# FDA Regulation of Pharmaceutical Marketing

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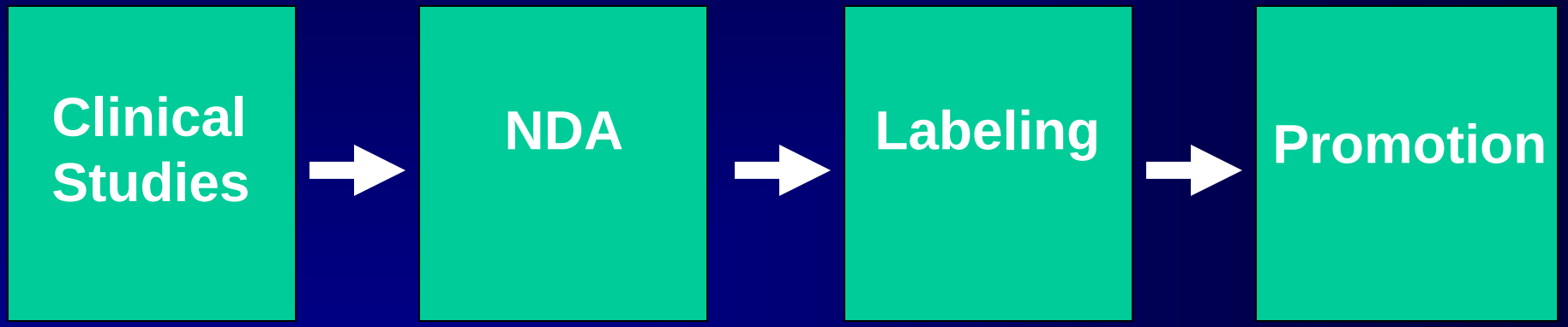
# Brief History of Rx Drug Regulation

- **1931- Food & Drug Administration Established**
- **1938 - Federal Food, Drug and Cosmetic Act**
  - Drugs must be shown safe before marketing
  - Pre-market notification to FDA
  - Manufacturer determines Rx status
- **1962 - Drug Amendments**
  - Pre-market approval of every new drug by FDA
  - New drugs must be demonstrated safe and effective by "substantial evidence"
  - FDA regulation of clinical testing/promotion

# Promotion Regulation
# The Conceptual Approach



# Regulation of Drug Promotion

Prescription drug promotion

- must be **consistent with and not contrary to** labeling
- must include **fair balance**
- may not be **false or misleading**
- must include **all material facts**
- must present a **true statement** of relevant safety/effectiveness
- must have **adequate directions** for use

# Promotion Regulations

- Promotion must be “consistent with and not contrary to” the FDA approved PI
  - May not “expand the indication” beyond approved use
  - May not minimize risks disclosed in the prescribing information

# “Expanding the Indication”

ZOCOR 40mg is proven to reduce the risk of major coronary events and CHD death in patients at high risk of coronary events because of CHD.

# “Minimizing Risk Information”

**Prescribing Information:**

- “Accutane may cause depression, psychosis…suicidal ideation, suicide attempts, and suicide.”

**Reps:**

- “We don’t feel it is an issue.”
- “News has hyped it up.”
- “Like any drug used in patients with depression, even penicillin, it could bring it out.”

# Regulation of Drug Promotion

**Must Include Fair Balance:**

- Sufficient emphasis on side effects and contraindications to balance effectiveness claims
- Inclusion of Prescribing Information or Brief Summary is not sufficient
- Located within promotional piece on same page/spread as benefit information
- Presented with prominence and readability reasonably comparable to claims of safety and efficacy
- Impossible to “balance” a misleading statement

# Regulation of Drug Promotion

**May not be False or Misleading:**

- Suggests use not permitted by label
- Use of tables and graphs to distort/misrepresent relationships
- Use of a headline or graphic in a way that is misleading
- References that are more favorable than overall evidence
- Use of inadequate study design
- Use of statistical significance where clinical significance not shown
- Retrospective analysis of a study/inappropriate statistical analysis
- Mechanism of action claims not generally regarded as established
- Failure to include material facts

# Promotion Regulations

## Support in Adequate Clinical Studies

Promotional claims about safety or effectiveness

– must be described in the PI (labeling)

*OR*

– supported by substantial evidence

- usually, 2 adequate and well-controlled trials
- consistent with the prescribing information

