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The Promise and Pitfalls of Adjusting Regulatory Standards to Promote Development of New CNS Drugs

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Agenda

- 1. Is flagging drug innovation a regulatory problem?
- 2. What can we expect from “innovative regulatory pathways” to incentivize CNS drug development?
- 3. How can we really incentivize CNS drug development?

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Basic statutory standards

- Food, Drug, Cosmetic Act (FDCA) of 1938, amended in 1962, requires evidence be collected before prescription drugs could be sold to public
  - Efficacy: “substantial evidence of efficacy” arising from “adequate and well-controlled investigations”
  - Safety: “Adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use”
- Why? Thousands of drugs marketed by manufacturers and widely used by physicians that were ineffective, unsafe, or both
- What sort of evidence?

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Meeting FDCA's ever-more-tolerant efficacy standard

- A single trial is sufficient
  - 1997 FDAMA: Amend FDCA to explicitly allow efficacy proven by "one adequate and well-controlled clinical investigation and confirmatory evidence."
- Comparison against placebo
  - Single-arm trials sufficient for rare disease drugs
- Show changes in a biomarker or surrogate endpoint rather than a real clinical endpoint
- Brief, highly protocolized setting that often excludes many patients who would get the drug after approval

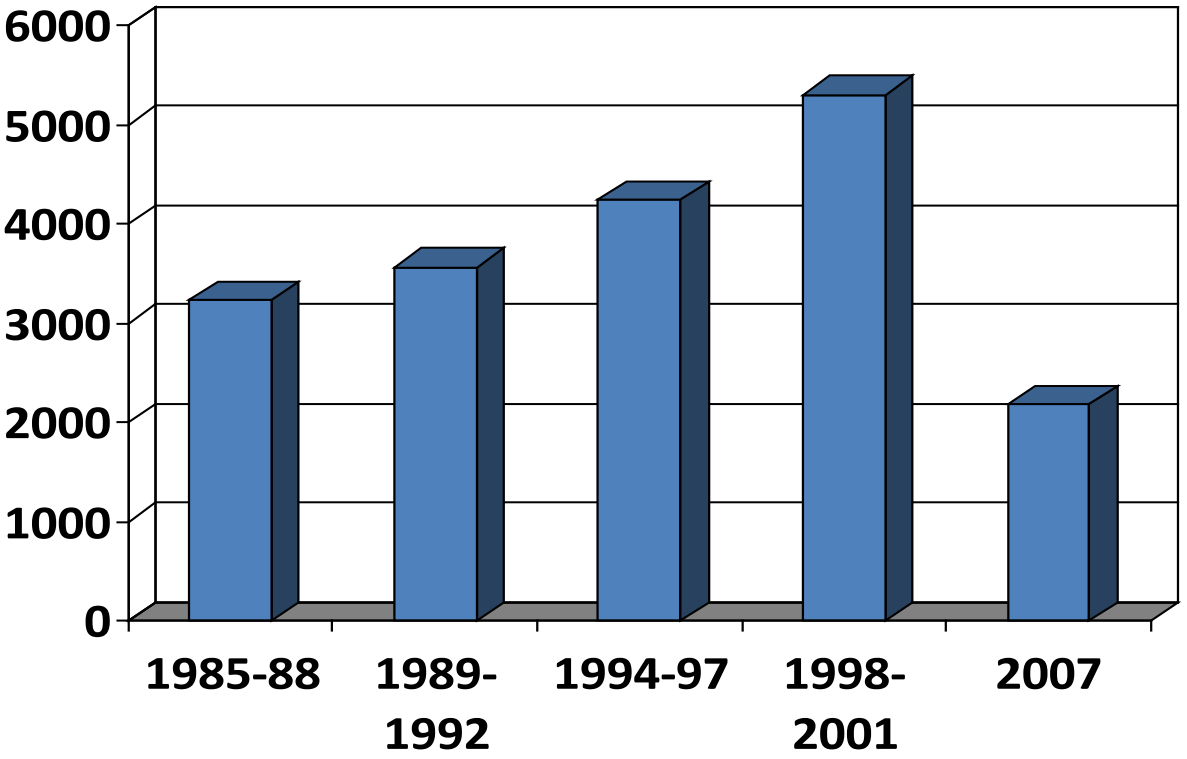
Agent/Indication Characteristic (Indications)	No. (%) [95% CI]						
		Trial Duration		Comparator		End Point	
	≥2 Pivotal Trials[b]	≥6 mo	≥12 mo	Active	Placebo	Clinical Outcome	Clinical Scale
All indications (N = 201)	127 (63.2) [56.5-69.9]	68 (33.8) [27.2-40.4]	17 (8.5) [4.6-12.3]	79 (39.3) [32.5-46.1]	119 (59.2) [52.4-66.0]	73 (36.3) [29.6-43.0]	39 (19.4) [13.9-24.9]

