The FDA Adverse Event Reporting System (FAERS) Explained

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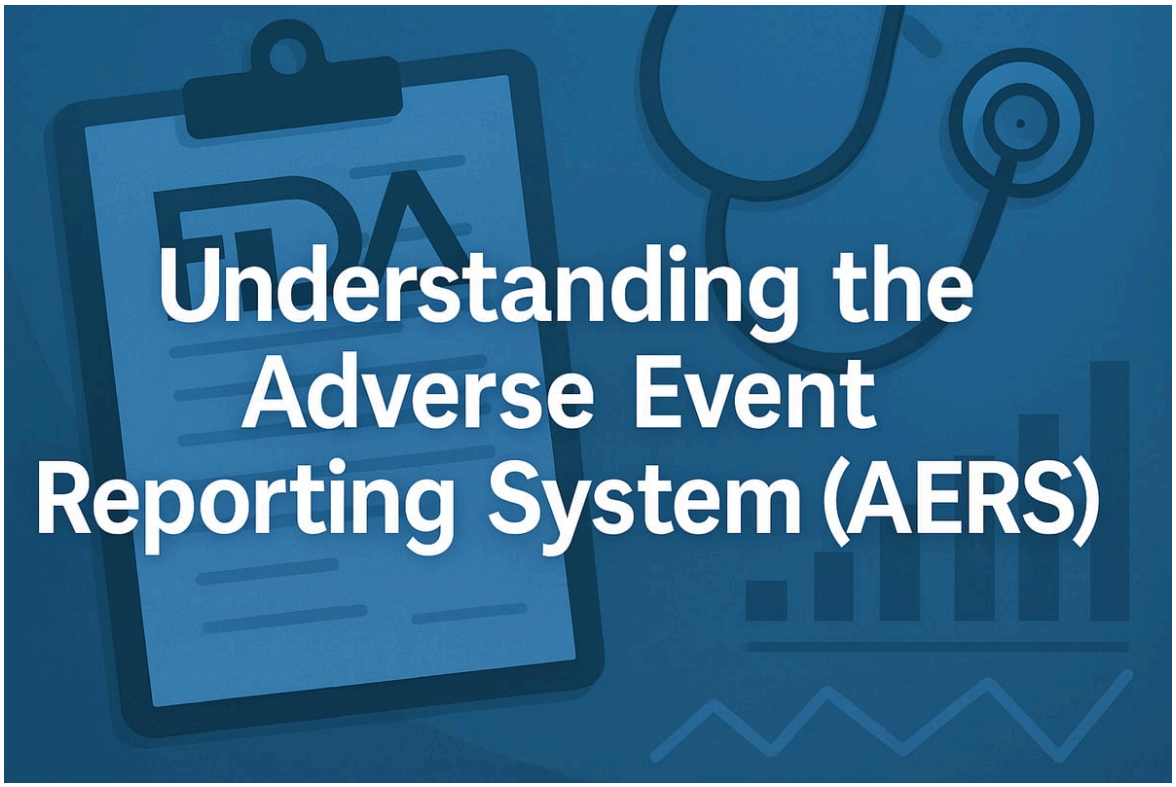

FDA's Adverse Event Reporting System (AERS): A Comprehensive Overview

1. Introduction

The **FDA's Adverse Event Reporting System (AERS)** – now known as **FAERS** (FDA Adverse Event Reporting System) – is a cornerstone of U.S. pharmacovigilance. It is a **computerized database** designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products open.fda.gov. AERS/FAERS collects reports of adverse drug events, medication errors, and product quality problems resulting in adverse events, submitted either directly to the FDA or via manufacturers open.fda.gov. This system is critically important for public health: it enables the FDA to **monitor the safety of products after approval** and to detect rare, latent, or serious adverse reactions that may not have been evident in pre-approval clinical trials govinfo.gov fda.gov. By aggregating reports from the broader patient population (now over one million reports are received each year fda.gov), AERS serves as an early warning system for potential drug safety problems. FDA safety evaluators use FAERS to look for **new safety signals**, evaluate manufacturers' compliance with reporting requirements, and inform regulatory actions to protect patients en.wikipedia.org. In essence, AERS/FAERS helps regulators continually assess whether a drug's **risk–benefit ratio** remains acceptable in real-world use en.wikipedia.org. The ultimate goal is to safeguard public health by enabling timely interventions – such as label changes, safety communications, or even product withdrawals – when significant risks are identified en.wikipedia.org.

(Table 1 provides a timeline of AERS's historical development and milestones.)

2. Historical Development

Origins (1960s–1980s): Modern pharmacovigilance in the U.S. has its roots in the early 1960s, catalyzed by the thalidomide tragedy and the 1962 Kefauver-Harris Drug Amendments. These events underscored the need for systematic adverse event monitoring for marketed drugs ashp.org. The FDA began operating a formal post-market **Adverse Drug Reaction (ADR) reporting program around 1961-1962**, initially relying on voluntary reports from healthcare professionals medscape.com. By **1969**, the FDA had established what became the **Spontaneous Reporting System (SRS)** – an early database (largely paper-based at first) to collect and manage adverse reaction reports ashp.org. This is often cited as the "inception" of FDA's spontaneous reporting database, which accumulated hundreds of thousands of reports in the following decades govinfo.gov. Throughout the 1970s and 1980s, the system remained

largely voluntary and paper-driven, with no requirement for most healthcare providers to report; manufacturers, however, were obligated to report serious adverse experiences from clinical use of their products under FDA regulations (e.g. **21 CFR 314.80** for drugs, established in the late 1980s). Reporting rates were low – studies estimate that **less than 1–10% of serious adverse events** ever get reported to FDA en.wikipedia.org pmc.ncbi.nlm.nih.gov – but the accumulating data still proved valuable. Notably, by the mid-1990s the FDA's spontaneous reporting database contained roughly **1.4 million adverse event reports** for human drugs and biologics govinfo.gov.

Launch of MedWatch (1993): In 1993, under FDA Commissioner Dr. David Kessler, the FDA launched the **MedWatch** program to improve the reporting process retinatoday.com. MedWatch established a single standardized **voluntary reporting form (Form FDA 3500)** and hotline, and promoted awareness among healthcare professionals to "voluntarily" report serious adverse events and product problems. As Dr. Kessler explained, *"MedWatch is not just a new form; it's a new approach to making adverse event reporting part of routine medical practice."* The MedWatch program streamlined how reports from clinicians and consumers were collected, creating a **central clearinghouse** for post-market safety data within FDA medscape.com. Importantly, while reporting remained voluntary for providers, **manufacturers were (and are) required by law** to report any adverse events they become aware of through a **mandatory system** (using Form FDA 3500A for mandatory reports) medscape.com. The MedWatch initiative led to a notable uptick in reporting; by the late 1990s the FDA was receiving on the order of 250,000 adverse event reports per year medscape.com – a number that would continue to climb. MedWatch set the stage for the next major evolution: a modern database to handle the growing volume.

Transition to AERS (1997–1998): In the mid-1990s, the FDA undertook a significant overhaul of its adverse event data systems. The old SRS, which had been largely manual-entry, was to be replaced by a more sophisticated, electronic system. In **September 1997**, the FDA rolled out the **Adverse Event Reporting System (AERS)** – a relational database that for the first time enabled electronic submission of Individual Case Safety Reports (ICSRs) by manufacturers govinfo.gov. **All historical SRS data were migrated into AERS** govinfo.gov. AERS was designed in alignment with new international standards: notably, its data structure conformed to the ICH's E2B guidelines for electronic case reporting, and it adopted the new standardized adverse event terminology, **MedDRA**, which was then being developed through the International Conference on Harmonisation govinfo.gov govinfo.gov. (Prior to MedDRA, FDA used the older COSTART dictionary for coding events; COSTART was phased out as AERS came online in 1997 ascpt.onlinelibrary.wiley.com.) The launch of AERS in 1997–98 was a watershed moment – the FDA's sprawling safety data were now in a unified, searchable electronic database, which facilitated more rapid ** signal detection and analysis** medscape.com. It also coincided with key legislation: the **Food and Drug Administration Modernization Act (FDAMA) of 1997**, which among other provisions, emphasized post-market surveillance and called for wider public access to safety data. By **1998**, AERS was fully operational and accepting both electronically transmitted ICSRs from industry and internally entered reports from MedWatch forms

medscape.com. Notably, AERS allowed inclusion of **all adverse events in a case report** (prior systems had capped the number of events per report) jamanetwork.com, improving data completeness.

