

Drug Discovery & Development

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Drug Discovery & Development: Bench, Bedside, & Beyond

I. Background

II. The R&D Landscape

III. Innovation and Transformation

IV. The Preclinical Development Process

V. Case Study: A Novel Antidepressant

VI. Ethical Issues: Money, Data, & Politics

Disclaimer

***“Those who have knowledge, don’t predict.
Those who predict, don’t have knowledge.”***

Lao Tzu, 6th Century BC Chinese Poet

Serendipity or Good Science: Building Opportunity

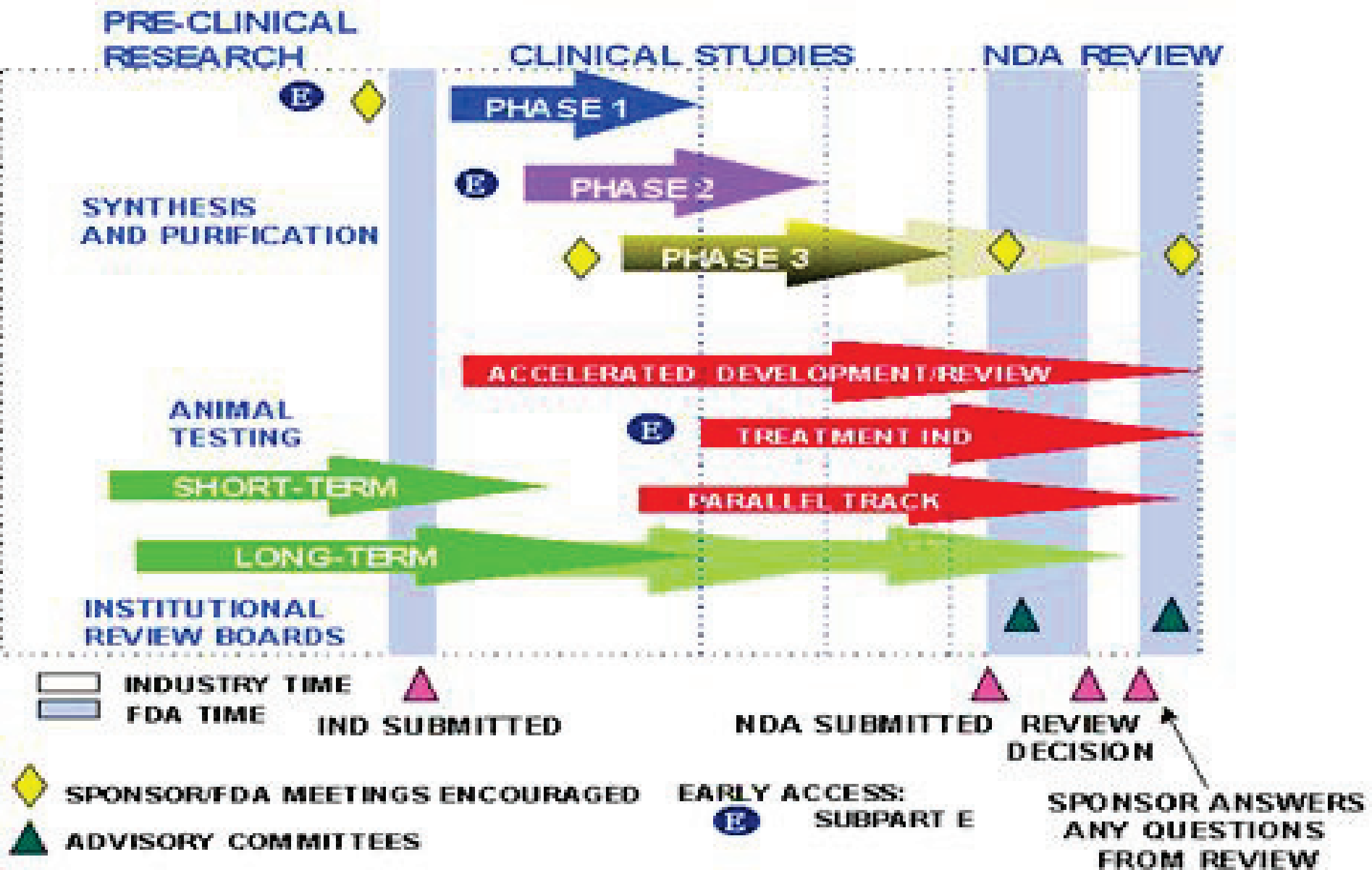
Hoffman



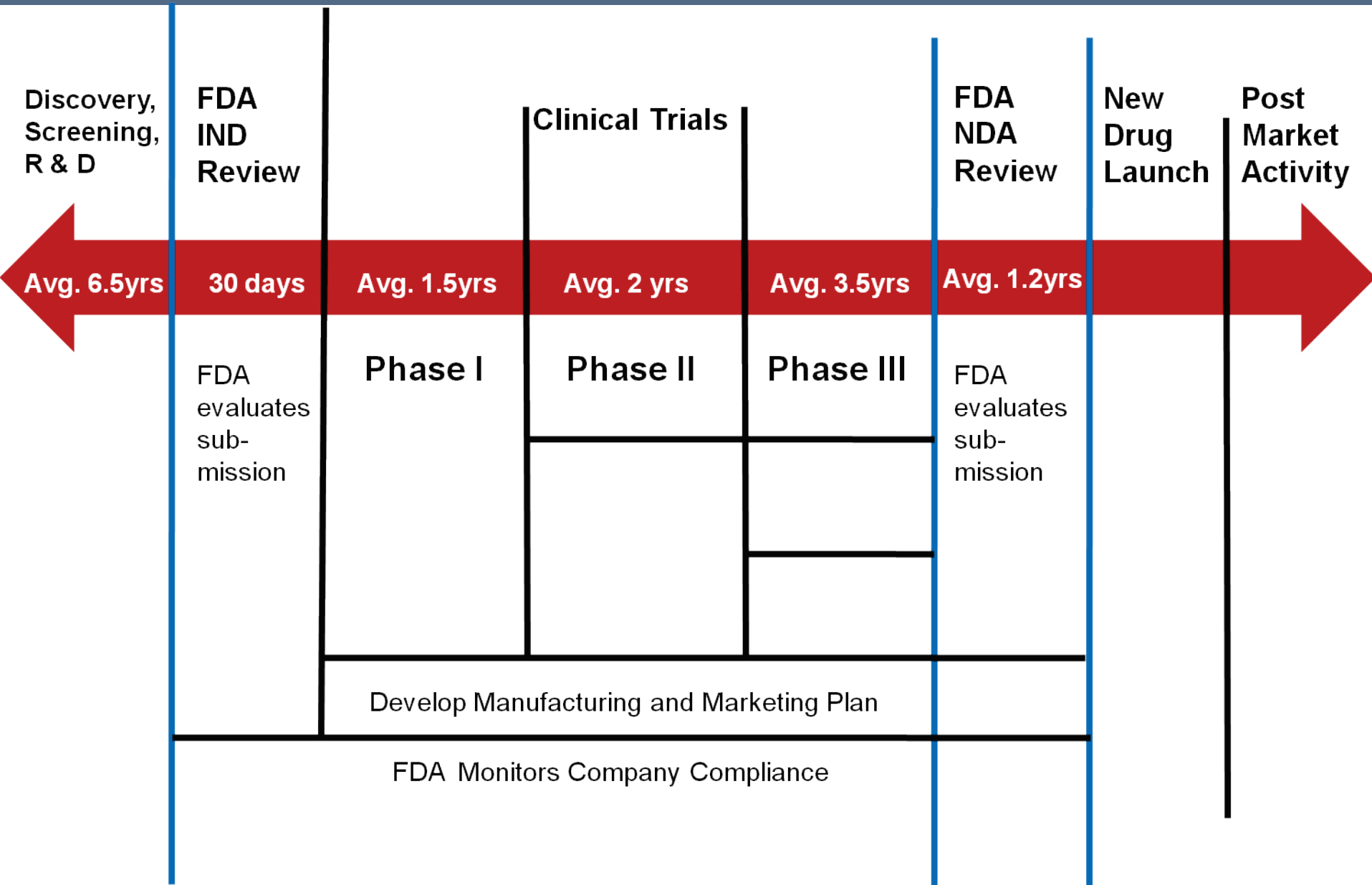
Osterloh

I. Background

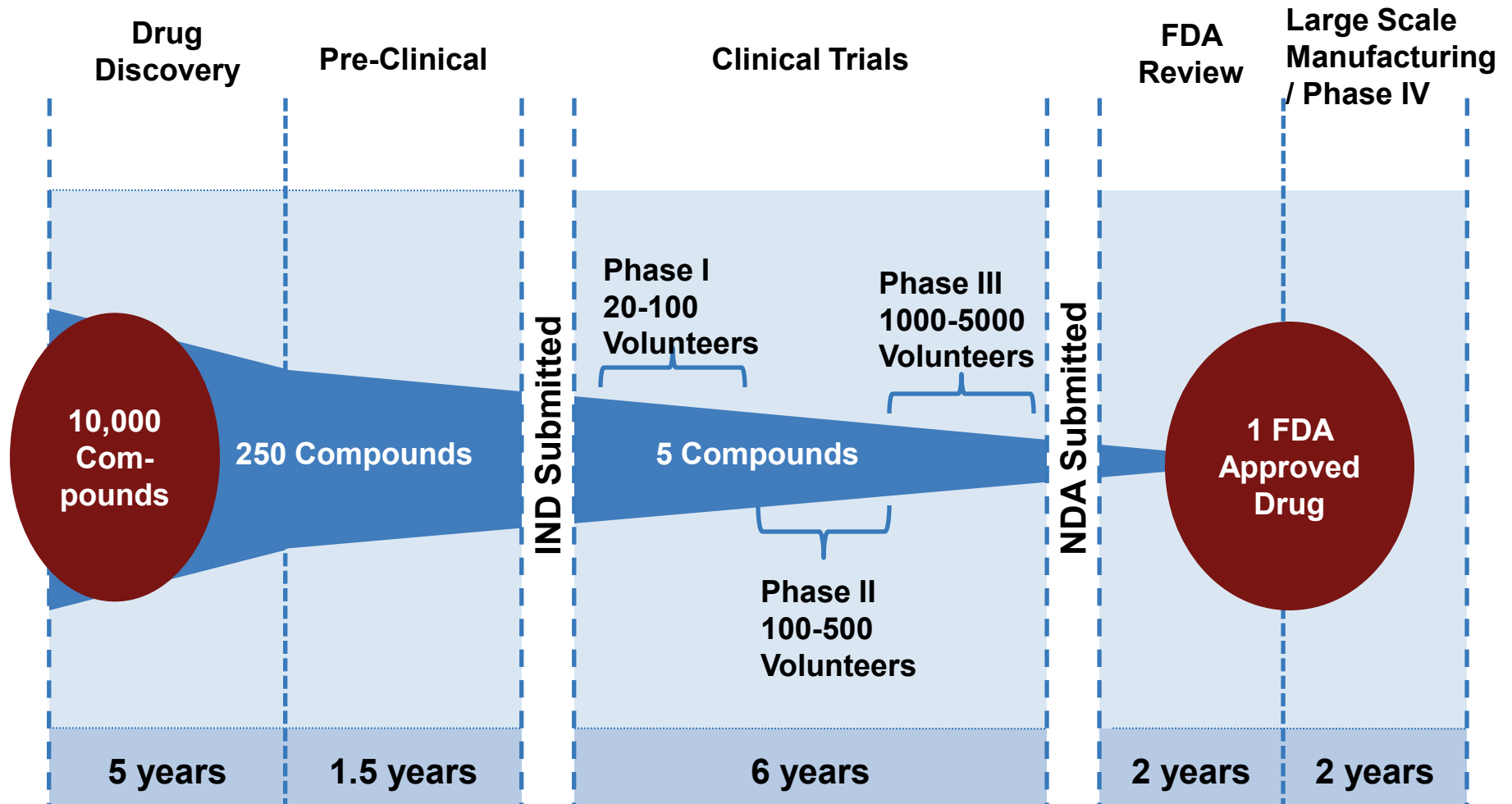
Drug Development Process: Stages



Drug Development Process: Phases

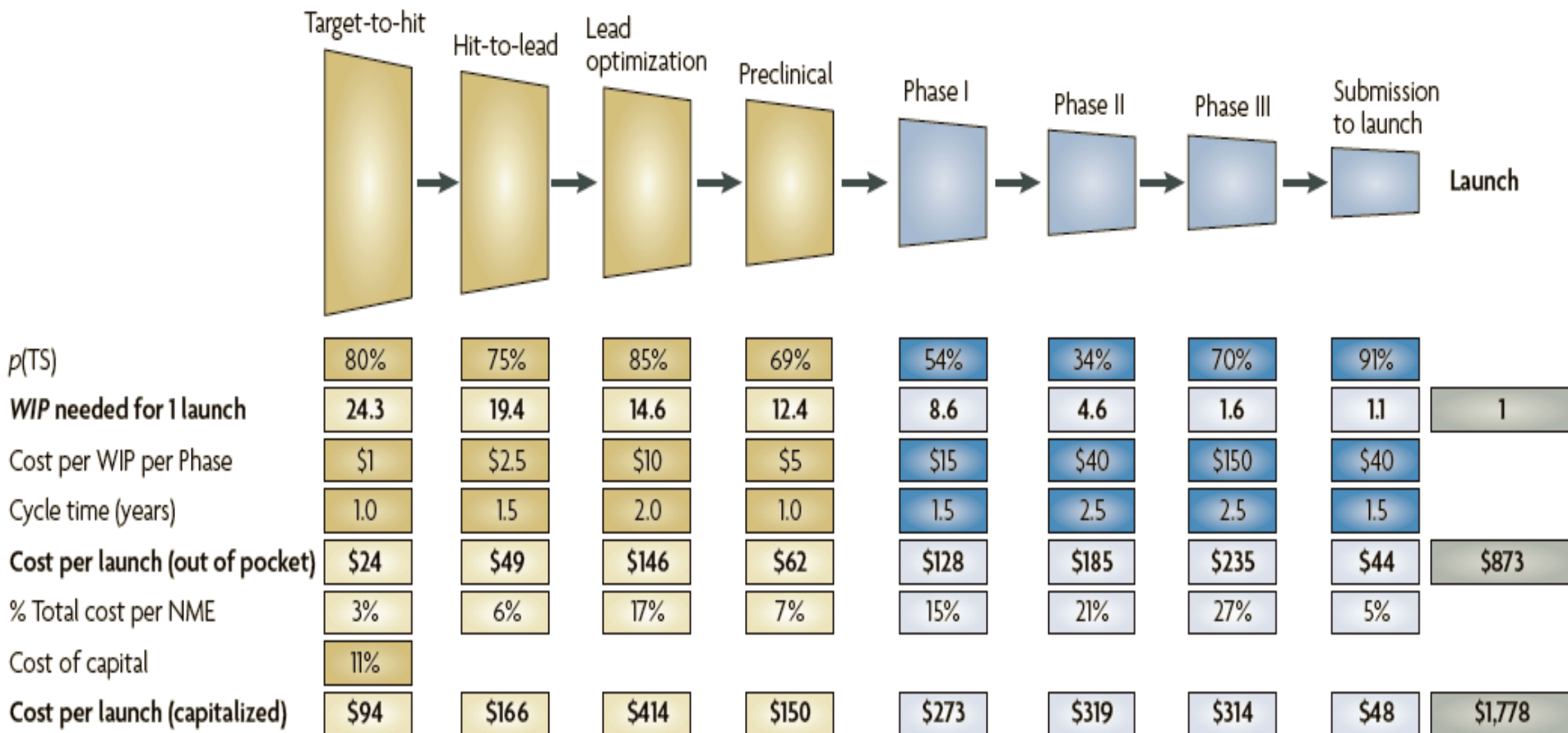


Biopharmaceutical Drug Development: Attrition



II. The Research & Development Landscape