Downing et al., NEJM, 2012

Average number of patients per NDA

Myth: Drug development saddled by FDA-imposed burdens on clinical trial design

Reality:

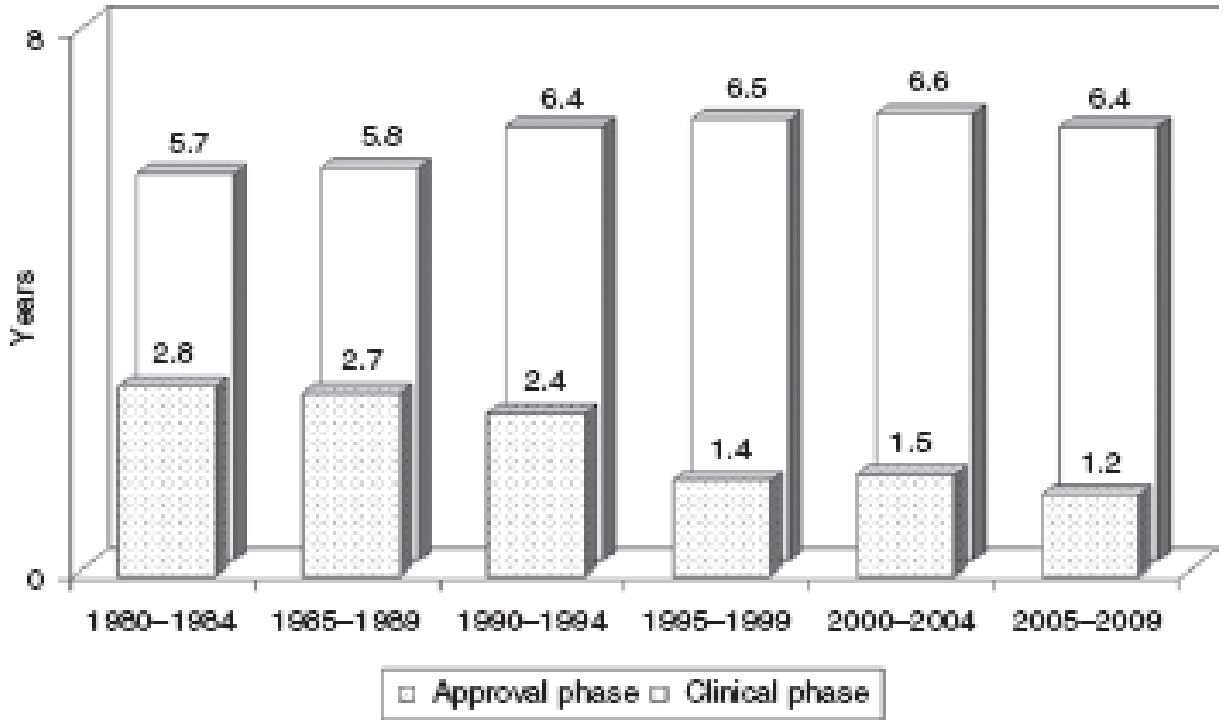


Tufts Center for the Study of Drug Development, 2002; Center for Information & Study of Clinical Research Participation, 2010

