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Introduction to Drug Safety

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Pharmacovigilance

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Prescription Drug Use Is High in the US

- 48.6% of US adults have taken a prescription drug in the past 30 days
- 88.5% of US older adults have taken a prescription drug in the past 30 days
- 6.3 billion prescriptions (~19 prescriptions for every American) in 2020

Sources: Centers for Disease Control and Prevention (CDC) National Center for Health Statistics. (2023). *Therapeutic drug use*. Accessed October 22, 2024, from https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm; IQVIA. (2021). *The use of medicines in the US*. Accessed October 22, 2024, from https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us; Towfiqu barbhuiya. (2021). [Photo]. Unsplash. Retrieved October 22, 2024, from https://unsplash.com/photos/orange-and-white-medication-pill-w8p9cQDLX7I

Adverse Event (AE)

- "Any untoward medical occurrence in a patient administered a medical product and which does not **necessarily have to have a causal relationship** with this treatment"

- An AE "can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product"

Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (2003). *ICH Harmonised Tripartite Guideline: Post-approval safety data management: Definitions and standards for expedited reporting (ICH-E2D)*. ICH. Accessed October 22, 2024, from https://database.ich.org/sites/default/files/E2D_Guideline.pdf

Adverse Drug Reaction (ADR)

- All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions
- “The phrase ‘responses to a medicinal product’ means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility”
- “A reaction, in contrast to an event, is characterized by the fact that a causal relationship between a drug and the occurrence is suspected”
  - However, “**if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction**”

Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (2003). *ICH Harmonised Tripartite Guideline: Post-approval safety data management: Definitions and standards for expedited reporting (ICH-E2D)*. ICH. Accessed October 22, 2024, from https://database.ich.org/sites/default/files/E2D_Guideline.pdf

Adverse Event Versus Adverse Drug Reaction

- The key difference between an adverse event and an adverse drug reaction is that a causal relationship is suspected of an adverse drug reaction, but it is not required for an adverse event
- Adverse drug reactions are a subset of adverse events
- In some countries, data on adverse drug reactions are collected in postmarketing pharmacovigilance reporting systems, while in others, data on adverse events are collected
  - E.g., the scope of reporting requirements in the US is “any adverse event associated with the use of a drug in humans, whether or not considered drug related …”

Source: Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications. 21 C.F.R. § 310.305. (2024). Accessed October 22, 2024, from https://www.ecfr.gov/current/title-21/section-310.305

Adverse Drug Reactions Constitute a Significant Health Care Burden in the US

- In 2022, there were more than 1.25 million serious adverse events and nearly 175,000 deaths reported in the US
- There were 6 emergency department visits for medication harms per 1000 patients and about 38% of such visits required hospitalization in the US (2017–2019)
- Adverse drug reactions may cost $136 billion annually in the US due to:
  - Increased hospitalization
  - Prolongation of hospital stay
  - Additional clinical investigations in more serious cases
  - May trigger prescription cascades when new medications are prescribed for conditions that are a consequence of another medication, which is often an unrecognized adverse drug reaction

Sources: US Food and Drug Administration (FDA). (n.d.). *FDA Adverse Event Reporting System (FAERS) public dashboard*. Accessed October 22, 2024; FDA. (2024). *FDA Adverse Event Reporting System (FAERS) public dashboard* [Qlik sheets]. Accessed October 22, 2024; Budnitz, D. S., et al. (2021). US emergency department visits attributed to medication harms, 2017-2019. *JAMA, 326*(13), 1299–1309. https://doi.org/10.1001/jama.2021.13844; Sultana, J., Cutroneo, P., & Trifirò, G. (2013). Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother, 4*(Suppl 1), S73–S77. https://doi.org/10.4103/0976-500X.120957

Pharmacovigilance: Etymology

Pharmakon (medical substance)

+

Vigilia (to keep watch)

Definitions

Pharmacovigilance	Pharmacovigilance	Postmarketing surveillance
"The science and activities relating to the detection, assessment, understanding, and prevention of adverse events or any other drug-related problems" –World Health Organization	"All scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events" –US Food and Drug Administration	"Practice of monitoring the safety of a pharmaceutical or device after it has been released on the market" –US Food and Drug Administration