Becoming FAERS and Data Transparency (2000s–2010s): Through the 2000s, AERS grew exponentially. By 2002, it had received **~2.3 million reports** in total, covering over 6,000 drug products ashp.org. High-profile safety withdrawals in the early 2000s (e.g., **troglitazone** in 2000, **cisapride** in 2000, **rofecoxib** in 2004, etc.) kept a spotlight on AERS data, and multiple regulatory reforms ensued. The **FDA Amendments Act (FDAAA) of 2007** significantly bolstered FDA's post-market authorities – mandating Risk Evaluation and Mitigation Strategies (REMS) for certain drugs, requiring better adverse event reporting for pediatrics and even dietary supplements, and crucially, calling for an **"active surveillance" system (the Sentinel Initiative)** to complement passive reporting fda.gov. Around this time, FDA also began sharing AERS data publicly. Starting in **2004**, the agency made anonymized AERS case data available on its website on a quarterly basis pmc.ncbi.nlm.nih.gov, enabling external researchers and the public to scrutinize the data. In **September 2012**, following a major database upgrade, the FDA rebranded AERS as **FAERS (FDA Adverse Event Reporting System)** en.wikipedia.org. FAERS represented continuity with AERS (the "legacy AERS") but with improved technology and integration across FDA centers. The database by then was enormous – containing roughly 10 million reports by 2012 – and continuing to grow rapidly as reporting became easier. The FDA issued a final rule in 2014 requiring that all postmarket adverse event reports from industry **must be submitted electronically** (this rule became effective in 2015) fda.gov, finally ending the era of paper 3500A forms from manufacturers. In 2017, to enhance transparency, FDA launched the **FAERS Public Dashboard**, a web-based query tool that allows anyone to search and filter FAERS reports in near real-time fda.gov. By the end of 2017, FAERS held over **14 million reports (1969–2017)** fda.gov; today (2025) it contains **well over 25 million reports**.

Table 1 – Timeline of AERS/FAERS Key Milestones

Year	Milestone
1962	*Kefauver-Harris Amendments* passed, laying groundwork for modern drug safety monitoring ashp.org. FDA begins systematic collection of post-market adverse event reports (early ADR program).
1969	FDA establishes the *Spontaneous Reporting System (SRS)* for adverse event collection – the precursor to AERS ashp.org.
1993	*MedWatch* program launched to encourage voluntary reporting and standardize forms retinatoday.com.
1997	FDA launches *AERS*, replacing SRS. AERS allows electronic ICSR submissions and uses ICH E2B format and MedDRA coding govinfo.gov govinfo.gov. FDAMA 1997 emphasizes improved post-market surveillance.
2004	FDA begins quarterly public release of AERS data, increasing transparency pmc.ncbi.nlm.nih.gov.
2007	*FDA Amendments Act* (FDAAA) expands post-market authorities, mandates Sentinel active surveillance (100 million patient data network) to complement AERS fda.gov.
2012	Legacy AERS upgraded to **FAERS** (FDA Adverse Event Reporting System) on Sept 10, 2012 pmc.ncbi.nlm.nih.gov.
2014	FDA mandates electronic submission of all postmarketing safety reports (Final Rule June 2014) fda.gov.
2017	FDA launches the **FAERS Public Dashboard**, a user-friendly web interface for querying FAERS data fda.gov.

Year	Milestone
2024	FDA begins transition to ICH E2B(R3) data standard for ICSRs; accepts IND safety reports electronically (modernizing FAERS for future) fda.gov fda.gov.

3. System Architecture and Functionality

Data Collection Workflow: FAERS operates by collecting **Individual Case Safety Reports (ICSRs)** of adverse events through multiple channels. Reports may originate from **healthcare professionals, consumers/patients, or manufacturers**, and can be submitted either *directly to FDA* (via the MedWatch program) or *indirectly via pharmaceutical manufacturers*. When a voluntary report is sent through **MedWatch**, it can be submitted online (through a web portal), by phone, fax, or mail using Form FDA 3500 (for health professionals) or the consumer-friendly Form 3500B retinatoday.com omicsonline.org. The FDA's Safety Reporting Portal (SRP) also supports direct online submissions. Manufacturers and other mandatory reporters typically submit **electronic ICSRs** via the FDA Electronic Submissions Gateway, following the ICH E2B XML format (currently transitioning from E2B(R2) to E2B(R3) standard) fda.gov. In practice, about *75% of reports come via manufacturers* (from healthcare providers or consumers who reported to the company), and the remaining come directly to FDA through MedWatch govinfo.gov. Each incoming report is triaged by FDA staff to ensure it contains the minimum required information (an identifiable patient and reporter, a suspect drug, and event) frontiersin.org. Reports are then entered into the FAERS transactional database. Key data fields include patient demographics, drug(s) used (with dose, start/stop dates), adverse event descriptions (coded terms), indication, outcome (e.g. hospitalization, death), and reporter information. If a report is initially submitted in narrative form (e.g. a written description), FDA staff or contractors will **code** the medical terms.

MedDRA Coding: All adverse events in FAERS are coded using the **Medical Dictionary for Regulatory Activities (MedDRA)** terminology open.fda.gov en.wikipedia.org. MedDRA provides standardized hierarchical terms for symptoms, diagnoses, lab abnormalities, etc., which allows aggregation and analysis. Trained coders or automated tools map the reporter's description (e.g. "heart stopped") to MedDRA terms (e.g. *"cardiac arrest"*). Drug names are also standardized – the FDA often uses a drug dictionary or **WHODrug** for consistency. One challenge is that the same drug can be reported under various names (brand, generic, typos). A known issue with FAERS is **drug name normalization**: reporters around the world use different names and spellings, so extensive data cleaning (mapping to a standard like RxNorm) is needed to aggregate reports for the same product pmc.ncbi.nlm.nih.gov pmc.ncbi.nlm.nih.gov. FDA and researchers have invested effort in creating cleaned FAERS datasets where drug names are standardized pmc.ncbi.nlm.nih.gov.

Database Structure: The FAERS database itself is a large relational data warehouse. Public FAERS data is provided in multiple tables (e.g. DEMO for patient/demo data, DRUG for suspect drugs, REAC for reactions, etc.), linked by case IDs. Internally, FAERS serves both **CDER** (drugs)

and **CBER** (biologics) reviewers. It adheres to the ICH E2B data format, meaning each ICSR can be exchanged internationally in a common structure open.fda.gov. The system is designed to handle the huge volume: as of 2024, FDA receives *over 1 million* new reports each year fda.gov, and the database holds 15+ million unique cases (over 29 million total report entries, including follow-ups) ema.europa.eu. Data storage and management are supported by Oracle-based solutions. FAERS also interfaces with the FDA's data analysis tools.

Processing and Quality Control: After entry, each case report may undergo **medical review** by FDA safety evaluators. FDA's Office of Surveillance and Epidemiology (OSE) has pharmacists and physicians who review serious reports, especially for new products medscape.com. Duplicate detection is an important function: the same adverse event might be reported by a consumer to FDA and by a physician to the manufacturer, resulting in two reports for one case. FAERS uses algorithms to **de-duplicate cases** (often by matching patient, event, and drug details) pmc.ncbi.nlm.nih.gov, but some duplicates persist in the raw data. The FDA also receives **follow-up reports** (when new information on a known case becomes available); these are linked to the original case in FAERS, though external datasets sometimes list them separately. Data quality checks (both automated and manual) are done to ensure key fields are populated and coded correctly. FDA even performs **quality assurance audits** on MedDRA coding – providing feedback to improve consistency frontiersin.org frontiersin.org.

Signal Detection and Analysis: One of the core functionalities of AERS/FAERS is to enable **signal detection** – spotting patterns that might indicate a new adverse reaction or a change in the frequency/severity of known reactions. Given the size of the data, FDA and researchers rely on **statistical data mining algorithms** to aid this process. FAERS data can be analyzed by **disproportionality methods** such as the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and the Empirical Bayes Geometric Mean (EBGM, used in the MGPS algorithm) to find drug-event pairs reported more frequently than expected pmc.ncbi.nlm.nih.gov pmc.ncbi.nlm.nih.gov. The FDA's analysts use tools like **Oracle Empirica Signal** (an industry standard software) to perform these analyses pmc.ncbi.nlm.nih.gov. For example, if drug X has 50 reports of liver failure, and in the entire database liver failure is rare, the PRR/ROR might signal a disproportionality, prompting further review. FAERS supports generating **automated signal summaries** – in the EU, for instance, over 14,000 statistical signal outputs were generated from their database in 2024 for review ema.europa.eu. In FDA, signals identified in FAERS are evaluated by multidisciplinary safety teams. An emerging practice is to supplement crude disproportionality with more advanced algorithms (e.g. logistic regression data mining pmc.ncbi.nlm.nih.gov), but these are largely research-stage. Once a potential safety signal is identified, FDA may conduct a targeted review: examining case series in detail, looking for a biologically plausible pattern, and perhaps *comparing FAERS data with real-world data* (such as insurance databases or clinical trial data). If the signal is deemed credible, it moves to regulatory action (see Section 5 and Case Studies).

