U.S. FOOD & DRUG ADMINISTRATION

Promises and Challenges of Screening for Adverse Events in Sentinel

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Plan for Talk

- When and why does FDA need safety screening approaches?
- How has Sentinel contributed to advancing these methods?
- What are some of the key remaining challenges?

FDA Amendments Act 2007

- "to provide for adverse event surveillance … to create a robust system to **identify adverse events** and **potential drug safety signals**"

- "develop validated methods for the establishment of a postmarket **risk identification** and analysis system to link and analyze safety data from multiple sources"

https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm

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ORIGINAL REPORT

The US Food and Drug Administration's Sentinel Initiative: Expanding the horizons of medical product safety

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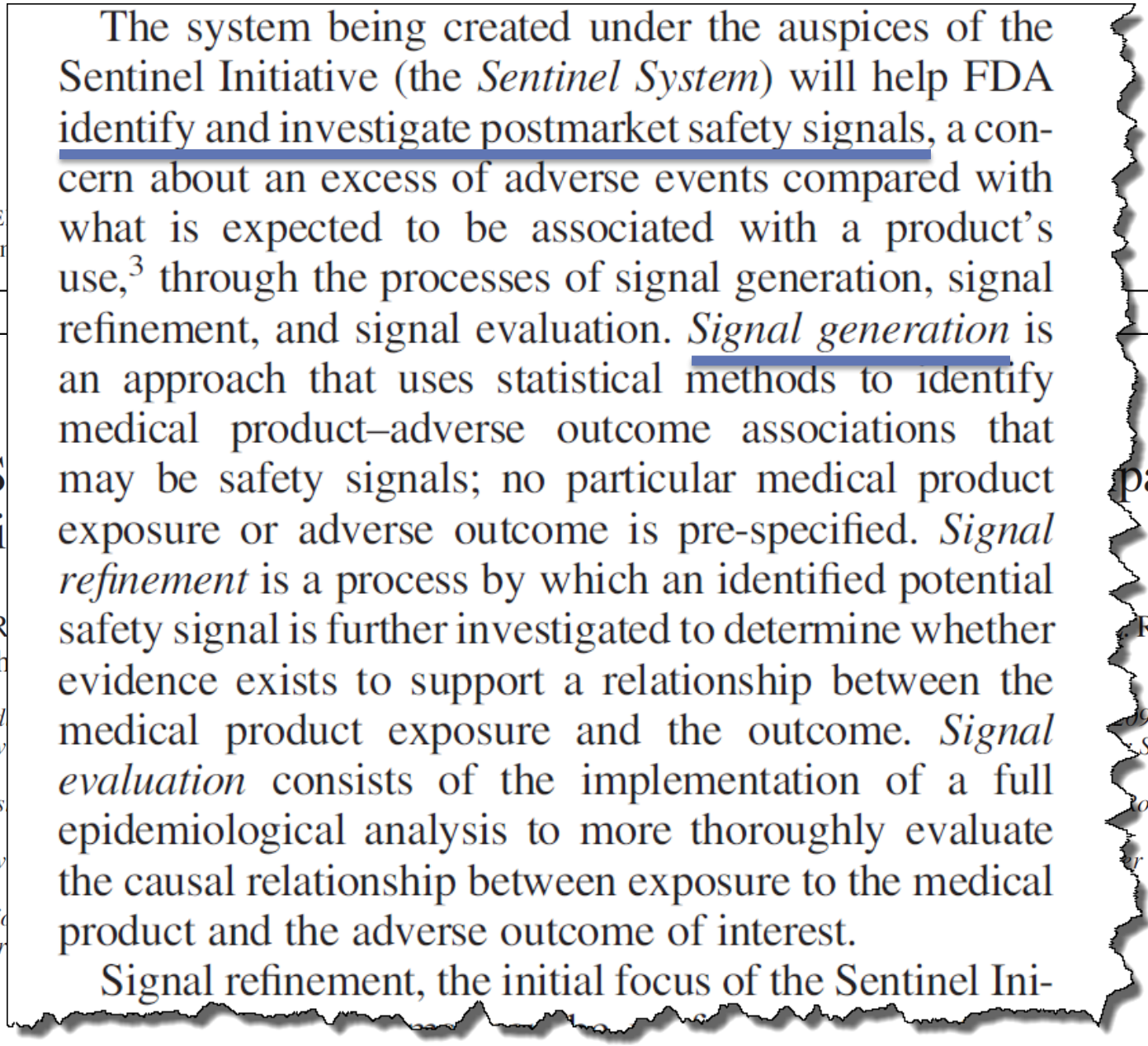