Sources: Uppsala Monitoring Centre. (2024). *Pharmacovigilance communications: Glossary*. Accessed October 22, 2024, from https://who-umc.org/pharmacovigilance-communications/glossary/; FDA. (2005). *Good pharmacovigilance practices and pharmacoepidemiologic assessment*. Accessed October 22, 2024, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment

General Steps in the Pharmacovigilance Process

1. Data collection and management
2. Safety signal detection
3. Risk assessment and quantification
4. Benefit and risk assessment
5. Intervention to reduce risk (if necessary)
   - Education campaign
   - Restrict access/guide prescribing (could be in form of a risk evaluation and mitigation strategy [REMS] program)
   - Withdrawal from market

Limitations of Preapproval Phases to Detect “Safety Signals”

- Preapproval studies are powered for efficacy
  - The number of patients treated with the drug limited, typically in the thousands
- Strict inclusion/exclusion criteria: patients in preapproval studies are more homogeneous than patients treated in clinical practice once a drug is marketed
  - Exclusion of patients with comorbidities
  - Exclusion of patients taking other medications
- Preapproval studies have limited duration of follow-up
  - This is very important for adverse drug reactions, which are cumulative
- Preapproval studies are standardized (in “controlled” research setting) with close monitoring

Postmarketing Safety Assessment

- After approval, there is a rapid increase in number of patients treated with the drug
- More complex patients receive the drug after approval
  - Patients with comorbidities
  - Patients taking concomitant medications
- Off-label use could be significant
- Clinical environment is less controlled

Pharmacovigilance: Passive Versus Active Surveillance

Passive surveillance	Active surveillance
▶ Spontaneous/voluntary reporting of cases ▶ National: MedWatch program (the FDA safety information and adverse event reporting program) ▶ Local or regional ▶ Scientific literature publications (e.g., a case report, a case series)	▶ Enhanced or targeted monitoring for certain events or drugs and seeks to ascertain the number of adverse drug reactions through a preplanned process (e.g., the FDA, Sentinel)

Sources: MedWatch. (n.d.). [Logo]. https://sentinelinitiative.org/; Sentinel Initiative. (n.d.). [Logo]. https://sentinelinitiative.org/

The Importance of Postmarket Safety Event Surveillance

- Among 222 novel therapeutics approved by FDA from 2001 to 2010, 71 (32%) were affected by a postmarketing safety event:
  - FDA safety communication: 59 safety communications affecting 44 therapeutics
  - New boxed warning: 61 new boxed warnings affecting 43 therapeutics
  - Withdrawal due to safety issue: 3

- Postmarket safety events were more frequent
  - Biologics
  - Psychiatric therapeutics
  - Drugs with accelerated approval and near regulatory deadline approval

Source: Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J. D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA*, *317*(18), 1854–1863. https://doi.org/10.1001/jama.2017.5150

Regulatory Requirements

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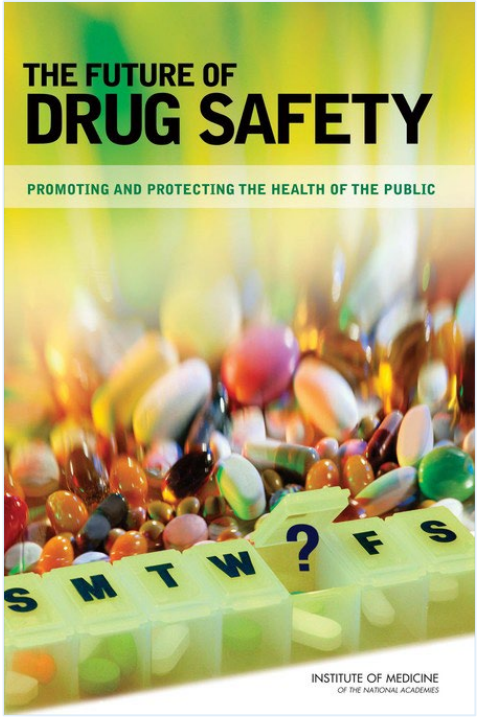
Concerns on US Drug Safety System in the Early 2000s

- The FDA and the Department of Health and Human Services (DHHS) asked the Institute of Medicine (IOM) to convene a committee to assess the US drug safety system and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs



FDA: US Food and Drug Administration
Source: Institute of Medicine (IOM). (2007). *The future of drug safety: Promoting and protecting the health of public*. National Academies Press.

