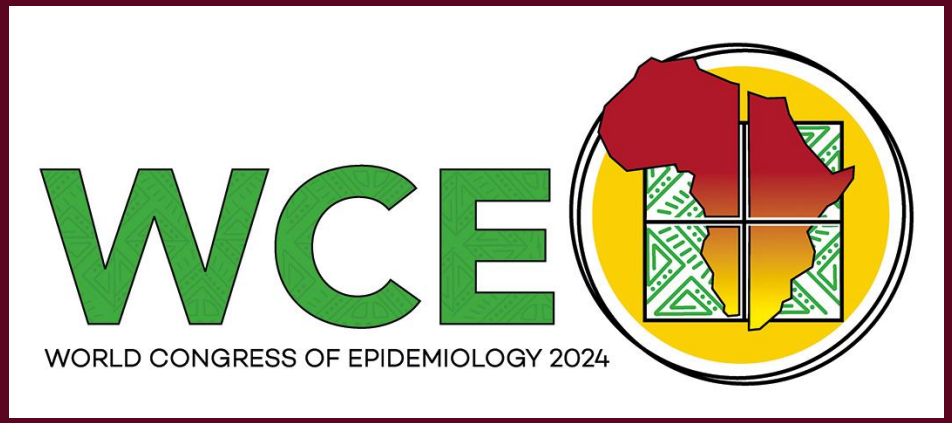


SESSION INT04

Pharmacoepidemiology – Insights and Challenges

Elaine H. Morrato, DrPH FISPE

Parkinson School of Health Sciences and Public Health

CAPE TOWN, SOUTH AFRICA | SEPTEMBER 25, 2024

LOYOLA
UNIVERSITY CHICAGO

Disclosure

The following personal or financial relationships relevant to this presentation existed during the prior 12 months:

Consultancy:

Xyrem (Sodium Oxybate) Antitrust Litigation, Class Plaintiffs including United Healthcare Services, Inc., Humana Inc., Molina Healthcare, Inc., and Health Care Service Corporation, Inc.

Division of Clinical Pharmacology, Department of Medicine
University of Cape Town

Karen Cohen,
MBChB, MMed, MSc

Ushma Mehta,
PharmD DrPH

LEARNING OBJECTIVES - AGENDA

1. Describe pharmacoepidemiology: evolution of the field, competencies and hot topics (presentation, 30 min)
2. Examine real-world application of pharmacoepidemiolgy (fire side chat with panelists, 30 min)
3. Discuss insights and challenges for the field of global pharmacoepidemiology (dialogue with audience, 20 min)
4. Share resources (summary presentation, 10 min)

pharmacoepidemiology (n)

INTERNATIONAL SOCIETY OF PHARMACOEPIDEMIOLOGY

The scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of medical products and interventions in human populations.

To accomplish this study, pharmacoepidemiology borrows from pharmacology, epidemiology … *and health services research*.

KNOW OUR AUDIENCE

Where in the world?

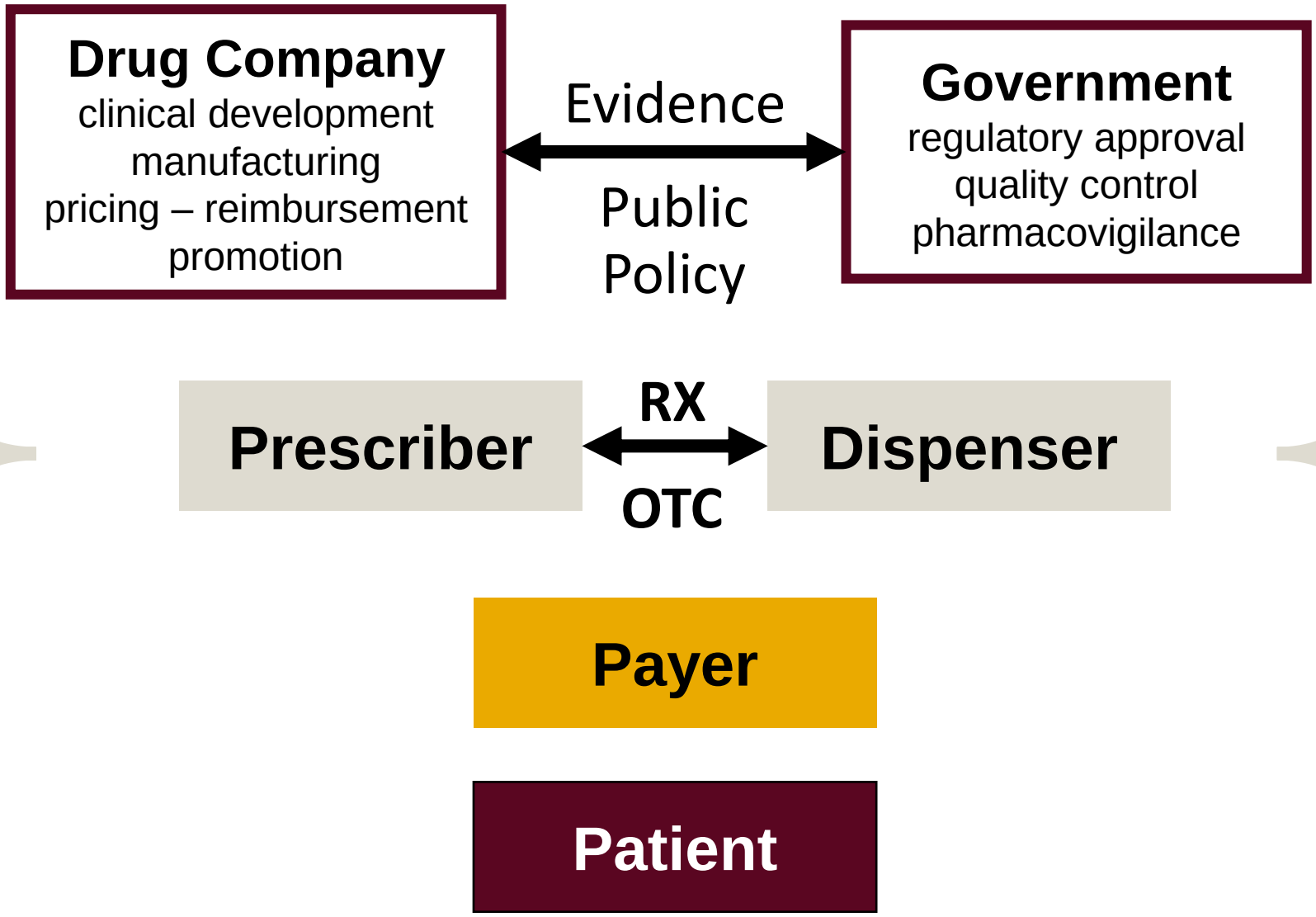
- Africa
- Asia-Pacific
- Europe
- South America
- North America

KNOW OUR AUDIENCE

Setting of research and practice?

- Academia – University
- Government
- Non-governmental Organization
- Private sector (industry, CRO)

Local Context Matters



Academics Evaluate Safety Signals and Policy Effects

KNOW OUR AUDIENCE

Level of expertise in pharmacoepidemiology?

- New to the field – keep it high level!
- Have some experience – give me practical advice!
- Have lots of experience – tell me the latest!

EVIDENCE FOR REGULATORY PUBLIC HEALTH DECISION MAKING

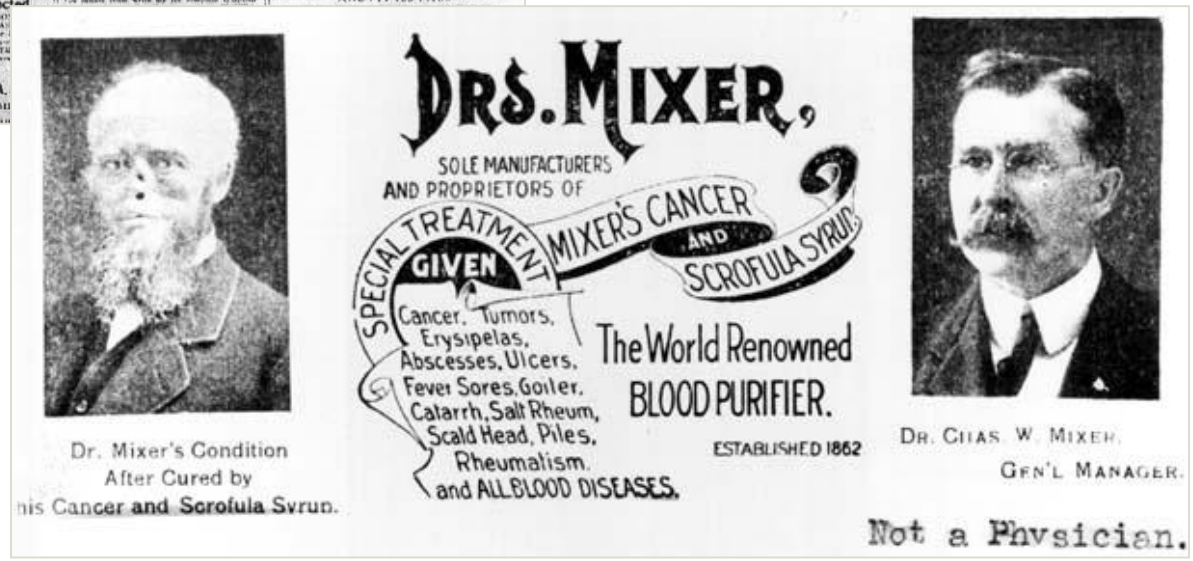
- Is the medicine safe and effective for the indicated use? Should I approve this medicine?
- What serious adverse events and risk(s) do I need to communicate? How generalizable are the findings?
- Are additional risk minimization measures required (beyond product labeling alone)?
- What pricing and reimbursement is warranted?
- Should I withdraw the medicine from the market?