MedWatch & Outreach: FAERS' functionality is also tightly linked with the MedWatch communication program. FDA uses the data not only internally but also to feed its **Safety**

Communications to healthcare providers and the public. For example, if FAERS reveals a new severe risk, FDA can issue MedWatch alerts, update the product's labeling (e.g. add a Boxed Warning), require the manufacturer to send out "Dear Healthcare Professional" letters, or convene advisory committees medscape.com medscape.com. Thus, the "back end" of FAERS (data analysis) connects to the "front end" of risk communication and regulatory enforcement.

In summary, the FAERS system architecture encompasses **data intake (MedWatch reports, electronic submissions)**, **data management** in a coded database (using ICH E2B format and MedDRA), and **analytics** for signal detection. It is a **massive, evolving IT system** that adheres to global standards and serves a critical public health function. Its success relies on the quality of reports submitted and the rigor of the FDA's analysis processes in translating data into actionable safety knowledge.

4. Data Submission and Stakeholders

Who Reports into AERS/FAERS: A variety of stakeholders submit reports to AERS, and the system accommodates both **voluntary** and **mandatory** reporting:

- **Healthcare Professionals (HCPs):** Physicians, pharmacists, nurses, and other clinicians may report adverse drug events either to the FDA (via MedWatch) or to the product's manufacturer. In the U.S., HCP reporting is **voluntary** – there is no legal requirement that physicians or hospitals must report most adverse events (unlike in some countries). However, FDA and professional societies encourage HCPs to report serious or unexpected events. HCPs can use the MedWatch Form 3500 (designed for health professionals) to send reports fda.gov. They are often the source of initial signals, since they may observe unusual patient reactions and connect them to drug therapy.

- **Consumers and Patients:** Patients and their caregivers can also submit reports voluntarily. Historically, consumer reports were underutilized due to complex forms, but FDA introduced a simplified **Form 3500B** in 2013 specifically for consumers ascpt.onlinelibrary.wiley.com. The 3500B form uses a Q&A format and plain language to make it easier for patients to describe what happened omicsonline.org omicsonline.org. Consumers can report events like side effects, product quality issues, or medication errors. These reports often provide crucial detail from the patient's perspective (symptoms, timing, etc.), and FDA has noted that consumer reporting has been increasing omicsonline.org. Even if consumer reports lack medical terminology, they are coded and entered into FAERS similarly. Importantly, **if a consumer reports an event to the manufacturer**, the manufacturer is obligated to forward it to FDA (thus it becomes part of mandatory reports) retinatoday.com.

- **Manufacturers (Industry):** Pharmaceutical manufacturers (and biologic product sponsors) are **required by law** to report adverse events associated with their products that they become aware of. U.S. regulations (e.g., 21 CFR 314.80 for drugs, 21 CFR 600.80 for biologics) mandate that manufacturers submit **expedited reports within 15 days** for any adverse experience that is *serious* and *unexpected* (not in the product's labeling) pmc.ncbi.nlm.nih.gov. These are often called "15-day Alert reports" or **FDA MedWatch 3500A reports**. Additionally, manufacturers must report **all other adverse events in periodic reports** – originally as quarterly reports for the first 3 years post-approval and annually thereafter (though FDA has moved toward ICH's Periodic Benefit-Risk Evaluation Reports, PBRER, format). Manufacturers typically fulfill these obligations by maintaining their own safety databases and sending electronic ICSRs to FAERS. If a patient or doctor reports an event to a company, the company's pharmacovigilance department will create a case and submit it to FDA. By law, **manufacturers must also search the scientific literature** and report any case reports of their drug causing adverse effects. They must report foreign adverse reports as well. In practice, this means that a large portion of FAERS cases originate from companies compiling information from various sources. In fact, as noted, ~75% of reports in FAERS are received from manufacturers who forward them on behalf of reporters govinfo.gov. Manufacturer submissions include both initial reports and follow-ups (e.g., if new information on a case emerges, companies file follow-up ICSRs). The FDA monitors compliance – failure of a company to report known adverse events can result in regulatory action.

- **Other Sources:** There are additional sources like **clinical trial sponsors** (who report serious unexpected suspected adverse reactions in IND trials to FDA, though those go into a separate IND safety system), **user facilities** (hospitals must report device-related adverse events under the FDA's device reporting regs, but drug-related events from hospitals are not mandatory to FDA), and **lawyers** (attorneys sometimes submit reports, often in context of litigation – these are treated as consumer reports). Notably, reports also come from **foreign regulatory agencies** through exchange agreements and the WHO program (see Section 8) – if an adverse event with a U.S.-marketed drug occurs abroad and the foreign regulator informs FDA, it may enter FAERS.

Voluntary vs Mandatory Reporting: The dichotomy of reporting is crucial. **Voluntary reporters (HCPs, consumers)** submit out of altruism or concern, so their reports may be sporadic. To facilitate voluntary reporting, FDA has tried to reduce barriers – e.g., toll-free phone (1-800-FDA-1088), simplified forms, online submission, and even a mobile app for reporting. The MedWatch program extensively educates clinicians on "when and what" to report: generally encouraging reports of *serious*, *unexpected*, or *unusual* events and any therapeutic failures or product quality issues omicsonline.org omicsonline.org. **Mandatory reporters (manufacturers)** have established processes and timelines enforced by regulation. For instance, if a company learns of a patient death potentially linked to their drug, they must investigate and send FDA a 15-day report with all details. They also submit **Follow-up reports** within 15 days of obtaining new info. This legal mandate ensures FDA gets critical reports, but it also means there can be redundancy (the same event might be voluntarily reported by a doctor and also reported by the company).

There is also a **distinction in forms**: *Form FDA 3500* is for voluntary reports (HCPs, consumers) and explicitly **notifies the reporter that it's voluntary**, whereas *Form FDA 3500A* is used by manufacturers (and user facilities or importers) for mandatory reports – it has additional fields

like manufacturer name, etc. The *3500B consumer form* (since 2013) is a simplified version of 3500 to drive up consumer participation ascpt.onlinelibrary.wiley.com.

Reporting Requirements & Regulations: In summary, the regulatory framework requires that: (1) any *serious and unexpected* adverse event must be reported by the company to FDA within 15 calendar days of receipt pmc.ncbi.nlm.nih.gov; (2) any *follow-up* information on a reported case must be submitted within 15 days of receipt; (3) *periodic safety reports* (which include summary tabulations of non-serious events and a narrative summary) must be submitted quarterly for new drugs (then annually). Additionally, **special reporting**: if an adverse event suggests an imminent hazard, FDA can be alerted immediately (e.g., "Alert Reports"). With the adoption of ICH standards, FDA aligned with the **CIOMS I form** internationally and now expects submission in electronic ICSR format (E2B). As of 2015, all manufacturers *must* submit electronically (no paper) fda.gov, which has streamlined the process. For investigational drugs (IND trials), FDA has a separate rule (21 CFR 312.32) requiring IND Safety Reports for serious unexpected suspected reactions in trials – those go to a different database but eventually, once the drug is marketed, such issues may be reflected in FAERS too.

Encouraging Reporting: FDA, through MedWatch, regularly reminds healthcare providers: "*If you don't report it, we can't know about it.*" Despite this, under-reporting is a perpetual challenge (Section 7). Over the years, FDA has engaged stakeholders via safety alerts, journal articles, and even Continuing Medical Education (CME) programs to improve reporting culture. They emphasize that **reporting a suspicion does not prove causality and does not incur legal liability** – providers sometimes fear reporting could imply blame. By fostering a non-punitive approach, FDA hopes more front-line clinicians will share their observations.

In summary, **stakeholders in AERS/FAERS range from the individual patient all the way to large pharmaceutical companies**. Each has a role: patients and providers as the eyes and ears detecting problems, and companies as obligated reporters consolidating global safety information. Through a combination of voluntary contributions and mandatory compliance, the system amasses the data needed for effective pharmacovigilance.

5. Data Access and Use

One of AERS/FAERS's most valuable aspects is that the data it collects do not simply disappear into an internal vault – they are actively **used by regulators** for decision-making and, in large part, made **accessible to the public and researchers** for independent analysis.