Key Findings: IOM Report 2006

- There is a **perception of crisis** that has compromised the credibility of FDA and of the pharmaceutical industry
- Most stakeholders—the agency, the industry, consumer organizations, Congress, professional societies, health care entities—seem to agree on the need for improvements in the system
- The drug safety system is impaired by serious **resource constraints** that weaken the quality and quantity of the science that is brought to bear on drug safety, **an organizational culture in the Center for Drug Evaluation and Research (CDER)** that is not optimally functional, and **unclear and insufficient regulatory authorities**, particularly with respect to enforcement
- The FDA, contrary to its public health mission, and the pharmaceutical industry, contrary to its responsibility to the users of its products (and its shareholders), **do not consistently demonstrate accountability and transparency** to the public by communicating safety concerns in a timely and effective fashion

FDA: US Food and Drug Administration

Source: Institute of Medicine. (2007). *The future of drug safety: Promoting and protecting the health of public.* National Academies Press.

Key Recommendation: IOM Report 2006—1

- The committee recommended that to improve the generation of new safety signals and hypothesis, CDER should:
  - Conduct a systematic, scientific review of the adverse events reporting system (AERS)
  - Identify and implement changes in key factors that could lead to a more efficient system
  - Systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals
  - Increase their intramural and extramural programs that access and study data from large automated healthcare databases
  - Include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest
  - Develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings

Source: Institute of Medicine. (2007). *The future of drug safety: Promoting and protecting the health of public.* National Academies Press.

Key Recommendation: IOM Report 2006—2

- All FDA drug product advisory committees include a pharmacoepidemiologist or an individual with comparable public health expertise in studying the safety of medical product

- Congress ensures that the FDA has the ability to **require** such **postmarketing risk assessment and risk management programs** as are needed to monitor and ensure safe use of drug products

Source: Institute of Medicine. (2007). *The future of drug safety: Promoting and protecting the health of public.* National Academies Press.

The 2007 Update to the FDA Amendments Act (FDAAA)

- The FDA **can require** manufacturers to conduct post-approval studies, such as giving it authority to impose monetary penalties for noncompliance

- This law also **mandate** the implementation of risk evaluation and mitigation strategies (REMS) which can require physician certification, mandatory risk communication, or laboratory testing when specific high-risk medications are used

Sources: Institute of Medicine. (2007). *The future of drug safety: Promoting and protecting the health of public*. National Academies Press.; Avorn, J., Kesselheim, A., & Sarpatwari, A. (2018). The FDA Amendments Act of 2007 - assessing its effects a decade later. *The New England journal of medicine*, *379*(12), 1097–1099. https://doi.org/10.1056/NEJMp1803910

Postmarketing Safety Reporting Requirements

- Under 21 Code of Federal Regular (CFR) 314.80, postmarketing safety reports must be submitted to FDA for the following:
  - Expedited reports: both serious and unexpected adverse events from all sources (domestic and foreign)
  - Non-expedited reports: domestic spontaneous adverse events that are:
    - Serious and expected
    - Non-serious and unexpected
    - Non-serious and expected
    - Quarterly for the first three years and then annually
- The time-frame for reporting is no later than 15 days after the sponsor's initial receipt of the safety information
- In the case of death or life-threatening event, the time-frame for reporting is no later than seven days
- Safety monitoring is an ongoing responsibility

Source: Postmarketing reporting of adverse drug experiences. 21 C.F.R. § 314.80. (2024). Accessed October 22, 2024, from https://www.ecfr.gov/current/title-21/section-314.80

