AMEF 2013

Expert Forum on Addiction Medicine

Nuove prospettive nell'assistenza ai tossicodipendenti.
Il ruolo delle nuove formulazioni farmaceutiche

Luca Pani
Direttore Generale
DG@aifa.gov.it

Pietrasanta, 8 Marzo 2013

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Dichiarazione di trasparenza/interessi*

Interessi nell'industria farmaceutica	NO	Attualmente	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società	x				
Consulenza per una società	x				
Consulente strategico per una società	x				
Interessi finanziari	x				
Titolarità di un brevetto	x				
Interessi indiretti:					
Sperimentatore principale	x				
Sperimentatore	x				
Sovvenzioni o altri fondi finanziari	x				
Corsi ECM				x	

* Luca Pani, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. Per questo intervento non ricevo alcun compenso

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How do we make/separate diagnosis?

1. Examine the associated physical changes (macroscopic, microscopic, molecular) and whether cause, effect or in some relationship with the disorder

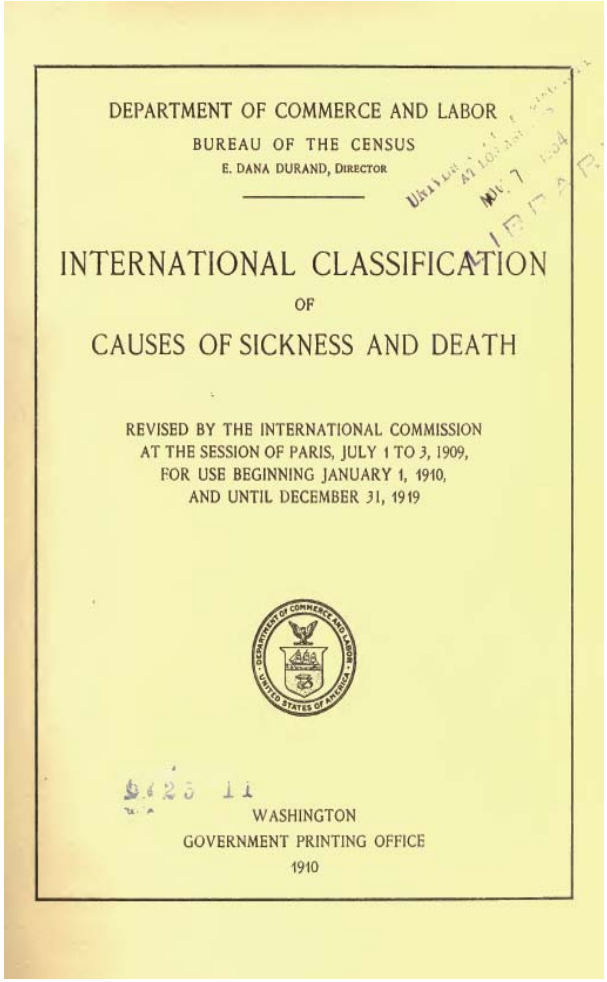
2. Follow the natural history and prognosis

3. Judge and evaluate the response to various treatments

4. Identify aetiology (cause). Usually this is the last element to be identified

This whole process is known as Validation

Evolution of the Classification



DEPARTMENT OF COMMERCE AND LABOR

BUREAU OF THE CENSUS

E. DANA DURAND, DIRECTOR

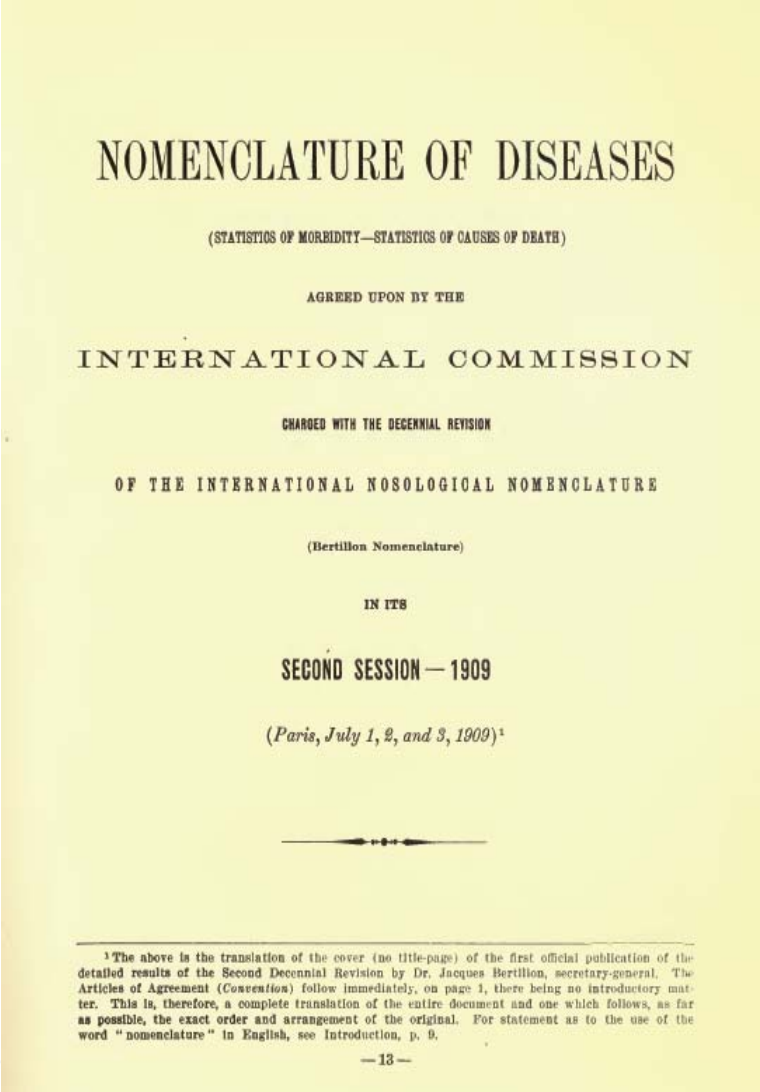
INTERNATIONAL CLASSIFICATION

OF

CAUSES OF SICKNESS AND DEATH

REVISED BY THE INTERNATIONAL COMMISSION
AT THE SESSION OF PARIS, JULY 1 TO 3, 1909,
FOR USE BEGINNING JANUARY 1, 1910,
AND UNTIL DECEMBER 31, 1919

WASHINGTON
GOVERNMENT PRINTING OFFICE
1910



NOMENCLATURE OF DISEASES

(STATISTICS OF MORBIDITY—STATISTICS OF CAUSES OF DEATH)

AGREED UPON BY THE

INTERNATIONAL COMMISSION

CHARGED WITH THE DECENNIAL REVISION

OF THE INTERNATIONAL NOSOLOGICAL NOMENCLATURE

(Bertillon Nomenclature)

IN ITS

SECOND SESSION — 1909

(*Paris, July 1, 2, and 3, 1909*)[1]

[1] The above is the translation of the cover (no title-page) of the first official publication of the detailed results of the Second Decennial Revision by Dr. Jacques Bertillon, secretary-general. The Articles of Agreement (*Convention*) follow immediately, on page 1, there being no introductory matter. This is, therefore, a complete translation of the entire document and one which follows, as far as possible, the exact order and arrangement of the original. For statement as to the use of the word "nomenclature" in English, see Introduction, p. 9.

—13—

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A.—DETAILED NOMENCLATURES—Continued.

1. DETAILED NOMENCLATURE INTENDED FOR STATISTICS OF THE SICK—Continued.

I.—General Diseases—Continued.

*4. Malaria.
*4a. —*Including:* Malarial cachexia.
*5. Smallpox.
*6. Measles.
*7. Scarlet fever.
*8. Whooping cough.
*9. Diphtheria and croup.
*9a. —*Including:* Croup.
*10. Influenza.
*11. Miliary fever.
*12. Asiatic cholera.
*13. Cholera nostras.
*14. Dysentery.
*15. Plague.
*16. Yellow fever.
*17. Leprosy.
*18. Erysipelas.
*19. Other epidemic diseases.
*20. Purulent infection and septichæmia.
*21. Glanders.
*22. Anthrax.
*23. Rabies.
24. Tetanus.
25. Mycoses.
26. Pellagra.
27. Beriberi.
28. Tuberculosis of the lungs.
29. Acute miliary tuberculosis.
30. Tuberculous meningitis.
31. Abdominal tuberculosis.
32. Pott's disease.
33. White swelling.
34. Tuberculosis of other organs.
35. Disseminated tuberculosis.
36. Rickets.
37. Syphilis:
A. *Primary.*
B. *Secondary.*
C. *Tertiary.*
D. *Hereditary.*
E. *Period not stated.*
38A. *Soft chancre.*

46041—10——2

2. DETAILED NOMENCLATURE INTENDED FOR STATISTICS OF DEATHS—Continued.

I.—General Diseases—Continued.

*4. Malaria.
*4a. —*Including:* Malarial cachexia.
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36. Rickets.
37. Syphilis.

A.—DETAILED NOMENCLATURES—Continued.

1. DETAILED NOMENCLATURE INTENDED FOR STATISTICS OF THE SICK—Continued.

I.—General Diseases—Continued.

