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MPL204T Clinical Research and Pharmacovigilance, M.Pharm Semester 2

Unit 4: Basic Aspects, Terminologies and Establishment of Pharmacovigilance

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4.1 What pharmacovigilance is

The WHO defines **pharmacovigilance** as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem. Each verb is a function: **detection** gathers reports of suspected harm; **assessment** weighs causality and importance; **understanding** characterizes who is at risk, by what mechanism and how often; **prevention** issues the warnings, labelling changes, restrictions and education that stop the next case. The discipline's product is not reports but decisions: a label amended, a dose revised, a population excluded, occasionally a drug withdrawn, and far more often, quiet reassurance that a medicine's balance remains favourable.

4.2 History and progress of pharmacovigilance

The modern discipline was born of one catastrophe and built by one system. In **1961** thalidomide, widely used in pregnancy, was linked by clinicians' case reports to an epidemic of limb reduction defects; the drug's withdrawal taught the permanent lesson that premarketing trials, small, short and conducted in selected patients, cannot exclude rare or delayed harm. Through the 1960s several countries built national reporting schemes, and in **1968 the WHO established its Programme for International Drug Monitoring**, pooling national reports into one global database so that a rare reaction invisible in any single country could become visible across many. Professionalization followed: the Uppsala Monitoring Centre in Sweden became the WHO collaborating centre operating the programme; standardized terminologies and, later, computerized individual case safety report management and statistical signal detection professionalized the work through the 1990s and 2000s; and the Indian programme of section 4.4 grew from a late start into one of the largest national systems. The arc of the history is from individual vigilance, to national systems, to a networked global one; the method, the suspected case report, has remained the atom throughout.

4.3 The significance of safety monitoring

Why must marketed drugs be watched at all, when licensing follows thousands of trial patients? Because arithmetic and reality conspire. A trial of three thousand patients will reliably show reactions occurring in about one patient in a thousand or more often; a reaction striking one in fifty thousand will almost certainly be missed, yet at ten million users it harms two hundred people. Trials are also short against chronic use, narrow against the elderly, the pregnant, the very young and the multiply ill who fill real practice, and clean against the interacting co medications real patients take. Safety monitoring therefore continues for the product's entire life, its intensity highest early, when knowledge is thinnest, and its justification permanent: every marketed medicine is, in this precise sense, still being studied.

4.4 Pharmacovigilance in India and international aspects

India joined the WHO Programme for International Drug Monitoring in 1998, and after early national efforts the durable system arrived with the **Pharmacovigilance Programme of India (PvPI)**, launched in 2010 by the Central Drugs Standard Control Organization and coordinated since 2011 by the **Indian Pharmacopoeia Commission (IPC), Ghaziabad**, as the National Coordination Centre. PvPI works

through a network of **ADR Monitoring Centres** in medical colleges and hospitals across the country, which collect reports from healthcare professionals and, increasingly, directly from patients, process them in the international reporting format, and transmit them to the national database and onward to the WHO global database. The programme also issues drug safety alerts and recommends regulatory action to CDSCO. Internationally, the architecture rhymes: national centres collect, the Uppsala Monitoring Centre pools and analyses globally, and regulators, the FDA in the United States, the EMA in Europe, CDSCO in India, act within their jurisdictions on shared evidence.