FDA's Use of FAERS Data: Within the FDA, FAERS is a daily tool for pharmacovigilance scientists. **Clinical safety reviewers** in CDER and CBER continuously screen incoming reports for signals en.wikipedia.org. They may use FAERS to generate case series (e.g., all reports of liver failure on a given drug) and to perform trend analyses. FAERS data inform a range of regulatory **actions**:

- **Labeling changes:** If a new adverse reaction is identified or a known one is found to be more frequent or severe than realized, FDA can update the product's labeling. Many drugs have had warnings, precautions, or even Boxed Warnings added based on post-market reports. For example, spontaneous reports of tendon rupture with certain antibiotics led to boxed warnings on fluoroquinolones.

- **Safety Communications:** FDA may issue *Drug Safety Communications* or MedWatch alerts to healthcare providers when a potential risk emerges that needs immediate attention (e.g., warning about a drug's interaction or a risk seen in certain populations). These communications often cite analysis of FAERS data.

- **Risk Evaluation and Mitigation Strategies (REMS):** If FAERS signals a serious risk that can be mitigated (say, severe birth defects), FDA can require a REMS program (like patient registries, restricted distribution, etc.). The decision to impose or modify a REMS is often supported by adverse event report trends.

- **Product withdrawals or suspension:** In rare but critical situations, FAERS data have tipped the balance on removing a drug from the market (see Case Studies in Section 6). If evidence from reports (often alongside other data) shows a drug's risks outweigh its benefits, FDA may request or require withdrawal. As noted in Section 3, either the manufacturer "voluntarily" withdraws (usually in negotiation with FDA) or FDA can initiate formal withdrawal procedures.

- **Compliance and Enforcement:** FAERS is also used to monitor **industry compliance** with reporting rules. If a company has an unexpectedly low number of reports for a drug (given its usage and known risks), it raises concern that they might be under-reporting. Conversely, if FDA finds cases in FAERS that a company should have reported but didn't (for instance, found via literature or other sources), it can lead to inspection findings.

- **Responding to inquiries:** FDA frequently gets inquiries from healthcare providers, researchers, or the media about drug safety issues. FAERS data are used to respond (with appropriate caveats) – e.g., how many reports of a certain adverse event exist for Drug X. These numbers often enter the public domain via FOIA requests or communications.

Public Access to FAERS Data: A major commitment of the FDA has been to improve transparency of adverse event data. Since the mid-2000s, the agency has provided multiple avenues for the public to access FAERS information:

- **Quarterly Data Extracts:** FDA posts FAERS case data files on its website for each quarter (since 2004). These are available in ASCII text (and more recently XML) format, containing anonymized case details (with personal identifiers removed). Researchers can download these and load into databases for analysis. The data files are segmented (demo, drug, reac, etc.) and can be quite large – reflecting thousands of reports per quarter. FDA provides a data dictionary to help interpret fields.

- **FAERS Public Dashboard:** Launched in September 2017, the FAERS Public Dashboard is a user-friendly web interface (hosted on FDA's website) that allows interactive querying of the FAERS database fda.gov. Through the dashboard, users can search by drug name, reaction, patient age, report year, outcome, etc., and generate dynamic charts and tables. It lowers the barrier for healthcare professionals or even patients to see aggregated safety data without needing database expertise. For example, one can quickly find how many reports of kidney failure have been submitted for Drug Y in the past year, etc. The dashboard updates quarterly (with a short lag) and includes data from 1969 up to the most recent available quarter fda.gov journals.sagepub.com. This initiative was part of FDA's push for greater transparency and was praised for making a very complex dataset accessible to non-experts. *(Notably, in response to emergent needs like COVID-19 therapies, FDA even launched special public dashboards focused on EUA (Emergency Use Authorization) products to monitor their safety in near real-time youtube.com.)*

- **OpenFDA API:** FDA also provides an **OpenFDA** platform – a set of APIs (Application Programming Interfaces) that allow developers and researchers to query FAERS data programmatically open.fda.gov open.fda.gov. OpenFDA FAERS data starts from 2014 (when OpenFDA began) and is updated quarterly. It outputs data in JSON format for easy integration into software applications. This has enabled the creation of third-party apps and visualizations of FAERS data.

- **FDA Adverse Event Reporting System Search (FAERS)**: Before the dashboard, FDA had an online search tool (AERS Search) but it was less user-friendly. The modern dashboard supersedes it.

When using FAERS public data, FDA **cautions users**: a report in FAERS does **not prove causation**, and numbers of reports cannot be taken as incidence of a problem en.wikipedia.org. The data have limitations (see Section 7). Nonetheless, academics, pharmacovigilance analysts, and even investors mine FAERS for signals. For instance, several peer-reviewed studies have used FAERS to identify disproportional reporting of certain adverse events leading to hypothesis generation (e.g., signal of an issue with a drug class). Organizations like the Institute for Safe Medication Practices (ISMP) publish a regular *QuarterWatch* report, which analyzes FAERS data to highlight emerging safety concerns. The availability of raw data has empowered external surveillance – effectively crowdsourcing pharmacovigilance analysis.

Data Restrictions: Certain aspects of FAERS data are **not public** due to privacy or proprietary concerns. Individual case narratives (the verbatim descriptions) are generally not released publicly to protect patient confidentiality. Personal identifiers (names, addresses) are stripped. Also, manufacturer identities for each case may be hidden in public data. However, researchers can request more detailed data or specific case narratives via **Freedom of Information Act (FOIA)** requests. The FDA often provides redacted narratives on request, which can be useful for in-depth analysis. Additionally, some data reside in **"protected" databases**: e.g., vaccine adverse event reports go to VAERS (managed with CDC) which has its own public interface; device events go to MAUDE. But for drugs/therapeutics, FAERS is the central repository.

Regulatory Decision Examples: FAERS data have played a role in many concrete regulatory decisions. For example, FDA's decision in 2013 to issue new warnings and dosing restrictions for zolpidem (Ambien) was influenced by FAERS cases of next-morning impairment (leading to accidents). The decision to withdraw the painkiller rofecoxib (Vioxx) in 2004, although primarily

prompted by clinical trial data, was supported by an accumulation of cardiovascular adverse event reports in AERS latimes.com latimes.com. The antidepressant suicidality warning in young people (Black Box added in 2004) was in part triggered by spontaneous reports and case series analysis. These examples show how **FAERS is used in concert with other data** (clinical studies, epidemiology) to drive safety actions. Typically, FAERS provides the *signal* and initial evidence, which may then be investigated via formal epidemiological studies (often using FDA's Sentinel system or other databases) before major regulatory moves. FDA's reviewers have an internal safety signaling workflow where FAERS signal -> review -> if signal is credible, it goes to the **Safety Signal Tracking system** and possibly to the **Pharmacovigilance Action Signal Evaluation (PASE) team**, and if warranted, to the **Drug Safety Oversight Board (DSB)** and/or an **Advisory Committee**. At each of those stages, FAERS data (counts, case narratives) are scrutinized.

In summary, **data from AERS/FAERS is actively leveraged both internally and externally**. Internally, it guides FDA's ongoing assessment of drug safety and regulatory interventions. Externally, it is shared to enable transparency, independent analysis, and public trust that safety issues are not being hidden. FAERS has essentially become a shared resource for the global pharmacovigilance community, albeit one that must be interpreted with caution.

6. Case Studies: Impact of AERS Data on Drug Safety

To illustrate the real-world impact of AERS/FAERS, this section highlights a few **notable case studies** where spontaneous adverse event reports led to significant regulatory action or safety interventions:

- **Troglitazone (Rezulin) – Liver Toxicity:** Troglitazone was a diabetes drug (a thiazolidinedione) approved in March 1997. Pre-approval trials had seen a few reversible liver enzyme elevations, but nothing alarming. After approval, however, the AERS quickly began accumulating reports of serious liver injury. By **October 1997 (just ~7 months on market)**, FDA had received **35 reports of idiosyncratic hepatocellular injury** with troglitazone, including one case requiring liver transplant and one death medscape.com. This was a clear signal emerging far earlier than expected. In response, FDA and the manufacturer (Parke-Davis) in late 1997 strengthened Rezulin's labeling with a new **"Warnings" section about hepatotoxicity** and recommended liver function monitoring medscape.com medscape.com. Despite these measures, reports continued into 1998, including additional deaths from liver failure – some in patients who may not have been adequately monitored medscape.com. By mid-1998, the estimated reporting rate for life-threatening hepatic events was about 1 case per 60,000 patients medscape.com, which was very concerning given the large patient population. FDA again responded by **extending the liver monitoring recommendations (label change July 1998)** and narrowing the drug's indication. In 1999, two newer (and seemingly safer) drugs in the same class (rosiglitazone and pioglitazone) were approved, allowing FDA to reconsider troglitazone's place. In early 2000, after reviewing all the data – notably that the new alternatives did not show the same liver toxicity profile – FDA convened an advisory committee. The accumulating AERS evidence tipped the balance. In **March 2000**, FDA requested the removal of troglitazone from the market medscape.com, and the manufacturer agreed, withdrawing Rezulin. This case exemplifies how **MedWatch reports alerted FDA within months of approval** to a lethal risk, prompting iterative risk management (warnings, Dear Doctor letters) and ultimately a withdrawal when the risk proved unmitigable medscape.com. Had those 35 initial reports not been submitted, the fatalities might have continued unchecked for much longer. Troglitazone's withdrawal was one of the first high-profile cases directly attributable to the AERS signaling process.