38B. Gonococcus infection.
*39. Cancer and other malignant tumors of the buccal cavity.
*40. Cancer and other malignant tumors of the stomach, liver.
*41. Cancer and other malignant tumors of the peritonæum, intestines, rectum.
*42. Cancer and other malignant tumors of the female genital organs.
*43. Cancer and other malignant tumors of the breast.
*44. Cancer and other malignant tumors of the skin.
*45. Cancer and other malignant tumors of other organs and of organs not specified.
*46. Other tumors (tumors of the female genital organs excepted).
*47. Acute articular rheumatism.
*48. Chronic rheumatism and gout.
*49. Scurvy.
*50. Diabetes.
*51. Exophthalmic goitre.
*52. Addison's disease.
*53. Leuchæmia.
*54. Anæmia, chlorosis.
*55. Other general diseases.
*56. Alcoholism (acute or chronic).
*57. Chronic lead poisoning.
*58. Other chronic occupation poisonings.
*59. Other chronic poisonings.

2. DETAILED NOMENCLATURE INTENDED FOR STATISTICS OF DEATHS—Continued.

I.—General Diseases—Continued.

38. Gonococcus infection.
*39. Cancer and other malignant tumors of the buccal cavity.
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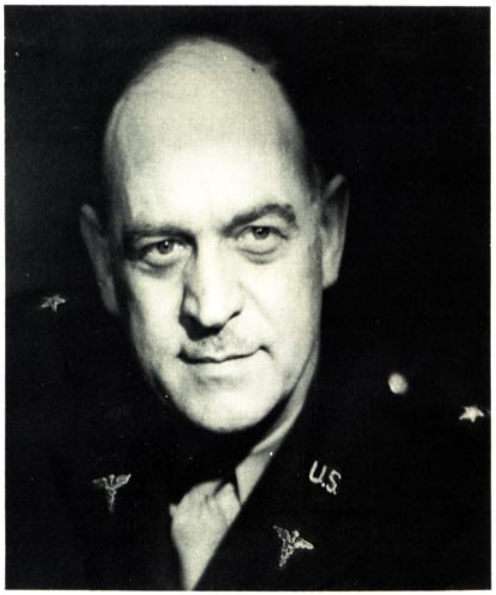


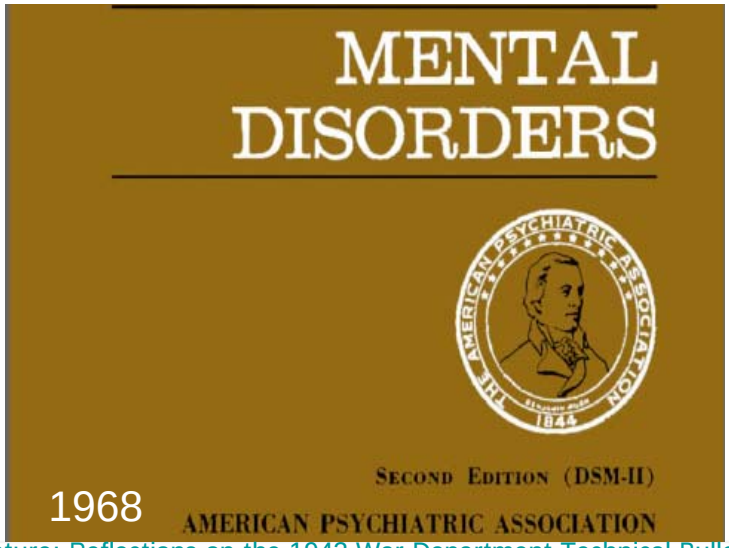
FIGURE 5.—Brig. Gen. William C. Menninger, Director, Neuropsychiatry Consultants Division, Surgeon General's Office, 10 December 1943–30 June 1946.

eveloped a "War Dept. Technical Document" called '**Medical 203' in 1943**

Led to the APA DSM-I in 1952.

295.3 Schizophrenia, paranoid type

This type of schizophrenia is characterized primarily by the presence of persecutory or grandiose delusions, often associated with hallucinations. Excessive religiosity is sometimes seen. The patient's attitude is frequently hostile and aggressive, and his behavior tends to be consistent with his delusions. In general the disorder does not manifest the gross personality disorganization of the hebephrenic and catatonic types, perhaps because the patient uses the mechanism of projection, which ascribes to others characteristics he cannot accept in himself. Three subtypes of the disorder may sometimes be differentiated, depending on the predominant symptoms: hostile, grandiose, and hallucinatory.



1968

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Houts, A.C. (2000) Fifty years of psychiatric nomenclature: Reflections on the 1943 War Department Technical Bulletin, Medical 203. Journal of Clinical Psychology, 56 (7), Pages 935 - 967

1968

1980

1987

1994

2000

182

265

292

297

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Ordering the Disorders: Classifications

- Both DSM (APA) and ICD (WHO) are etiology neutral
- They specify Criteria for each Psychiatric disorder, name them and put them into broad categories
- This allows:
  - the collection of statistical data about them
  - the communication among professionals
  - the study of these syndromes for prognosis and treatment

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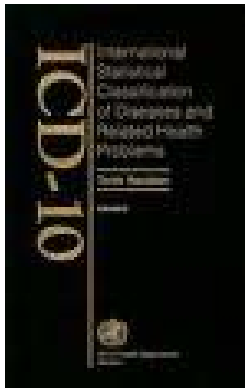
DSM-5 and clinical trials in psychiatry: challenges to come?

Florence Butlen-Ducuing, Manuel Haas, Luca Pani, Barbara van Zwieten-Boot and Karl Broich

The publication of the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013 raises important questions for clinical trials and associated regulatory decisions on new drugs for psychiatric disorders.



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Substance-Related Disorders Working Group (SRDWG)

American Psychiatric Association
DSM-5 Development

Home | About DSM-5 | Meet Us | Research Background | General Resources | Newsroom

Home / Meet Us / Substance-Related Disorders

Substance-Related Disorders

The Substance-Related Disorders Work Group is chaired by Charles O'Brien, M.D., Ph.D. Also, Thomas Crowley, M.D co-chaired the group until late 2011. Its members are listed below.

Members

O'Brien, Charles, M.D., Ph.D.
Crowley, Thomas, M.D.
Auriacombe, Marc, M.D.
Borges, Guilherme, M.D., DrSc
Bucholz, Kathleen, Ph.D.
Budney, Alan, Ph.D.
Grant, Bridget, Ph.D., Ph.D.
Hasin, Deborah, Ph.D.
Ling, Walter, M.D.
Manson, Spero M., Ph.D. (2007-2010)
Petry, Nancy, Ph.D.
Schuckit, Marc A., M.D.

Addiction

"Persistent use of a substance despite negative consequences. It is a complex disease, the course of which is influenced by the interaction of genetics and environmental factors. Addiction is a chronic and treatable disease."

Charles O'Brien, SRDWG Chair

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The new criterion

The symptoms listed in DSM V under “Substance use disorder” are the result of the combination of the symptoms listed in DSM-IV under “Substance abuse” and ‘’Substance dependence”

Another change was the removal of legal problems from the “Substance abuse” list, since these legal problems are not included in the WHO-ICD classification

“*3. Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)”*

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The main changes

"Beginning in 2013, for the first time in history, the word "addiction" will be used as a category by the authority of mental health in America, the DSM".

DSM-5

DSM-5 enlarges from 7 to 11 the list of recognized symptoms for a Substance Use Disorder and reduces from 3 to 2 the number of symptoms needed for a diagnosis.

DSM-5 includes Gambling as a Behavioral Disorder (Internet Use Disorder is included as condition requiring further study before it should be considered disorders).

http://www.thefix.com/content/dvm-5-definition-addiction9110?page=all

Addictive Disease Classifications

DSM IV
(Artificial distinction)

Substance Abuse
At least 1 symptom of 4 listed

Substance Dependence
At least 3 symptoms of 7 listed

DSM 5

Substance Use Disorder
At least 2 symptoms of 11 listed

In every case it is needed clinically significant impairment or distress

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http://www.sis.indiana.edu/DSM-IV-Criteria.aspx

Which changes?

Substance Abusers → **DSM 5** → Diagnosis

- Mild
- Moderate
- Severe

} *Substance Use Disorder*

↓

Characterization of severity levels

↓

A potential better guide to the treatment

↓ **DSM IV**

Not categorized as *'Addicts'*

↓

~~Artificial distinction between *'Abuse'* and *'Dependence'*~~

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More diagnoses=more costs/incomes=less safety?

- More than 20 million people in the U.S. (more than 3 million people in Italy) could be classified as ‘Addicts' according to the DSM-5

- It is feared an unnecessary and not safe increase of the diagnoses and the drug prescriptions

More diagnoses=more costs/incomes=less safety?

- It is feared the 'medicalization' of everyday behavior and the explosion of false epidemics

- Have been raised doubts about the fairness and transparency of the specialists who have updated the DSM since they are related to the Pharmaceutical Companies

What important consequences will there be?