# Promotion Regulations

Adequate and well-controlled studies:

- scientifically sound, clinically meaningful, and statistically significant
- randomized and blinded
- valid comparison with a control
- clear statement of study objectives
- pre-specified endpoints
- pre-specified statistical analysis plan

# Substantial Evidence

These are usually not considered adequate to support claims beyond PI:

- *In vitro* evidence
- Computer modeling
- Mechanism of Action
- Clinical Practice Guidelines
- Consensus documents

# ***Comparative* Claims**

- Both products approved for indication studied
- Comparable patient populations
- Doses consistent with PI and in same part of dosage range
- Comparisons of clinically meaningful endpoints
- Formulation identical to U.S. formulation
- Two adequate and well-controlled studies

# Rx Drug Communications

Promotional Labeling  Advertising

"Promotional Activities"

# Rx Drug Communications

- Promotional Labeling
  - All labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying a drug
  - Disseminated ***by or on behalf*** of manufacturer
  - Communicated to healthcare professionals (HCP's) to promote the sale of a drug
- **Promotional Labeling must be accompanied by FDA approved Prescribing Information**

# Rx Drug Communications

- Advertising
  - Advertisements in published journals, magazines, periodicals, newspapers
  - Advertisements broadcast through media
    - Television, radio, Internet, telephone and fax
  - Requires “information in brief summary relating to side effects, contraindications, and effectiveness” from PI

# 1997 Guidance on Broadcast Direct-to-Consumer Advertisements

**Broadcast Product-Claim Ads**

- Include a *major statement* of risk information
- Adequate provision to disseminate the product labeling
  - 800 Phone #
  - Website
  - Concurrent Print
  - Healthcare Professional

# Types of Advertising

- Product-claim ad
  - Includes product name and indication/use
- Unbranded Ad (Help-Seeking/Disease Awareness)
  - Discusses a disease or health condition but does not mention or suggest any particular treatment
  - Fair balance and Brief Summary not required
- Reminder Ad (not boxed warning drugs)
  - Contains proprietary and established name
  - No representation or suggestion of product use
  - Fair balance and Brief Summary not required
-