The system being created under the auspices of the Sentinel Initiative (the *Sentinel System*) will help FDA identify and investigate postmarket safety signals, a concern about an excess of adverse events compared with what is expected to be associated with a product's use,[3] through the processes of signal generation, signal refinement, and signal evaluation. *Signal generation* is an approach that uses statistical methods to identify medical product–adverse outcome associations that may be safety signals; no particular medical product exposure or adverse outcome is pre-specified. *Signal refinement* is a process by which an identified potential safety signal is further investigated to determine whether evidence exists to support a relationship between the medical product exposure and the outcome. *Signal evaluation* consists of the implementation of a full epidemiological analysis to more thoroughly evaluate the causal relationship between exposure to the medical product and the adverse outcome of interest.

Signal refinement, the initial focus of the Sentinel Ini-

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Comprehensive Approach

The FDA's Sentinel Initiative—A Comprehensive Approach to Medical Product Surveillance

R Ball[1], M Robb[1], SA Anderson[2] and G Dal Pan[1]

In May 2008, the Department of Health and Human Services announced the launch of the Sentinel Initiative by the US Food and Drug Administration (FDA) to create the Sentinel System, a national electronic system for medical product safety surveillance.[1,2] This system complements existing FDA surveillance capabilities that track adverse events reported after the use of FDA regulated products by allowing the FDA to proactively assess the safety of these products.

successes of the Mini-Sentinel pilot[4] and leverage the Sentinel Infrastructure, a distributed database with a Common Data Model to enable the creation of analytical programs to be run remotely in participating data partner's secure data environment for analysis. The FDA is also seeking to develop the use of the Sentinel Infrastructure for questions outside of safety surveillance, but of importance to the FDA in the protection and promotion of public health. All these elements are defined in Table 1.

Assessment of the Sentinel System's current capabilities

The Sentinel Program Interim Assessment mandated by the Prescription Drug User Fee Act (PDUFA) V concluded that "In the implementation and execution of Mini-

The FDA's Sentinel Initiative—A Comprehe Medical P

R Ball[1], M Robb[1], SA

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Early warning system

The FDA is focusing on projects to refine existing methodologies and develop new and innovative approaches to support safety surveillance. For example, several projects are underway to test methods of identifying unexpected safety concerns. CBER conducted a pilot study on a vaccine to evaluate one statistical approach, TreeScan, and has launched another pilot study, a prospective evaluation of a recently licensed vaccine to further evaluate the tool in conducting general safety studies.[10]