Length of time of investigational process

Myth: FDA keeps raising the bar for what's needed to prove efficacy, which lengthens the time of clinical investigation and makes drug development unsustainable

Reality:



Kaitin and DiMasi, CPT, 2011

FDA's Expedited Development and Review Pathways

- Fast track
  - Reduce development time by 3.3 years
- Accelerated Approval
  - Total IND->approval time of under 5 years
- Orphan Drug
- Priority Review within 6 months
  - FDA acts on 95% of its NDAs within the statutory time window
- Breakthrough Therapy
- (Permissive 'expanded access'/experimental use program)

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Darrow et al., NEJM, 2014; Darrow et al., NEJM, 2015

Over half of new molecular entities approved in 2012 qualified for at least one expedited development or review program

2012 NMEs	Orphan	Fast Track	Priority Review	Accelerated Approval
Amyvid				
Aubagio				
Belviq				
Bosulif				
Choline c-11				
Cometriq				
Elelyso				
Eliquis				
Erivedge				
Fulyzaq				
Fycompa				
Gattex				
Iclusig				
Inlyta				
Jetrea				
Juxtapid				
Kalydeco				
Kyprolis				
Linzess				
Myrbetriq				
Neutroval				

2012 NMEs	Orphan	Fast Track	Priority Review	Accelerated Approval
Omontys				
Perjeta				
Picato				
Prepopik				
Raxibacumab				
Signifor				
Sirturo				
Stendra				
Stivarga				
Stribild				
Surfaxin				
Synribo				
Tudorza Pressair				
Voraxaze				
Xeljanz				
Xtandi				
Zaltrap				
Zioptan				

Conclusions

- Current FDCA standards are rigorous but far from insurmountable, highly flexible for unmet medical needs, and exist because without them, we would be deluged with ineffective or unsafe therapies
- While new drug development is an increasingly challenging task, FDA evaluation leads to approval in the vast majority of cases, particularly for drugs that are innovative or treat life-threatening conditions, and compares favorably with the evaluation process in other industrialized countries

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Some characteristics of an innovative regulatory pathway for CNS drugs

- 1. Avoid time-consuming later-stage clinical trials
- 2. Adapt Accelerated Approval pathway, relying on biomarkers with “greater uncertainty”
- 3. Restrictions on advertising/label/use while collecting data from post-approval studies
- 4. Limit new pathway to “only a few best-case classes of drugs”

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Choi et al., Neuron, 2014

1. Avoid time-consuming, later-stage trials

- Survival of CNS vs. Non-CNS Drugs, 1990-2012
- Similar survival Phase 1->2 and Phase 2->3
- CNS drug significantly lower survival Phase 3-> approval
- Suggests that barrier is *not* at decision to undertake complicated/expensive late-stage trials
- But does suggest that if these late-stage trials are not done, more unsafe or ineffective drugs will be approved

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Unpublished data (for now)

2. Greater use of “uncertain” biomarkers and surrogate endpoints

- Accelerated approval standard
  - Surrogate endpoints **reasonably likely** to predict patient benefit
- Risk of using insufficiently validated biomarkers

Problematic surrogates

Drug	Use	Surrogate	Actual Outcome
Aprotinin	High-risk cardiac surgery	Decreased need for transfusion	Mortality
Clofibrate	Increased cholesterol in healthy men	Decreased cholesterol	Mortality
Doxazosin	Hypertension and other CV risk factors	Decreased blood pressure	Congestive heart failure
Encainide	Ventricular premature beats post-MI	Decreased ventricular ectopic beats	Mortality
Erythropoietin	Anemia due to chronic renal failure	Increased hemoglobin to >12.0	Mortality
Estrogen/ progestin	Cardiovascular disease prevention in postmenopausal women	Decreased LDL cholesterol and increased HDL cholesterol	CV disease and breast cancer
Flecainide	Post -MI patients with ventricular premature beats	Decreased ventricular ectopic beats	Mortality