Modern pharmacoepidemiology evidence

TYPES OF INVESTIGATIONS

- Surveillance - pharmacovigilance, drug utilization
- Retrospective studies – effect size, causal inference
- Prospective studies - post-marketing safety registries
- Risk management design, implementation, assessment (e.g., labeling changes, FDA REMS, EMA aRMMS)
- Benefit-Risk assessment (evidence synthesis, real-world evidence, patient preferences)

United States, turn of the 20th century…



Patent Medicines

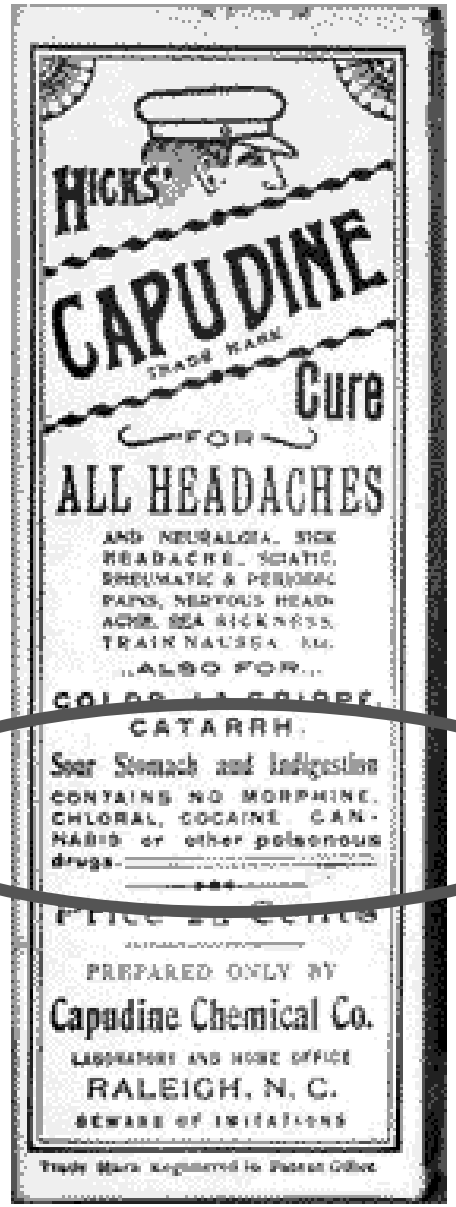
Protecting America's Health Philip Hilts (2003)

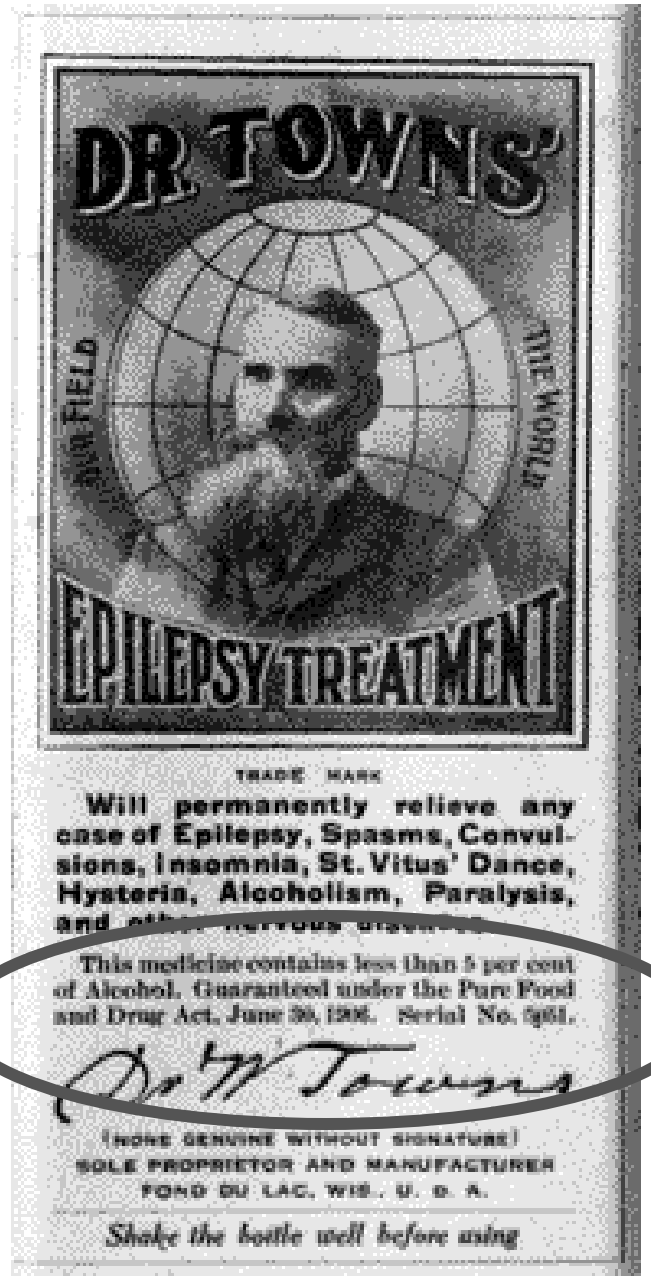
U.S. Food and Drug Act (1906)

- The FDA is the first federal public health regulatory agency.
- The Act established official standards of strength and purity.
- The Act banned adulterated or impure contents, but ingredient listing not required (except narcotics and poisons)

… pre-cursor to today's Chemistry, Manufacturing and Control (CMC) requirements

“Pure” Drugs


HICKS'
CAPUDINE
TRADE MARK
Cure
FOR
ALL HEADACHES
AND NEURALGIA, SICK HEADACHE, SCIATIC, RHEUMATIC & PERIODIC PAINS, NERVOUS HEADACHE, SEA SICKNESS, TRAIN NAUSEA, &c.
...ALSO FOR...
CATARRH.
Sour Stomach and Indigestion
CONTAINS NO MORPHINE, CHLORAL, COCAINE, CANNABIS or other poisonous drugs.
PREPARED ONLY BY
Capudine Chemical Co.
LABORATORY AND HOME OFFICE
RALEIGH, N. C.
BEWARE OF IMITATIONS
Trade Mark registered in Patent Office


DR. TOWNS'
OUR FIELD
THE WORLD
EPILEPSY TREATMENT
TRADE MARK
Will permanently relieve any case of Epilepsy, Spasms, Convulsions, Insomnia, St. Vitus' Dance, Hysteria, Alcoholism, Paralysis,
This medicine contains less than 5 per cent of Alcohol. Guaranteed under the Pure Food and Drug Act, June 30, 1906. Serial No. 981.
Dr W Towns
(NONE GENUINE WITHOUT SIGNATURE)
SOLE PROPRIETOR AND MANUFACTURER
FOND DU LAC, WIS., U. S. A.
Shake the bottle well before using

Elixir Sulfanilamide

- Sulfanilamide, a “wonder” drug
- Demand for liquid formulation
- Diethylene glycol chosen solvent
- Case Fatality Rate = 105/353 = 30%
- Drug seized after 4 weeks because misbranded (no alcohol)

Wax, PM *Annals of Internal Medicine* (1995)

Food, Drug and Cosmetic Act (1938)

