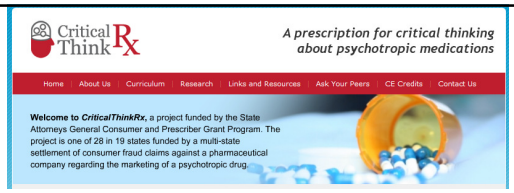

A Critical Curriculum on Psychotropic Medications

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www.CriticalThinkRx.org

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Module 3

The Drug Approval Process

All drugs intended for prescription in this country must be ***approved*** by the U.S. Food & Drug Administration (FDA)

There are huge financial and health stakes in drug approvals

7

The FDA was established by Congress in 1906 to enforce standards on purity of medicinal compounds

Today, the FDA's **Center for Drug Evaluation and Research (CDER)** oversees testing and approval of medications

8

The CDER conducts no drug tests of its own—drug firms (sponsors) pay for and conduct all tests

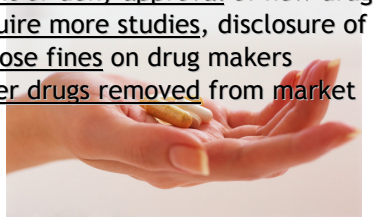
Based on data submitted by sponsors, CDER judges a drug's "efficacy" and "safety"

(Avorn, 2004)

9

Some FDA mandates

- ☑ grant permission to test drugs on humans
- ☑ review data on safety and efficacy
- ☑ set criteria for drug approval
- ☑ grant or deny approval of new drugs
- ☑ require more studies, disclosure of risks
- ☑ impose fines on drug makers
- ☑ order drugs removed from market



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1938 Federal Food, Drug and Cosmetic Act:

Basis for FDA regulation of drugs

- Passed after 100 deaths in 1937 from a toxin in a batch of sulfa drugs

(Ballentine, no date)

11

FDA's drug testing rules tightened after **thalidomide**, prescribed to pregnant women in Europe in 1960, caused birth defects

12

As a result, 1962 amendments to *Food, Drug, & Cosmetic Act* of 1938 required sponsors to:

- ✓demonstrate efficacy in controlled trials
- ✓report serious adverse effects to FDA
- ✓list all known risks (on drug label and in drug ads to doctors)

13

More recent FDA laws have been controversial

Some scientists, advocacy groups, and legislators often accuse the FDA of treating industry, not the public, as its client

(Hawthorne, 2005; Sharav, 2007)

14

Prescription Drug User Fee Act, 1992

To speed up approval times, FDA collects fees from sponsors

User fees now make up over 50% of CDER's budget

(Avorn, 2007)

Impact of user fees

Since 1992 and the birth of user fees, the FDA has slashed its own testing laboratories and network of independent drug safety experts in favor of hiring more people to approve drugs for the pharmaceutical industry

(Harris, 2004)

16

"User fees have undoubtedly constrained the FDA's independence and influenced its decisions."

Marcia Angell, former editor, *New England Journal of Medicine*

FDA's User-Fee Habit
washingtonpost.com
By Cindy Skrzycki
Tuesday, April 3, 2007; D01

17

Draft Guidance on Direct-to-Consumer Advertising, 1997

After 15 years of industry pressure, the FDA allowed sponsors to advertise prescription drugs directly to consumers

- *DTCA is praised for providing drug information to consumers*
- *DTCA is criticized for increasing drug costs and promoting least effective drugs*

(Gellad & Lyles, 2007; Hollon, 1999)

18

Pediatric Research Equity Act, 2003 & *Pediatric Exclusivity Act*, 2004

FDA can request studies to be conducted on children, giving sponsors an extra 6 months of exclusive marketing for every drug studied

- *Acts are praised for stimulating research on drug effects and indications in children*
- *Acts are criticized for griving drug firms unneeded profits and using kids as guinea pigs for unnecessary drug testing*