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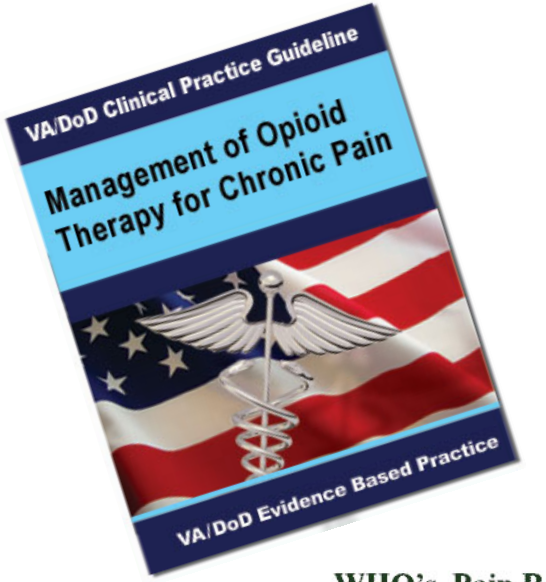
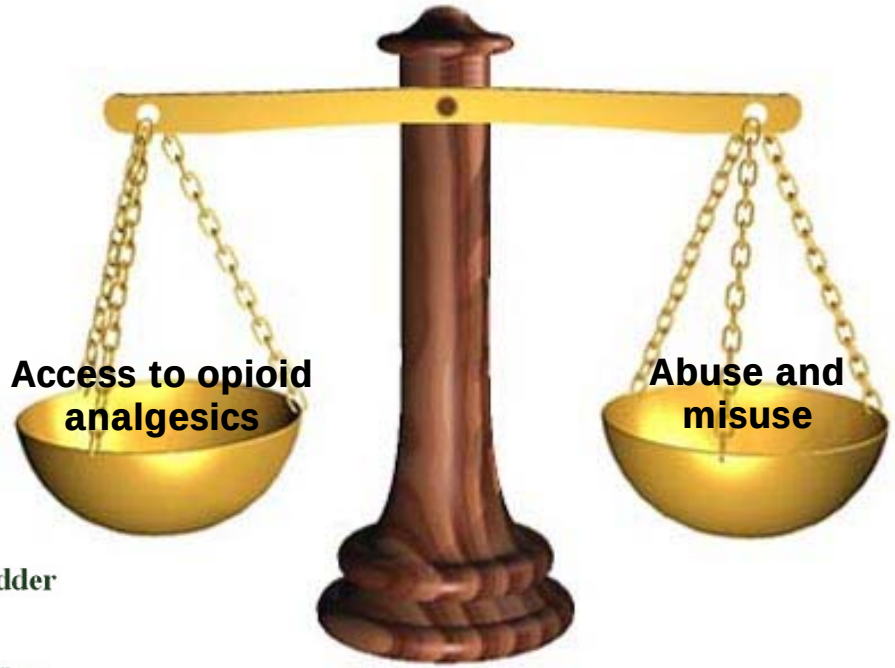
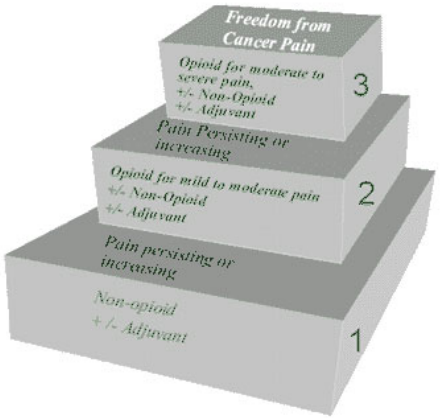
The prescription of opioids





WHO's Pain Relief Ladder



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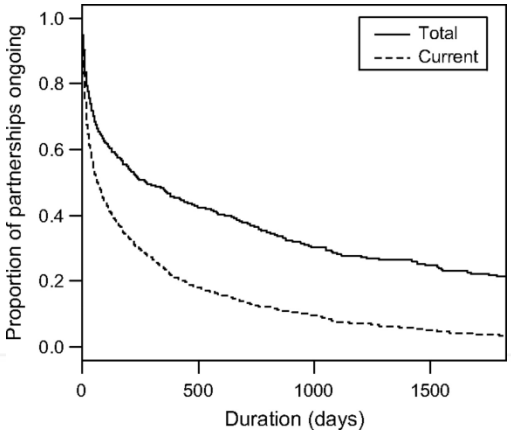
Regulatory evaluation of a Dossier

1. Population(s)
2. Endpoint(s)
3. Comparator(s)
4. Duration of Effect(s)



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So, when evaluating a dossier we make sure that:

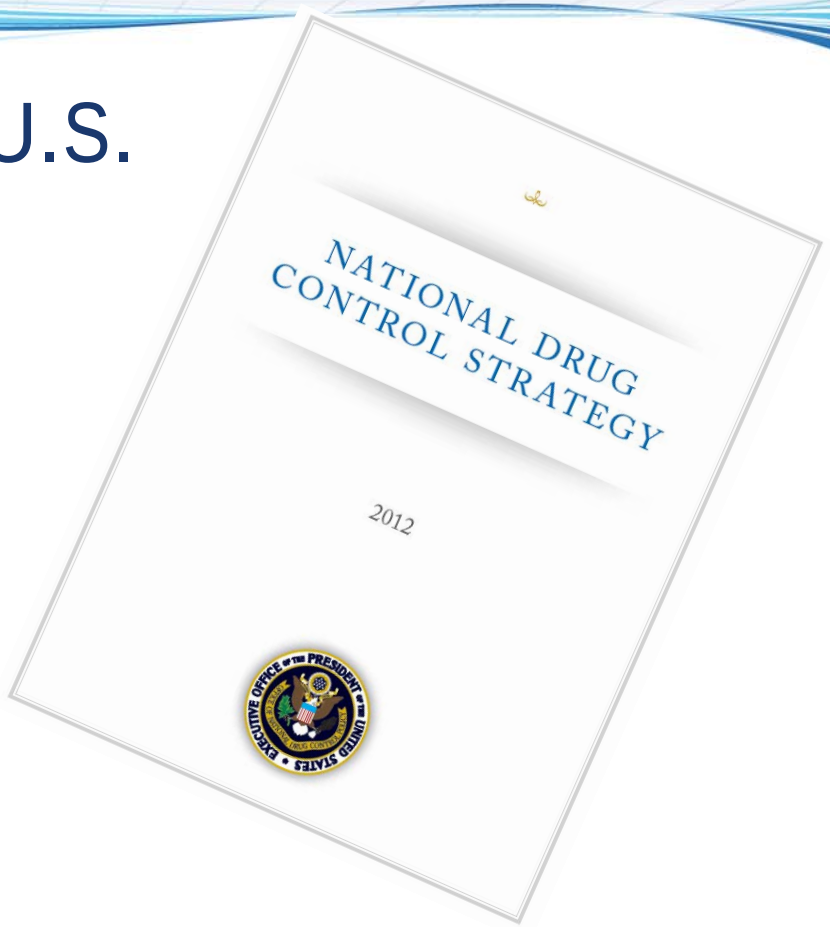
- Regulatory validated scales have been used;
- The population has been accurately defined;
- The endpoint(s) has/have been carefully selected;
- An adequate comparator(s) has/have been chosen;
- The trial has been conducted for a significant amount of time;
- An effect on function is measurable;
- Statistics are run in line with the clinical significance of the claim(s) the Applicant is trying to make.

A challenge for Europe…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CPMP/EWP/612/00 21 November 2002	Note for Guidance on clinical investigation of medicinal products for treatment of nociceptive pain
Doc. Ref. CPMP/EWP/252/03 rev.1 24 January 2007	Guideline on clinical medicinal products intended for the treatment of neuropathic pain
Referral art. 31 20 April 2011	Assessment report for Authorised modified –release oral medicinal products of the WHO level III scale for the management of pain (intense sustained pain resistant to previous medications) (containing morphine, oxycodone, and hydromorphone)
EMA/728909/2010 rev.1 20 April 2011	Question and answers on the review of modified-release oral opioid medicines of the WHO level III scale management of pain
EMA/CHMP/210477/2011 22 September 2011	Concept paper on the need for revision of Note for Guidance on Clinical Medicinal Product for Treatment of nociceptive Pain and Guideline on clinical investigation of products intended for the treatment of neuropathic pain

...and U.S.