- **Cisapride (Propulsid) – Cardiac Arrhythmias:** Cisapride, a pro-motility drug for nighttime heartburn, was approved in 1993. Even during its first few years, AERS data showed some cardiac adverse events (QT prolongation, arrhythmias). FDA repeatedly updated cisapride's label – **five separate labeling changes between 1995 and 1999** – to restrict use and add contraindications as reports came in medscape.com medscape.com. Despite risk management steps (contraindicating cisapride in patients with certain conditions or on interacting drugs), serious **arrhythmias including Torsade de Pointes and sudden death** kept occurring in clinical practice. By December 31, 1999, FDA had on record **341 cases of serious heart rhythm abnormalities with cisapride, including 80 deaths** medscape.com. This was an alarming number for a drug that wasn't life-saving. Many cases involved patients who had risk factors or were on contraindicated medications (meaning the safety warnings weren't fully preventing dangerous use). In January 2000, FDA – in conjunction with the manufacturer (Janssen) – issued a further alert advising ECG screening before cisapride use medscape.com. Nevertheless, **reports continued to stream in** of arrhythmias and fatalities, even in patients who apparently met the screening criteria. Facing mounting evidence that the risk could not be controlled in general practice, Janssen and FDA agreed to withdraw cisapride. In March 2000, FDA announced that **Propulsid would be pulled from general sale as of July 14, 2000**, making it available only via a limited-access IND program for those with no alternatives medscape.com. This effective removal was directly driven by the accumulation of AERS reports. Cisapride's case is often cited in pharmacovigilance as an example of "**labeling inadequacy**" – i.e., even 5 warning revisions couldn't mitigate the risk, and the spontaneous reports (over 300 serious cases) were pivotal in forcing a market withdrawal for safety. The cisapride saga also pushed regulators to demand more thorough pre-marketing cardiac safety studies for similar drugs.

- **Cerivastatin (Baycol) – Rhabdomyolysis:** Cerivastatin was a cholesterol-lowering statin introduced in 1998. While all statins carry a low risk of muscle injury (rhabdomyolysis), within months of Baycol's launch, AERS data indicated **a disproportionately high rate of rhabdomyolysis**, especially when cerivastatin was combined with gemfibrozil (another lipid-lowerer) latimes.com latimes.com. In the first year, several deaths from rhabdomyolysis were reported. FDA and the manufacturer (Bayer) reacted by contraindicating the combo with gemfibrozil and issuing warnings in late 1999 latimes.com. Despite that, cases kept coming – including fatalities – even on cerivastatin alone at higher doses. By mid-2001, AERS had about **52 deaths** confirmed due to cerivastatin-associated rhabdomyolysis (and thousands of reports of muscle damage) trialsjournal.biomedcentral.com. This was far beyond what was seen with other statins. In August 2001, Bayer "voluntarily" withdrew Baycol worldwide, in agreement with FDA cdn.who.int cdn.who.int. A later analysis showed that the FAERS data signaled trouble as early as 3 months post-launch (with 7 serious cases in that span) latimes.com, raising questions if action could have come sooner. Nonetheless, **the decision to withdraw was heavily influenced by the pattern and severity of AERS reports**, which showed Baycol had a ~10-fold higher reporting rate of severe muscle injury than other statins latimes.com latimes.com. The Baycol case underscored how critical it is to detect "**disproportionate toxicity**" in a drug class.

- **Rofecoxib (Vioxx) – Cardiovascular Events:** Rofecoxib's withdrawal in 2004 is often attributed primarily to a randomized trial (the APPROVe study) showing increased heart attacks. However, it's worth noting that the FDA's AERS had accumulated numerous reports of myocardial infarction and stroke in patients on rofecoxib even before 2004. In 2001, an FDA safety officer (Dr. David Graham) used AERS and other data to estimate an elevated risk, but interpretation was confounded by the drug's widespread use. The decisive evidence came from clinical data, but **AERS provided supporting real-world evidence** that cardiovascular thrombotic events were being seen in practice. The subsequent controversy led to changes in how FDA monitors for "common but serious" adverse events – often requiring a combination of FAERS signal detection and epidemiological studies (via Sentinel or others).

- **Drug-Drug Interaction Signals:** FAERS has also revealed critical drug interaction risks. For example, the discovery that the antihistamine terfenadine (Seldane) could cause fatal arrhythmias in combination with erythromycin or ketoconazole in the 1990s was aided by case reports in AERS. Those reports, combined with in vitro studies, led to Seldane's removal in 1997. Similarly, FAERS helped identify the interaction between SSRIs and triptans causing serotonin syndrome (leading to a warning in 2006), and between clopidogrel and PPIs reducing efficacy. Each of these came to light because practitioners or companies reported clusters of adverse events that pointed to an interaction.

These case studies demonstrate a few general points: **(1)** AERS/FAERS often detects signals within the first year or two of marketing – a period often called the "**Weber effect**" where reporting peaks for new drugs. Early signals (troglitazone, cerivastatin) can be life-saving if acted upon. **(2)** Regulatory responses can be incremental: strengthen warnings, restrict use, and only if needed, withdraw – with each step guided by incoming data. **(3)** Many signals involve **serious events that were too rare to observe in clinical trials** (e.g., 1 in 10,000 incidence), highlighting FAERS's role in uncovering rare risks. **(4)** Causality assessment is difficult (as FAERS lacks control groups), but when a clear clinical syndrome repeatedly appears and no other explanation fits, the "weight of evidence" from case series can be compelling. **(5)** International

collaboration matters: Often the FDA learned of some cases from overseas (via foreign regulators or literature) which got integrated into AERS; likewise, FDA's actions informed other countries' decisions.

In all, **AERS data have prompted label changes for hundreds of drugs and the withdrawal of dozens of products over the decades ashp.org ashp.org**. The system's effectiveness is exemplified by these cases where patient harm was mitigated by detecting the signal and taking action. Each adverse event report, as FDA emphasizes, can make a difference – *"a single well-documented case report can lead to a drug safety breakthrough"*. The troglitazone case – one report of liver failure leading to a transplant – arguably saved many lives by triggering early warnings.

7. Limitations and Challenges of AERS

While AERS/FAERS is an indispensable tool, it has well-recognized limitations that pose challenges to interpreting the data and using it optimally for public health decisions:

Under-Reporting: Perhaps the biggest challenge is that only a small fraction of actual adverse events are reported to the system. It's often cited that **FDA receives reports for <10% of adverse events**, and possibly **less than 1% of all serious events** pmc.ncbi.nlm.nih.gov. There are multiple reasons for under-reporting: health professionals may not link the event to the drug (especially if it's a common problem in general), they may assume someone else will report it, or they may simply lack time. Patients often don't know they can or should report, or might only tell their doctor (and the doctor might not forward it). This means FAERS data cannot be used to calculate true incidence rates of adverse effects en.wikipedia.org. A spike in FAERS reports of an event doesn't necessarily mean the event is happening more – it might mean more are being reported. **Under-reporting is variable**: serious, unusual events are more likely to be reported than mild or expected ones. Newly marketed drugs often have relatively higher reporting (due to heightened awareness), whereas older drugs' events might be under-reported (the so-called "Weber effect" of declining reporting over time). The FDA tries to combat under-reporting via outreach (MedWatch campaigns, etc.), but it remains a fundamental limitation that FAERS captures only the "tip of the iceberg" of drug safety problems.

Reporting Biases: The data in AERS are subject to various biases that can distort signal detection. **Stimulated reporting** occurs when publicity or emerging concerns cause a flood of reports. For example, if a safety alert is issued about Drug X causing kidney injury, patients and doctors may suddenly send in historical and new cases of kidney injury on Drug X, creating a spike unrelated to a true change in frequency. Media coverage of an issue can greatly increase reporting (sometimes termed the "notoriety effect"). Conversely, **lack of awareness** can lead to under-reporting of certain events for years. There's also **reporting bias related to a drug's newness**: new drugs often see a flurry of reports (both because every adverse event is "news" and because manufacturers are very vigilant in early phase of marketing) – this can make new

drugs look riskier in FAERS than older drugs, not necessarily because they are, but because of differential reporting rates en.wikipedia.org. Another bias is **comorbidity/confounding**: very sick patients tend to be on many drugs, so adverse events in them might get attributed to a drug by suspicion but could be disease-related or due to another drug. FAERS reports rely on the reporter's suspicions of causality, which may not always be correct (they might report all drugs the patient was on, or just one they think is culprit – either way can bias analysis).