Drug	Use	Surrogate	Actual Outcome
Flosequinan	Chronic congestive heart failure	Improved ventricular function	Mortality
Fluoride	Fracture prevention in postmenopausal women with osteoporosis	Increased bone mineral density	Nonvertebral fractures
Ibopamine	Severe congestive heart failure	Increased exercise tolerance and decreased vascular resistance	Mortality
Metoprolol	Patients with CV risk factors undergoing non-cardiac surgery	Decreased postoperative myocardial ischemia	Increased mortality
Milrinone	Severe congestive heart failure	Increased cardiac contractility	Mortality
Moxonidine	Congestive heart failure	Decreased plasma norepinephrine	Mortality
Rosiglitazone	Type 2 diabetes	Decreased HbA1c	MIs

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Adapted from Svensson et al. JAMA IM, 2013

2. Greater use of “uncertain” biomarkers and surrogate endpoints

- Accelerated approval standard
  - Surrogate endpoints **reasonably likely** to predict patient benefit
- Risk of using insufficiently validated biomarkers
- The correct response to poorly understood biomarkers in the study of CNS diseases isn’t to change regulatory standards to allow us to approve more drugs based on them with the hope that they pan out, but to invest more in validating them ahead of time

3. Focus on testing efficacy and safety of CNS drugs in post-approval period

- Reality: Difficulty enforcing post-approval commitments
- Practical limits in doing post-approval efficacy studies to confirm the conditions for which the drug is approved
  - Bedaquiline given 10 years to complete post-market study requirements
- FDA's limited authority to require post-approval testing and then to withdraw a drug if does not meet goals
  - Bevacizumab (Avastin) for metastatic breast cancer
- Limited power of insurers to refuse use of FDA-approved product
- 1st Amendment limits on commercial speech restrictions

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4. Restrict pathway to “best-case classes”?

- Expedited pathway creep
- Increasing number of drugs with expedited development and approval designations in last 2 decades
  - Due to application to more non-first-in-class drugs

Unpublished data (for now)

Breakthrough Therapy

- 2012 to speed approval of drugs showing "exceptional results for patients"
- 244 applications, 68 approvals in 2 years
- Sen. Bennet: "Rollout has been faster than I expected"

Name	Indication	Name	Indication
Nintedanib	IPF	Obinutuzumab	CLL
Pirfenidone	IPF	Pembrolizumab	Melanoma
Trumenba	Meningitis B vaccine	Ibrutinib	CLL
Eltrombopag	Severe aplastic anemia	Ceritinib	NSCLC
Idelalisib	CLL	Ivacaftor	CF monotherapy
Sofosbuvir	HCV	Ofatumumab	First-line CLL combination therapy

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New Phase 1, 2, 3 trials started, 1990-2012

- Substantially fewer new Phase 1 trials of CNS drugs vs cancer drugs

Final thoughts

- We need more potentially active agents targeting neuropsych conditions *to enter* investigational trials
  - Transformative science often comes from NIH/NIMH/NSF labs and funded investigators – see Kesselheim et al. Health Affairs, forthcoming Feb 2015
  - Funding for these agencies is doing poorly in current budget process – ***the*** major threat to new CNS drug development
  - New cures do not generally arise initially in large pharmaceutical companies, though they are integral in moving these products forward

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Final thoughts

- It is true that if a promising cure for Alzheimer's disease was invented tomorrow, the long latency period needed to test it may not garner interest from revenue-minded large pharmaceutical companies
  - Need to figure out better ways to support academic/NFP research centers, start-up firms, or patient organizations that will step in to bear the risk

Final thoughts

- But we do **not** necessarily need to weaken the process for gathering evidence on new treatments
  - Changing regulatory hurdles to eliminate later-phase studies will increase the number of new CNS drugs introduced that are ineffective or unsafe
  - Let's not bend over backwards to approve new drugs before they've been shown to work
  - It is not in the interests of patients, however sick they may be or however great their unmet medical need, to have faster, easier access to products that are ineffective and may actually worsen their clinical status

THANK YOU

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