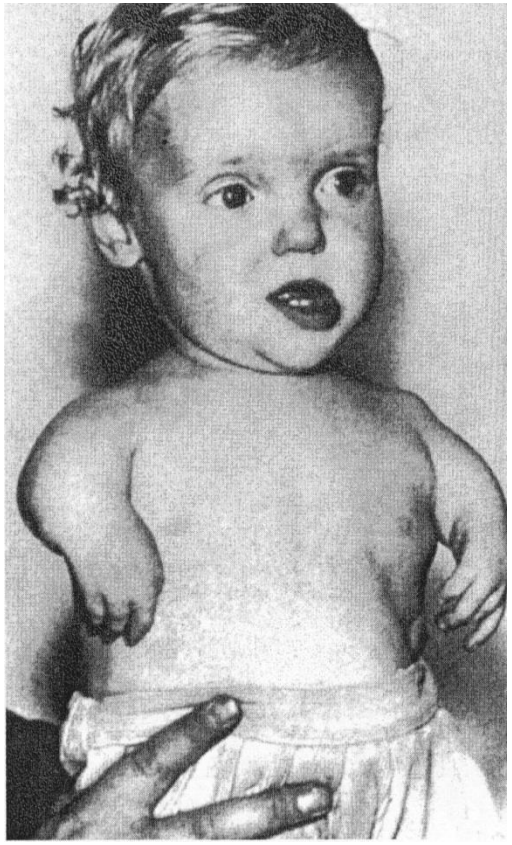
- 1st law requiring the testing of drug safety before marketing
- Pre-cursor to today's pre-clinical testing, ushers in the field of toxicology

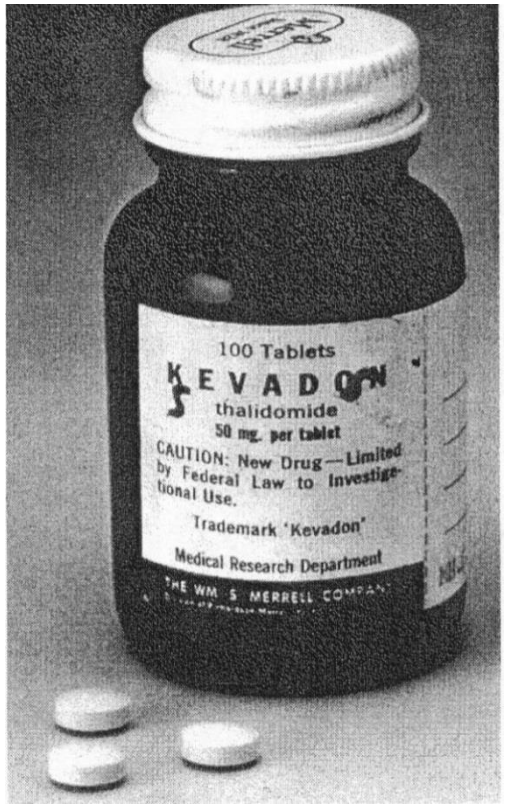
… but …

Automatic approval unless FDA blocks the application; FDA owns legal burden of proof

No standards for patient experimentation

Thalidomide *A Modern Tragedy*





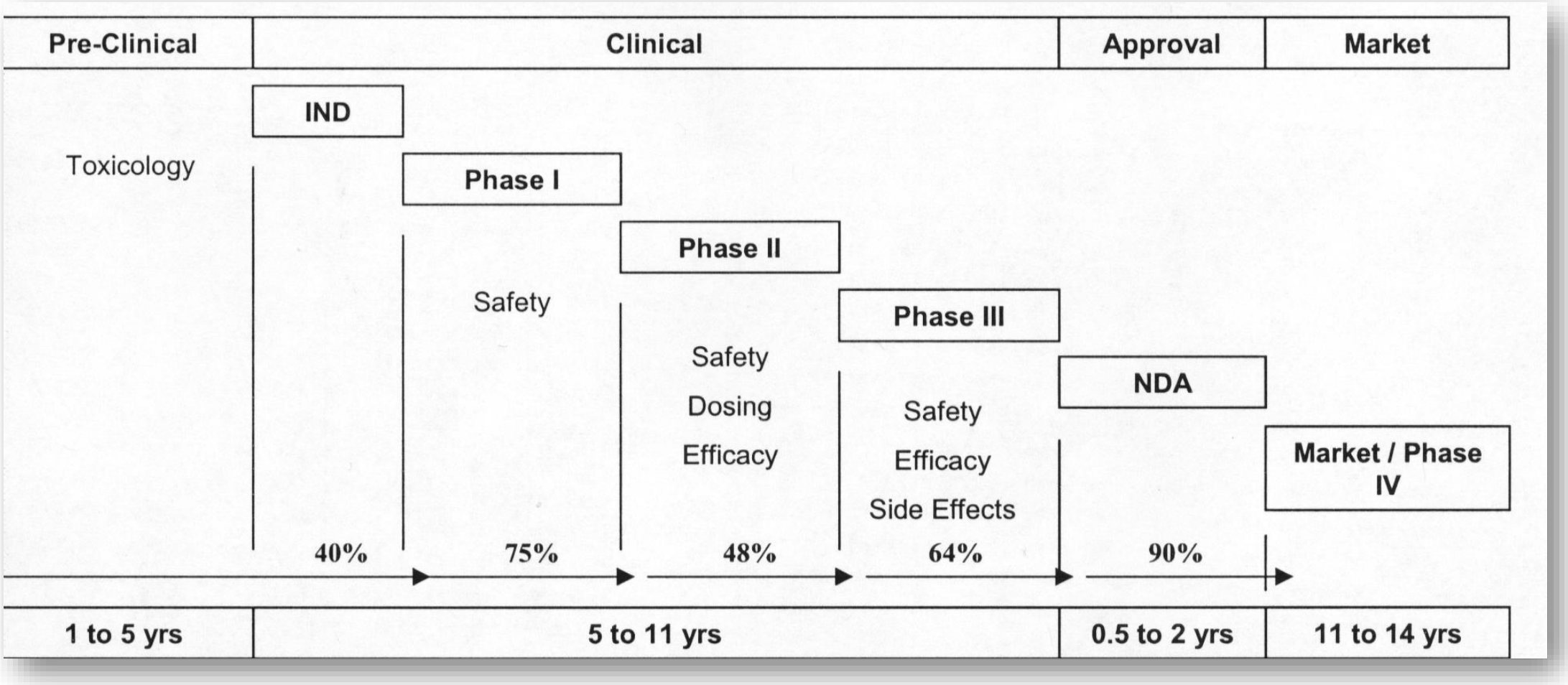
Protecting America's Health Philip Hilts (2003)

Kefauver-Harrison Amendments (1962)

- Human experiments required before approval
- Pharmaceutical manufacturer owns the burden of proof (safety and efficacy) before marketing
- “Adequate and well-controlled” studies
- Currently marketed drugs must be safe and effective, too.

… leads to the Investigational New Drug (IND) and New Drug Application (NDA) review process

Modern drug development



AEI-Brookings Joint Center Conference (2005)