Examples of Requested Studies

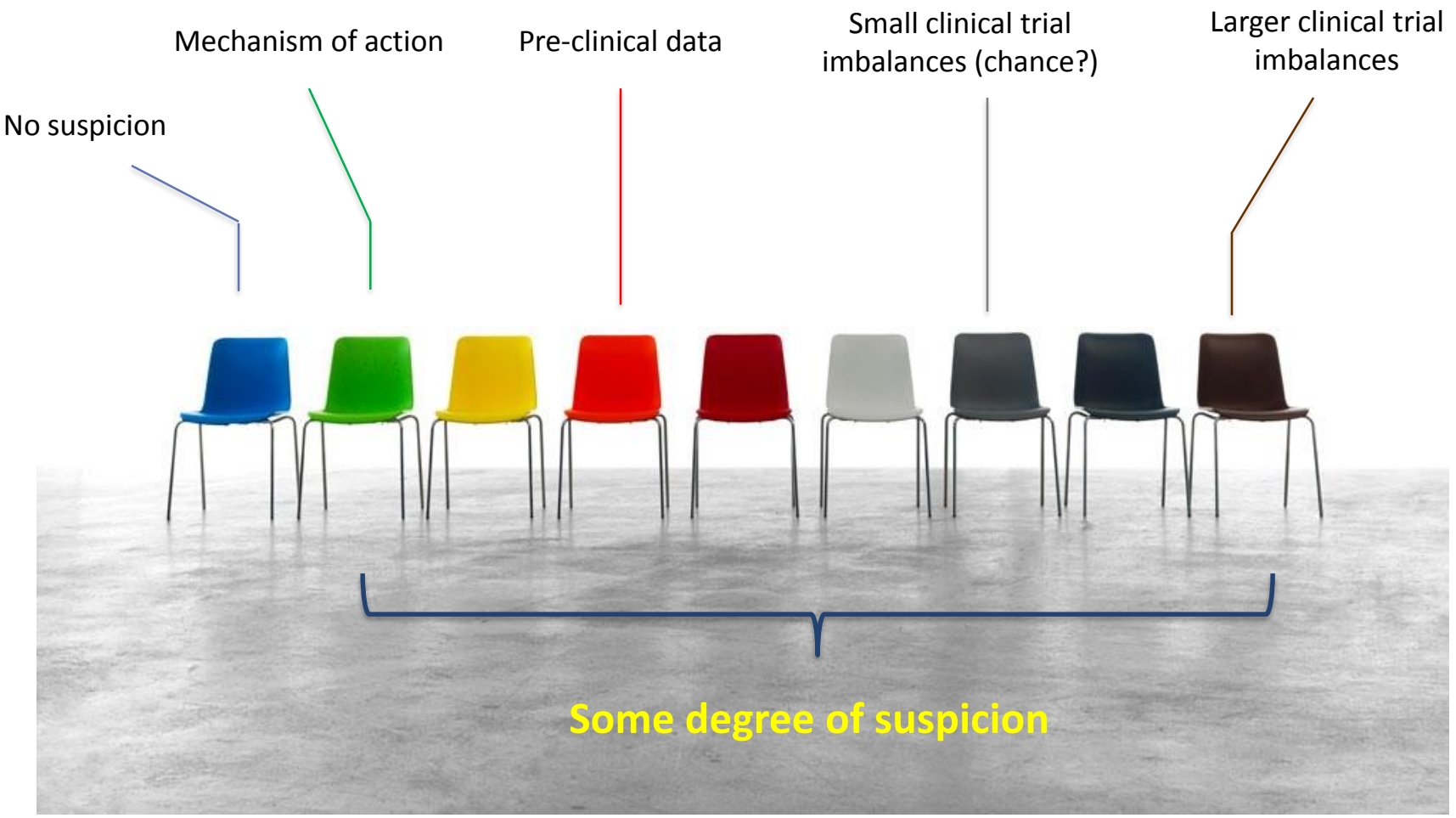
- “The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births.”
- “The study’s primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.”
- “drug-induced liver injury, serious infections, and immune-mediated disorders, including hepatitis, noninfectious colitis, serious skin reactions, Type I diabetes, thyroid disease, sarcoidosis, and other immune disorders”
- “chronic kidney disease, periampullary cancer, gastric polyps, dementia, AMI, celiac disease”
- “Events for monitoring would include serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events, eye disorders, herpes virus infections, parasitic infections, and atopic conditions (e.g., asthma)”

Common Themes of Requests

- **Desire for depth within a single clinical area**
  - Numerous outcomes within a single anatomic, disease or pathophysiologic area
- **Yet span across organ systems**
  - Outcomes that span across multiple organ systems, disease processes, signs and symptoms
- **With a variety of degrees of clinical suspicion**
  - Origin of need and clinical index of suspicion differs by health outcome
  - Duration and size of safety database pre-approval differs
- **In other words…**
  - Concern is often specific enough to name ≥1 disease entity, but not specific enough to focus a study on that entity
  - A single concern drives a set of concerns that are biologically plausible