Science of Safety Signal Detection

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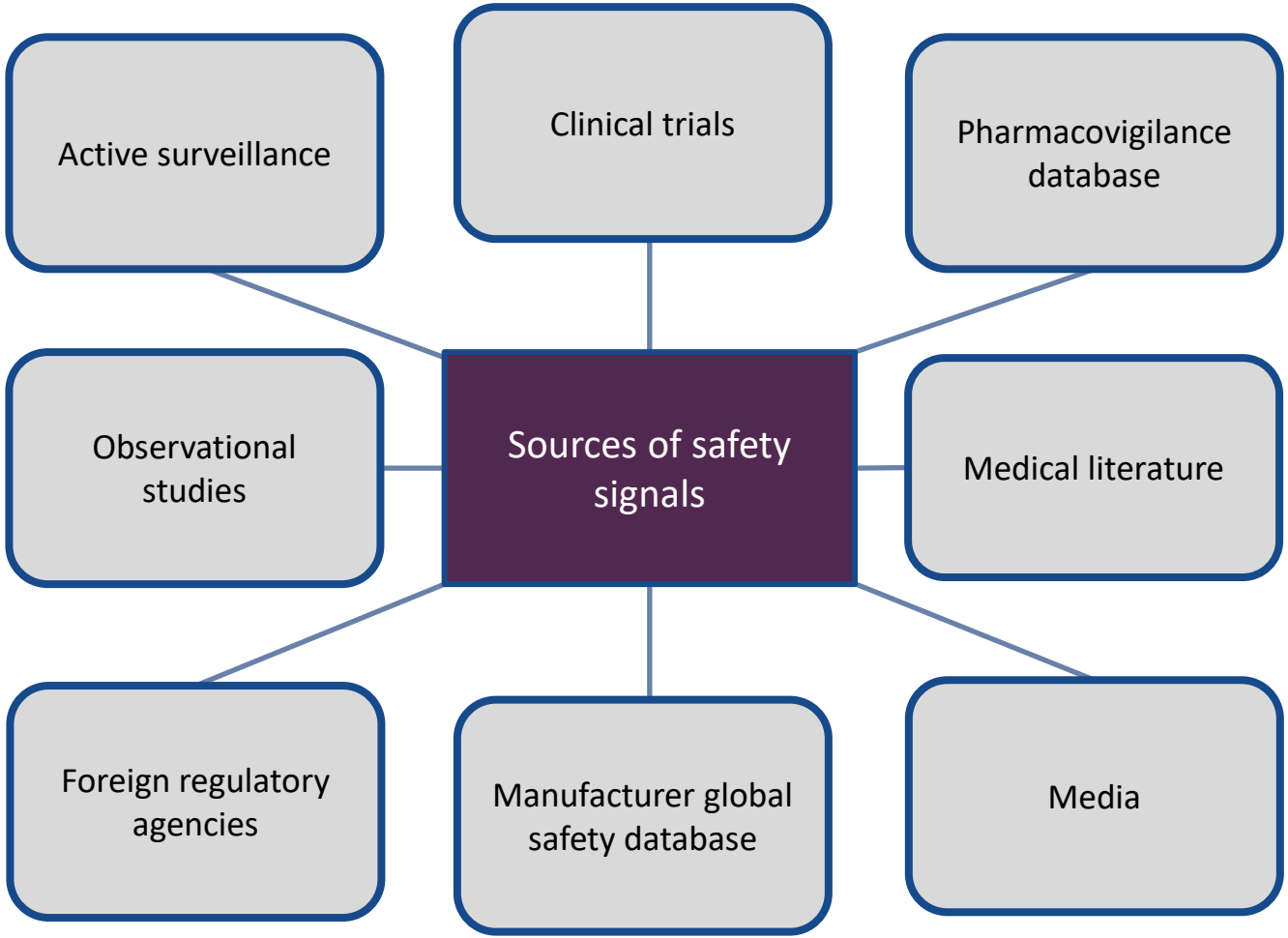
Safety Signal

- Reported information on a **possible causal relationship** between an adverse event and a drug, the relationship being unknown or incompletely documented previously (WHO, 2002)
  - Usually supported by multiple case reports
  - New unlabeled adverse events
  - An observed increase in a labeled event or a greater severity
  - New interactions
  - Newly identified at-risk population

- Generates hypothesis that calls for future work to be performed to evaluate that hypothesis

Source: World Health Organization (WHO). (2002). *The importance of pharmacovigilance*. Accessed October 22, 2024, from https://www.who.int/publications/i/item/10665-42493

Sources of New Safety Questions for a Marketed Product



Signal Detection Methods

- Manual review of reports
  - Has been a standard method in the setting of a relatively small number of reports
    - E.g., review a list of all reports where the outcome was “death”
  - May not be practical or reproducible for detecting signals from large databases

