

5.1 International Classification of Diseases

Safety data must be sorted before it can be counted, and the world's sorting frame for diseases is the **International Classification of Diseases (ICD)**, maintained by the WHO and now in its eleventh revision, ICD 11. Every disease, injury and cause of death carries an ICD code, so diagnoses written in any language and style resolve into standardized entries that statistics can aggregate across hospitals, regions and countries. In pharmacovigilance the ICD complements MedDRA: MedDRA codes the reaction as reported and coded for regulatory work, while ICD coding supports mortality and morbidity statistics, hospital records research and the pharmacoepidemiological studies of Unit 6, whose databases are built on ICD coded diagnoses. One vocabulary for the event, another for the disease burden: both exist so that comparisons are between like and like.

5.2 International Nonproprietary Names for drugs

Drugs need the same treatment as diseases. An **International Nonproprietary Name (INN)** is the WHO assigned generic name by which a pharmaceutical substance is known worldwide, one substance, one name, displacing the thicket of brand names and national variants: the substance sold under dozens of trade names is paracetamol in INN terms in most of the world, acetaminophen in the United States Pharmacopoeia tradition. INNs are built with stems, suffixes and prefixes that declare pharmacological family, so a name itself carries information: the stem "olol" announces a beta blocker, "pril" an ACE inhibitor. In pharmacovigilance the INN is the aggregation key of section 4.6: reports against every brand of a substance meet in the database under its INN, and a signal for the substance emerges that no single brand's reports could have shown.

5.3 Passive surveillance: the spontaneous reporting foundation

Passive surveillance is the system that waits for reports: healthcare professionals and patients who suspect a reaction complete a report, and the system receives whatever the field sends it. The spontaneous reporting system of section 5.8 is its machinery. Passive surveillance is cheap, covers every drug and every patient in the country, runs for the product's whole life, and is unmatched at generating hypotheses about rare and unexpected harm, since any observant clinician anywhere can contribute a case that no study would have been funded to find. Its limitations are structural and must be taught with it: **under reporting**, the celebrated weakness, only a small fraction of reactions, often estimated in the literature at well under one in ten, are ever reported, and reporting is uneven, rising after publicity and for new drugs, and falling for familiar and mild reactions; **no denominator**, the system counts reports, not users, so it cannot by itself give incidence; and **variable quality**, reports arrive with missing doses, dates and histories that assessment must chase. Passive surveillance finds signals; it cannot measure risks. Measurement belongs to the active and analytic methods that follow.

5.4 Active surveillance

Active surveillance goes out and looks. Instead of waiting for reports, the system solicits them: defined populations of drug users are identified and followed deliberately, through prescription event monitoring, in which prescribers are asked systematically about events in patients on a new drug; through registries that

enrol every exposed patient; through sentinel hospital sites with staff tasked to hunt reactions on the wards; and through routine record linkage of the databases of Unit 6. Because ascertainment is systematic, active systems can approach true incidence and characterize the exposed population that passive reporting lacks. The costs are money, organization and time, so active surveillance is deployed selectively: new drugs of wide expected use, drugs with a suspected serious problem, and special populations such as pregnancy, where exposure registries are the standard instrument.

Safety Surveillance: From Detection to Measurement

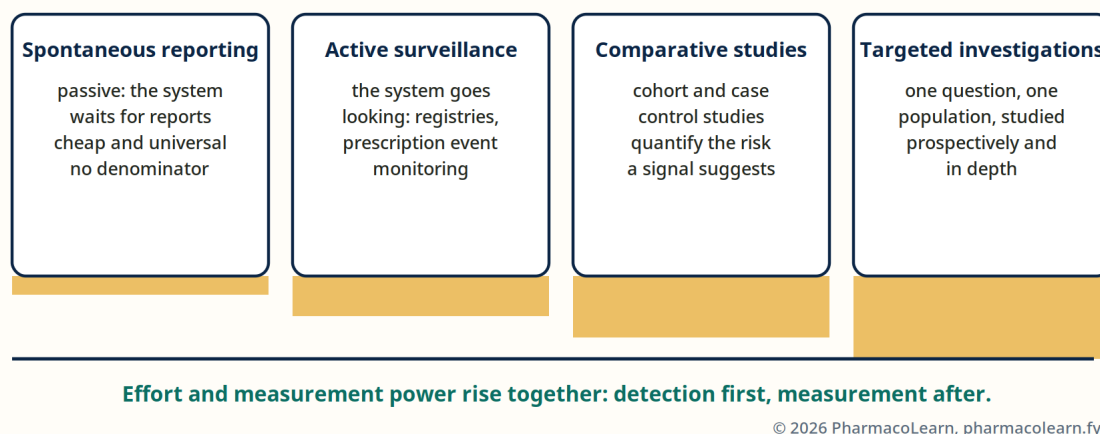


Figure: The methods of safety surveillance range from waiting for reports to following whole exposed populations, gaining measurement power as effort rises.