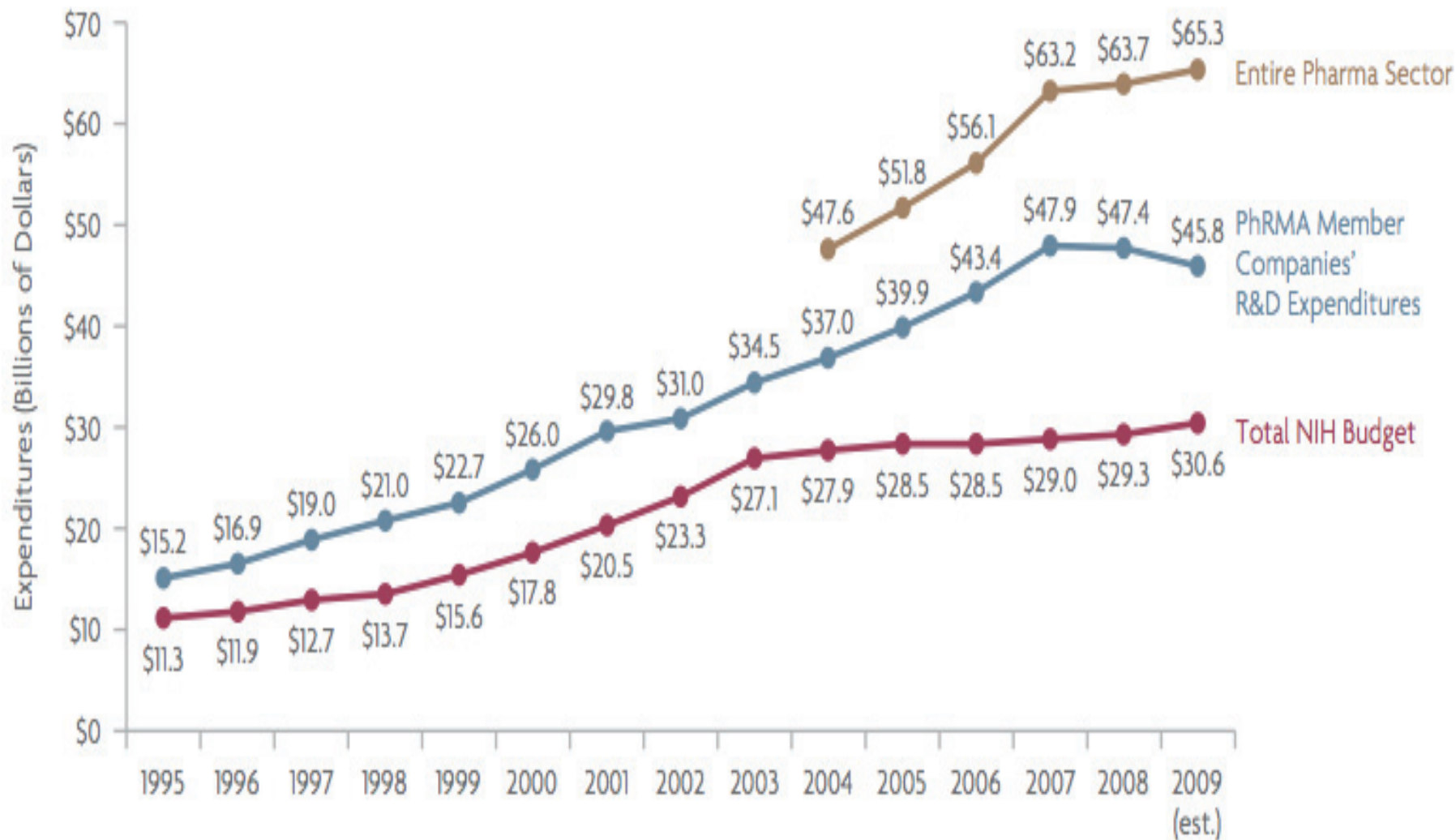
New Chemical Entities: R&D Cost Model



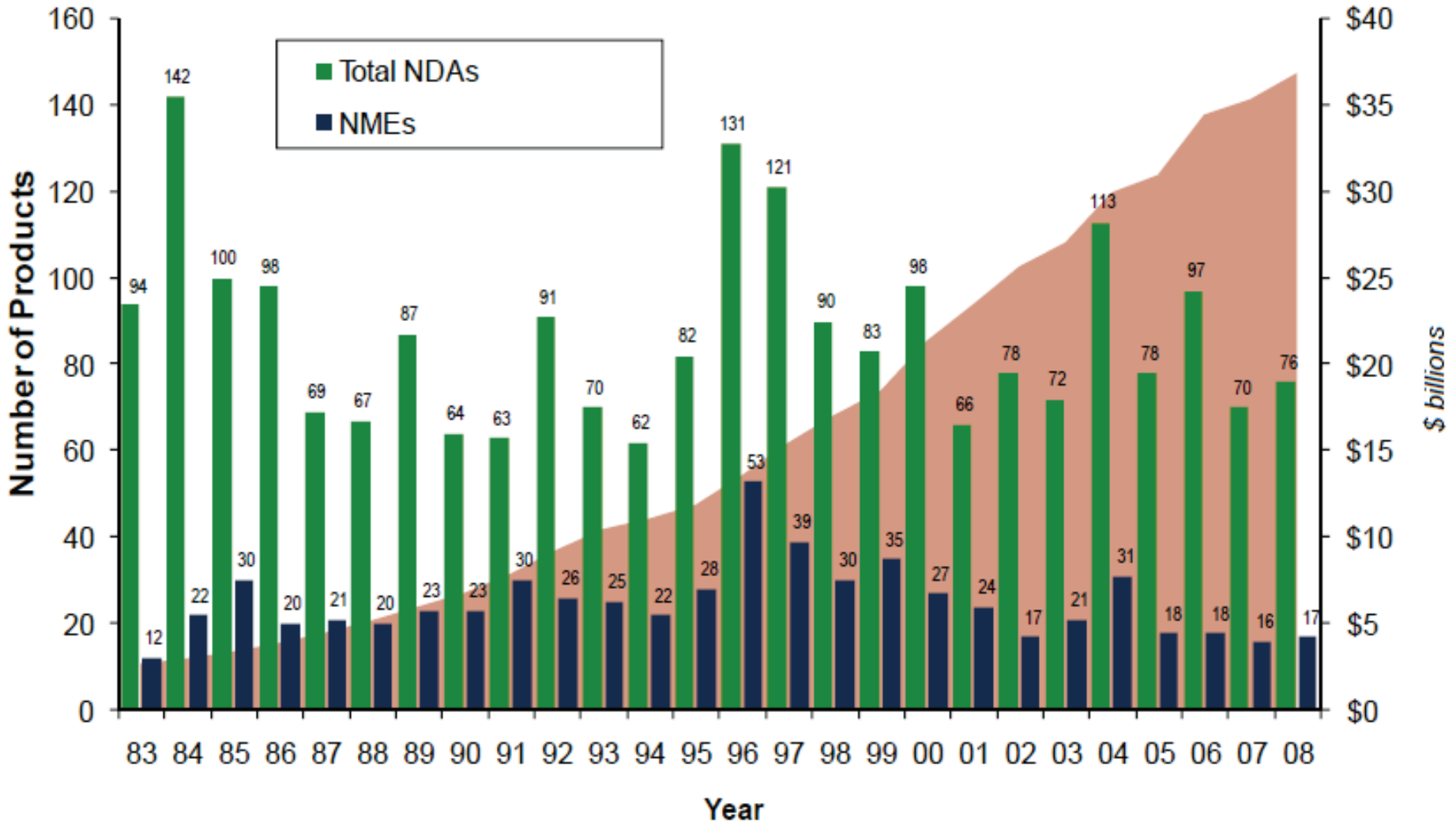
Discovery: \$263/\$824 million

Development: \$632/1054 million

Annual Private & Public R&D Spending

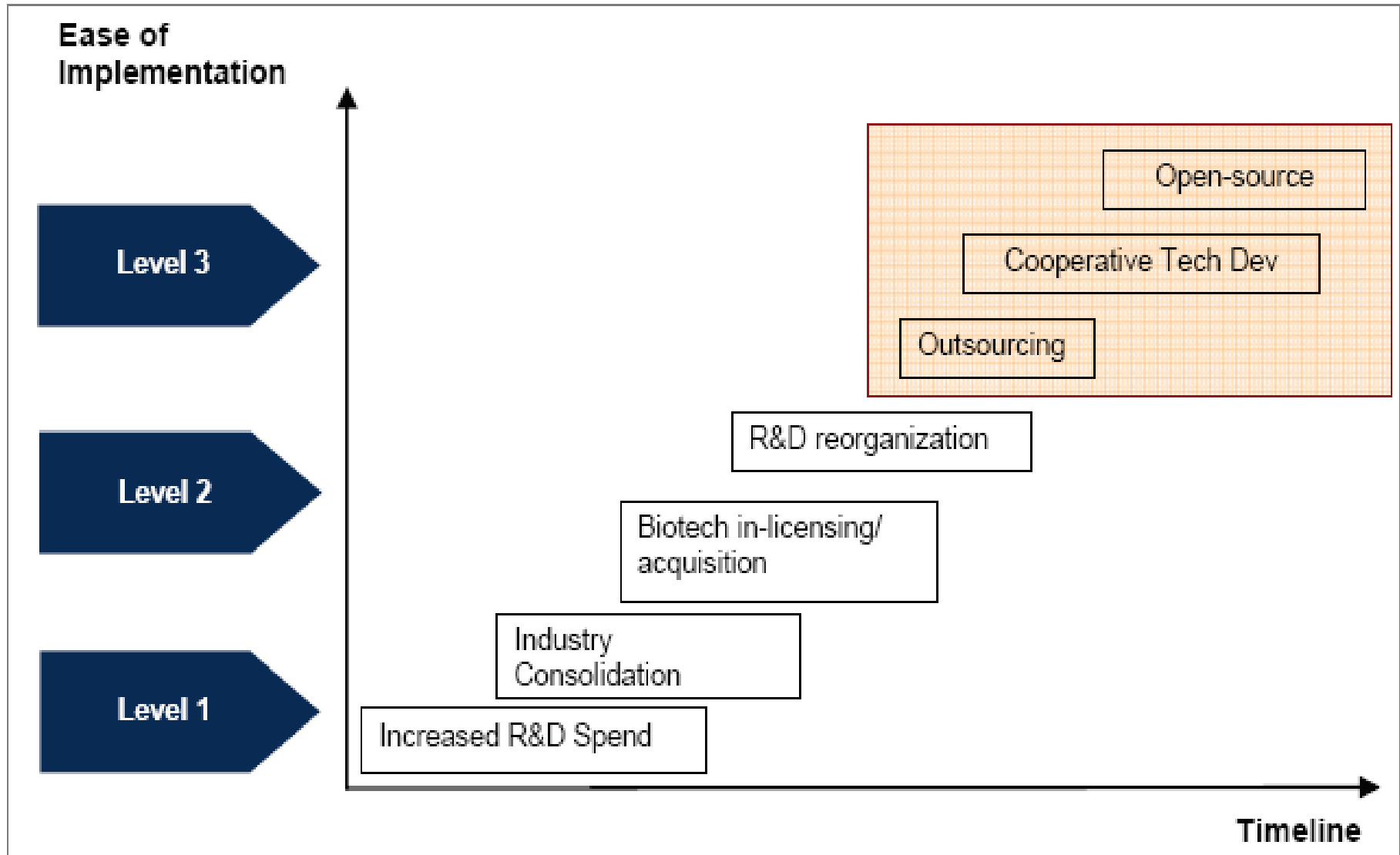


Research & Development Spending: Return on Investment



III. Innovation & Transformation

Innovation Models and Transformation

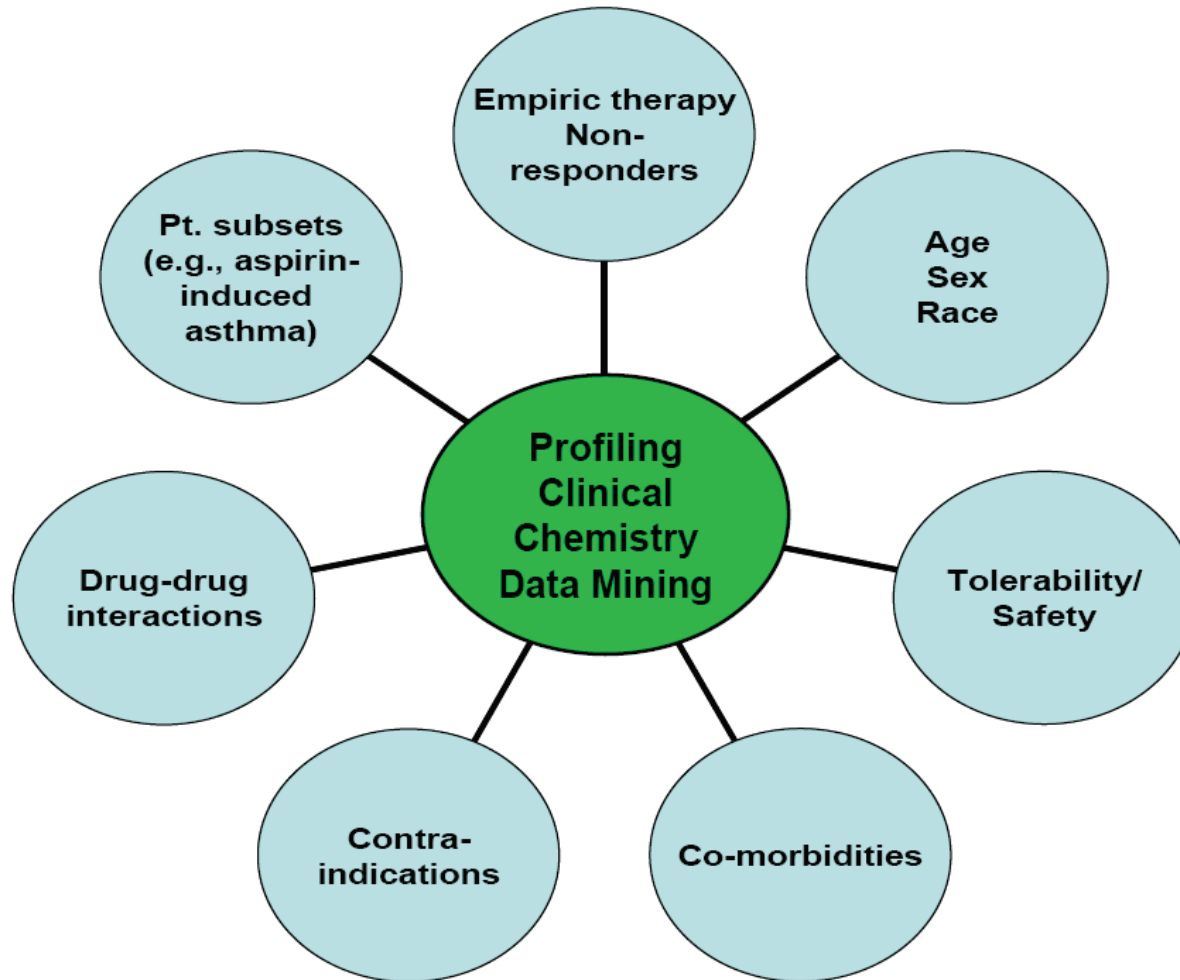


Antidepressants: Me Too Drugs