Range of Different Starting Points

Assume: Pre-approval scenario, issues can occur in combination and not mutually exclusive*



* For illustration purposes; not a comprehensive list

ICH E2C(R2) Signal Definition

Both the Endpoint and the Context

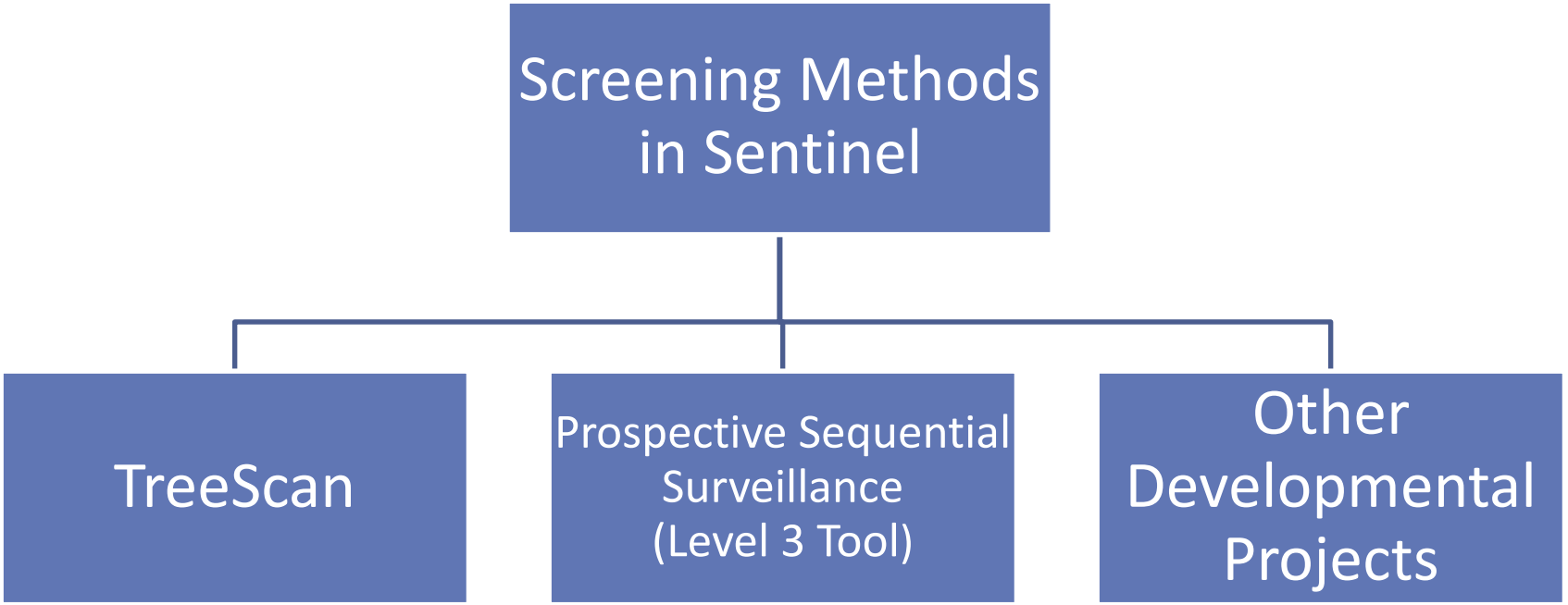
"Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify."

Guidance for Industry: E2C(E2) Periodic Benefit Risk Evaluation Report, July 2016
https://www.fda.gov/downloads/drugs/guidances/ucm299513.pdf

Plan for Talk

- When and why does FDA need safety screening approaches?
- How has Sentinel contributed to advancing these methods?
- What are some of the key remaining challenges?