- Data mining technique: essential in modern pharmacovigilance
  - A process of analyzing data to find patterns using statistically based, computerized algorithms
  - **Disproportionalities** in data: whether a given adverse event/adverse drug reaction (AE/ADR) reported for a particular drug is more often than would be expected, based on the number of reports of that AE/ADR for all other drugs in the database
  - These methods rely on reports within the database—understanding the characteristics of database is important

Data Mining Technique

- The degree of disproportionality for a given drug-event pair may vary from one database to another
- As the background information for all drugs in the database changes over time, the expected number of reports of a specific AE/ADR for a given drug (and the proportionality of the drug-event pair) also changes
- A signal of disproportionality is a measure of statistical association within a collection of AE/ADR reports, rather than in a population
  - **It is NOT a measure of causality**
  - **Data mining is for hypothesis generation and future work is needed to evaluate the signal**
- The absence of a signal of disproportionality is not evidence that an important AE/ADR is not associated with a particular drug

Several Test Statistics to Examine Disproportionality

- Proportional reporting ratio (PRR)
- Reporting odds ratio (ROR)
- Empirical bayes geometric mean (EBGM)
- Bayesian confidence propagation neural network (BCPNN)
- The choice of signaling criteria (e.g., case definition) had a greater impact on signal detection performance than the choice of disproportionality methods

Reporting Ratio (Sometimes Called a Reporting Rate)

- Using postmarketing safety reporting systems, it is not possible to calculate an incidence rate for a particular drug-event pair because the information on the frequency of a particular drug use is not available

- Reporting ratio = (the number of cases of a particular AE/ADR reported to a drug safety database during a specific time period)/(the number of dispensed prescriptions for a particular drug)

- Limitations
  - The numerator (the number of individual case safety report) and the denominator (derived from product utilization data) are from different data sources
  - Underreporting of AEs is common
  - Product utilization data are based on national estimates, not actual counts

How to Assess Causal Effects Between a Drug and an Adverse Event?

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Causal Assessments

- The process of assessing potential causal effects between an adverse event and a product has many challenges

- Causal assessments should be conducted
  - At the individual case safety report level
  - At the overall product-adverse event level

Source: US Department of Health and Human Services, US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024). *Best practices for FDA staff in the postmarketing safety surveillance of human drug and biological products*. Retrieved October 23, 2024, from https://www.fda.gov/media/130216/download

Five Key Factors in Assessing a Case Report for Causal Effects

1. Chronologic data (e.g., plausible temporal sequence, dechallenge, rechallenge)
2. Precedents (e.g., a causal relationship has been determined for other products with common structural features)
3. Biological or pharmacological plausibility (e.g., toxic drug concentration in body fluid, occurrence of a recognized pharmacodynamic phenomenon)
4. Alternative etiologies (e.g., concurrent diseases or conditions, concomitant medications)
5. Information quality

Source: US Department of Health and Human Services, US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024). *Best practices for FDA staff in the postmarketing safety surveillance of human drug and biological products*. Retrieved October 23, 2024, from https://www.fda.gov/media/130216/download

World Health Organization Causality Categories

- Causal relationship between adverse event and a suspected drug can be
  - Certain
  - Probable/likely
  - Possible
  - Unlikely
  - Conditional/unclassified
  - Unassessable/unclassifiable

Source: The Uppsala Monitoring Centre. (2013). *The use of the WHO-UMC system for standardized case causality assessment*. Accessed October 23, 2024, from https://www.who.int/publications/m/item/WHO-causality-assessment

Causal Effects Between Product and Adverse Event

- This determination should be based on the strength of evidence from the totality of data for the product under postmarketing review
  - Preclinical data
  - Literature
  - Other safety databases
  - Clinical trials and studies from preapproval development programs
  - Epidemiological studies
  - Product utilization data
  - Reporting ratios (rates)

- The number of well-documented cases, the consistency of the safety findings among the data sources, precedents, and biological and pharmacological plausibility should also be considered

Source: US Department of Health and Human Services, US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024). *Best practices for FDA staff in the postmarketing safety surveillance of human drug and biological products*. Retrieved October 23, 2024, from https://www.fda.gov/media/130216/download