1986	Fluvoxamine	(Luvox; Solvay) SSRI
1987	Fluoxetine	(Prozac; Lilly) SSRI
1992	Sertraline	(Zoloft; Pfizer) SSRI/NRI
1993	Venlafaxine	(Effexor; Wyeth) SSRI/NRI
1996	Bupropion	(Wellbutrin; Wyeth) SNRI/DRI
2002	Escitalopram	(Lexapro; Forrest) SSRI
2004	Duloxetine	(Cymbalta; Lilly) SSRI/NRI
2008	Desvenlafaxine	(Pristiq; Wyeth/Pfizer) SNRI
2011	Vilazidone	(Vybrid; Forest Labs) SSRI/5HT1a

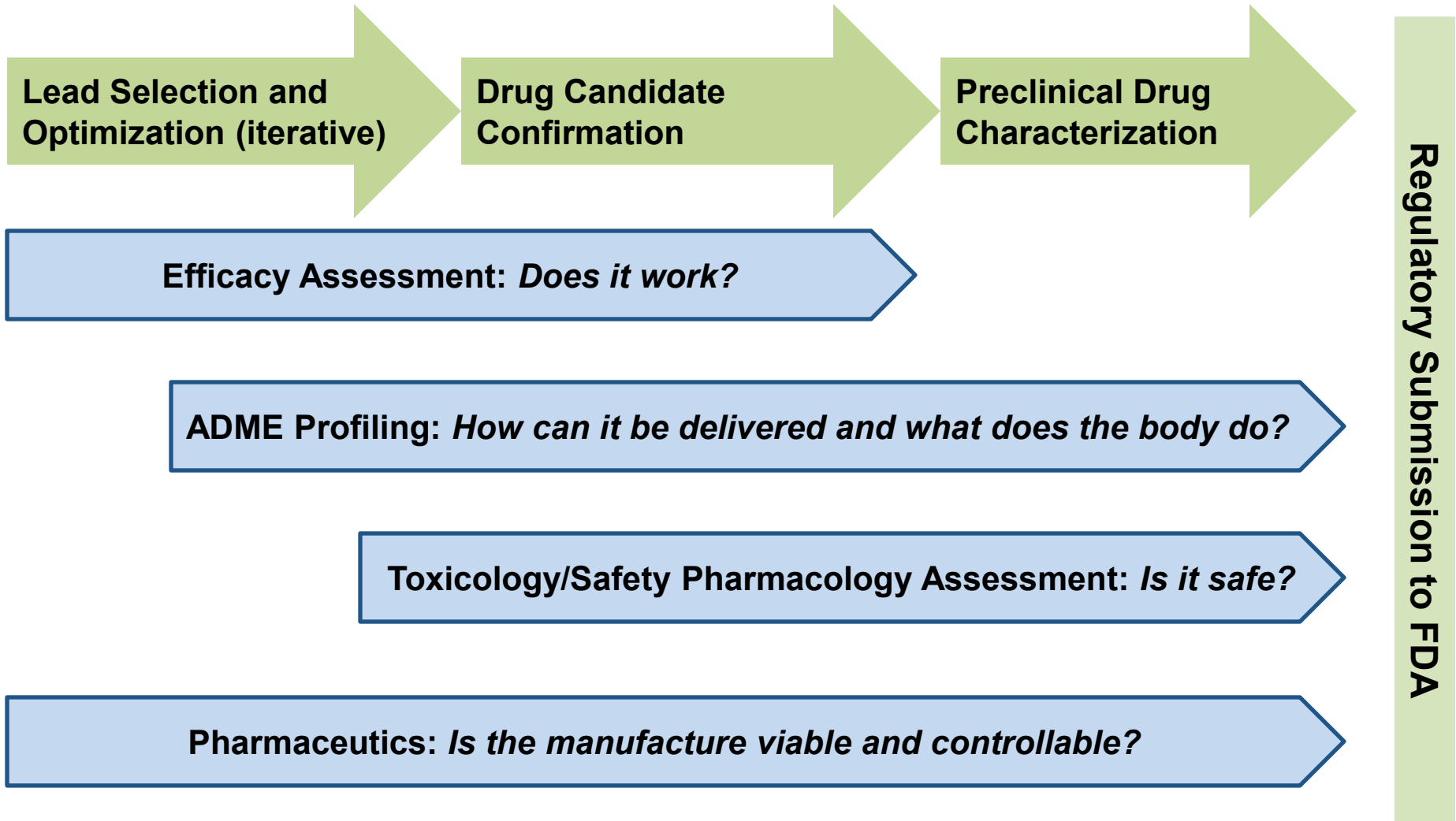
Personalized Medicine (sort of)