Categories of Projects in Sentinel



One of earliest decisions is whether to select a broad-based approach (e.g., TreeScan) or an approach with a pre-defined outcome (e.g., Level 3).

Varieties of TreeScan Methods

	Exposure Indexed	Outcome Indexed
Self controlled	-Self control risk interval (Bernoulli) -Tree-temporal (SCRI + temporal scan)	Case-crossover (DrugScan)
Cohort-based	-Cohort (Poisson) -Propensity scored matched TreeScan	None

Each type can condition on pre-exposure healthcare utilization rates, to control for temporal trends before and after exposure

Select Ongoing Projects

- **TreeScan**
  - Tree-temporal pilot with long acting contraceptives
  - Propensity score based TreeScan simulation
  - Enhancing TreeScan for long-term follow-up
- **L3 sequential surveillance**
  - Pilot of angioedema after ACE inhibitors
- **Other developmental projects related to screening**
  - Evaluation of Patient Episode Profile Retrieval (PEPR) to manage alerts
  - Switching of between brand and generic medications
  - Medication error detection (e.g., name confusion, dose errors)

https://www.sentinelinitiative.org/sentinel/methods

Plan for Talk

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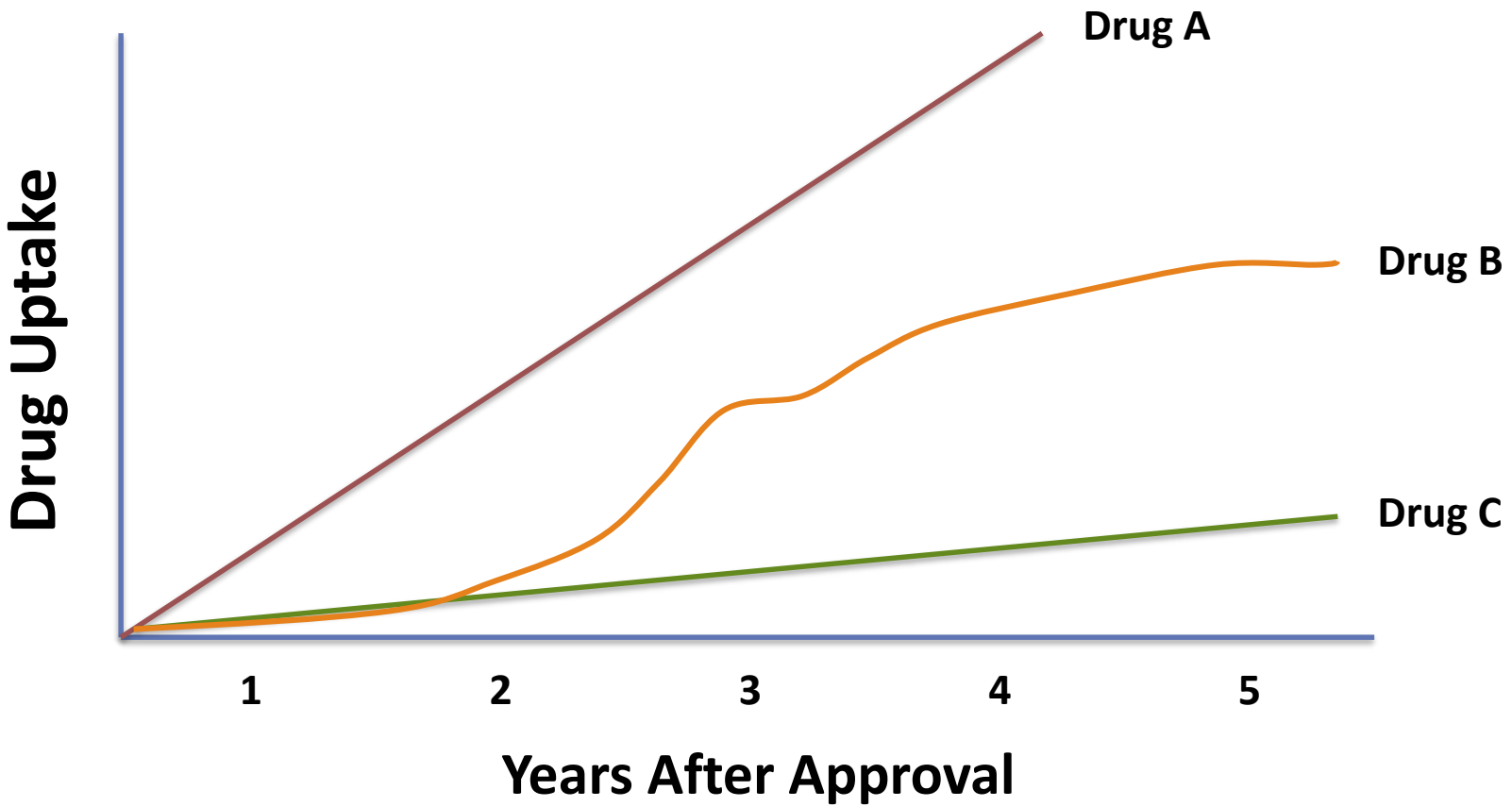
Intuitively Simple; Deceptively Difficult