''Science shows that drug addiction is not a moral failing on the part of the individual but a disease of the brain that can be prevented and treated''

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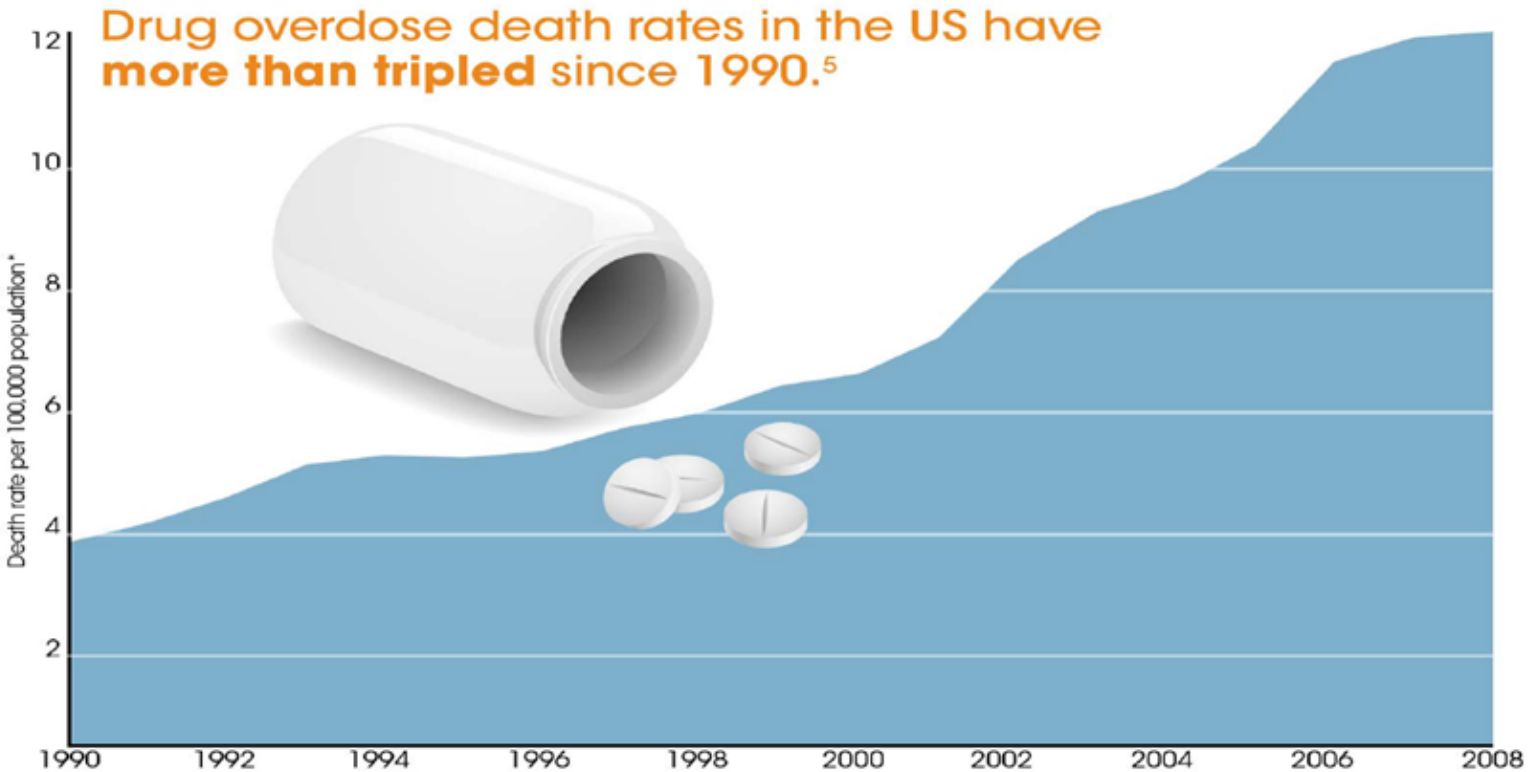
A Major Public Health Problem



*Deaths are those for which poisoning by drugs (illicit, prescription, and over-the-counter) was the underlying cause.

Source: CDC NCIPC November 2011

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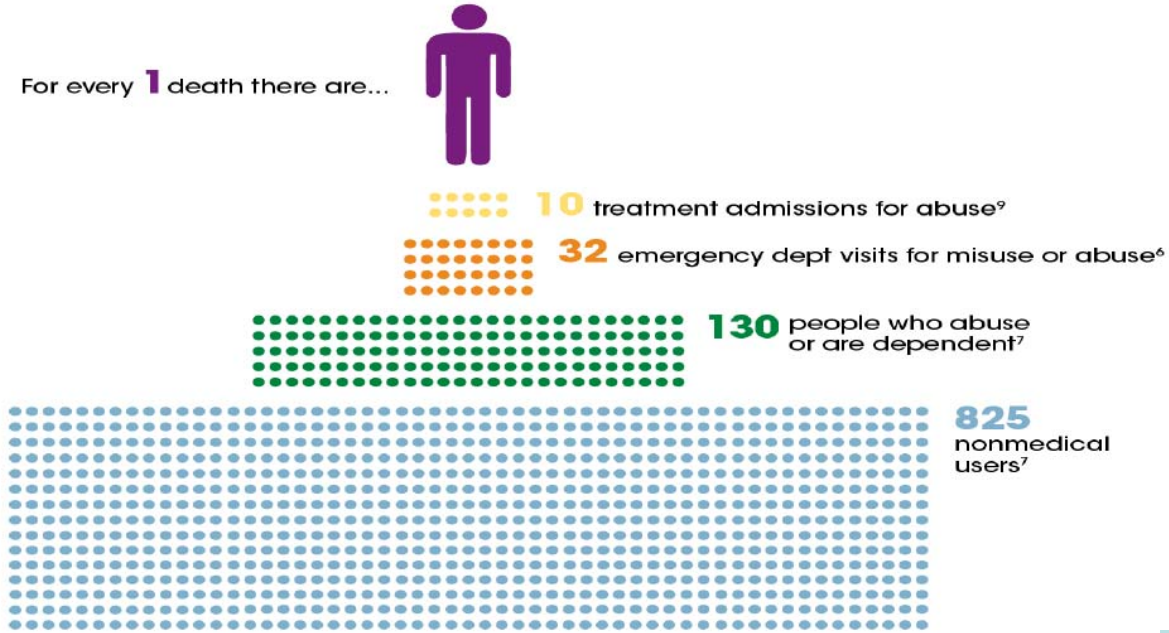
Fonte: "FDA and Opioids: What's a regulator to Do? Throckmorton Director CDER, FDA. June 14, 2012"

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Opioid Deaths Are the "Tip of the Iceberg"

In 2008, there were **14,800** prescription painkiller deaths.[4]

For every **1** death there are...



Source: CDC NCIPC November 2011

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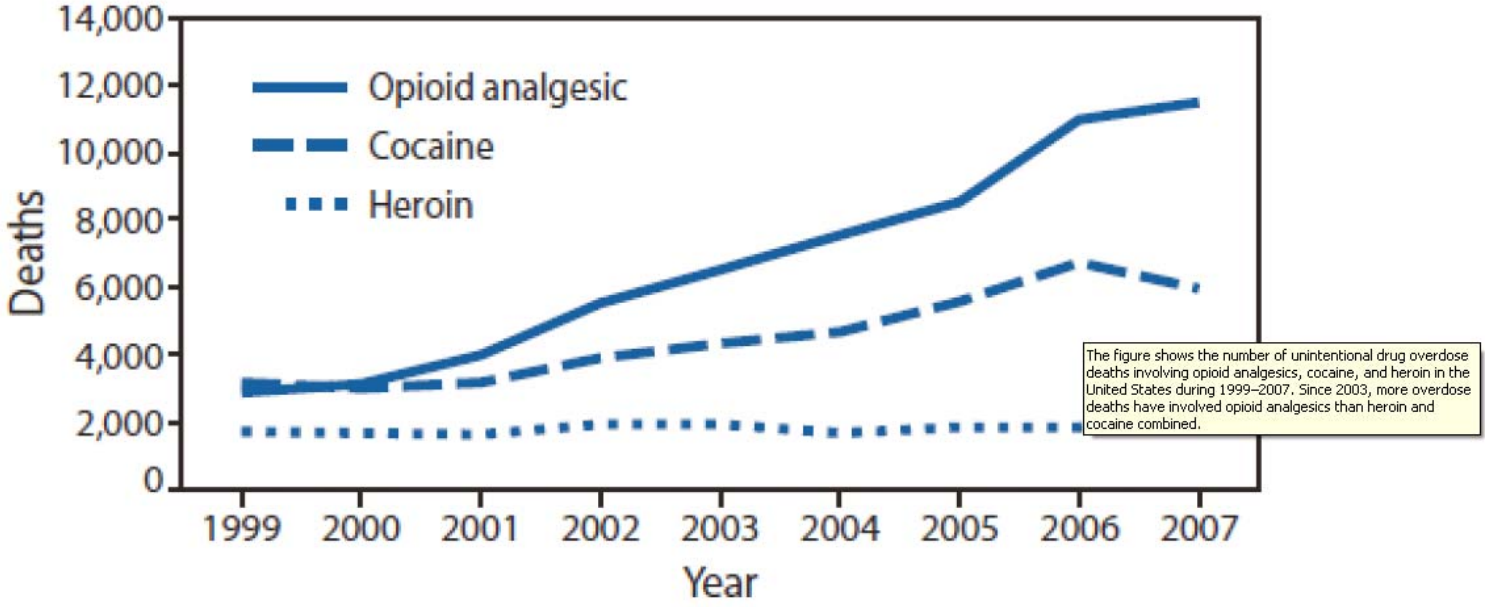
Fonte: "FDA and Opioids: What's a regulator to Do? Throckmorton Director CDER, FDA. June 14, 2012"

Causes of Unintentional Drug Overdose Deaths — United States, 1999–2007



Source: National Vital Statistics System

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Fonte: "FDA and Opioids: What's a regulator to Do? Throckmorton Director CDER, FDA. June 14, 2012"

The need for careful screening practices

ELSEVIER

Drug and Alcohol Dependence

Available online 9 February 2013

In Press, Corrected Proof — Note to users

Risk factors for incident nonmedical prescription opioid use and abuse and dependence: Results from a longitudinal nationally representative sample

Cara Katz[a], Renée El-Gabalawy[a, b], Katherine M. Keyes[c], Silvia S. Martins[c], Jitender Sareen[a, b]