Less Impersonal Medicine: Clinical Segmentation Instead of Pharmacogenetic Segmentation

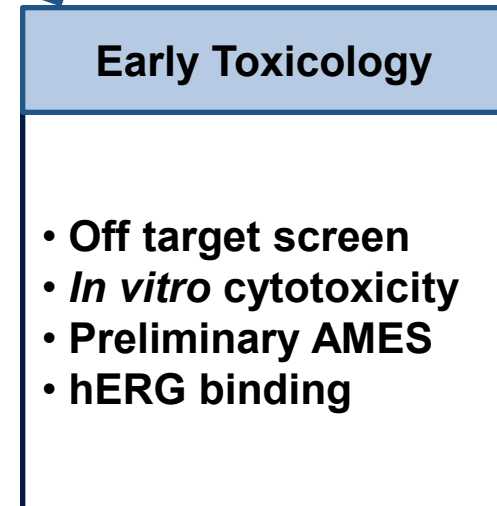
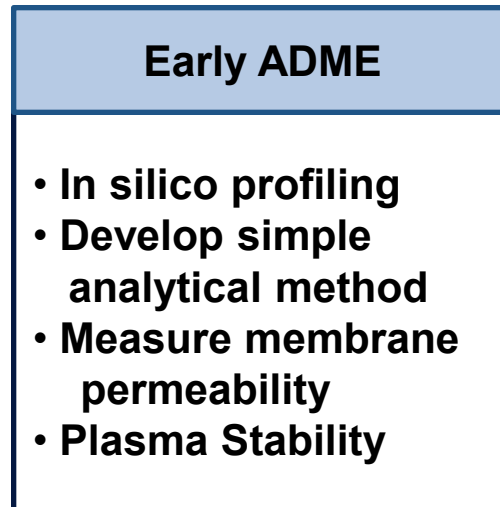
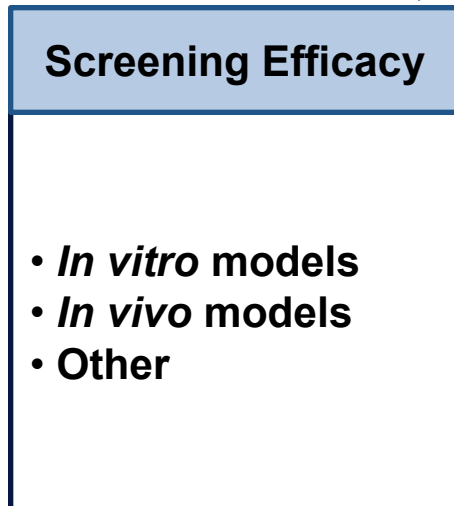
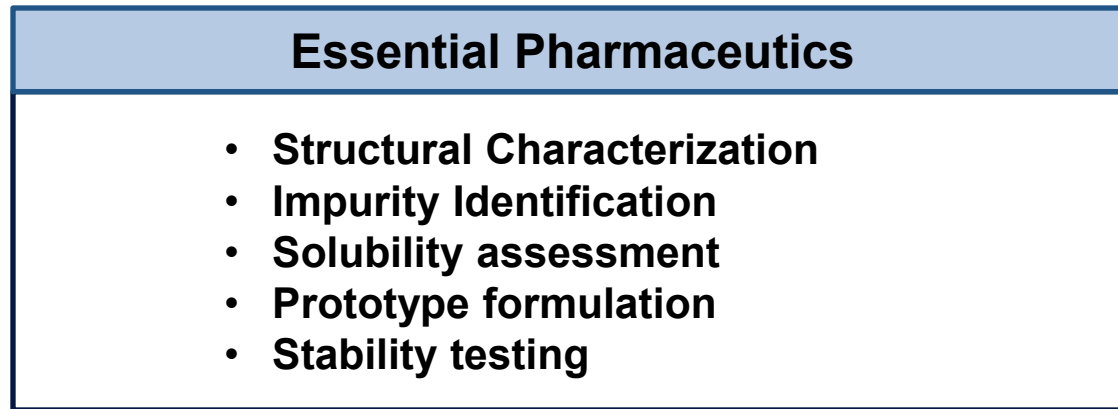


IV. Discovery & Development

Preclinical Development



Stage 1: Lead Selection and Optimization



Stage 2: Drug Candidate Confirmation

Data from Lead Optimization Stage

Preliminary CMC (Chemistry, Manufacture and Control)

- Formulation for GLP Toxicology
- Stability testing of active ingredient
- Detailed physicochemical characterization
- Impurity analysis

“Benchmark” *in vivo* Models

- *In vivo* models
- Validated models
- Models in other disease areas

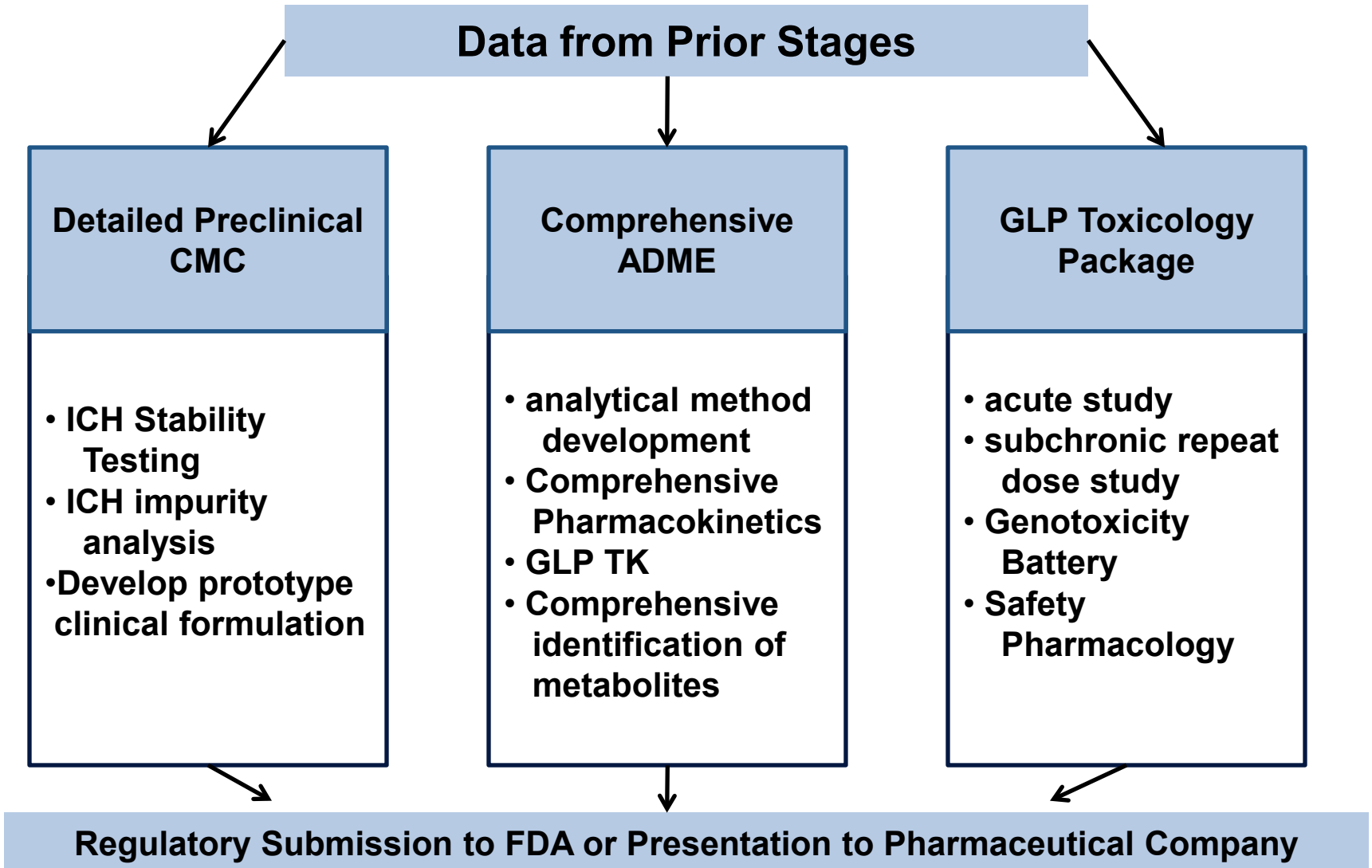
ADME Profiling

- Optimized analytical method development
- Basic pharmacokinetics (PK) & Oral Bioavailability
- Determine metabolism of drug