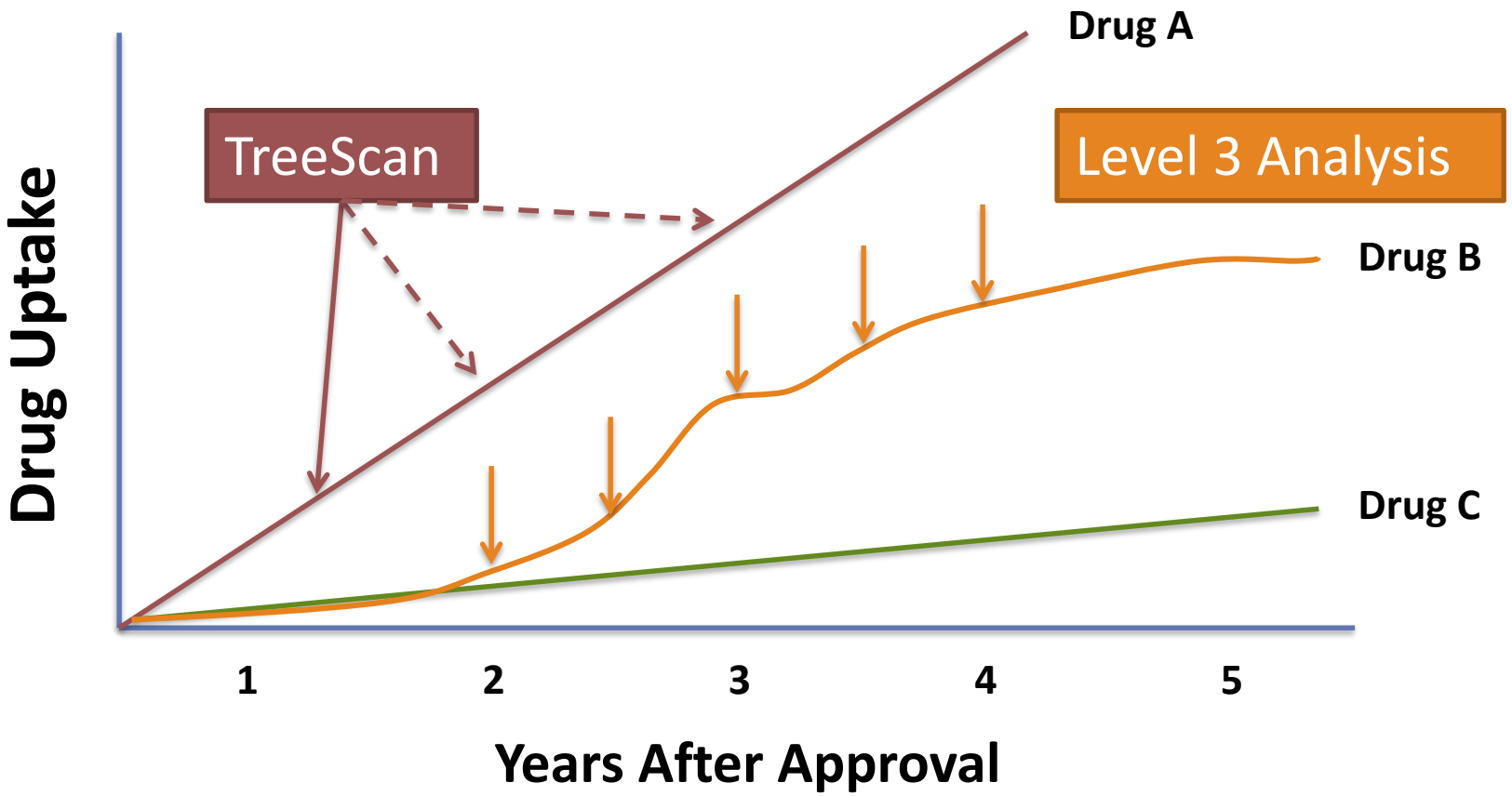
	FAERS	Sentinel
Data source	• Reports with some clinical suspicion for association • Known limitations of spontaneous reports	• All healthcare encounters; longitudinal data • Known limitations of claims data
Required Decisions	• "Always on" • Few design decisions	• Need "to activate" • Many design decisions
Analytic Approach	• Universal approach • "All drugs by all outcomes"	• Many statistical methods • Choice of drug(s) and outcomes
Alert Investigation	• Well established • Case series approach	• Under development