U.S. FOOD & DRUG ADMINISTRATION

New Drug Development and Review Process

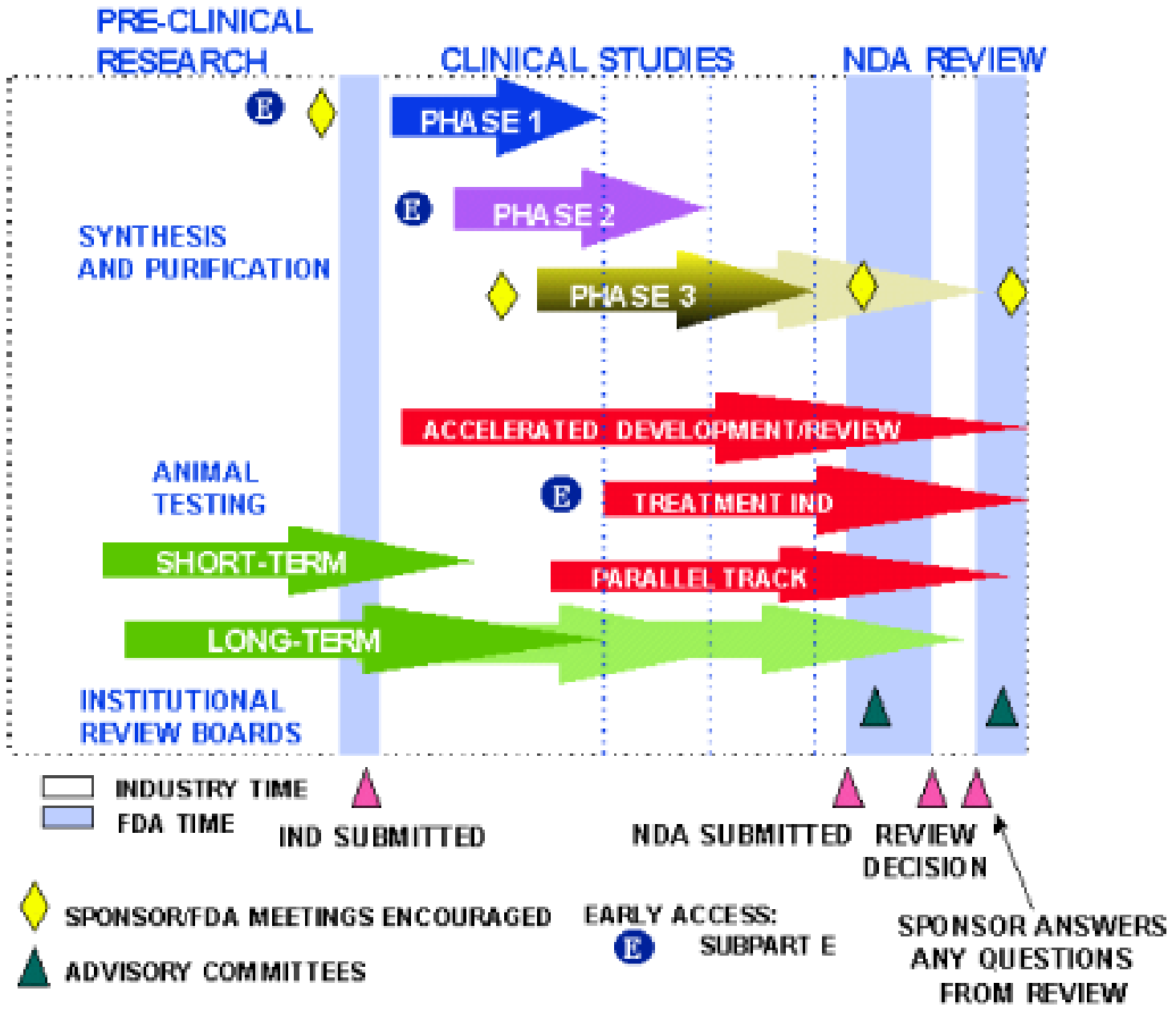


Figure 1: FDA's Benefit-Risk Framework

Benefit-Risk Integrated Assessment		
Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Role of pharmacoepidemiology

DURING EARLY PHASES OF DRUG DEVELOPMENT

- Understand determinants of disease (unmet medical need)
- Interpret safety profile (historical comparators)
- Summarize post-marketing observational data (global safety profile in support of new indications)

The package insert (product labeling) is the culmination of drug development...

… and informs pharmacoepi investigation.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIPITOR safely and effectively. See full prescribing information for LIPITOR.

LIPITOR® (atorvastatin calcium) Tablets for oral administration

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

LIPITOR is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
LIPITOR has not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

DOSAGE FORMS AND STRENGTHS

10, 20, 40, and 80 mg tablets (3).

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).
Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

WARNINGS AND PRECAUTIONS

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine, fibrates, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1).

Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the LIPITOR 80 mg group vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with LIPITOR in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (1-800-438-1985 and www.pfizer.com) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

- Digoxin: Patients should be monitored appropriately (7.5).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.6).
- Rifampin should be simultaneously co-administered with LIPITOR (7.4).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [6/2009]

Traditional Drug Safety Communication Tools

Contraindications

Only for clinical situations in which the risk from use clear outweighs any possible therapeutic benefit.
Only known hazards, and not theoretical possibilities.

Warnings and Precautions

Clinically significant adverse reactions observed in association with the use of a drug for which there is reasonable evidence of a causal association:

- serious
- preventable
- affects compliance
- interferes with a laboratory test
- requires dose adjustment or management

Boxed Warnings

A means to highlight for prescribers

- Adverse event so serious in proportion to the potential befit that it is essential that it be considered

Food and Drug Administration Amendment Act (FDAAA) of 2007

Enhanced authority regarding postmarket safety of drugs

- Postmarket studies to examine real-world safety
- Enhanced MedWatch program and Active Safety Surveillance
- Risk Evaluation and Mitigation Strategies (REMS)
- Expanded use of the Drug Safety and Risk Management Advisory Committee

FDA Office of Surveillance and Epidemiology

MedWatch (passive surveillance, pharmacovigilance)

Only 4 elements are needed to report an AE: (1) identifiable patient; (2) identifiable reporter; (3) suspect drug or biologic product; and (4) adverse event or fatal outcome

FDA Adverse Events Reporting System (FAERS) Public Dashboard

U.S. FOOD & DRUG ADMINISTRATION

Home | Search | Disclaimer | Report a Problem | FAQ | Site Feedback

Total Reports 29,153,222

Serious Reports (excluding death) 16,130,758

Death Reports 2,650,057

Reports by Report Type

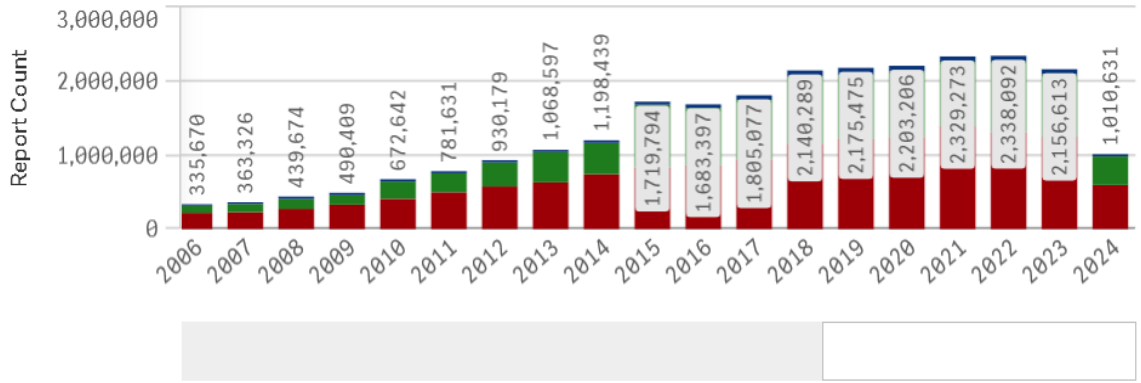
All Years | Last 10 Years

Reports received by Report Type

Year | Report Type

	Total Reports	Expedited	Non-Expedited	Direct	BSR
Total Reports	**29,153,222**	**15,957,059**	**11,911,258**	**1,284,042**	**863**
2024	**1,010,631**	595,177	385,238	30,216	-
2023	**2,156,613**	1,249,616	838,367	68,630	-