Preliminary Toxicology

- Maximum tolerated dose (MTD)
- Repeat Dose (non-GLP)
- Preliminary Cardiovascular Safety Pharmacology

Stage 3: Preclinical Drug Characteristics

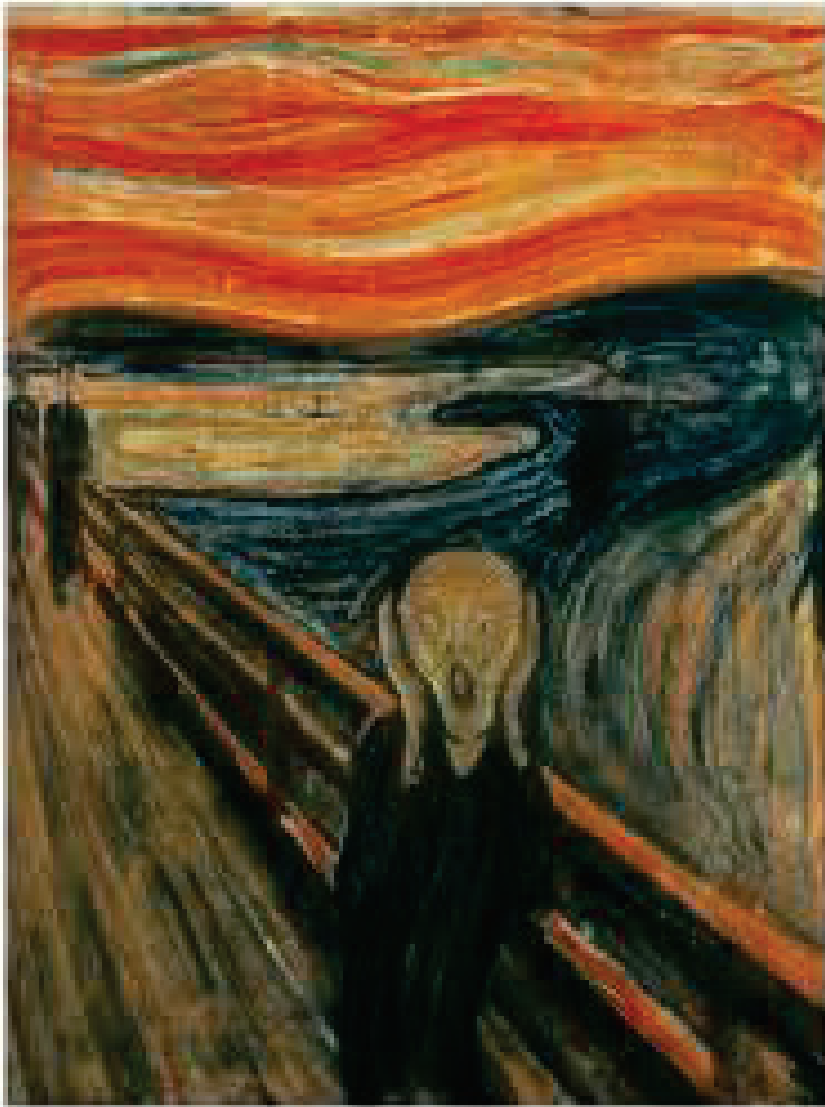


V. Case Study: Agomelatine

Major Depression: Symptoms

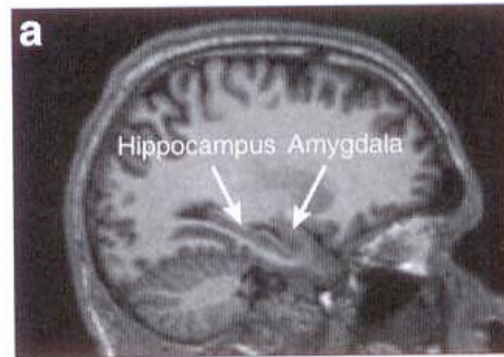
- **Anhedonia**
- **Blunted Affect**
- **Disturbed Sleep**
- **Weight Gain/Weight Loss**
- **Compromised Social Interactions**