5.5 Comparative observational studies in safety evaluation

When a signal needs measuring, the observational designs of Unit 2 return as analytic instruments, now called **comparative observational studies**. Cohort studies compare incidence of the suspected harm in users and non users of the drug, or against users of an alternative drug for the same disease, the comparison that corrects for the disease itself causing the outcome. Case control studies test whether cases of a rare established harm were more often exposed, the design that confirmed several historic reactions in pregnancy and childhood. Their pharmacoepidemiological discipline, confounding control, bias analysis, and very large record databases, is Unit 6's subject; here they are placed in the toolkit as the methods that convert a spontaneous reporting suspicion into a quantified relative risk a regulator can act on.

5.6 Targeted clinical investigations

Between passive reporting and full epidemiology sits the **targeted clinical investigation**: a focused study, often small and quick, aimed at one defined safety question in one defined population. A cluster of reports suggesting liver injury leads to a study measuring liver enzymes prospectively in exposed patients; a question about a drug in renal impairment leads to a pharmacokinetic and tolerability study in that group; a suspected interaction leads to a formal interaction study. The investigation is targeted in question, population and measurement, and its place in the sequence is characteristic of good pharmacovigilance: signal from reports, quantification by observation, mechanism and boundaries by targeted study, then regulatory action proportioned to the assembled evidence.

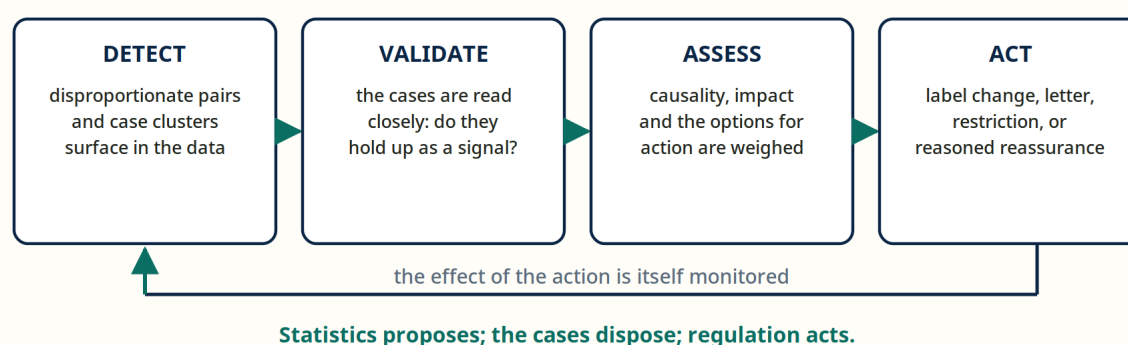
5.7 Vaccine safety surveillance

Vaccines break several assumptions of drug pharmacovigilance: they are given to healthy people, often children, in mass campaigns; the public tolerance for harm is therefore near zero; and coincidental events, illnesses that would have occurred anyway in the days after vaccination, are guaranteed in large numbers. **Vaccine safety surveillance** is built for this terrain. Its core event category is the **adverse event following immunization (AEFI)**: any untoward medical occurrence after immunization, not necessarily caused by it, classified by cause as vaccine product related, vaccine quality defect related, immunization error related, immunization anxiety related, or coincidental. India runs a dedicated AEFI surveillance system under its immunization programme, with district and state committees performing structured causality assessment of serious cases, because the cost of a mishandled scare is measured not only in individual harm but in collapsed vaccine coverage and returning disease. The lesson generalizes: causality communication is itself a safety intervention.

5.8 The spontaneous reporting system and reporting to regulatory authorities

The **spontaneous reporting system** is the organized machinery of passive surveillance: standard report forms distributed everywhere care is given; collection points in hospitals and pharmacovigilance centres; a national database; assessment; and feedback. A report qualifies as a valid individual case safety report when it carries the four minimum elements: **an identifiable patient, an identifiable reporter, a suspect product, and an event**. In India the reporter, professional or patient, completes the suspected ADR reporting form of PvPI; reports flow from ADR Monitoring Centres to the National Coordination Centre at IPC, where they are processed and transmitted to CDSCO for regulatory use and to VigiBase for the world's. Industry reports run on a parallel regulated track into the same authorities. Reporting guidelines, section 5.9, exist to raise the completeness and speed of this flow, because a spontaneous system's sensitivity is set less by its software than by the willingness of busy clinicians to spend three minutes on a form.