Reports received by Report Type

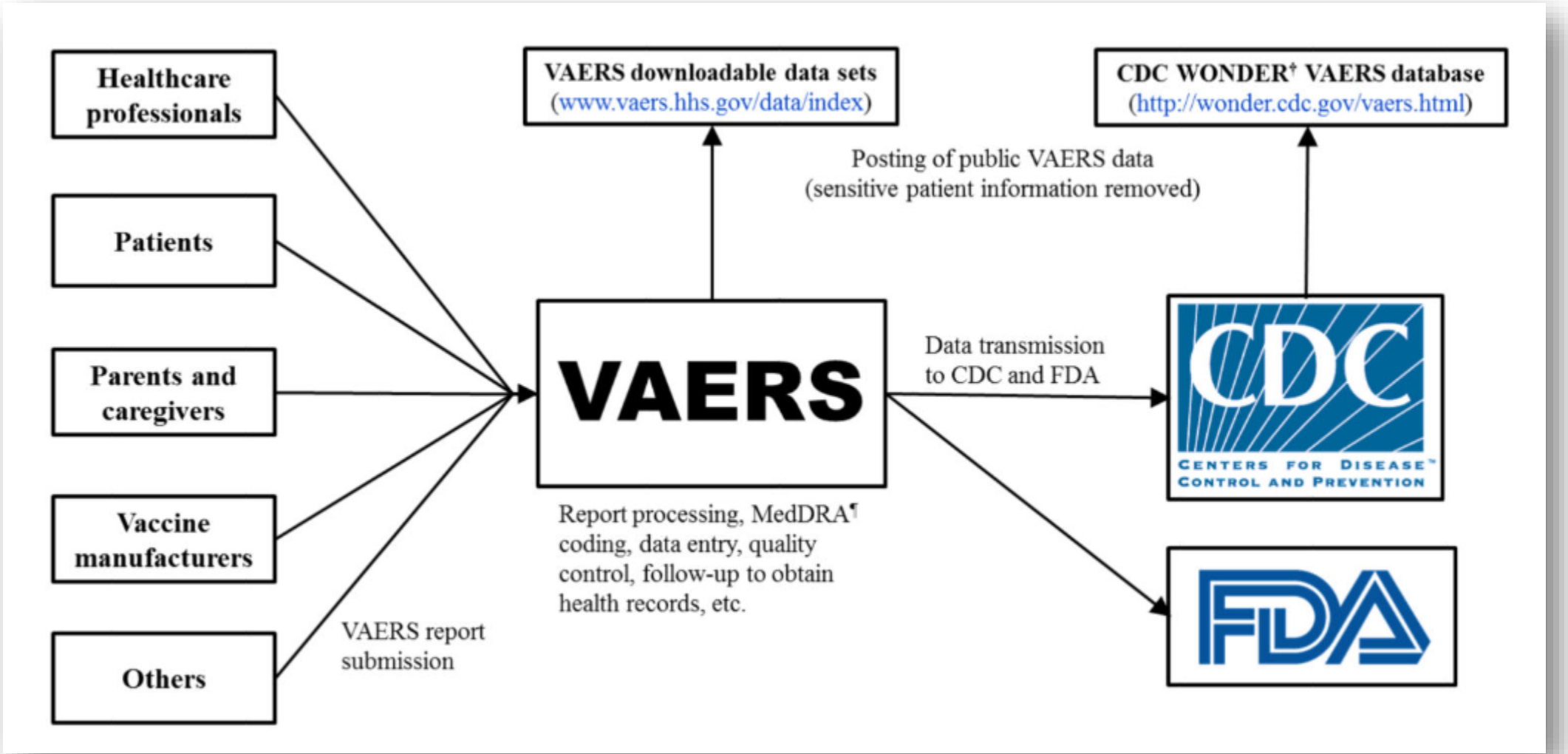


Data as of June 30, 2024

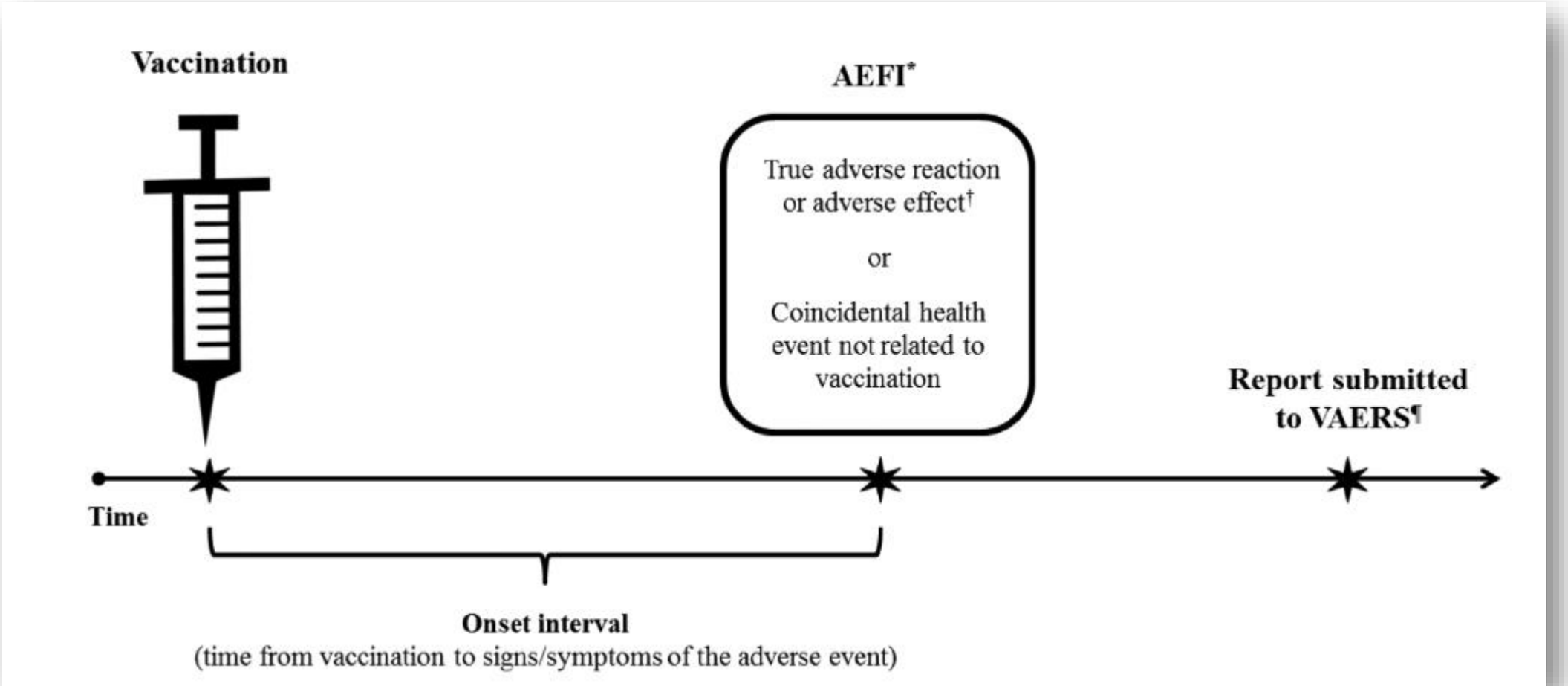
Vulnerability Disclosure Policy

This page displays the number of adverse event reports received by FDA for drugs and therapeutic biologic products by the following Report Types.

- Direct Reports are voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals.



Vaccine. 2015 August 26; 33(36): 4398–4405.
doi:10.1016/j.vaccine.2015.07.035



Vaccine. 2015 August 26; 33(36): 4398–4405.
doi:10.1016/j.vaccine.2015.07.035

FDA Sentinel Initiative, active surveillance

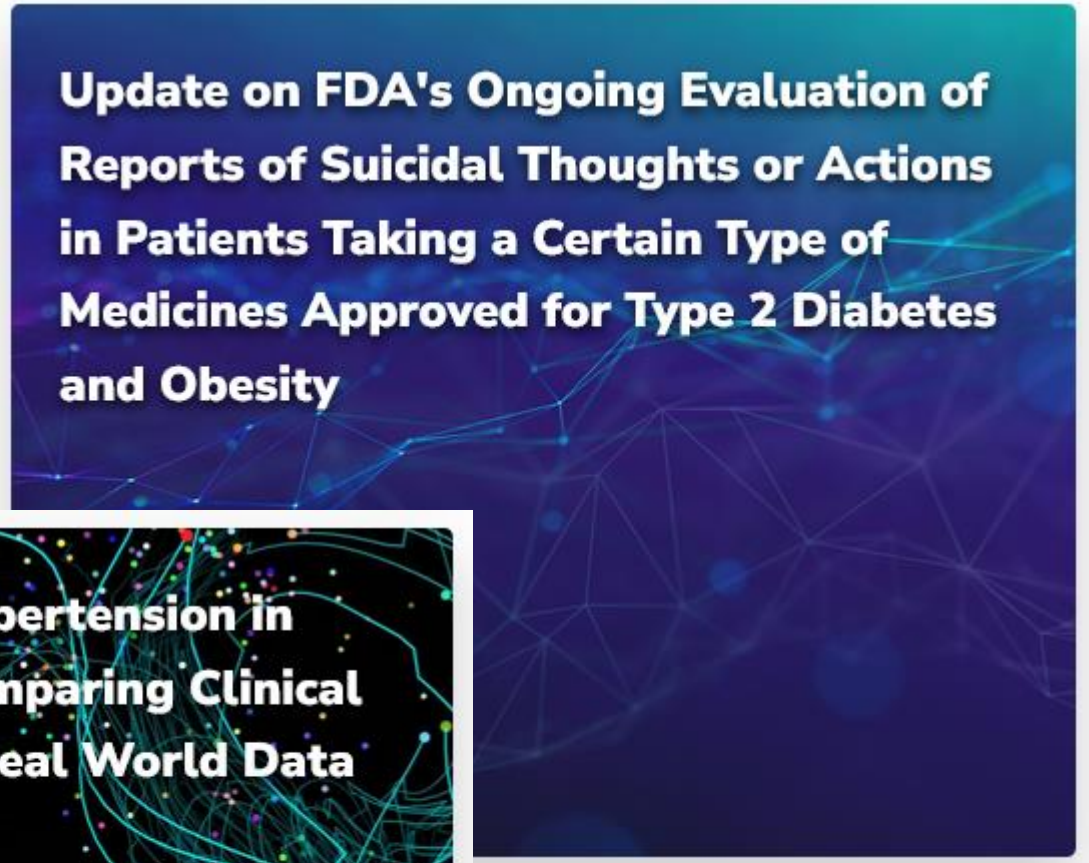
Data sources are electronic health records and administrative claims data in the U.S. (2000 – 2024)

