importation

Registration & Listing

Requirements apply to:

- **Manufacturers of finished products and Active pharmaceutical Ingredients (APIs)**
- **Repackers**
- **Relabelers**
- **Control laboratories (registration only)**

Registration & Listing

- An establishment is required to register before any NDA or ANDA is approved.
- An establishment must register within five days after beginning manufacture or processing of a drug product for commercial distribution.
- Registration information shall be renewed annually

Registration & Listing

- When operations are conducted at more than one establishment which are jointly owned and controlled, the registration and listing information may be submitted by the parent, subsidiary and/or affiliate company.
- Drugs imported or offered for import into the United States (U.S.) must be listed with FDA

Registration & Listing

- Listed products are assigned a National Drug Code (NDC #)
- The NDC # identifies the manufacturer or distributor, the drug, and the trade package size and type
- Non-listed products are misbranded under FD&C Act Section 502(o)

Registration & Listing-Exemptions

- Inactive Ingredients
- Non-API intermediates used to synthesize APIs
- Drugs not for importation into the U.S.
- Drugs imported under the Import for Export provisions (801(d)(3))
- Drugs imported or offered for import under the IND regulations

U.S. Agent

- 21 CFR 207.40

  Foreign firms that manufacture, prepare, propagate, compound or process a drug imported or offered for import into the U.S. are required to:

  – Register their name & place of business
  – List all drug products imported or offered for import
  – Designate a U.S. Agent

U.S. Agent

- Definition:

  "Person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent."

- Cannot be a mailbox, answering machine or service, or other places where the person acting as agent is not physically present.

U.S. Agent

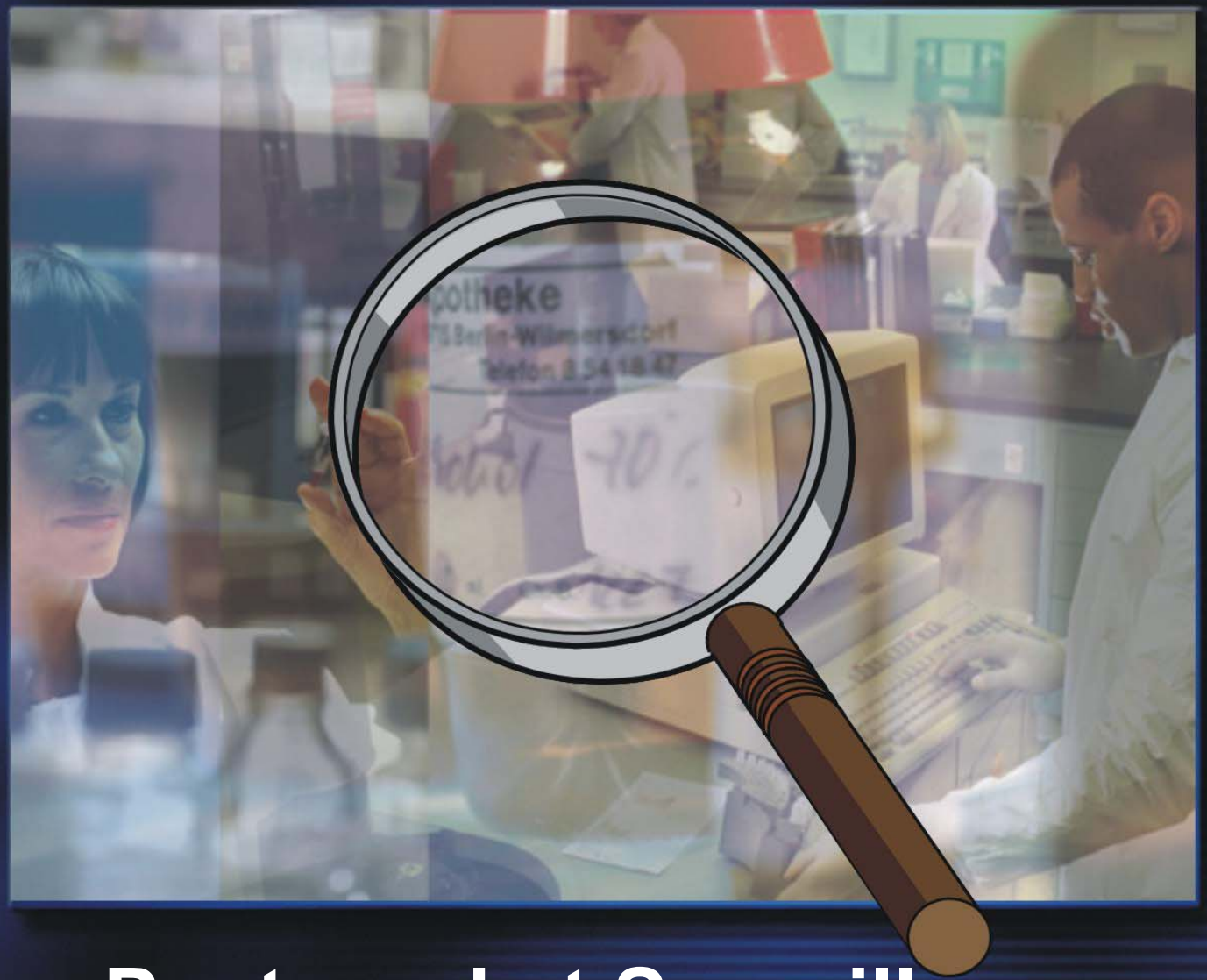
- Registration:
  - Submit letter with annual registration form with the name of U.S. Agent (firm, address, telephone number, email & fax)
  - Letter on company letterhead, signed by authorized company official
  - Changes must be reported within 10 business days of change by firm or U.S. Agent