[a] University of Manitoba, Department of Psychiatry, Winnipeg, Manitoba, Canada

[b] University of Manitoba, Department of Psychology, Winnipeg, Manitoba, Canada

[c] Columbia University, Department of Epidemiology, 722 West 168th Street, Room 1608, New York, NY 10032, United States

http://dx.doi.org/10.1016/j.drugalcdep.2013.01.010, How to Cite or Link Using DOI

Permissions & Reprints

"These results suggest the importance of mental and physical comorbidity as a risk for nonmedical prescription opioid use (NMPOU) and abuse/dependence, emphasizing the need for careful screening practices when prescribing opioids"

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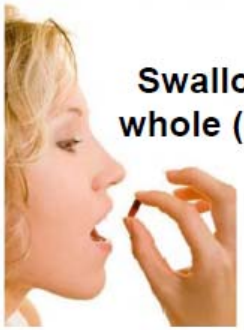
Modalities of opioid abuse



Swallowing whole (intact)

Injecting

Snorting

Crushed (tampered) product

Smoking

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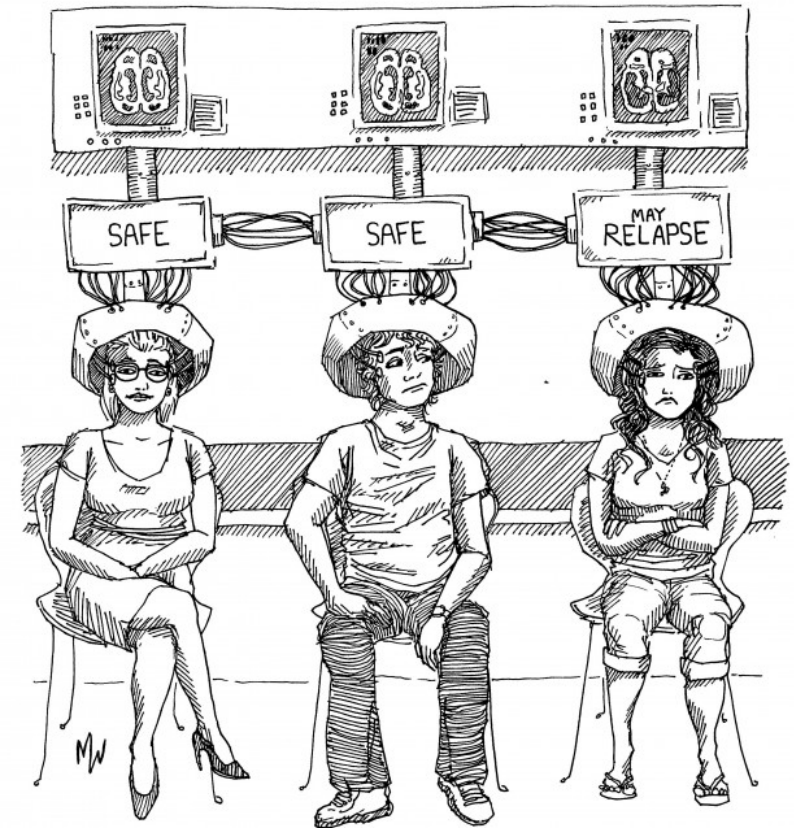
http://www.radars.org/Portals/1/Brown.pdf

Can the addiction be predicted?



The FDA considers the development of the Abuse-Deterrent Formulations (ADFs) a public health priority

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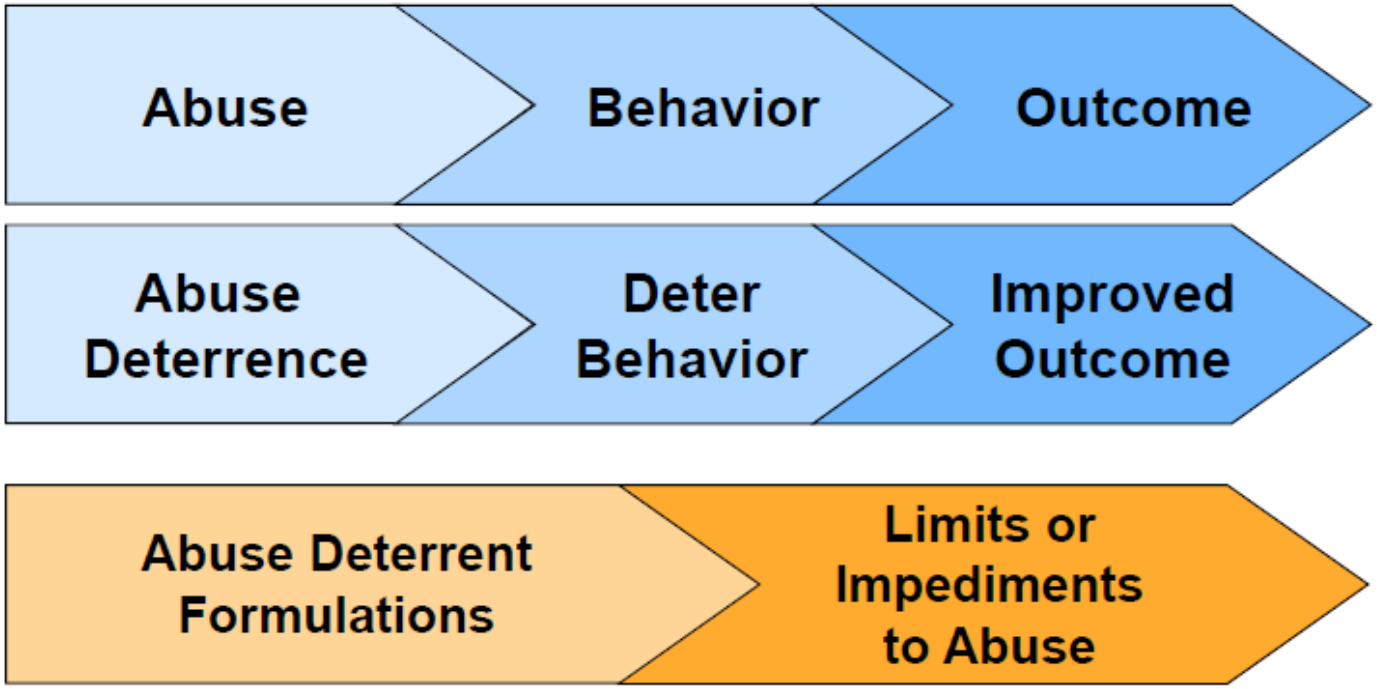
Underlying Principles of the Role of an ADF



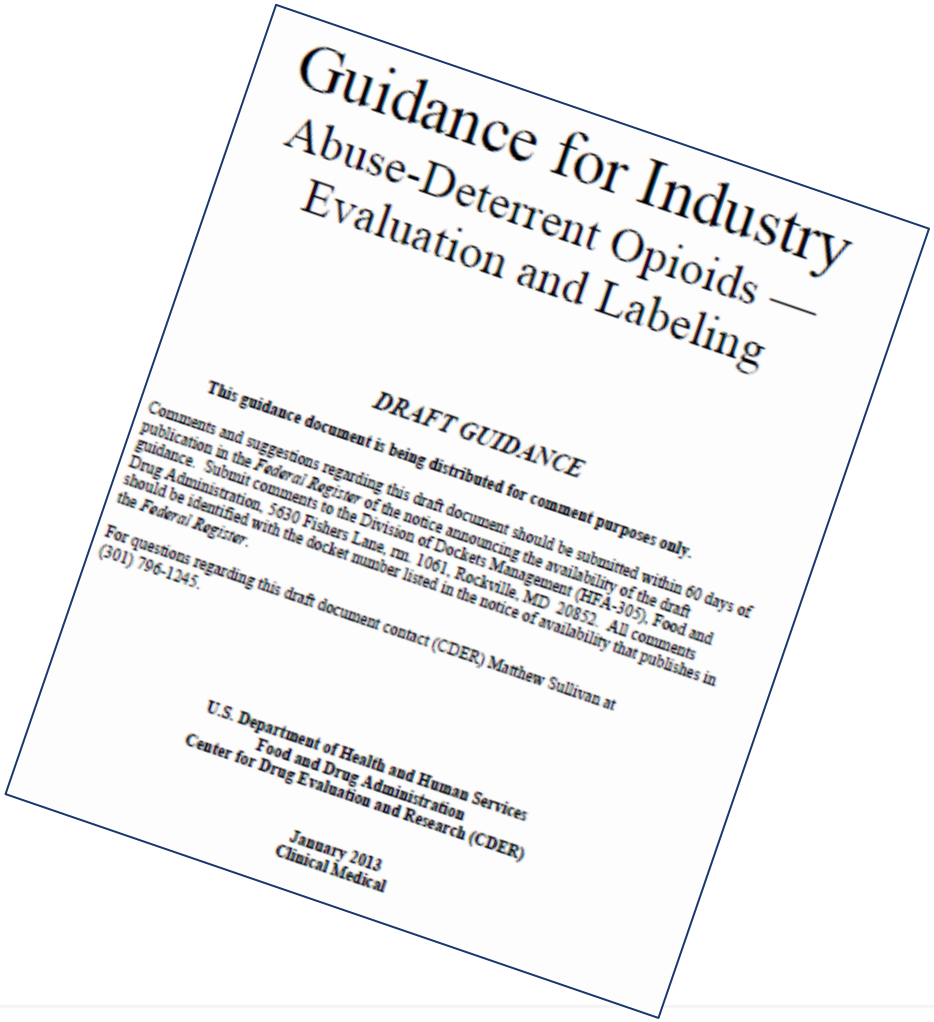
Incremental Benefit

From Epidemiology Advisory Committee Meeting (Oct .2010)

http://www.radars.org/Portals/1/Brown.pdf

FDA interventions

January 2013



Guidance for Industry
Abuse-Deterrent Opioids —
Evaluation and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Matthew Sullivan at (301) 796-1245.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2013
Clinical Medical

The Guidance key points

This Guidance → explains FDA's thinking about → the studies that should be conducted to demonstrate that a formulation has abuse-deterrent properties

→ how those studies will be evaluated

→ what label claims may be approved based on the results of those studies

does not addresses

~~the manufacture evaluation of products designed to have abuse-deterrent properties.~~

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The purpose

To make product manipulation more difficult

To make abuse of the manipulated product...

less actractive

less rewarding

State of the art

Are these technologies proven successful at deterring the most common form of abuse?