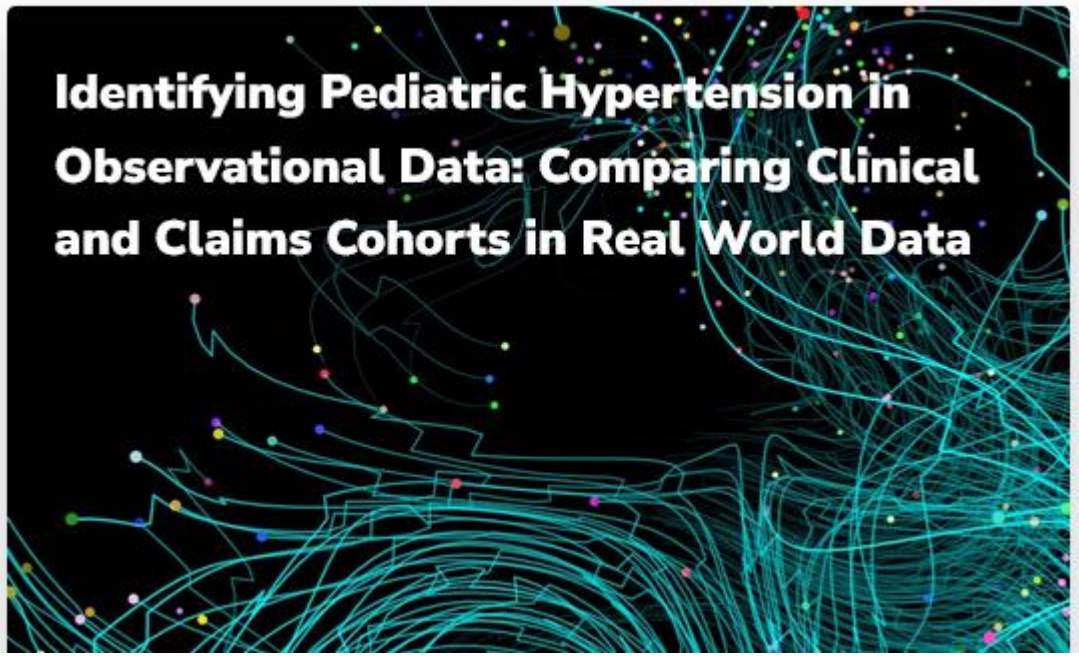
The Sentinel Distributed Database has a total of 500.1 million unique patient identifiers. A total of 371.5 million patients have at least one day of drug and medical coverage.

Of those with both medical and drug coverage, there are:

- 1.3 billion person-years of data
- 22.3 billion pharmacy dispensings
- 24 billion unique medical encounters
- 73.2 million members with at least one laboratory test result


Research in Action Podcast:
Transforming Public Health with
Unstructured Data and NLP in FDA's
Sentinel Initiative


Update on FDA's Ongoing Evaluation of
Reports of Suicidal Thoughts or Actions
in Patients Taking a Certain Type of
Medicines Approved for Type 2 Diabetes
and Obesity


Identifying Pediatric Hypertension in
Observational Data: Comparing Clinical
and Claims Cohorts in Real World Data

Sentinel

U.S. Risk Evaluation and Mitigation Strategy (REMS)

A drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication.

FDA Risk Evaluation and Mitigation Strategy (REMS) Publ…

Active REMS | Total REMS | ETASU | Shared REMS | Modifications | REMS Revisions | REMS Released | REMS Summary

Ever Approved

320

User Selection

-NA-

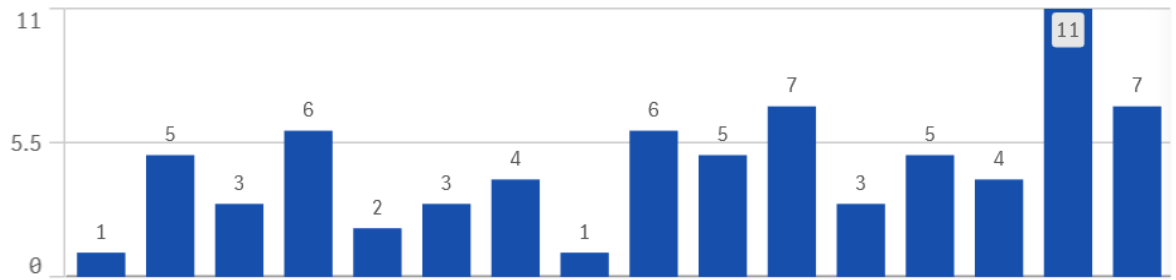
Currently Active

73

Yearly | Quarterly | Monthly

Active REMS

Currently Active REMS



The elements of the REMS reflected in the graph are the latest elements of the REMS, not the elements with which the REMS was initially approved.

Currently Active REMS

Name	Application ...	REMS ...	Lates...	El...	Com...
Abecma	BLA #125736	03/26/2021	04/04/2024	Yes	No
Adasuve	NDA #022549	12/21/2012	01/27/2022	Yes	No
Addyi	NDA #022526	08/18/2015	10/09/2019	No	No
Alvimopan Shared S...	Multiple Applicati...	12/19/2019	06/12/2023	Yes	No

The elements of the REMS reflected in the table are the latest elements of the REMS, not the elements with which the REMS was initially approved.

Data as of August 7, 2024

REMS Logic Model: A Framework to Link Program Design With Assessment

Guidance for Industry

DRAFT GUIDANCE

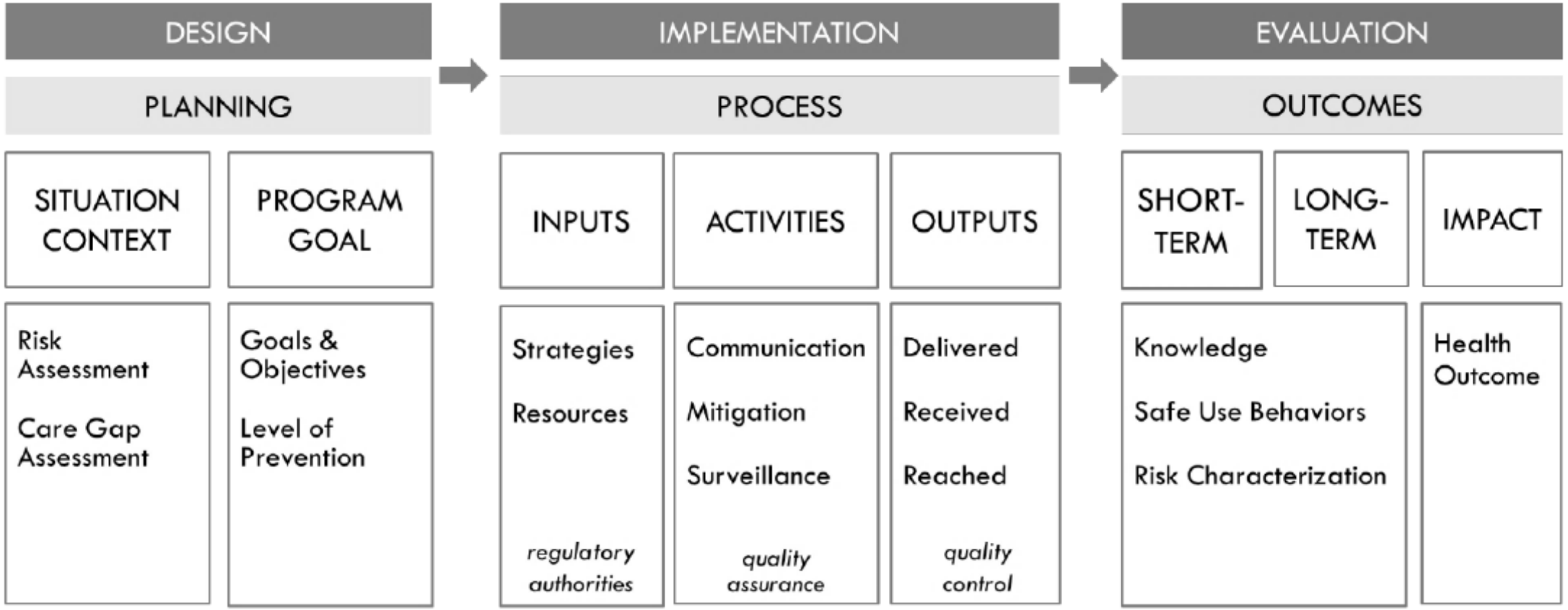
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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) Gita Toyserkani, Office of Surveillance and Epidemiology, at OSE.PMKTREGS@fda.hhs.gov or 301-796-2380 or (CBER) James Myers, at 240-402-7911.