The Scream

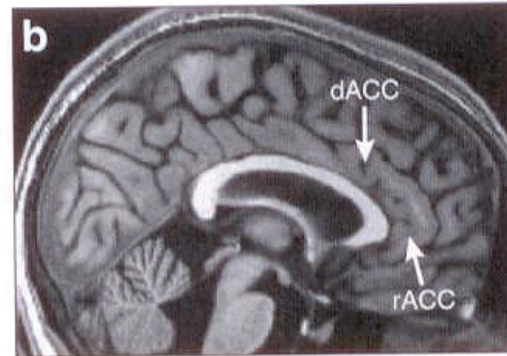


Edvard Munch, 1893

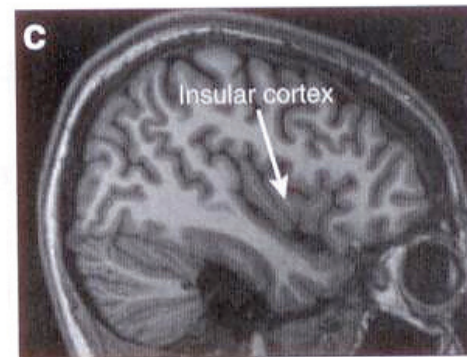
Fear Circuits: Core Components



Hippocampus and Amygdala

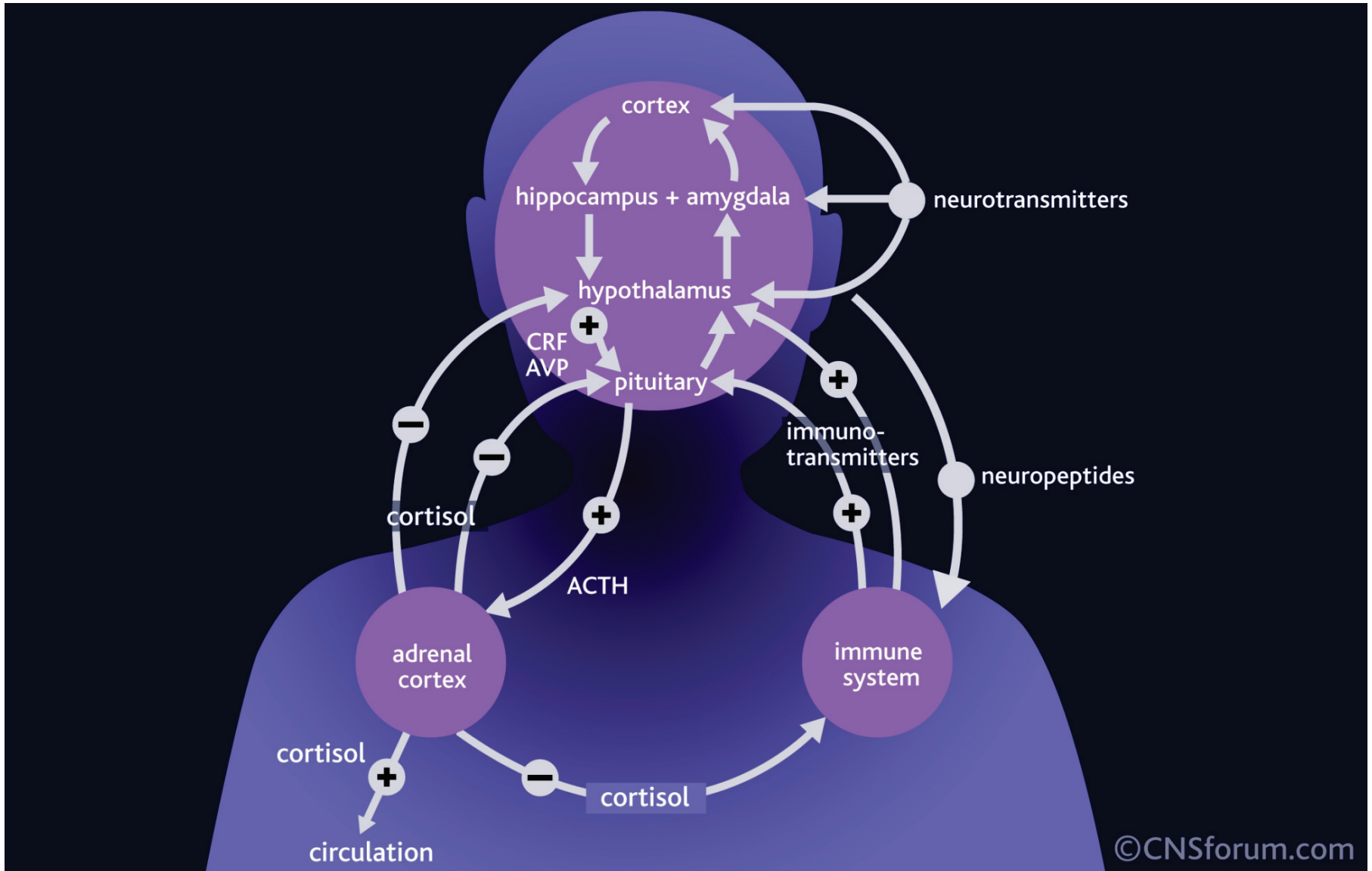


Anterior & Rostral Cingulate Cortex

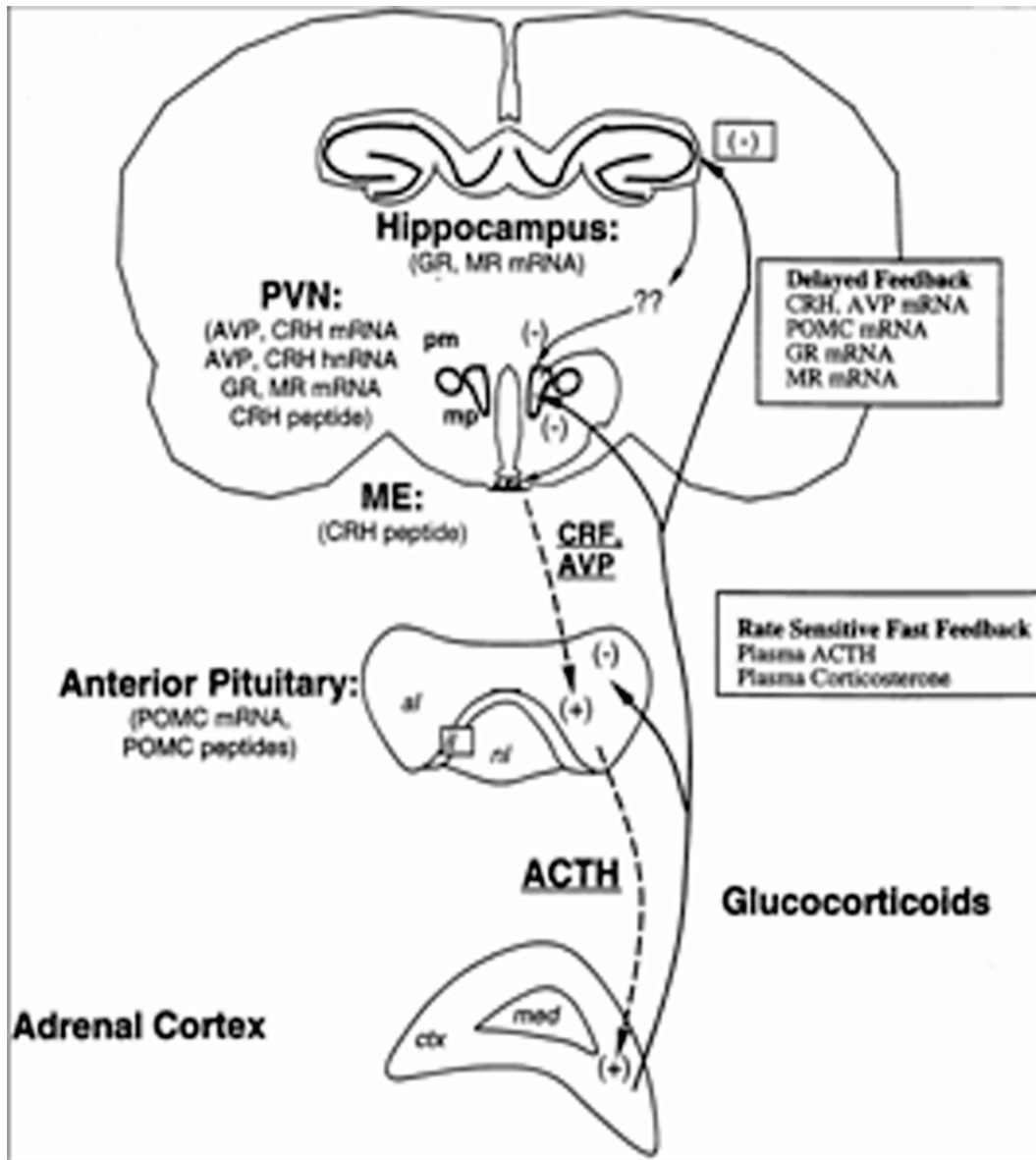


Insular Cortex

Hypothalamic-Pituitary-Adrenal Axis



Hypothalamic-Pituitary-Adrenal Axis



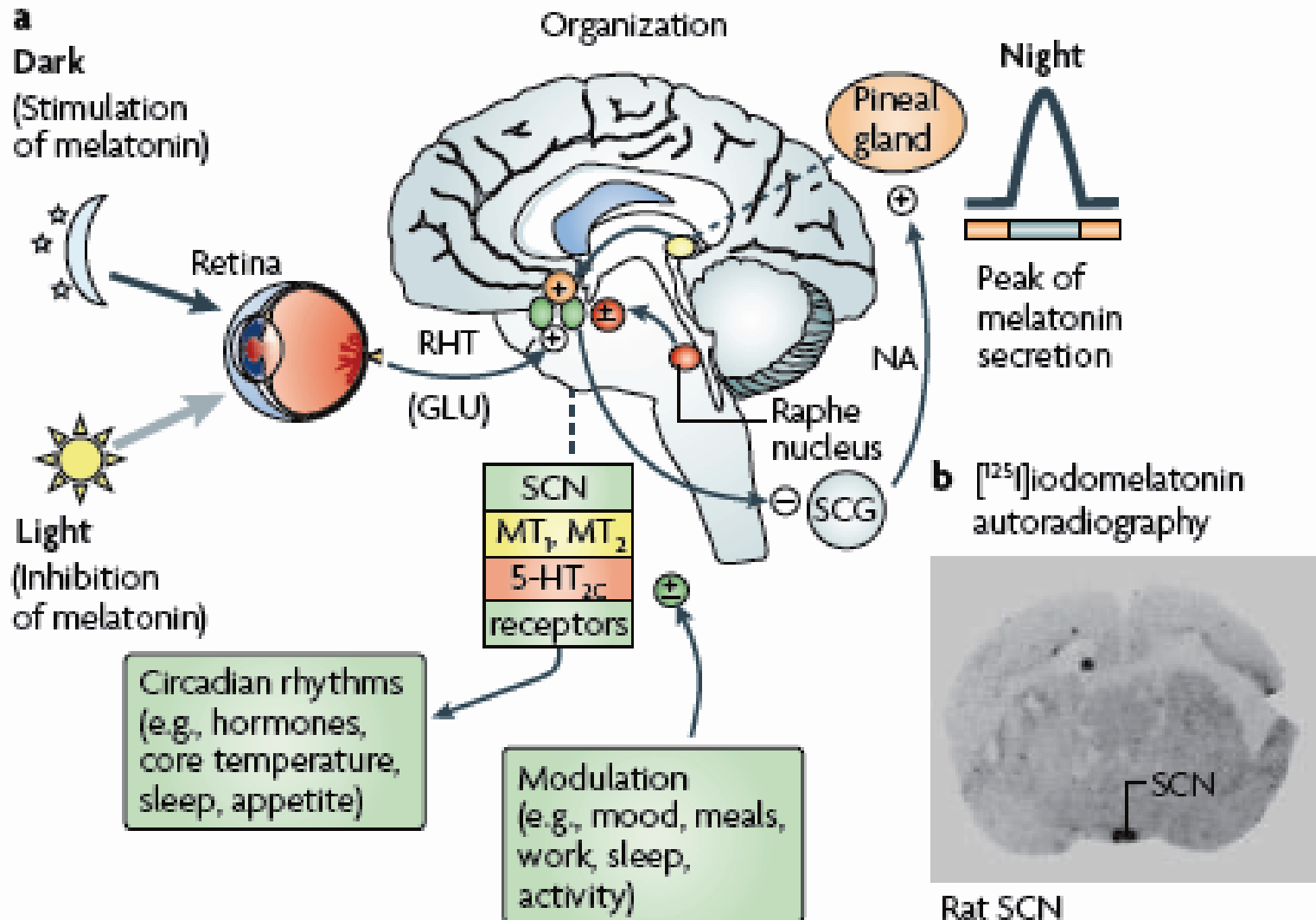
Key Considerations

- **Regulatory Peptides**
 - CRF
 - AVP
- **Feedback Regulation**
 - Glucocorticoids
- **Biorhythm Disturbance**
 - Sleep
 - Temperature
 - Cardiac
 - HPA axis