Challenges of Deciding When to Activate



Depends on drug characteristics: NME vs. follow-on, drug indication, disease treatment tier, etc.

When to Activate Depends On Many Factors

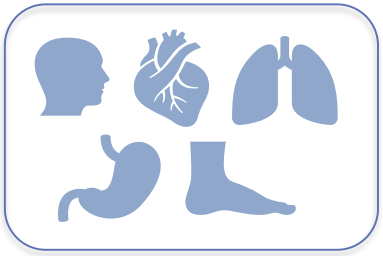


Reasons to Be Careful

	Traditional Retrospective Study	Screening for Unexpected Events
Regulatory Setting	Evidence of safety concern	Variable underlying clinical suspicion
Outcome	Use of complex, validated algorithm or chart review	• Outcome codes with variable specificity • Mixture unintended + intended effects • Finite resources for chart review
Power	Powered to a single drug-event pair	• Variable power across many outcomes • Subject to false reassurance
Confounding	Tailored to drug-event pair	Single nonspecific confounding control strategy
Multiple comparisons	N/A	Baseline rate of false positives
Communication of Results	Clear communication point at end of study	• Generates results with uncertainty • Alert fatigue; potential to confuse study approaches with screening approaches

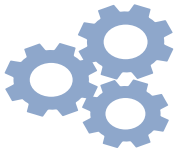
How it Might Work

1 drug



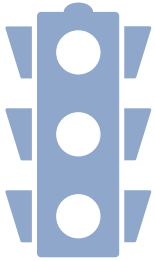
Use TreeScan
Screen for all outcomes

All Sentinel
Data Partners



Generate
statistical alerts

Clinician review
of claims profiles
+
Follow-up
sensitivity analyses



- Categorized alerts
- Uncategorized alerts

Further
study

Confirmed or
unconfirmed alerts

Summary

- There is a clear regulatory need and public expectation for signal detection in Sentinel
- FDA is invested in and has invested in approaches to detect unexpected adverse events in Sentinel
  - Prospective sequential surveillance (L3)
  - TreeScan
  - Other screening approaches (medication errors, switching)
- Such methods draw inspiration from sophisticated study designs but are configured to achieve either increase speed (Level 3 analysis) or breath of surveillance (TreeScan)
- Numerous trade-offs emerge in order to achieve these desirable characteristics, and their performance needs to be better characterized before routine implementation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