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

May 2024
Safety - Issues, Errors, and Problems



REMS Logic Model (2024)

https://www.fda.gov/media/178291/download

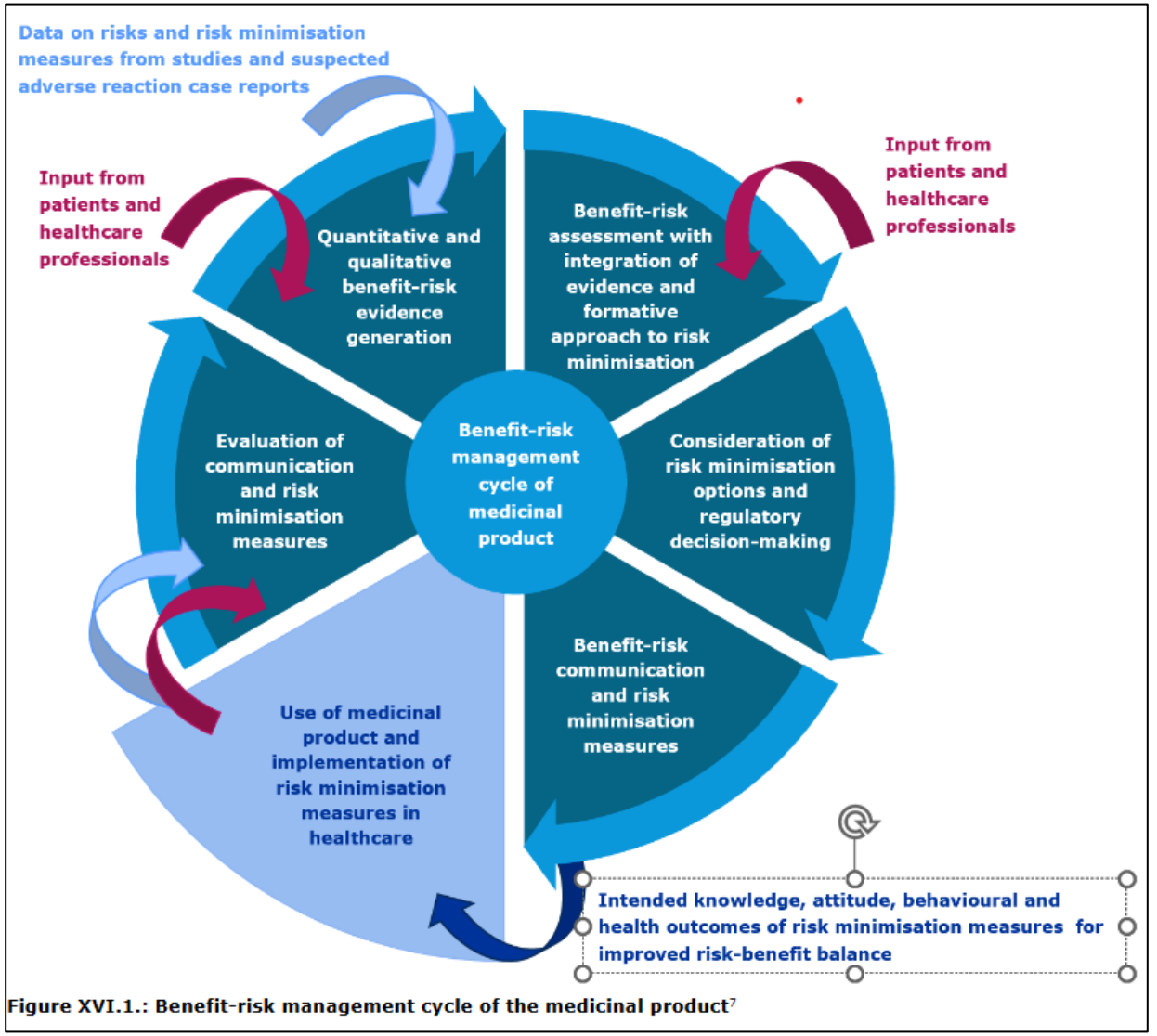


Figure XVI.1.: Benefit-risk management cycle of the medicinal product[7]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on good pharmacovigilance practices (GVP)

Module XVI – Risk minimisation measures (Rev 3)

equator network

Enhancing the QUAlity and Transparency Of health Research

The Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE)

Smith MY, Morrato EH, Mora N, Nguyen V, Pinnock H, Winterstein AG. The Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE). Drug Saf. 2024.

Include Design and Implementation knowns and unknowns (limitations) in the Evaluation Report

Pharmacoepi Hot Topic

Real-World Data (large datasets) and Real-World Evidence (rigorous methods)

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

VALUE IN HEALTH 20 (2017) 1003–1008

Original Report

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2,], Sebastian Schneeweiss[1,2], Marc L. Berger[3], Jeffrey Brown[4], Frank de Vries[5], Ian Douglas[6], Joshua J. Gagne[1,2], Rosa Gini[7], Olaf Klungel[8], C. Daniel Mullins[9], Michael D. Nguyen[10], Jeremy A. Rassen[11], Liam Smeeth[6], Miriam Sturkenboom[12], on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making*

VALUE IN HEALTH 20 (2017) 1009–1022

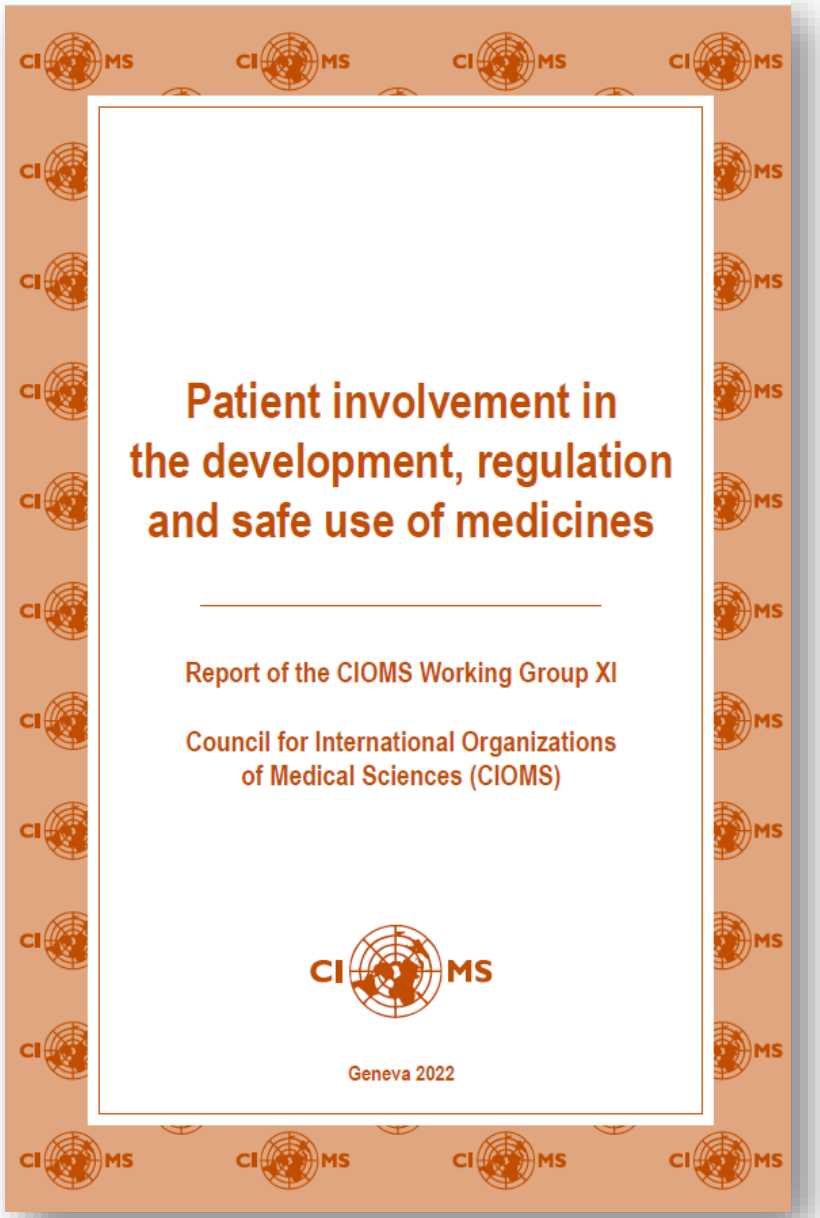
BEST PRACTICES FOR RWE OBSERVATIONAL STUDIES

- ✓ Study transparency. Publicly register protocol and analysis plan.
- ✓ Publication transparency. Deviation(s) from protocol. Allow open critique of observational methods used.
- ✓ Reproducibility. Full data sharing.
- ✓ Replication. Value of confirming findings.
- ✓ Stakeholder engagement. Interpreting the findings.