Post-Authorization Safety Studies, Phase 4

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PMRs Versus PMCs

- Before 2007 FDA Amendment Act (FDAAA), the FDA has used the word “commitment” to cover both required and not required studies and clinical trials
- Postmarketing requirements (PMRs): studies or clinical trials that sponsors are ***required*** to conduct under one or more statues or regulations
- Postmarketing commitments (PMCs): studies or clinical trials that a sponsor has agreed to conduct, but that are ***not required*** by a statue or regulation

Source: US Food and Drug Administration (FDA). (2024). *Postmarketing requirements and commitments: Introduction*. Accessed October 23, 2024, from https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarketing-requirements-and-commitments-introduction

Before 2007 FDA Amendment Act (FDAAA)

- FDA could require postmarketing studies or clinical trials only in the situations described below:
  - **Accelerated approval PMRs**: Under the Accelerated Approval Pathway, FDA may approve a drug based on a surrogate or intermediate clinical endpoint. These approvals require postmarketing studies or clinical trials to verify the clinical benefit.
  - **Pediatric Research Equity Act (PREA) PMRs**: FDA may approve a drug that is ready for approval for use in adults but has not been studied in a relevant pediatric population. In these cases, FDA may defer pediatric studies under PREA.
  - **Animal efficacy rule PMRs**: When human clinical trials cannot be conducted ethically, FDA may approve a drug based solely on animal studies. In these cases, FDA may require the sponsor to conduct postmarketing studies in humans, when feasible and ethical.

Source: US Food and Drug Administration (FDA). (2024). *Postmarketing requirements and commitments: Introduction*. Accessed October 23, 2024, from https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarketing-requirements-and-commitments-introduction

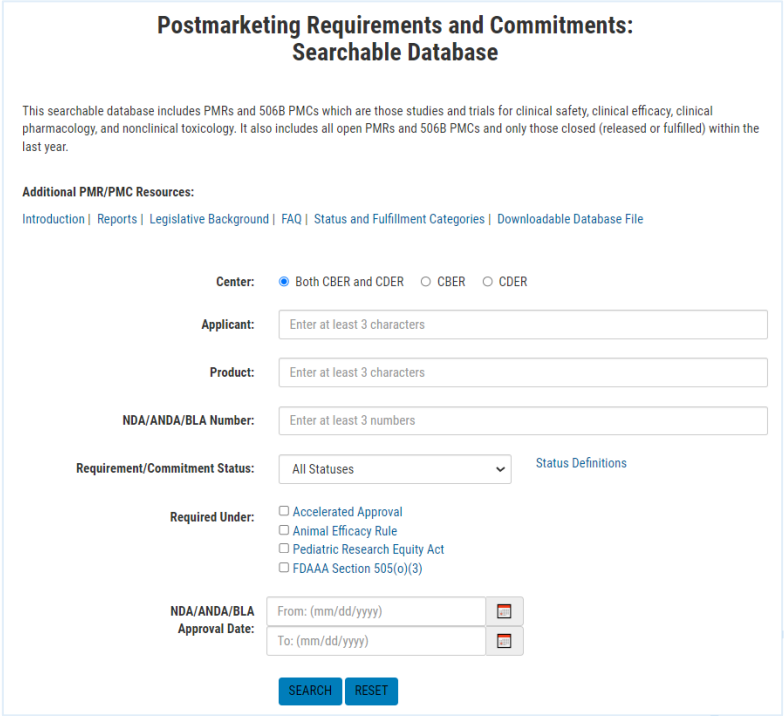
After 2007 FDA Amendment Act (FDAAA)

- FDA **may require** postmarketing studies or clinical trials at the time of approval or after approval **if FDA becomes aware a new safety information**
  - To assess a known serious risk related to the use of the drug
  - To assess signals of serious risk related to the use of the drug
  - To identify an unexpected serious risk when available data indicate the potential for serious risk

Source: US Food and Drug Administration (FDA). (2024). *Postmarketing requirements and commitments: Introduction*. Accessed October 23, 2024, from https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarketing-requirements-and-commitments-introduction