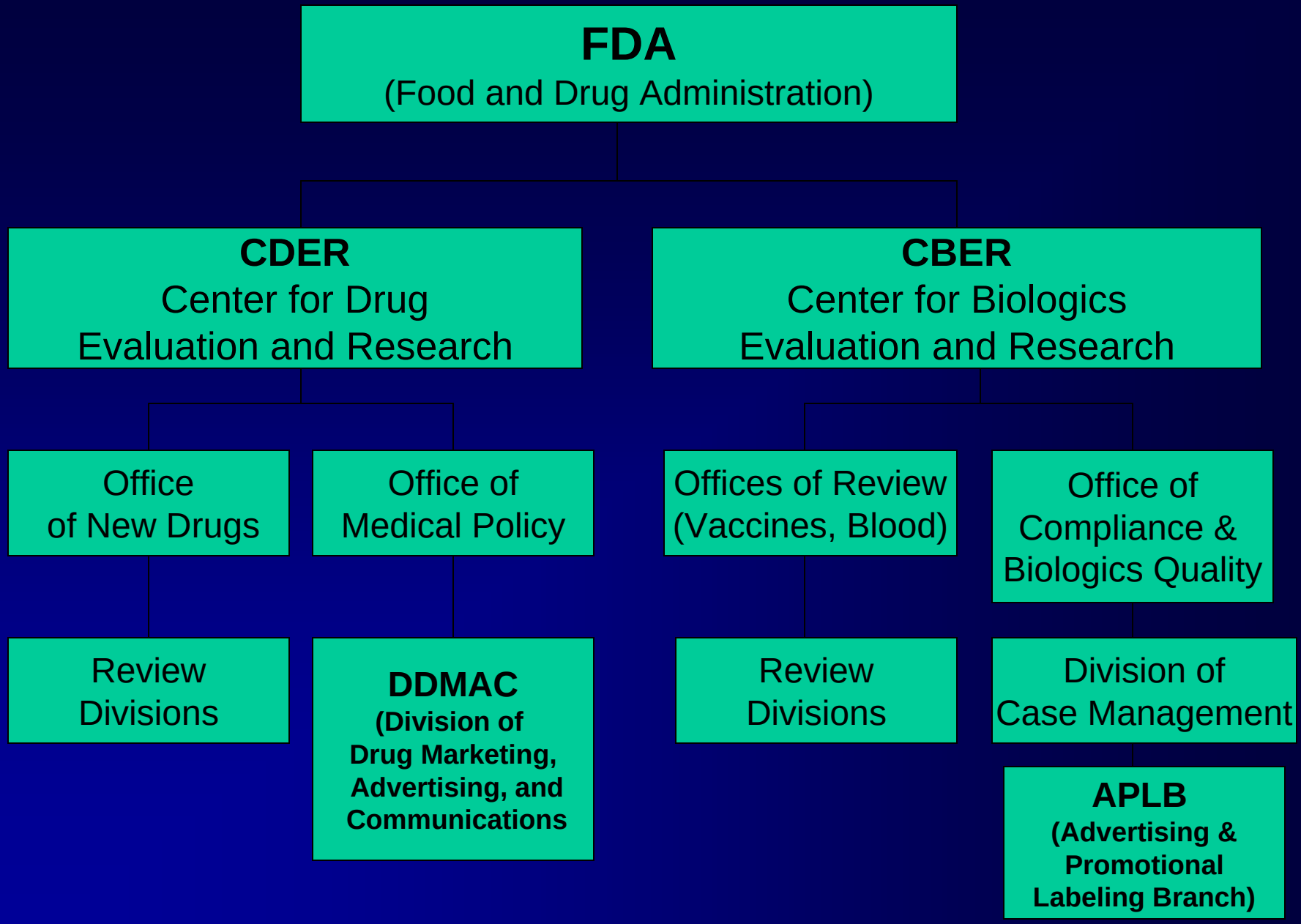
# Pre-Approval Promotion

**Sponsor shall not represent in a promotional context that an investigational drug is safe or effective**

- Institutional:
  - Company X is doing research in Y area of medicine
  - Cannot mention any drug by brand or generic name
- Coming soon:
  - Announce name of a new product that will be available soon
  - May not make written, verbal, or graphic representations or suggestions concerning the safety, efficacy, or intended use of the product

# ***Scientific Communications***

- Publications
- Presentations & Poster sessions
- Scientific Exchange Press Releases
  - Present the results of a study but do not draw conclusions or include any promotional efficacy/safety claims
- Clinical Study Reprints under ~~FDAMA~~
  - Restricted to new uses of an approved drug
  - Peer-reviewed articles in a scientific or medical journal considered "scientifically sound."
  - Sponsor must have plans to pursue approval of new use discussed in reprint
  - Obtain FDA approval to disseminate reprint