19

Part B

FDA's Drug Approval Process

20

Few drugs make it to market

5,000 molecules screened in the lab = 1 obtains FDA approval as a medication

From start to finish, sponsor will spend $100 - $400 million to obtain FDA approval

(Goozner, 2004; Ng, 2004)

21

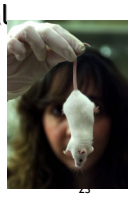
FDA requires that drugs intended for prescription undergo pre-clinical and clinical testing

22

Pre-clinical testing: 2-4 years

A promising molecule is tested in laboratory and on animals

- to establish its main biological activity and
- to rule out that it causes cancer, mutations, and birth defects



23

If drug remains promising after pre-clinical testing, sponsor may apply to start clinical trials on humans

Phase I trials: 1-2 years

Drug is given to 20-80 healthy volunteers to establish safe dosage levels, main adverse effects, "abuse potential"

25

Phase II trials: 2-3 years

Drug is given to 300-500 people with the illness for which the drug is supposed to be marketed

- The goal is to show promising therapeutic effects in order to justify the next phase of trials

26

Phase III trials: 2-4 years

In *randomized controlled trials* (RCTs), 1000-3000 diagnosed patients from many sites are *randomly* assigned to receive either the drug or a placebo

- Neither investigators nor patients are supposed to know who is receiving what ("double-blind")

27

FDA approval requires only 2 positive Phase III trials, even if more trials are negative

Positive trial: on a symptom rating scale, drug-treated group shows *statistically significant* advantage over placebo-treated group

(FDA, 1998)

A drug showing "efficacy"

✓has shown <5% chance of being worse than placebo

✓has *not* shown that it helps patient's condition to remit, or that it works better than another drug

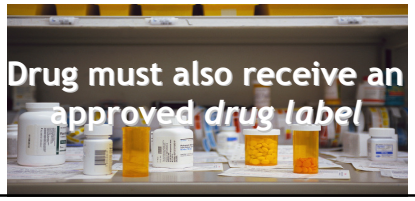
(Avorn, 2004)

29

With 2 positive Phase III trials, sponsor can make a **New Drug Application (NDA)**, requesting FDA approval to market drug for a specific indication and age group covered in the trials

30

FDA reviews pre-clinical and clinical studies and decides whether the drug's benefits outweigh its risks



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Drug label

- Label summarizes information from pre-clinical and clinical trials
- Exact contents are negotiated in private by FDA and sponsor
- A shortened form must appear in all drug packaging and advertising, except broadcast
- Label is considered the authoritative drug information

32

Phase IV trials: Post-marketing surveillance

- As a condition for approval, FDA usually requests sponsor to conduct post-marketing trials
- These trials evaluate the drug under ordinary conditions, with ordinary patients
- Phase IV trials give more realistic view of drug's harms and benefits

33

Part C

Limitations of Clinical Trials

34

To discover new drugs for physical diseases

Researchers start with a *target* of drug action identified by understanding how a disease affects the body at the cellular/molecular levels

35

Not the same process for mental disorders…

- Cellular/molecular biology of mental disorders is *unknown*—drugs tested for these problems don't target known biological anomalies
- These drugs are selected based on their *effects on animal behavior* and *expected effects on people's complaints and behavior*

(Moncrieff & Cohen, 2005)

36

No biological markers exist

To repeat – mental and emotional problems ***are not*** equivalent to physical diseases

No cause has been shown to be exclusively biological

There is ***no biological marker*** for any DSM "primary mental disorder," including schizophrenia

(Charney et al., 2002)

37

Flaws in clinical trials

Analysts and critics have revealed many problems with the design and conduct of clinical trials of psychotropic drugs

Overall conclusion:

Clinical trials do not provide definite basis to determine benefits or risks of drugs

(Cohen, 2002; Safer, 2002)

38

Trials at all phases neglect most psychoactive effects

Practice: Trials focus on measuring narrowly selected complaints and behavior

Problem: Main psychological alterations produced by drugs remain unknown

(Jacobs & Cohen, 1999; Cohen & Jacobs, 2007)