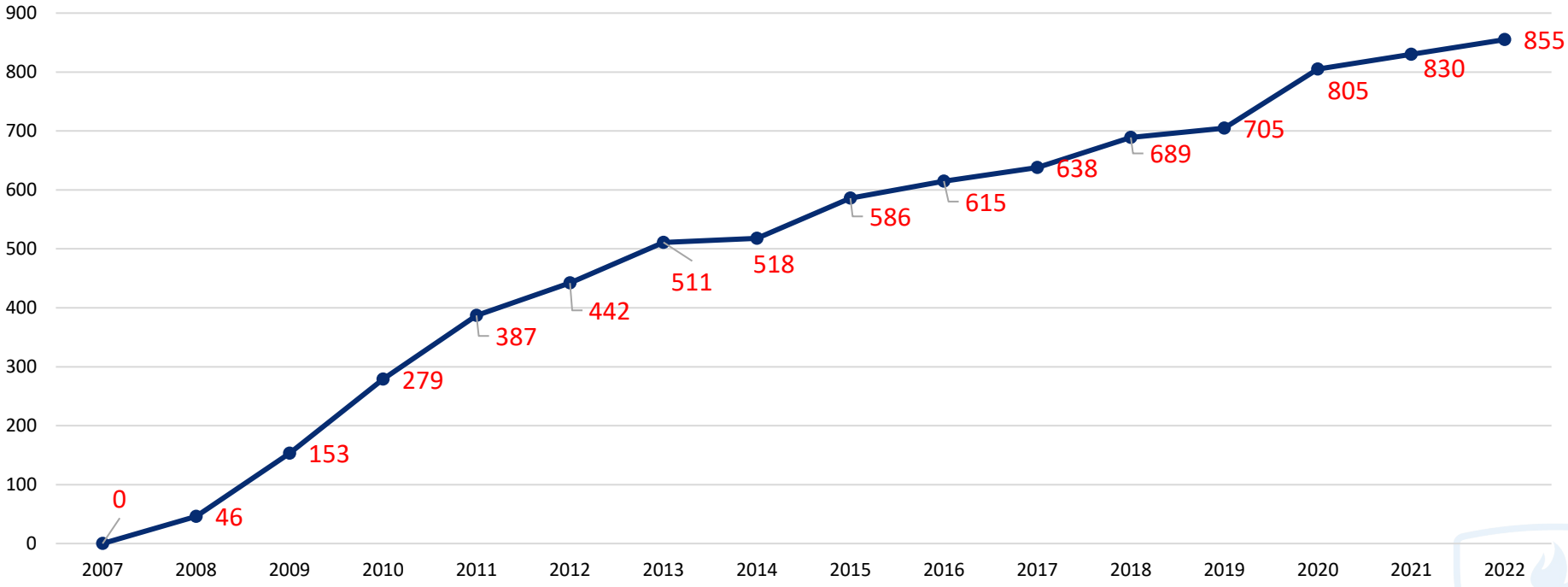
FDA's Data on Postmarketing Studies and Clinical Trials

- **FDA's internal PMR/PMC databases**
  - By the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER)
- **Publicly available PMR/PMC data**
  - Online searchable and downloadable database
  - A subset of all PMRs/PMCs: only include studies that had an open status or were closed within the past year at the time of data retrieval



Source: FDA. (2013). *Postmarketing requirements and commitments: Searchable database*. Accessed October 23, 2024, from https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

The Total Number Studies Required Under the FDAAA: 2007–2022



Data sources: FDA. (2024). [Annual reports in Federal Register (FY2007–FY2022)]. *In Postmarketing requirements and commitments: Reports*. Retrieved August 15, 2024, from https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports; Fain, K., Daubresse, M., & Alexander, G. C. (2013). The Food and Drug Administration Amendments Act and postmarketing commitments. *JAMA, 310*(2), 202–204. https://doi.org/10.1001/jama.2013.7900

Summary

1. **Pharmacovigilance**: the science and activities relating to the detection, assessment, understanding, and prevention of adverse events or any other drug-related problems
   - Passive versus active

2. **The 2007 update to the FDA Amendments Act (FDAAA)**
   - FDA may require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of new safety information

3. **Safety signal**: a signal of disproportionality
   - It is NOT a measure of causality
   - For hypothesis generation and future work is needed to evaluate the signal

4. **Causal assessments**: well-documented cases, the consistency of the safety findings among the data sources, precedents, and biological and pharmacological plausibility