U.S. Agent

- Responsibilities:
  - assists FDA in communicating with foreign firm
  - responds to questions from FDA about firm's imported products
  - assists FDA in scheduling inspections of foreign firm
  - accepts documents from FDA if foreign firm cannot be contacted

U.S. Agent

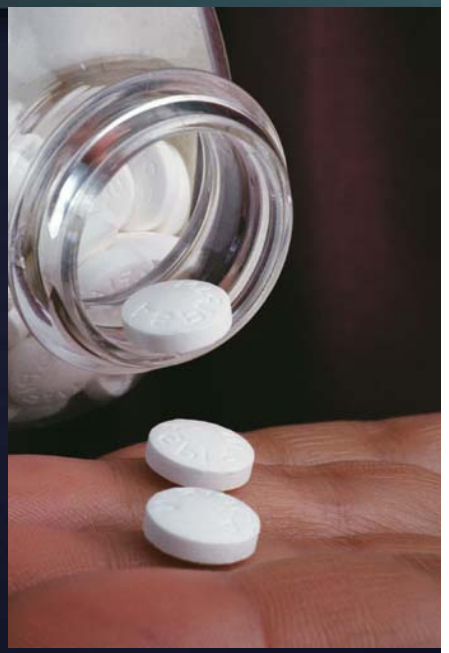
- FDA intentionally imposed few duties on U.S. agent
- Agent is not required to submit any particular documents for foreign firm
- U.S. Agent intended to meet FDA's needs to communicate quickly and efficiently with the foreign firm



Post-market Surveillance

Office of Drug Safety

- Division of Drug Risk Evaluation
- Division of Medication Errors and Technical Support,
- Division of Surveillance, Research, and Communication Support



MedWatch Website

- Safety Information Retrieval
- Adverse Event Reporting for Drugs,Devices, Biologics and Dietary Supplements

www.fda.gov/medwatch

Adverse Event Reporting System (AERS)

- Database
- Internationally compatible

Office of Drug Safety (ODS) uses AERS to:

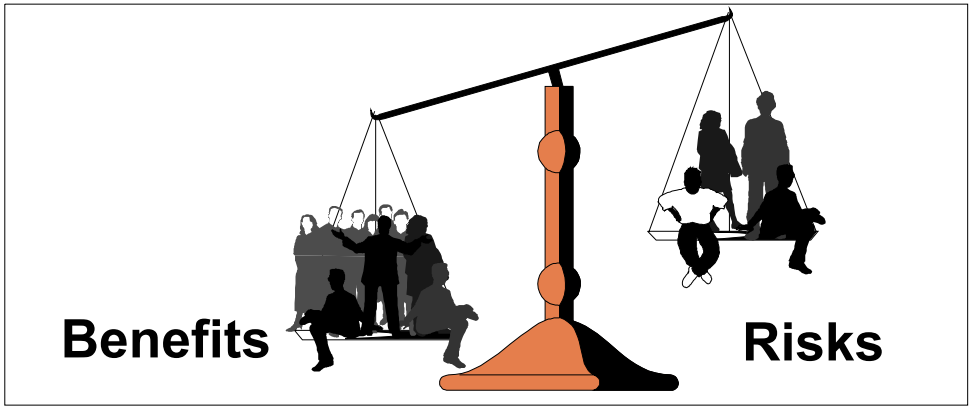
- triage
- review
- assess risk

Potential Regulatory Action for Postmarketing Safety Issues

- Labeling Change
- Scientific publication
- "Dear Doctor" letter (for specific warnings)
- Restricted use
- Restricted distribution
- Patient Medication guide
- Product withdrawal