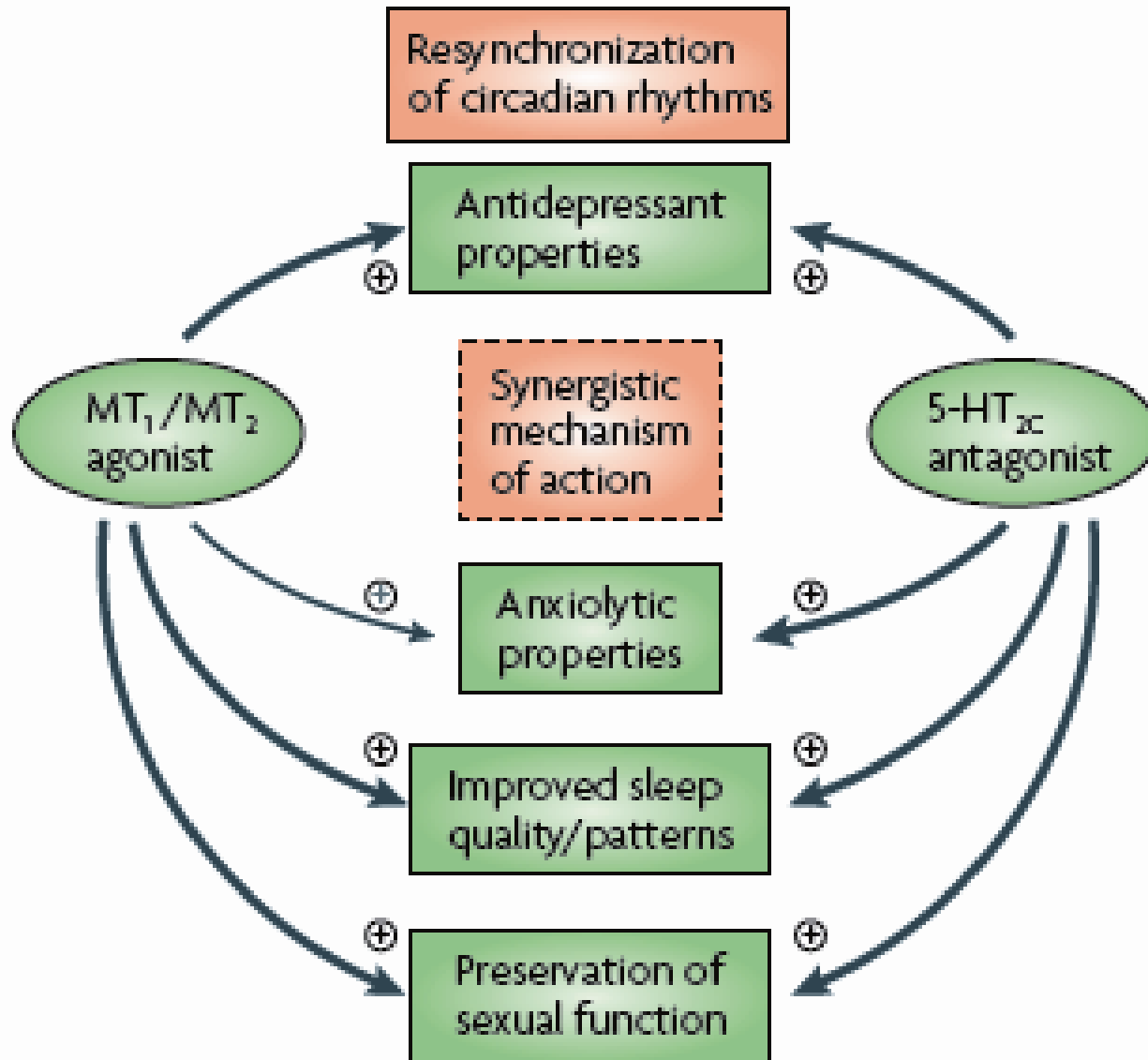
Major Depression & Biorhythms

- **Alterations in circadian rhythms of behavior, sleep, core temperature and the secretion of cortisol and other hormones**
- **Blunted amplitude of daily rhythms and poor responsiveness to environmental entraining stimuli.**
- **Circadian desynchronization may also be triggered by disorganization of the suprachiasmatic nucleus**
- **Circadian disturbances may be provoked by an abnormal pineal output of melatonin, a key synchronizer of biological rhythms and sleep**
- **Depression is associated with an altered diurnal rhythm of melatonin output, including a blunted night time surge**
- **Administration of melatonin itself is ineffective in major depression**
- **Re-coordination of biological rhythms by recruitment of melatonergic mechanisms may be a therapeutically relevant strategy for improving depressed states.**

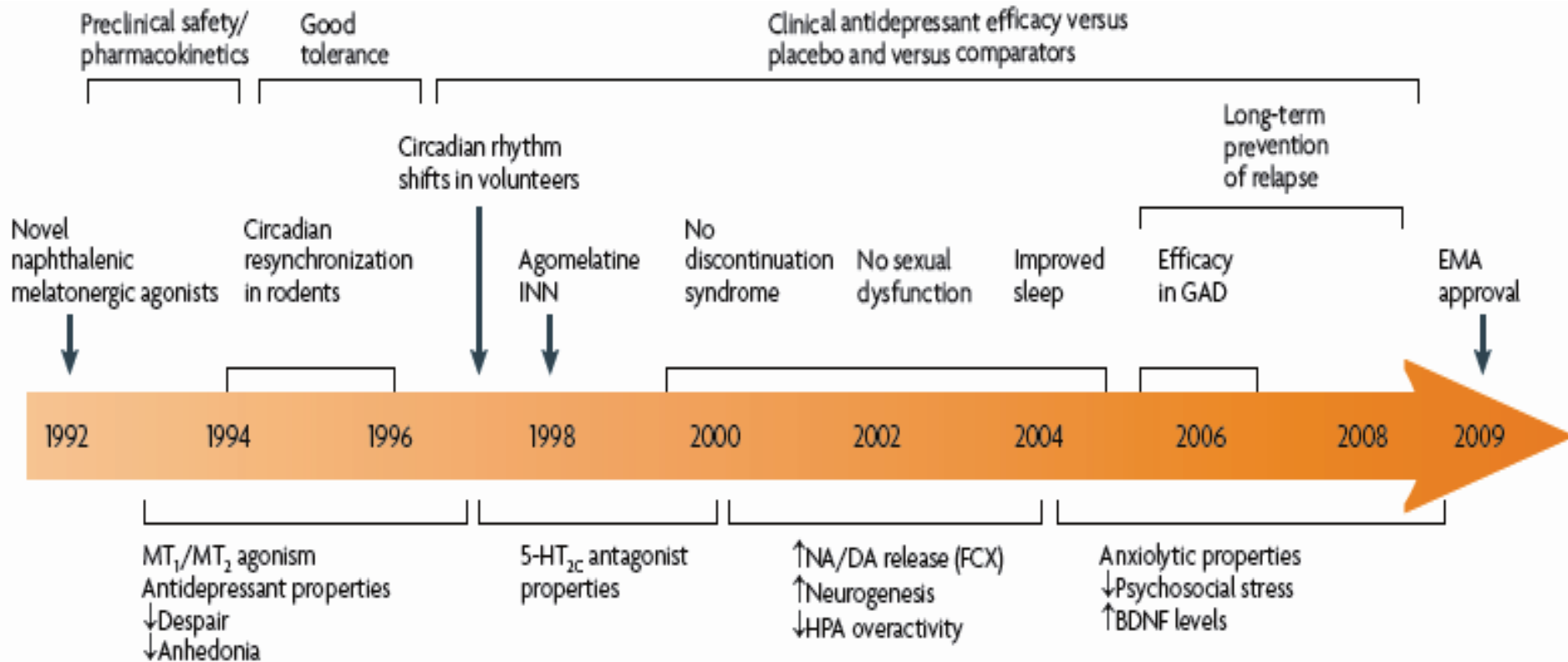
Melatonin, Circadian Rhythms, & Agomelatine



Agomelatine: Mechanism of Action



Discovery, Development, Characterization, & Approval of Agomelatine



Key Pharmacological Observations

V. Ethics

Neurontin

PFIZER LOSES A ROUND OVER MARKETING OF NEURONTIN

By BLOOMBERG NEWS

A judge in Boston upheld a jury decision that Pfizer illegally promoted Neurontin for unapproved uses. Pfizer said it would appeal. January 29, 2011

EXPERTS CONCLUDE PFIZER MANIPULATED STUDIES

By STEPHANIE SAUL

The drug maker manipulated the publication of studies to bolster use of its epilepsy drug Neurontin, according to expert witnesses in a lawsuit against the company. Oct 8, 2008

PFIZER TO PAY \$430 MILLION OVER PROMOTING DRUG TO DOCTORS

By GARDINER HARRIS

Pfizer pleads guilty and agrees to pay \$430 million to resolve criminal and civil charges that it paid doctors to prescribe epilepsy drug Neurontin to patients with ailments that drug was not federally approved to treat. May 14, 2004

Politics, Medicine, & Responsibility

<http://www.youtube.com/watch?v=pPZn9mRQIq4>

Serendipity or Good Science: Building Opportunity

Hoffman



Osterloh

Thank you for your time and attention