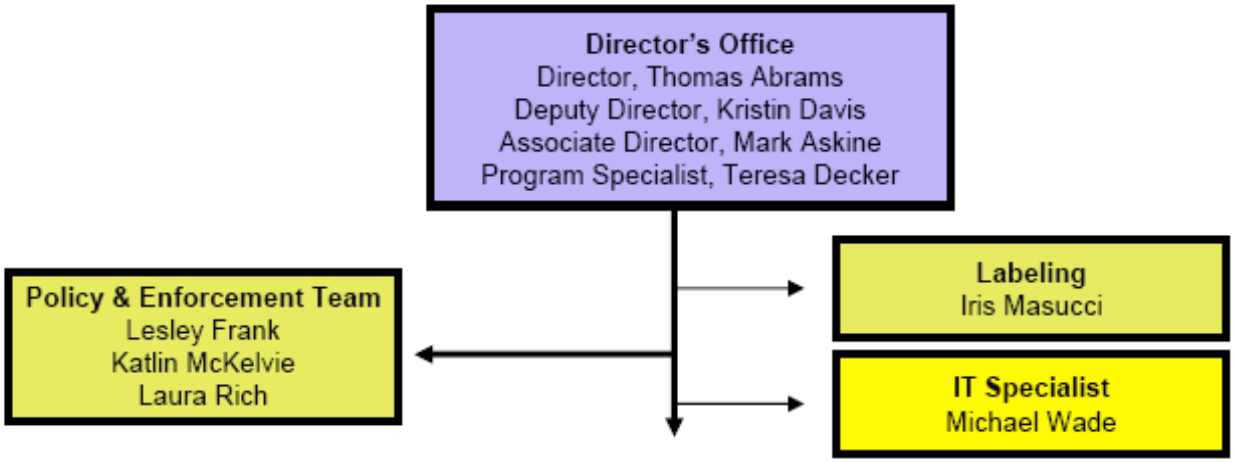

FDA
(Food and Drug Administration)
CDER
Center for Drug
Evaluation and Research
CBER
Center for Biologics
Evaluation and Research
Office
of New Drugs
Office of
Medical Policy
Offices of Review
(Vaccines, Blood)
Office of
Compliance &
Biologics Quality
Review
Divisions
DDMAC
(Division of
Drug Marketing,
Advertising, and
Communications
Review
Divisions
Division of
Case Management
APLB
(Advertising &
Promotional
Labeling Branch)

# DDMAC's Mission

To protect the public health by assuring prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both health professionals and consumers.

# The Division of Drug Marketing, Advertising, and Communications

( 5/1/07)




| Professional Review Group I<br>Leader<br>Jialynn Wang | Professional Review Group II<br>Leader<br>Catherine Gray | Professional Review Group III<br>Leader<br>Elaine Hu | Professional Review Group IV<br>Acting Leader<br>Lynn Panholzer | Training and Support Group<br>Leader<br>Barbara Chong | Direct-To-Consumer Review Group I<br>Leader<br>Christine Smith | Direct-To-Consumer Review Group II<br>Leader<br>Marci Kiester |
|---|---|---|---|---|---|---|
| Neurology<br>(Amy Toscano) | Oncology Drugs<br>(Joseph Grillo,<br>Kathy Oh) | Pulmonary & Allergy<br>(Michelle Safarik) | Anti-Infectives & Ophthalmology<br>(Sheila Ryan) | (Sangeeta Vaswani) | Groups 2 & 3<br>(Shefali Doshi,<br>Joan Hankin) | Groups 1 & 4<br>(Aline Moukhtara,<br>Carrie Newcomer,<br>Vacancy) |
| Psychiatry<br>(Robert Dean) | Oncology Biologics<br>(Carole Broadnax) | Analgesics, Anesthetics, & Rheumatology<br>(Vacancy) | Special Pathogens & Transplant<br>(Suzanne Berkman) | | **Research Team**<br>(Kathryn Aikin,<br>Amie Braman) | |
| Cardiovascular & Renal<br>(Lisa Hubbard) | Dermatology & Dental<br>(Andrew Haffer) | Evidence Review and Metabolism & Endocrinology<br>(Kanika Vij) | Antivirals<br>(Jennifer Fan) | | | |
| Reproductive & Urology<br>(Corrinne Kulick) | | Evidence Review and Gastroenterology<br>(Michael Brony) | Medical Imaging & Hematology<br>(Sean Bradley) | | | |
| TIA, Sharon Smith | | | TIA, Guyann Toliver | | | |

# DDMAC "Hotbuttons"

**Most common reasons for enforcement letters:**

- Inadequate Fair Balance
- Minimization or omission of risk information
- Overstatement of Efficacy
- Expansion of approved Indication
- Omission of material facts
- Unsubstantiated claims
- Unsubstantiated comparative efficacy and safety claims

# DDMAC Enforcement

Enforcement Letters

- **Untitled Letter** (Notice of Violation)
  - Remove materials with violative messages
- **Warning Letter**
  - Remove materials with violative messages
  - Corrective advertising to same audience

# “2253” Submissions

***Federal regulations require drug manufacturers to submit samples of any and all advertising and promotional materials to FDA at time of first use***

# Things We Did Not Cover

- DTC TV
- The Internet
- Conventions
- Press Releases
- Use of Celebrities
- Patient Testimonials
- Product Placements
- Use of Generic Names
- Competitive Complaints
- CME vs Paid Physician Speakers
- Solicited vs Unsolicited Questions
- Requests for DDMAC Review & Comment

# Resources

- DDMAC Website
  - Homepage – www.fda.gov/cder/ddmac
  - Enforcement Letters - www.fda.gov/cder/warn
- APLB Website
  - Enforcement Letters - www.fda.gov/cber/efoi/adpromo.htm
- PhRMA website - www.phrma.org
- ACCME website - www.accme.org
- thomas_casola@merck.com