39

Phase II & III trials are very short

Practice: Most last only 3-8 weeks, and up to 70% of subjects drop out before trial's end

Problem: Only some acute effects are detected—not those emerging over a longer time

(Cohen & Jacobs, 2007)

40

Subjects are wrongly assumed to have the "same" disorder

Practice: In a depression drug trial, a subject meeting DSM criteria for depression is eligible

Problem: 200 distinct symptom combinations = DSM diagnosis of depression

Also, subjects usually meet DSM criteria for *several* diagnoses

The "sameness" of subjects' problems—needed for a valid comparison of treatments—is not established

(Beutler & Malik, 2002; Cohen & Jacobs, 2007; Emslie et al. 2002)

41

Inert pills are used as comparisons

Practice: Drugs with psychoactive effects are compared to inert sugar pills

Problem: Placebos can be active (causing physical sensations) or inert (no sensations)

Because they are more powerful, active placebos are almost never used

Also, sponsors routinely screen and exclude placebo responders from clinical trials

(Abboud, 2004; Fisher & Greenberg, 2003)

42

The "blind" is often broken

Practice: It's assumed that patients and investigators are "blind" to treatment status

Problem: Obvious side effects in drug-treated subjects cue everyone about which treatment they're getting. This breaks the "blind"—making objective studies impossible

(Fisher & Greenberg, 1993)

43

High doses of comparison drugs are used

Practice: When comparing a new drug to an older drug, very high doses of the older drug are used

Problem: The older drug produces more side effects, making the newer drug appear safer

(Geddes et al., 2000)

44

Outcomes are researcher-rated rather than patient-rated

Practice: Main outcome measures are rated by *researchers*

Problem: In all Phase III pediatric trials of antidepressants, *not one of 10* parent- or child-rated scales showed advantage for the drug

(Jureidini et al., 2004)

45

Adverse effects are carelessly investigated

Practice: Most trials elicit side effects by asking subjects general questions once a week, or waiting for subjects to report them *spontaneously*

Problem: This *underestimates* rates of side effects, especially psychological and behavioral ones, giving false impression of drug's safety

(Greenhill et al., 2003)

46

Adverse effects are mis-coded

Practice: Sponsor decides which effects qualify as "adverse drug events" and how to name them

Problem: Many adverse events are coded as something else, giving false impression of drug's safety

(Breggin, 2002)

47

Strattera pediatric trial:

Mis-coding why patients dropped out

What the researcher wrote	How the sponsor coded it	How it was re-coded after FDA reanalysis
"Parents felt 'too many side effects'; stopped drug early; Abdominal pain, nausea, anxiety"	*Protocol Violation*	*Adverse Event*
"Increasing behavior problems, worsening oppositional behavior; depression"	*Physician Decision*	*Adverse Event*

(Lillytrials.com, 2007)

48

Post-treatment ratings unreported

Practice: Sponsor gathers data for weeks *after* subjects stop treatment, but does not submit them to FDA

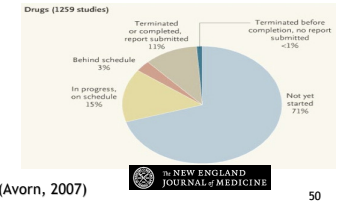
Problem: How subjects rate their treatment *once they're off drugs* may contradict their ratings while *on* drugs. This discrepancy is rarely discussed or explored

(Healy & Farqhar, 1998)

49

Post-marketing trials rarely conducted

As of late 2006, more than 70% of promised Phase IV trials had not yet started…



(Avorn, 2007)

50

The preceding limitations of clinical trials give clinicians and policymakers false ideas about how medications can help and how they can harm people

- FDA approval by itself does not guarantee that a drug is either *safe* or *efficacious* for its intended uses

(Strom, 2006)

51

The increasing involvement of industry in clinical trials has further muddled this worrisome situation