Not yet

Why?

The formulation must be able to deliver the opioid to patients for the management of pain

What's problem?

In an abuse deterrent product the abuse reduction will never be absolute

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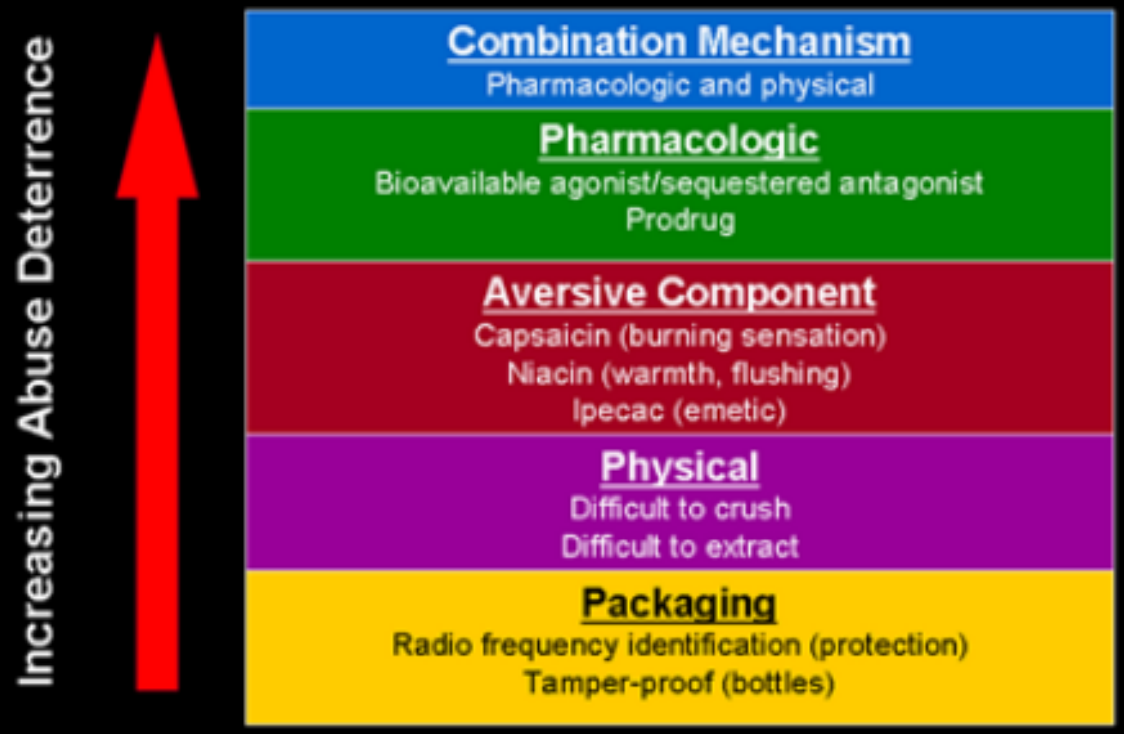
Categories of ADFs



FDA approvals

Table Abuse-Deterrent Opioid Formulations

Trade name	Opioid	Mechanism	FDA status
OxyContin	Oxycodone	Hard plastic polymer that renders the tablet difficult to crush or dissolve	Approved in 2010
Remoxy	Oxycodone	Very viscous liquid intended to resist crushing, dissolution, injection, or inhalation	Under FDA review
Suboxone	Buprenorphine	Contains sequestered naloxone (an opioid antagonist), which is released when product is chewed/crushed and cancels the euphoric effects of buprenorphine	Approved in 2002
Embeda	Morphine	Contains sequestered naltrexone (an opioid antagonist), which is released when the product is chewed/crushed and cancels the euphoric effects of morphine	Approved in 2009
Acurox	Oxycodone (immediate release)	Contains an aversive agent (niacin) that causes unpleasant effects when injected, inhaled, or taken orally in high doses	Under FDA review

FDA indicates US Food and Drug Administration.

Evaluation of ADFs

RADARS® SYSTEM News
Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System

The epidemiologic triangle is routinely used to conceptualize the evaluation of the complex interaction between the Host, the Agent and the Physical Environment.
RADARS extended this approach to provide a framework for evaluating the effect of extended opioids for the management of chronic pain.

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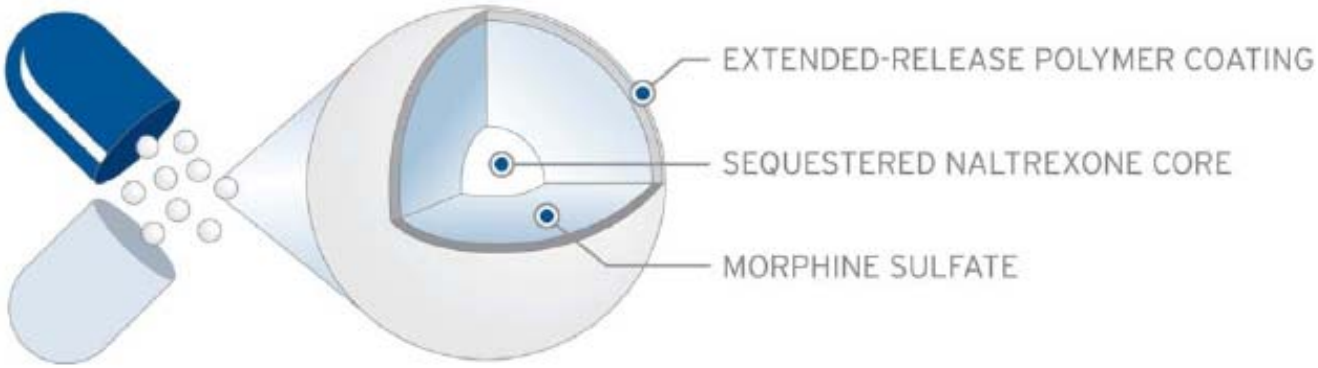
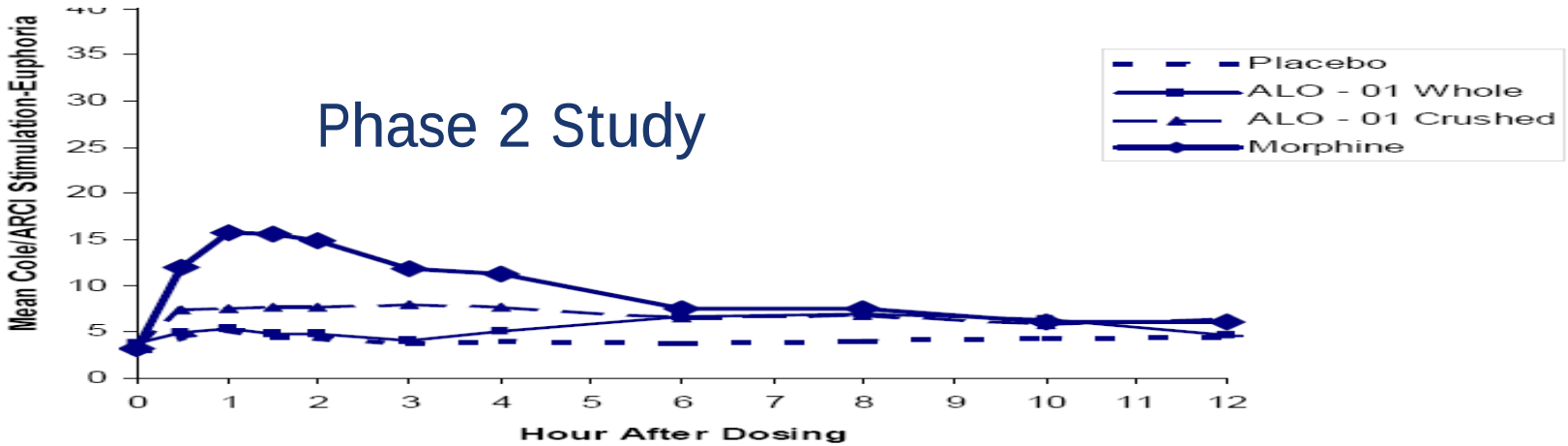
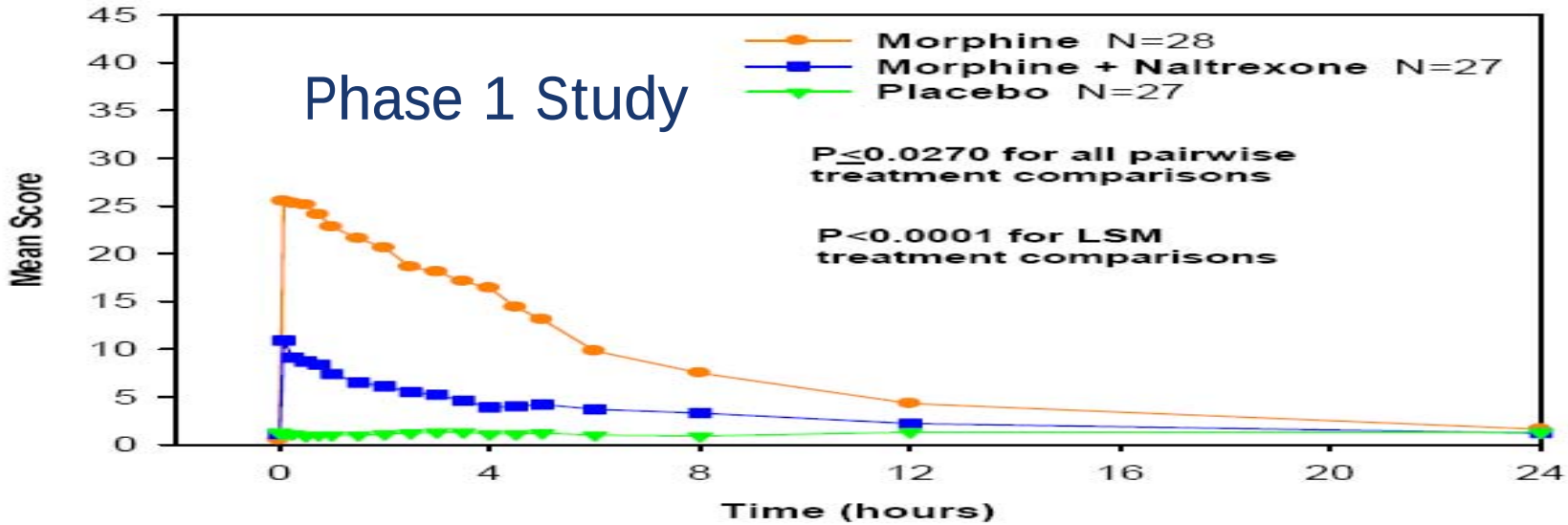
An example: Embeda