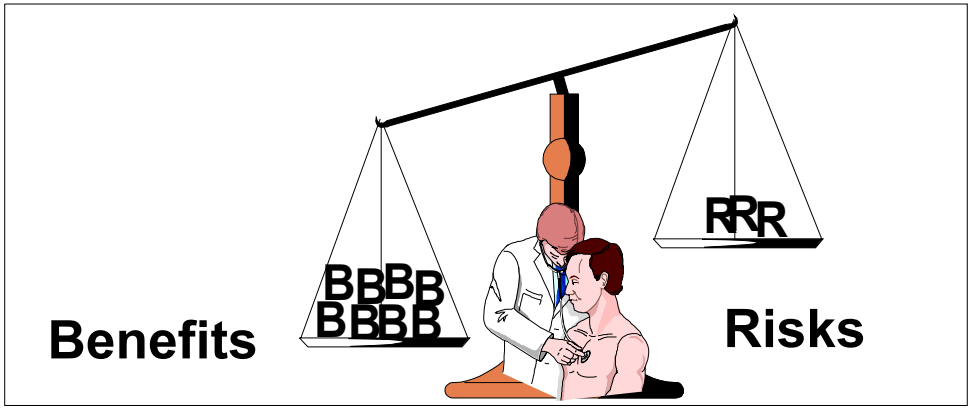
FDA

evaluates
benefits/risks
for the population



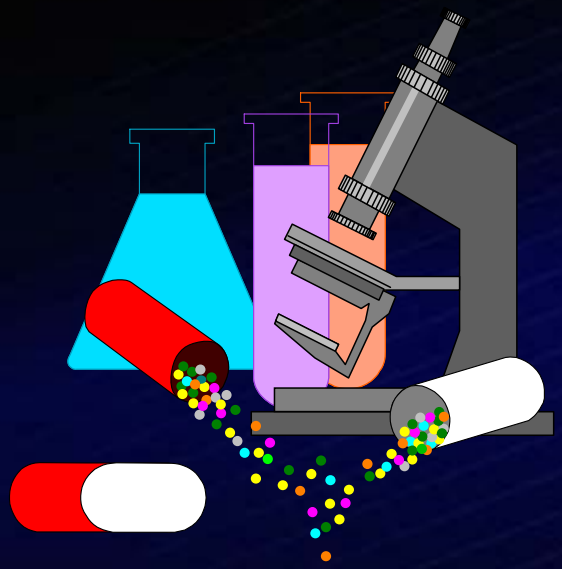
Provider

evaluates
benefits/risks
for a patient



Patient

evaluates
benefits/risks
in terms of
personal values

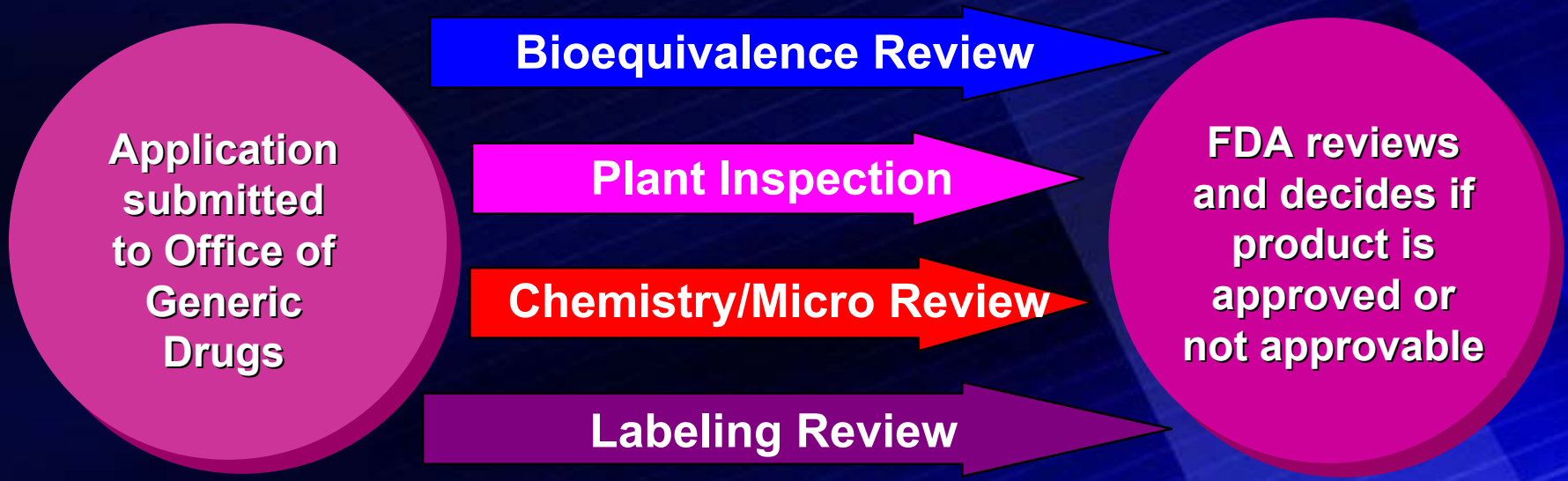


CDER's Office of Compliance

- Sets labeling, manufacturing, and testing standards
- Monitors the quality of marketed drugs
- Evaluates, classifies, and recommends human drug recalls

Generic Drug Review Process

Determine if application is acceptable



NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies 7. Clinical Studies 8. Bioavailability	6. Bioequivalence

Definition of Bioequivalence

A generic drug is considered to be bioequivalent if:

- The rate and extent of absorption do not show a significant difference from listed drug, or
- The extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant

What are the requirements for a generic drug?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use

Compared to reference listed drug (RLD)
- (brand name product)

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS "Orange Book"

http://cdsmlweb1/ob/index.htm

Orphan Drug Products

www.fda.gov/orphan

- Rare diseases or conditions affecting fewer than 200,000 people in the U.S.
- 7 years exclusively after approval
- Special financial incentives
- Grants
- Protocol Assistance

Working with Partners to Meet the Challenge

www.fda.gov/cder

/http://www.fda.gov/cder/handbook/

CDER's Internet Home Page

http://www.fda.gov/cder

Drug Information

888-INFO-FDA or 301- 827-4573

druginfo@cder.fda.gov