52

Part D

Blurring Science and Marketing

53

Huge payoffs can follow an FDA drug approval

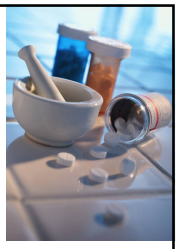
Zyprexa sales since 1996: ***$20 billion***

These create enormous incentives to turn clinical trials into marketing tools

(Smith, 2005)

For the FDA, a clinical trial is a limited test of the efficacy of a product

For the sponsor, it's a ticket to get its product past the FDA hurdle—and possibly to blockbuster status



(Smith, 2003)

55

How sponsors turn trials into marketing tools

- ☑ design studies solely to get positive results
- ☑ suppress and twist negative results
- ☑ publish positive results multiple times

(Quick, 2001)

56

The NEW ENGLAND JOURNAL of MEDICINE (2008)

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

"According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive."

57

Contract Research Organizations (CROs)

To get drugs approved by the FDA, sponsors outsource clinical trials to CROs, a $15 billion/year business

These private firms make it easier to:

- Enroll thousands of subjects
- Conduct more multi-site trials
- Shield trials from public scrutiny

(Hunley, 2007)

58

Conflicts in research

"It's a house of cards built on a fundamental conflict of interest. The problem is that drug companies have inordinate influence over the evaluation of their own products. That, on the face of it, doesn't make sense."

- **Marcia Angell**, former editor, *New England Journal of Medicine*, author, *The Truth About the Drug Companies*

59

Funder's drugs come out ahead

In 90% of studies pitting one newer antipsychotic against another, the best drug was the study sponsor's drug

THE AMERICAN JOURNAL OF PSYCHIATRY

(Heres et al., 2006)

60

Independent studies don't favor newer drugs

NIMH's (CATIE) study compared 5 antipsychotics in largest schizophrenia trial. Older, cheaper drug worked as well (or as poorly)

- Regardless of drug, ¾ of patients stopped treatment because they did not improve or had intolerable side effects

The NEW ENGLAND JOURNAL of MEDICINE

(Lieberman et al., 2005)

61

The New York Times

November 22, 2002

Madison Ave. Has Growing Role In the Business of Drug Research

By MELODY PETERSEN

"You cannnot separate advertising and marketing from the science anymore."

- **Arnold S. Relman, MD**, Professor Emeritus, Harvard Medical School, and former editor, *New England Journal of Medicine*

THE WEEK

The Best of the U.S. and International Media

The Corruption of Medicine

Several top medical journals recently admitted that studies they published on new medications have been tainted by undisclosed financial ties between researchers and drug companies. Does Big Pharma have too much influence over drug research?
9/22/2006

63

Part E

Problems in Drug Safety After Marketing

64

Because of the limitations of clinical trials, detecting adverse effects from drugs falls to **post-marketing surveillance**, when drugs are commonly prescribed, and used for longer periods, in more natural conditions, by more varied patients

(Strom, 2006)

This is when most adverse effects, and a more accurate portrait of the drug's risk-benefit ratio, emerge

Yet such post-marketing monitoring also appears spotty

(Lasser et al., 2002)

66

Newer drugs more likely to have hidden risks

50% of warnings occur within 7 years of a drug's introduction

Half of the withdrawals occur within 2 years

(Lasser et al., 2002)

67

Black Box Warnings

If the adverse drug reaction is serious enough to require extraordinary monitoring or special screening, the FDA will ask the drug sponsor to insert a "*black box warning*" in all marketing and product information to alert clinicians and consumers of the nature of the risk

68

Safety questions are "answered" post-marketing

51% of drugs get label changes

20% of drugs get new black box warnings

3-4% of drugs are withdrawn

(Strom, 2006)

69

Former and current FDA officials, outside scientists, and advocates for patients say the FDA's efforts to monitor the ill effects of drugs on the market are insufficient