Duplicate and Incomplete Data: As mentioned, **duplicate reports** are common. The same adverse event might be reported by the patient to FDA and by the physician to the company (and then to FDA), resulting in two entries. FDA deduplication efforts are imperfect; public data likely contain some duplicates, which can inflate counts. Also, **follow-up reports** can appear as separate entries if not properly linked. In AERS's "legacy" days, case matching algorithms had to be applied by researchers to consolidate duplicates pmc.ncbi.nlm.nih.gov. **Incomplete information** is another frequent issue: Many reports lack critical details – e.g., no concomitant medication list, or incomplete medical history, or the exact timing of drug exposure relative to event is missing. Some reports might just say "Patient died" without clear cause. This makes causality assessment difficult. Additionally, **quality of reports varies** widely: some are thorough (especially those from manufacturers or devoted clinicians), others are sketchy (a single sentence from a consumer).

No Certainty of Causation: AERS is a **spontaneous reporting system**, so it inherently cannot prove that the drug caused the event. As FDA reminds users, **the existence of a report doesn't establish causality** fda.gov. Patients on medications often have underlying illnesses or other risk factors. FAERS lacks a comparison group of non-exposed people, so one cannot readily distinguish drug-caused events from background incidence. For example, if 100 heart attacks are reported in patients on Drug Y, is that more than expected by chance? It's hard to say without knowing how many patients in total take Drug Y (denominator problem) and what their baseline risk is. This is why signals from FAERS are considered hypothesis-generating, not confirmatory. Regulators often need to turn to epidemiological studies or controlled data to confirm a signal's reality and magnitude en.wikipedia.org. However, certain adverse events with clear drug "signatures" (like anaphylaxis right after dose, or a unique syndrome in a plausible timeframe) can be strongly suggestive even from single case reports – but those are exceptions.

Incidence and Reporting Rates: As noted, FAERS cannot be used to calculate **incidence** or frequency of an adverse event in the population en.wikipedia.org. The numerator (reports) is incomplete and biased, and the denominator (total patients exposed) is often unknown to FDA (they may have sales data approximations, but not precise patient counts or usage patterns). This complicates risk assessment. One work-around is using reporting odds or proportional ratios internally (comparing within FAERS: does Drug A have a higher proportion of liver injury reports than all other drugs?). That's useful for signal detection but still doesn't give absolute risk. FDA's Sentinel initiative (see Section 9) was in part to address this limitation by providing databases where both exposure and outcome are known, to calculate real incidence.

Temporal Trends and Weber Effect: There is a phenomenon observed where adverse event reporting for a new drug often peaks in its second year post-launch and then declines (Weber effect). This might be due to initial extensive use and intense reporting interest, which wanes as issues become known. The decline may mislead one to think the drug got "safer" later, when in fact it's just less reported. Conversely, a sudden increase in reports might not mean the drug got more dangerous – it could be due to stimulated reporting (e.g., increased awareness). Analysts must carefully account for such trends when interpreting FAERS data.

Biases in Who Reports: Certain adverse events are more likely to be reported by certain reporters. **Physicians** might under-report things they consider "known" (e.g., common side effects), but are more likely to report unusual or severe reactions. **Patients** might report effects that impact quality of life (like sexual dysfunction, or withdrawal symptoms) that doctors might not report. **Lawyers** may report cases that turn into lawsuits (which could bias towards severe outcomes). Also, some companies have more robust surveillance than others, possibly affecting the volume of reports from their products (differences in company engagement can mimic differences in drug safety).

Data Overload and Noise: As FAERS has grown, distinguishing meaningful signals from background "noise" is harder. There are many coincidental drug-event associations reported. With millions of reports, **statistical noise** can produce false-positive signals. For instance, almost every drug in FAERS has at least one report of "death" simply because patients die for various reasons – disproportionality analysis helps filter, but not perfectly. On the flip side, *data overload* can lead to missed signals if not analyzed promptly – an important signal could be buried among thousands of reports. FDA has limited staff relative to the data volume, so prioritization algorithms are crucial.

Quality of Coding: Although MedDRA provides a standard, the **quality of coding** can affect analysis. If reporters choose overly general terms (or coders map to high-level terms inconsistently), signals might be masked. For example, if liver failure cases are coded sometimes as "hepatic failure" and sometimes as "hepatic necrosis" or "liver disorder", the counts for any one term may seem low unless grouped appropriately. FDA analysts have to use groupings like SMQs (Standardized MedDRA Queries) to capture broad concepts. Incomplete coding of drug names (e.g., misspellings) can lead to under-counting events for a drug until data cleaning is done pmc.ncbi.nlm.nih.gov.

Legal and Causality Considerations: Another challenge is **causality assessment** in FAERS. FDA does not require proof of causality in reports – **reports are accepted even if the relationship is only suspected** en.wikipedia.org. Thus, FAERS contains some reports that may eventually be deemed unrelated to the drug (after investigation). But FDA cannot dismiss reports a priori; they evaluate patterns. They also cannot easily quantify a drug's risk from FAERS alone; instead, they look at the *totality* of evidence. This is why for many signals, FDA uses FAERS as a starting point and then examines other data sources or asks the company for further analysis.

International Data Differences: FAERS primarily contains US reports (though manufacturers must submit foreign reports for US-marketed drugs as well). Meanwhile, other countries have their own databases (which may feed into WHO's VigiBase). Sometimes an issue might appear first in another country's data before FAERS (or vice versa). Harmonization efforts (Section 8) seek to improve inter-database communication, but historically, a safety problem could be visible in Europe's data but not flagged in FAERS because of differences in reporting rates or drug usage patterns.

Misuse of FAERS data: A practical challenge is preventing **misinterpretation** by the public or media. Raw FAERS data can be misused – e.g., someone finds "1000 reports of outcome X with Drug Y" and concludes drug Y is dangerous, without context that maybe 20 million people take drug Y and 1000 events might be background or duplicates. FDA often has to temper such interpretations by emphasizing the caveats en.wikipedia.org. They include disclaimers in dashboard and data files. Nonetheless, sensational headlines sometimes occur, which can skew public perception.

In summary, **AERS/FAERS is a powerful but imperfect tool**. Under-reporting means signals might be missed or delayed; biases mean some signals can be spurious. FDA addresses these limitations by *augmenting FAERS with other surveillance methods*: more active surveillance (Sentinel), targeted studies, and international data pooling. They also invest in improving data quality (encouraging complete reports, developing AI to assist coding – see Section 9). Understanding the limitations is crucial for anyone analyzing FAERS: it prevents drawing erroneous conclusions and highlights why FAERS signals are typically just the first step, not the final proof, in regulatory science. Despite its flaws, FAERS's strengths (breadth of data, real-world scope, early detection potential) ensure it remains the backbone of FDA pharmacovigilance, as long as its data are interpreted judiciously.

8. Global Comparisons and Harmonization Efforts

Medicines safety is a global endeavor. Adverse event reporting systems analogous to AERS exist around the world, and there are concerted efforts to harmonize these systems and share data for a more comprehensive view of drug safety. Here we compare AERS/FAERS to key international systems and highlight harmonization initiatives:

WHO Programme and VigiBase: The World Health Organization (WHO) coordinates an international pharmacovigilance effort called the **Program for International Drug Monitoring (PIDM)**, which started in 1968 (partly in response to thalidomide). Under this program, over 180 countries' regulatory agencies contribute their adverse event reports to a global database called **VigiBase**. VigiBase, maintained by the Uppsala Monitoring Centre (UMC) in Sweden, is the world's largest collection of ADR reports – as of February 2025, it holds **over 40 million reports** from member countries who-umc.org. Notably, the FDA (representing the US) is a member of the WHO program and does contribute data to VigiBase (FDA sends domestic reports, and

conversely, receives reports from other countries via the companies or WHO). VigiBase allows detection of global signals, especially for rare events that might be too infrequent in any single country's data. It also helps identify issues that might be specific to certain regions or genetic populations. The WHO program has facilitated **data standardization** by promoting the use of common terminologies (UMC created the WHO-ART dictionary originally, but many countries have shifted to MedDRA) and sharing **signal detection findings** among regulators. For example, if UMC's signal detection on VigiBase finds a notable disproportionality (a potential signal) for a drug, it issues a *"WHO Pharmaceutical Newsletter"* item or a Signal Report that is circulated to all member countries. This can prompt FDA and others to check their own data. A famous example: WHO's system picked up early signals of pergolide (a Parkinson's drug) causing valvular heart disease, which then FDA verified in AERS and led to action. Harmonization here means **being alerted to global signals quickly and using standardized methods to analyze them**.