Making Real-World Evidence More Useful for Decision Making
Greenfield, Sheldon
Value in Health, Volume 20, Issue 8, 1023 - 1024

Hot Topic

Patient and Stakeholder Engagement and (Re)Strengthening Societal Trust



Free download from

https://cioms.ch/publications/product/patient-involvement/

Medical product decision making
Patient Preferences

“Nothing about us, without us.”

https://www.imi-prefer.eu/

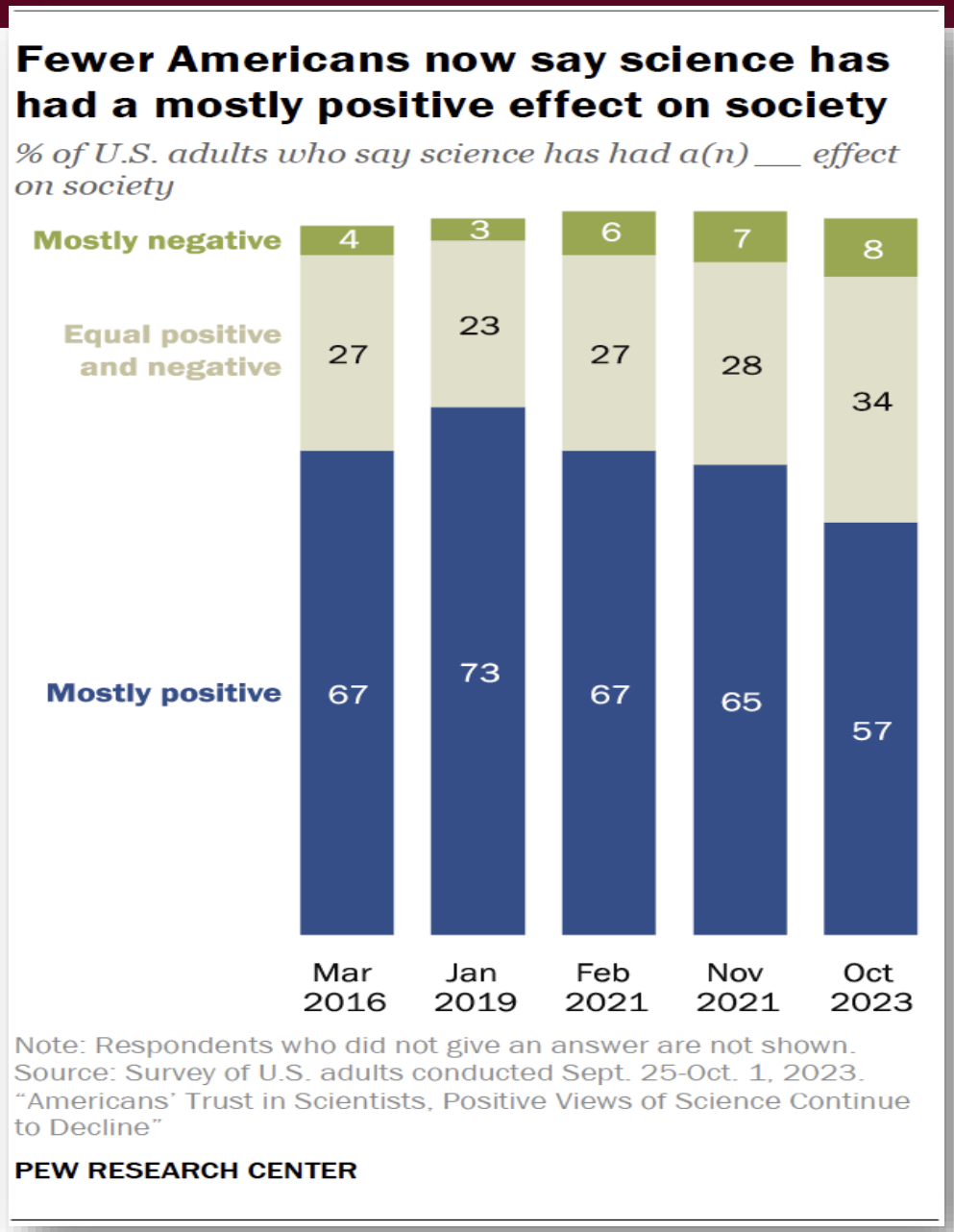
FY23 FDA Broad Agency Announcement (BAA)

Research Areas of Interest

I. Modernize development & evaluation
   - H. Methods for assessing behavioral, economic, or human factors
   - I. Approaches to incorporate patient and consumer input

II. Strengthen post-market surveillance
   - E. Methods to improve communication about risk to patients and consumers

III. Invigorate public health preparedness and response
   - C. Patient and consumer engagement



Covid-19 Vaccine Warp Speed Development

*****

Changing Societal Risk Perceptions Post Public Health Emergency

Pharmacoepi Hot Topic
Expanding workforce capacity

Workforce Gap

Recognizing the limited staff capacity in regulatory authorities and companies having the requisite expertise in psychometrics, related statistics, and decision sciences …

Source: Patient-Focused Drug Development Reflection Paper (2021)

5 Core Domains	1. Epidemiology 2. Clinical pharmacology 3. Regulatory science 4. Statistics and data science 5. Communication and other professional skills

New Skill Development for Many

Stakeholder Engagement

Mixed Methods – qualitative, survey, observational epidemiology

Implementation Science

External Validity - Social Determinants of Health

Pharmacoepi Hot Topic

Digital data and Large-Language Models (AI/ML)

Emerging Digital Data Advances

Merging multi-modal data, more quickly

Regulatory-grade clinical endpoints from wearables

AI/ML for clinical decision making at bedside

And increasing cybersecurity concerns from the electronic health record "data sharers"

JAMA Network | Open

Original Investigation | Health Informatics

Randomized Clinical Trials of Machine Learning Interventions in Health Care
A Systematic Review

Deborah Plana, BS; Dennis L. Shung, MD, PhD; Alyssa A. Grimshaw, MSLIS; Anurag Saraf, MD; Joseph J. Y. Sung, MBBS, PhD; Benjamin H. Kann, MD

… despite the large number of medical machine learning–based algorithms in development, few RCTs for these technologies have been conducted. … most did not fully adhere to accepted reporting guidelines and had limited inclusion of participants from underrepresented minority groups.

Replace pharmacoepi humans?

Automate pharmacovigilance (first pass)

Automate causal inference testing (first pass)

PANEL DISCUSSION

REAL WORLD APPLICATION INSIGHTS AND CHALLENGES

Karen Cohen

Ushma Mehta

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CLOSING COMMENTS

PHARMACOEPIDEMIOLOGY RESOURCES

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PDS Pharmacoepidemiology & Drug Safety

Review Series: Core Concepts in Pharmacoepidemiology

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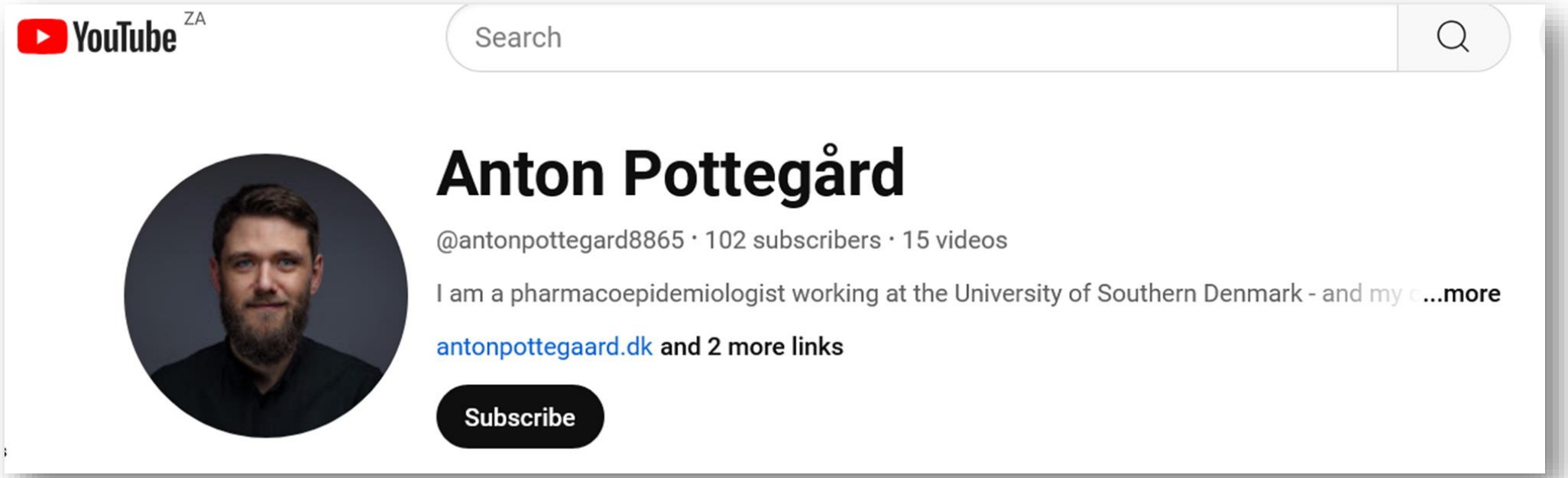
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Thank you!

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