The Signal Management Cycle



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Figure: Signal management is a cycle: detection in accumulated data, validation against the cases, assessment of the evidence, and action whose effects are then monitored.

5.9 Guidelines for ADR reporting

Reporting guidelines answer the practitioner's four questions. **What to report**: any suspected adverse reaction, with emphasis on reactions that are serious, unexpected, or associated with new drugs, but without excluding the rest, since reporters cannot know in advance which case completes a pattern; in India all suspected reactions to all drugs, including those from traditional systems where the form allows, may be reported. **Who reports**: physicians, pharmacists, nurses, dentists and other healthcare professionals, and patients themselves, whose reports the Indian programme accepts directly. **When and where**: as soon as

the suspicion forms, to the nearest ADR Monitoring Centre, hospital pharmacovigilance unit, or directly to the national programme, using the standard form or its electronic equivalents; suspicion, not proven causality, is the reporting threshold, and waiting for certainty is how signals are strangled. **How completely:** with patient particulars in anonymized form, full drug details including dose, dates and batch where known, the reaction's onset, course, investigations and outcome, dechallenge and rechallenge information, and concomitant medicines and diseases, because the value of a report is set by its assessability, and an unassessable report is a signal that failed to arrive.

5.10 Argus: the industry safety database

Case reports at industry scale number in the hundreds of thousands, and the discipline runs on specialized safety databases. **Oracle Argus Safety**, universally called **Argus**, is the most widely deployed of them in pharmaceutical companies: a validated software system for the intake, processing, medical review, coding in MedDRA, duplicate checking, and regulatory submission of individual case safety reports, with the audit trails and electronic records controls that regulated software requires. Argus automates the clocks of section 4.9, flagging expedited deadlines, generates submissions in the international electronic format (the ICH E2B standard) to regulators, and holds the case data from which aggregate reports and signal detection draw. Knowing what Argus is belongs to this subject because a large fraction of M.Pharm pharmacovigilance employment consists of working inside it or its rivals.

5.11 Aris G and the family of safety systems

Aris G (styled ArisG), the safety system of ArisGlobal, is the other classic name the syllabus pairs with Argus: a pharmacovigilance database for case intake, processing, coding, reporting and signal support, used by companies and some regulatory and contract research organizations. The two systems differ in vendor, architecture and interface, not in function: both exist to keep every case valid, coded, assessed, submitted on time and auditable, and skills transfer between them. Around them stands a small family of related tools the working professional meets: electronic data capture and submission gateways through which cases pass to authorities, literature screening tools, and the signal detection platforms of section 5.13.

5.12 VigiFlow: the national centre workhorse

VigiFlow is the web based case management system provided by the Uppsala Monitoring Centre to national pharmacovigilance centres: a secure online tool in which a centre enters, codes, assesses and manages its individual case safety reports, and from which reports pass electronically into VigiBase, the WHO global database. PvPI's ADR Monitoring Centre network works in this ecosystem, so a case entered at a medical college in India becomes, after national processing, part of the world's pooled experience with that drug. VigiFlow's significance for the student is architectural: national systems need not buy industry scale software, because the WHO programme supplies a shared platform, one more way the international system lowers the cost of joining it.

5.13 Statistical methods for evaluating medication safety data

Case by case assessment reaches its limit where counts grow large; statistics takes over, not by replacing judgement but by ranking where judgement should look first. The working family is **disproportionality analysis**, which asks whether a drug event pair is reported more often than the database's background would predict. The standard measures compare the pair's share of the drug's reports with its share among all other drugs: the **proportional reporting ratio (PRR)** and the **reporting odds ratio (ROR)** work on the two by two table of reports, while Bayesian methods, the information component used with VigiBase and the empirical Bayes measures used with the FDA database, shrink unstable small counts toward the

background so that three reports do not outrank three thousand. A pair standing out disproportionately is a **statistical signal of disproportionate reporting**: an instruction to read the cases, not a verdict, since disproportionality is inflated by publicity, by newness and by the reporting biases of section 5.3. Around these sit the supporting crafts: duplicate detection, time to onset analysis, stratification by age, sex and region, and the review of observed to expected counts where exposure denominators exist. The craft's rule closes the unit and the subject's method: statistics proposes, cases dispose, epidemiology measures, and only then does regulation dispose finally.

FROM REPORT TO SIGNAL: THE EVALUATION LADDER

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Individual reports arrive (spontaneous, literature, studies)
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Case assessment: causality, seriousness, expectedness
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v
Disproportionality screening across the database
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v
Signal validation: do the cases, read closely, hold up?
|
v
Analytic studies and targeted investigations quantify risk
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v
Regulatory action and communication, then continued
monitoring of the action's effect
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