EudraVigilance (EU): Europe has its own regional system: **EudraVigilance**, managed by the European Medicines Agency (EMA) since 2001. EudraVigilance serves the EU/EEA member states for both post-marketing and clinical trial (pre-marketing) adverse event reporting. It's similar in concept to FAERS but spans many countries, languages, and a regulatory network of national authorities. As of early 2024, EudraVigilance contained **over 29.3 million ICSRs** (16.9 million unique cases) ema.europa.eu – a dataset comparable to FAERS in size. The EU made reporting of certain adverse events mandatory for healthcare professionals in some countries (in addition to company reporting), and also allows **direct patient reporting** in the EU (since around 2012, EU law mandated members to accept patient reports). EudraVigilance uses the same ICH standards (MedDRA, E2B) as FAERS, which greatly facilitates **data exchange**. The EMA and FDA regularly exchange information: there is a confidentiality agreement and collaborative efforts so that signals detected in one system can be assessed in the other. For instance, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and FDA's OSE often share analyses. A safety issue might lead to a discussion at the International level if it affects multiple regions. The EU also has a public interface for safety data: **ADRreports.eu**, where one can view aggregated EudraVigilance data by drug and reaction (similar to FAERS dashboard). Harmonization through ICH ensures that a company can send an ICSR in the same format to FDA and EMA. This reduces discrepancies and duplicate work. Moreover, EMA and FDA both use MedDRA's multilingual capabilities to allow reporting in native languages but analysis in a unified medical terminology.

Other National Systems: Many other countries have their own databases – e.g., **Health Canada** has the Canada Vigilance database, **Japan's PMDA** has JADER, **Australia's TGA** has the DAEN, etc. These systems are all conceptually similar (collect spontaneous reports) but may have differences in reporting culture and rules. For example, France historically required all serious ADRs be reported by law, so their database had a high volume from hospitals. Some countries' systems feed directly into EudraVigilance (EU members report to both their agency and EudraVigilance). The UK's **Yellow Card Scheme** (one of the oldest, started in 1964)

continues today and also contributes to the WHO; it's notable for allowing patient reports early on.

CIOMS and ICH Harmonization: Global harmonization primarily comes via two entities:

- **CIOMS (Council for International Organizations of Medical Sciences):** CIOMS has issued influential consensus guidelines on pharmacovigilance. In the early 1990s, CIOMS Working Group I introduced the standard **CIOMS I reporting form** for adverse drug reaction reporting internationally, which essentially became the template for ICH's E2B fields. CIOMS also tackled periodic reporting (CIOMS II guided the development of periodic safety update reports – PSURs) and other topics (like CIOMS III on core safety data sheets). These efforts predate and complement formal ICH guidelines.

- **ICH (International Conference on Harmonisation, now the International Council for Harmonisation):** ICH brings together regulators and industry from the US, EU, and Japan (with others now participating) to harmonize drug regulatory guidelines. In the realm of pharmacovigilance, the **ICH E2 series** are key:

- **E2A:** Definitions and standards for expedited reporting (establishing what is a "serious" event, what is "unexpected", timelines – much of which FDA and others then codified in regulations) govinfo.gov.

- **E2B:** Data elements for transmission of ICSRs govinfo.gov. This standard defines the electronic message structure (fields, dictionaries) for case reports. FDA's AERS was built to adhere to ICH E2B from the start govinfo.gov. Over time, E2B has been revised – currently E2B(R3) is the latest, which FDA is now adopting fda.gov fda.gov. Having a common format allows a company to report the same case to multiple regulators easily and enables systems like FAERS and EudraVigilance to "talk" to each other.

- **E2C:** Periodic Safety Update Reports (PSUR) – now evolved into PBRERs. This harmonized the schedule and content of periodic reports so companies could submit a single global periodic report. FDA historically used its own Periodic Adverse Drug Experience Report (PADER) format, but post-ICH it accepts PSUR/PBRER for alignment.

- **E2D, E2E:** Cover topics like post-approval safety data management and pharmacovigilance planning.

- **M1 (MedDRA):** ICH also facilitated the creation of **MedDRA** as a globally accepted dictionary for adverse event coding govinfo.gov. MedDRA's maintenance is overseen by an ICH committee (now managed by an MSSO – Maintenance and Support Services Organization). FDA's adoption of MedDRA in AERS (replacing older terminologies) was a major harmonization milestone govinfo.gov. Now regulators worldwide speak the same "language" when discussing adverse events (e.g., "Stevens-Johnson Syndrome" has one MedDRA code used everywhere).

- **M2 (ESTRI):** Electronic Standards for Transfer of Regulatory Information – ensures that the technical infrastructure (like message exchange protocols) are compatible govinfo.gov. FDA's electronic gateway and EMA's EVWEB were developed per these standards.

These harmonization efforts mean that **pharmacovigilance is increasingly a collaborative, global enterprise**. A single case that occurs in one country can be rapidly known to others if it's serious enough. Companies have to submit serious unexpected reports from any market to all regulators where the product is approved (in practice, through E2B transmissions to each). This

creates overlapping safety nets. For example, if a serious event with a drug occurs in India, the manufacturer will report it to Indian authorities and also to FDA if the drug is US-approved – thus FAERS can contain foreign cases. Indeed, about **28% of reports in FAERS come from outside the US** pmc.ncbi.nlm.nih.gov, reflecting global data sharing.

Signal Detection Collaboration: Regulators often compare notes on signals. There are international forums (like the ICH Pharmacovigilance Working Group, or WHO's annual meetings of pharmacovigilance centers) where issues are discussed. If Europe is seeing a safety trend, they will ask the company and FDA if similar is seen in US data, and vice versa. A notable collaboration is in the area of **medicine exposure during pregnancy** – FDA's FAERS and EMA's data contribute to joint assessments of teratogenic risk. Another is **pediatric ADRs** – signals in children are so rare that pooling global data (via WHO or joint analyses) is crucial.

Differences in Systems: Despite harmonization, differences remain. For instance:

- **Reporting culture:** Some countries mandate certain reporting by HCPs (like France), whereas US relies on voluntary reporting. This can lead to differences in volume and type of reports.
- **Data access:** FDA and EMA have open public dashboards; some countries do not publicly share data or do so in limited ways.
- **Vaccines:** The U.S. splits out vaccine AE reporting to VAERS (joint FDA-CDC system), whereas some other countries include vaccines in their main database. WHO's VigiBase includes both drugs and vaccines, but FAERS is drugs/biologics only.
- **Resources:** Smaller regulatory agencies may not have dedicated signal detection teams; they rely on WHO's signals or literature. FDA and EMA have large teams and advanced data mining in-house.

ICH & WHO synergy: ICH harmonizes the technical and regulatory aspects, while WHO's program harmonizes the *practice* of pharmacovigilance, especially for developing countries, and provides a global view. The two complement each other. WHO also provides tools like **VigiLyze** for member countries to analyze VigiBase data (similar to how FDA has FAERS dashboard). Through WHO, a country with few resources can still detect if their country's reports plus global data suggest an issue.

In conclusion, **AERS/FAERS is part of a worldwide network of pharmacovigilance systems**. Harmonization efforts like ICH E2B and MedDRA have allowed seamless data exchange, and collaborative bodies like CIOMS, ICH, WHO ensure regulators are (more or less) on the same page regarding definitions and reporting practices. This greatly amplifies the power of any single country's safety monitoring – a signal can be strengthened by consistent findings in multiple regions. FDA's system, being one of the largest contributors of reports, plays a major role in the global safety dataset; conversely, FDA benefits from learning about issues identified abroad. Today's pharmacovigilance is truly without borders – a necessary reality in an era where drugs are globally marketed and post-market data from everywhere must be considered to fully understand a product's safety profile.