Combination of extended-release morphine and sequestered naltrexone



Trials on Embeda



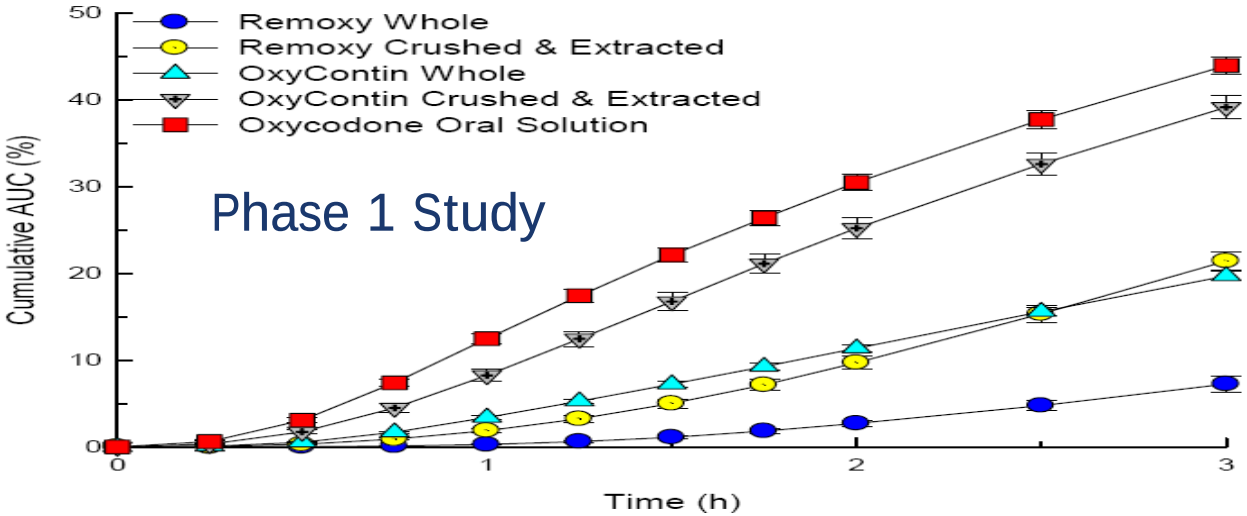


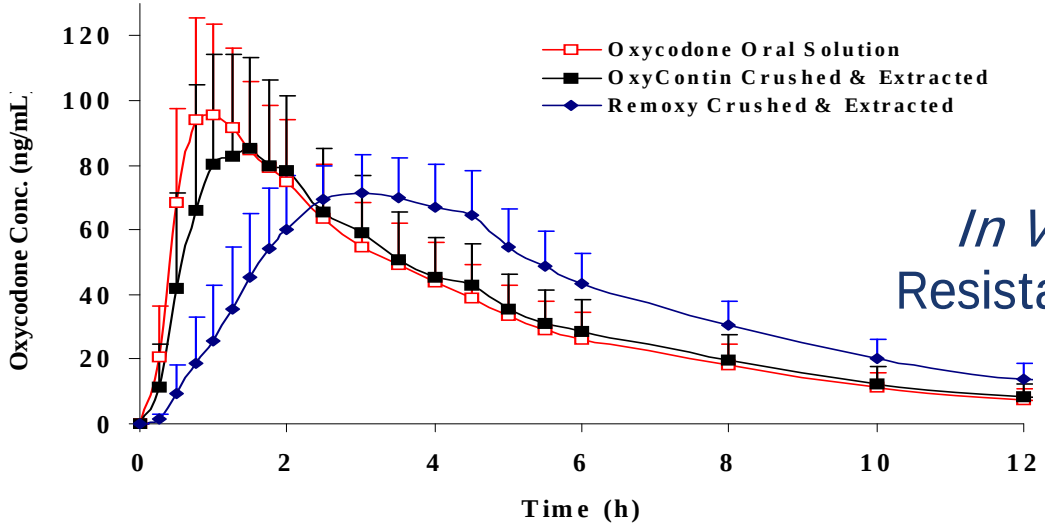
LSM=least square means

An example: Remoxy

Extended-release oxycodone in a high viscosity hard gelatin capsule

Trials on Remoxy





In Vivo Abuse Resistance Studies

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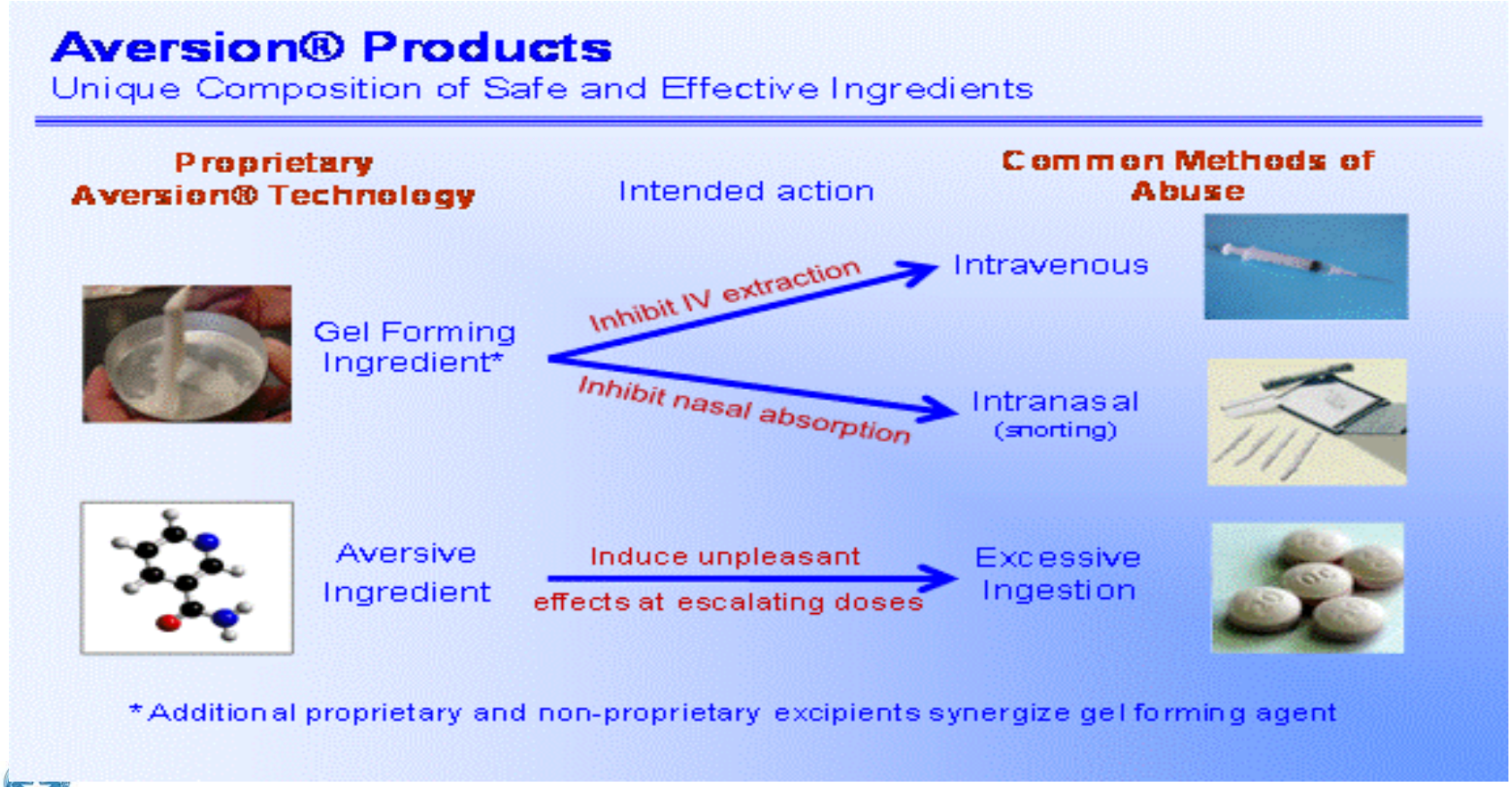
An example: Acurox