70

USA TODAY

Report: FDA so underfunded, consumers are put at risk

(December 3, 2007; http://www.usatoday.com/news/washington/2007-12-02-fda_N.htm)

abc NEWS

FDA Is Broken, Endangers American Lives

Report Blames Congress for Cutting FDA's Budget

December 6, 2004

The New York Times

At F.D.A., Strong Drug Ties and Less Monitoring

Example: Prozac, 2004

Prozac was on the market for 17 years before FDA warned of increased suicidality

Sponsors of several SSRIs have been accused of not disclosing all the data from clinical trials

72

Example: Vioxx, 2004

Vioxx was taken by 20 million Americans before Merck withdrew it after links to heart attacks and strokes

Merck accused of not disclosing all the data from clinical trials

FDA Public Health Advisory: Safety of Vioxx

73

Serious Adverse Events (SAEs)

- Fatal or life-threatening, cause disability or require hospital stay

Only 1% to 10% of all drug-related SAEs are actually reported to the FDA through MedWatch

Medwatch The FDA Safety Information and Adverse Event Reporting Program

(Moore, Cohen & Furberg, 2007)

74

Thousands die annually

Reports to Medwatch of fatal drug reactions tripled between 1998-2005

- Over **80,000** deaths suspected from medications were reported by health professionals and others during that 7-year period

(Moore, Cohen & Furberg, 2007)

75

26,000 deaths suspected to be linked to 15 drugs, including:

3 antipsychotics and

1 antidepressant

Clozaril, Risperdal, Zyprexa, Paxil

(Moore, Cohen & Furberg, 2007)

76

Table 4. Most Frequent Suspect Drugs in Death and Serious Nonfatal Outcomes, 1998-2005

Drug Name	Rank/Deaths	Drug Class
Death outcome		
Oxycodone	1/5548	Opioid analgesic
Fentanyl	2/3545	Opioid analgesic
Clozapine	3/3277	Antipsychotic
Morphine	4/1616	Opioid analgesic
Acetaminophen	5/1393	Analgesic
Methadone	6/1258	Opioid analgesic
Infliximab	7/1228	DMARD
Interferon beta	8/1178	Immunomodulator
Risperidone	9/1093	Antipsychotic
Etanercept	10/1034	DMARD
Paclitaxel	11/1033	Antineoplastic
Acetaminophen-hydrocodone	12/1032	Combination analgesic
Olanzapine	13/1005	Antipsychotic
Rofecoxib	14/932	NSAID
Paroxetine	15/850	Antidepressant

77

(Moore, Cohen & Furberg, 2007)

Part F

Conclusions and Recommendations

78

FDA's independence in question

As a result of inordinately close ties to drugmakers, the FDA appears to have compromised its independence and its mandate to protect the public from dangerous products

79

Clinical trials provide skewed portrait of drug risks and benefits

Predictable limitations of trials suggest that their positive findings cannot generalize to real-life clinical conditions

Trials are especially poor at detecting adverse effects

80

Most psychological alterations produced by drugs are unstudied

Drugs' main psychological and behavioral effects can remain unknown even years after their approval by FDA and use by millions of people

Clinical trials ≠ objective evaluations of drug effects

Excessive involvement of sponsors in testing drugs may have tainted the research process, turning many clinical trials into "infomercials"

82

Conflicts of interest = suppression of negative trial findings

"Selective reporting of clinical trial results may have adverse consequences for researchers, study participants, health care professionals, and patients."

(Turner et al. 2008)

83

Need for skepticism and vigilance

Professionals should view announcements of clinical trial findings with skepticism and review them critically

84

Use new drugs cautiously

The first users of a newly marketed FDA-approved drug are the true research subjects

Public Citizen recommends waiting 7 years after marketing to use new drugs

"The public misunderstands drug safety, believing that a drug is safe at the time of marketing."

(Strom, 2006)

85

Your role in post-marketing surveillance?

Non-medical professionals and consumers can play an important role in *observing* and *reporting* adverse drug reactions to FDA, thus helping to create a more accurate portrait of medications and their impact on people's lives

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A Critical Curriculum on Psychotropic Medications

Module 3

The End

www.CriticalThinkRx.org

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