9. Future Directions for AERS/FAERS and Pharmacovigilance

Pharmacovigilance is evolving rapidly, and systems like FAERS must adapt to new technologies, data sources, and analytical methods. Looking ahead, several key trends and initiatives are shaping the future of AERS/FAERS:

Integration of Real-World Data (RWD) and Active Surveillance: Traditional spontaneous reporting will be increasingly supplemented by proactive mining of electronic health records (EHRs), insurance claims, and other real-world data to identify safety signals. The FDA's **Sentinel Initiative** (mandated by FDAAA 2007) is a flagship effort in this domain – essentially creating a giant distributed database of healthcare data (from insurers, healthcare systems, etc.) to monitor drug safety in near real-time. Sentinel has already met the goal of accessing data on over **100 million patients by 2012** fda.gov and continues to grow. Sentinel is used for targeted analyses, for example to investigate a signal that emerged from FAERS in a more quantitative way (providing incidence rates and relative risks by comparing users vs. non-users in claims data). The future vision is that **FAERS and Sentinel (and other RWD sources) work in tandem**: FAERS flags a potential issue, then an active surveillance query rapidly tests whether that issue is showing up at higher rates in clinical practice data. Alternatively, active surveillance might itself generate signals (especially for adverse events that are common background occurrences, like heart attacks, where spontaneous reports might not be useful). A likely future step is a closer **integration of FAERS with hospital EHR systems** – for instance, if a clinician notes an adverse reaction in an EHR, that could automatically generate a report to FAERS (with appropriate consent/privacy). Pilot projects are exploring this to reduce under-reporting. Real-world data can also enhance FAERS case quality – e.g., linking FAERS reports to patient records (with de-identification) to gather more details.

Advanced Analytics and Artificial Intelligence: With the sheer volume of data now in FAERS, FDA and others are turning to **machine learning (ML) and AI** to improve signal detection and data processing. AI can be applied in several ways:

- **Natural Language Processing (NLP):** Many FAERS reports contain narrative text (especially in the case descriptions). NLP algorithms can scan through narrative to identify relevant clinical details or even identify un-coded adverse events mentioned in the text that the coder might have missed. For example, NLP might pick out that "the patient's skin turned yellow" in a narrative, suggesting jaundice, and ensure it's coded properly as "hyperbilirubinemia" if not already. NLP can also help in case clustering – grouping similar case reports together.

- **Auto-Coding of Reports:** Currently, coding each report (mapping free-text to MedDRA terms) is labor-intensive. AI could assist by automatically suggesting MedDRA terms. In fact, FDA researchers have identified that two key opportunities for AI in FAERS are **(A)** improving **MedDRA coding** of incoming reports and **(B)** enhancing the **quality assurance review** of reports frontiersin.org. An AI system could potentially learn from past coding decisions and code new reports consistently, or flag when a report's coding seems inconsistent with the text.

- **Signal Detection Algorithms:** Traditional disproportionality methods generate many signals (with high noise). Machine learning models (like logistic regression, random forests, etc.) have been tested on FAERS data to see if they can better differentiate true signals from noise by considering multiple features of data simultaneously pmc.ncbi.nlm.nih.gov pmc.ncbi.nlm.nih.gov. Research suggests that more complex algorithms (e.g. LR) can outperform simple disproportionality in certain validation studies pmc.ncbi.nlm.nih.gov. In the future, FDA might use a hybrid of methods – continuing disproportionality for transparency, but using ML to prioritize which signals to review first based on likelihood of being real.

- **Predictive Safety and AI:** The concept of *"predictive pharmacovigilance"* is emerging – using algorithms on multi-source data (clinical trials, structure-activity relationships, FAERS, literature) to predict what adverse events might occur even before they are seen, or to detect signals extremely early. AI could identify subtle patterns (e.g., a drug where all the adverse event reports, though few, have a common thread like all in young females, etc.) that might be missed by human eyeballing.

- **Automation in Triage:** AI could help prioritize incoming reports. Currently, all serious reports are looked at, but within non-serious, there could be hidden clues. An AI might flag a non-serious report that has an unusual feature as worth a closer look. Also, AI could help link duplicate reports (by matching based on case details) more efficiently than current algorithms.

FDA is actively exploring these technologies. For example, FDA's Center for Drug Evaluation and Research (CDER) has an informatics group working on **"Artificial Intelligence in Pharmacovigilance"** to see how tools can be integrated without missing signals or adding false signals pmc.ncbi.nlm.nih.gov. There are challenges: AI algorithms need training data, and in pharmacovigilance, labeled datasets (with known causal vs non-causal cases) are limited. Nonetheless, FDA has collaborated in public challenges (like an NLP challenge on FAERS data) to stimulate development.

Enhancing Reporting and Data Quality: The future will also see efforts to improve the **quality and richness of reports**. For instance, incorporating **electronic health record extraction** – rather than a clinician manually filling a MedWatch form, a system might pull structured data from the EHR (labs, meds, outcomes) to attach to the report. This could greatly enrich data (fewer "unknown" fields for things like doses, dates, etc.). Additionally, FDA might incorporate patient-generated data streams – e.g., reports via mobile apps where patients can also allow use of fitness tracker data or other contextual info if relevant. The goal is to move beyond the relatively sparse data in a typical FAERS report to a more comprehensive adverse event " dossier " that could be analyzed. However, privacy and data standardization issues come along with that.

Global Data Integration: We can expect even tighter **global collaboration** in signal detection. There may be a future where a single global pharmacovigilance portal exists for regulators to jointly evaluate signals using data from all regions in real-time. While jurisdiction and data privacy issues make a single global database for public use unlikely soon, behind the scenes the sharing might increase. Already, EMA and FDA have run joint signal workups on several drugs. Harmonizing reporting requirements globally (so that what must be reported and when is

uniform) is another possible outcome – making it easier for companies and clearer for healthcare providers internationally.

Social Media and New Data Sources: Beyond EHRs and claims, there's interest in mining **social media, patient forums, and wearables** for adverse event information (sometimes called "Web-ADR"). People often share experiences on Twitter, Reddit, health forums about side effects. AI can sift through these unstructured data to find mentions of drug names and adverse effects. While this is still experimental, it could provide an earlier or complementary signal source, especially for issues that patients discuss but don't formally report (for instance, patient-reported issues like mood effects or quality-of-life effects might surface on social media first). FDA has done some research in this area but is cautious due to noise and validation problems.

Electronic Reporting Worldwide: As more countries adopt electronic ICSR reporting, the speed of pharmacovigilance improves. FDA in 2024 began accepting even **premarket IND safety reports electronically in E2B(R3)** fda.gov, which means clinical trial SUSAR reports will be databased similarly. Over the next few years, essentially **all pharmacovigilance reporting will be digital and structured**, phasing out paper entirely. This paves the way for near-real-time analysis across systems.

Pharmacogenomics and Precision PV: A future area is incorporating **pharmacogenomic data** into adverse event analysis. E.g., if genetic data (when available) could be included in reports or linked, one might detect that a certain HLA allele is present in all reports of liver injury for a drug, pointing to a genetic susceptibility (like was found for abacavir hypersensitivity). As precision medicine advances, PV systems may need to capture certain patient biomarkers to allow detecting subpopulation-specific risks.

Transparency and Communication: In the future, not only will data be more available, but communication of risk will be more targeted. For example, if an emerging signal is seen, regulators might use modern channels (text alerts, app notifications) to reach healthcare providers and even patients directly (opt-in systems) rather than the relatively passive web postings used today. Patients might also be able to query personalized risk (with appropriate safeguards) – e.g., "Given my profile and meds, are there any new safety advisories?" which would require integration of PV data with clinical decision support.

Continuous Benefit-Risk Assessment: Ultimately, tools like FAERS are evolving from a reactive model (report comes in, signal detected, action) to a more continuous **benefit-risk monitoring** model. The FDA has spoken about leveraging "Big Data" and AI not just to find risks, but to contextualize them with benefits and patient preferences. For instance, linking efficacy data or patient-reported outcomes data with safety data to assess overall impact. While FAERS itself is just safety data, its future may involve connecting to benefit data (e.g., via registries or other studies) to allow a more holistic regulatory decision framework.

In summary, the **future of AERS/FAERS** will be defined by **technological enhancement and data integration**: AI to analyze reports smarter and faster, new data sources (EHRs, social

media) to capture events that go unreported, and global data sharing to catch signals anywhere they occur. These advances aim to address current limitations – e.g., under-reporting might be mitigated by EHR auto-reports; causality might be clearer with active surveillance data linkage; duplicate/incomplete data might be resolved with AI and better tools.

The FDA's vision, as reflected in strategic plans, is a **"21st Century Pharmacovigilance System"** that is not just passively collecting reports but proactively detecting and even predicting drug safety issues, using all available data. In this vision, AERS/FAERS remains a central component – a hub of curated safety reports – but one that is augmented by a web of complementary systems (Sentinel's big data, international databases, AI analytics). The result should be *earlier detection of safety problems, more precise understanding of risk factors, and faster, more tailored regulatory interventions* to protect patients while minimizing unnecessary alarm. FAERS is poised to evolve from a large but somewhat siloed database into an **interconnected, intelligent pharmacovigilance platform** for the future.

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(Additional sources available upon request)

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