Immediate release oxycodone/subtherapeutic niacin (*aversive ingredient)*



ADFs: advantages and disadvantages

Mayo Clin Proc

Table 1

Current Tamper-Resistant Opioid Formulations: Advantages and Disadvantages

Opioid formulation	Advantage	Disadvantage
Physical barriers	Prevent abusers from crushing or chewing their opioid to facilitate rapid release into the system Prevent accidental crushing or chewing in compliant patients No AEs in compliant patients FDA-approved formulation available	Does not deter abuse of intact tablets Only 1 FDA-approved formulation available
Aversive components	May prevent abuse by chewing or crushing opioids May limit abuse of intact tablets because taking too much will amplify niacin AEs	Potential for AEs in compliant patients who take the product as intended Adverse events with intact tablets may prevent legitimate dose increases to address increasing pain or decreasing efficacy over time Adverse events of niacin may not be sufficient to deter a motivated abuser No FDA-approved formulation
Sequestered antagonist	Prevents abuse by chewing or crushing opioids FDA-approved formulation available	Does not deter abuse of intact tablets Chewing or crushing the tablet may precipitate severe withdrawal symptoms

AE = adverse event; FDA = Food and Drug Administration.

Mayo Clin Proc

Stanos SP et Al. Strategies to reduce the tampering and subsequent abuse of long-acting opioids: potential risks and benefits of formulations with physical or pharmacologic deterrents to tampering. Mayo Clin Proc. 2012 Jul;87(7):683-94

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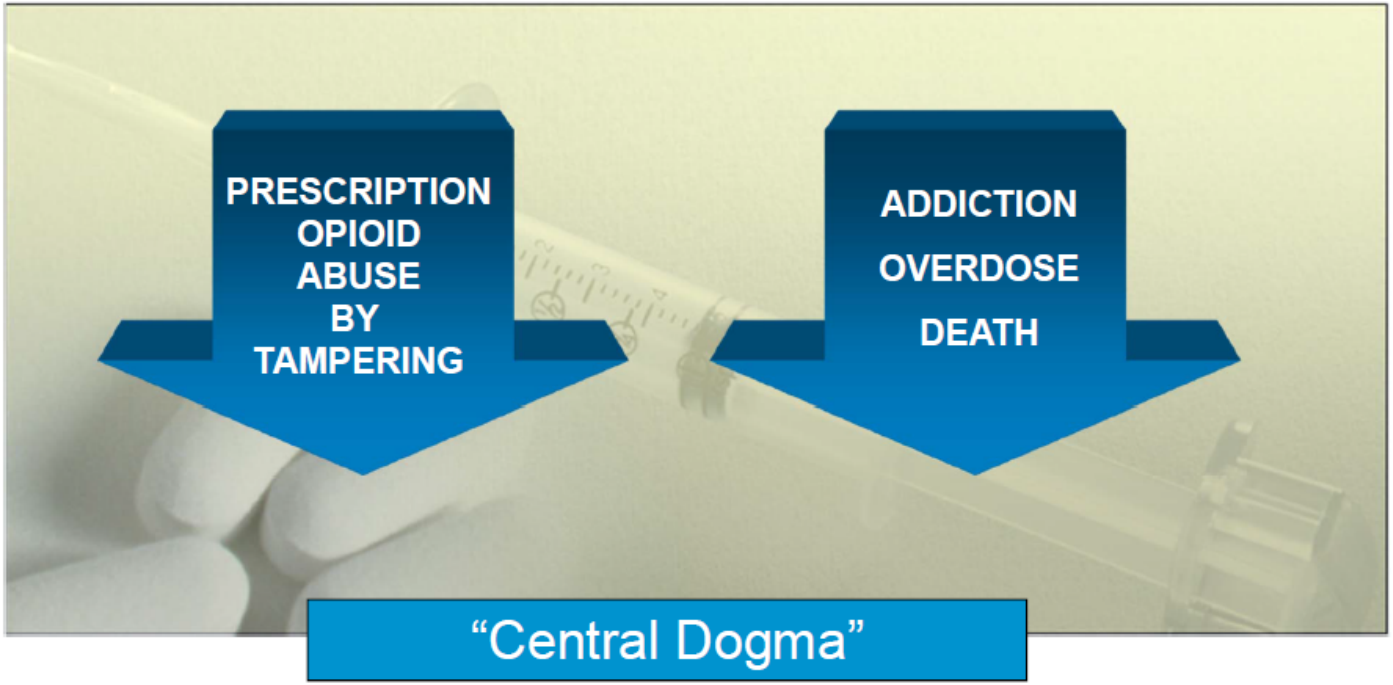
The goal

Demonstrate that ADF deters abuse by tampering



From Epidemiology Advisory Committee Meeting (Oct .2010)

http://www.radars.org/Portals/1/Brown.pdf

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Please enter Regulator's dilemma

Industry
Require favourable conditions for innovation

Payers/prescribers/HTA organizations
Request comparative efficacy/ effectiveness data

Patient groups
Demand early access to potentially life-saving drugs (for example, Abigail Alliance)

Media/scientific community
Demand stricter safety assessment after series of market withdrawals

Unmet medical need
For example, epidemiology of obesity, diabetes

Excess medicalization
For example, obesity, metabolic syndrome, mood disorders

Time to marketing authorization

Shorter timelines
Higher level of uncertainty

More studies/patients
Delayed market access

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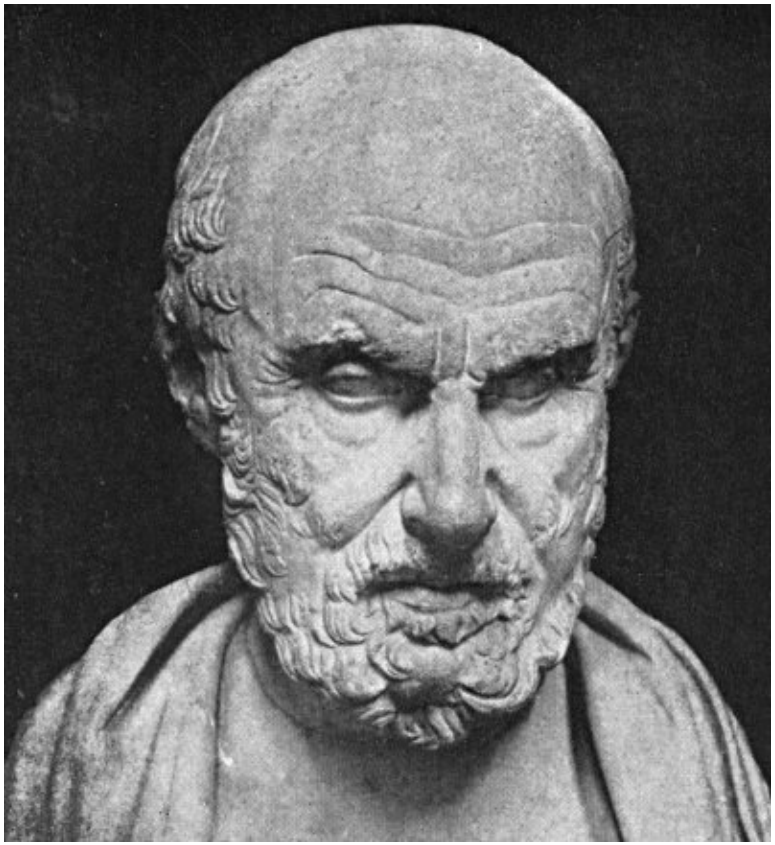
Eichler HG et al. Nature Rev Drug Disc 2008

...and a much older Dilemma

Ὁ βίος βραχὺς,
ἡ δὲ τέχνη μακρὴ,
ὁ δὲ καιρὸς ὀξὺς,
ἡ δὲ πεῖρα σφαλερὴ,
ἡ δὲ κρίσις χαλεπή



Hippocrates of Kos (Aphorisms 1, 1)

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Life is short, Art is long, Moment escapes, Esperiment dangerous, Judgment difficult