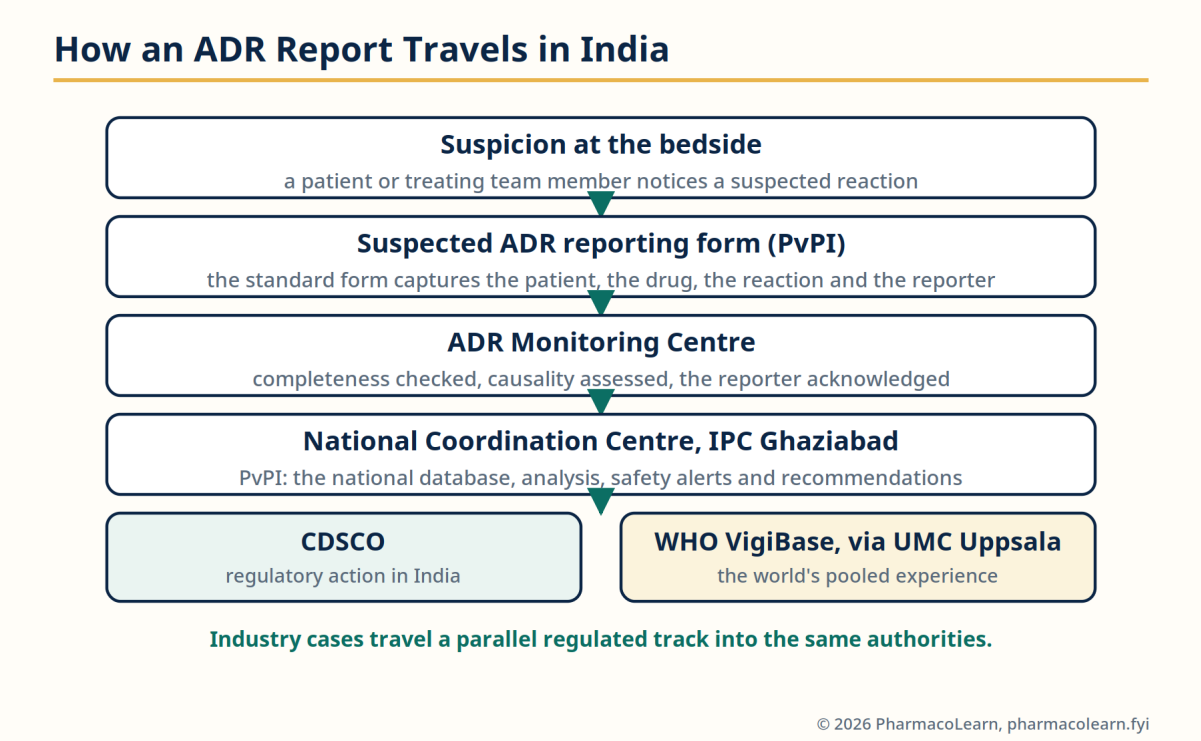

Figure: The journey of a suspected ADR report in India, from the reporter's form to the national programme and the WHO global database.

4.5 The WHO international drug monitoring programme

The **WHO Programme for International Drug Monitoring**, established in 1968, is the global collaboration of national pharmacovigilance centres, coordinated by WHO in Geneva with the **Uppsala Monitoring Centre (UMC)** as its operational arm. Member countries submit individual case safety reports in a common format; UMC maintains them in **VigiBase**, the global database holding tens of millions of reports, returns feedback and analyses to members, and supports the statistical signal detection of Unit 5. Membership obliges a country to run a national centre and a spontaneous reporting system; in return it receives the world's experience with its drugs, including signals first visible elsewhere. Most of the world's population is now covered by member programmes, and the programme's quiet achievement is standardization: one vocabulary, one report format, one database, so that a case reported in Ghaziabad can be analysed in Uppsala beside a case reported in Stockholm.

4.6 WHO and regulatory terminologies of ADR

Shared work requires shared words, and pharmacovigilance has built terminologies at three levels. **Reaction terms**: the WHO Adverse Reaction Terminology historically, and now **MedDRA**, the Medical Dictionary for Regulatory Activities, a hierarchical medical terminology (from system organ class down through high level group, high level and preferred terms to lowest level terms) into which every reported event is coded, so that a report written as "liver failure", "hepatic failure" or "liver function abnormal" in different places becomes one countable concept. **Drug names**: the WHO Drug Dictionary codes products

to the international nonproprietary names of Unit 5, so brand variants collapse to one substance. **Case definitions and seriousness criteria** follow ICH E2A, and causality language the categories of section 4.7. Terminology work looks clerical and is in fact the discipline's infrastructure: signal detection can only count what coding has made identical.

4.7 Evaluation of medication safety: causality assessment

A report asserts that a patient took a drug and suffered an event; evaluation asks whether the drug caused it. **Causality assessment** weighs, case by case, the time relationship (did the event follow the drug plausibly?), dechallenge and rechallenge, alternative explanations in disease and other drugs, prior knowledge of the reaction, and dose relationship. Two standard instruments structure the judgement. The **WHO-UMC system** sorts cases into categories: **certain, probable or likely, possible, unlikely, conditional or unclassified, and unassessable or unclassifiable**, according to how completely those tests are satisfied. The **Naranjo scale** scores ten questions about the case, previous reports, timing, dechallenge, rechallenge, alternatives, placebo response, drug levels, dose response and prior similar exposure, into a total read as definite, probable, possible or doubtful. Neither instrument manufactures certainty from a single case, and that is not their purpose: they make thousands of individual judgements consistent enough that the aggregate, a cluster of "probable" cases of the same rare event, can constitute a signal. Causality at case level, severity, seriousness, predictability and preventability together are the complete evaluation of a medication safety report, after which it is fit for the statistical methods of Unit 5.

4.8 Establishing a pharmacovigilance centre in a hospital

A hospital pharmacovigilance centre, in India typically an ADR Monitoring Centre under PvPI, is established by assembling the same elements anywhere: **sponsorship** from the institution's leadership and a named coordinator, usually a pharmacologist or clinical pharmacist; a **multidisciplinary ADR committee** drawing in clinicians of the major departments, pharmacy and nursing; **infrastructure**: the standard suspected ADR reporting form (in India the PvPI form), access to the reporting software, and a defined route for reports to travel to the national centre; **promotion**, because reporting is voluntary and competes with workload: launch meetings, posters, pocket reminders, a simple answer to the reporter's question "what happens to my report"; **feedback**, the element most often omitted and most decisive: reporters who receive acknowledgement, causality outcomes and safety news keep reporting, and those who report into silence stop; and **routine work**: ward rounds that hunt reactions, review of reports for completeness, causality assessment by the committee, monthly transmission and analysis, and periodic hospital bulletins. A centre is judged by sustained reporting quality, not by inauguration.

4.9 Pharmacovigilance in industry

For a marketing authorization holder, pharmacovigilance is a legal system, not a service. An industry pharmacovigilance unit must collect every adverse event its company learns of, from trials, literature, sales representatives' field reports, patient support programmes and the web; process each case against the minimum validity criteria (an identifiable patient, an identifiable reporter, a suspect drug and an event); assess seriousness, expectedness and causality; expedite serious cases to regulators within the prescribed clocks; maintain the company safety database (the systems of Unit 5); write the periodic aggregate reports that review the product's whole safety experience at intervals; and detect and evaluate signals continuously, feeding labelling changes and risk minimization measures back to regulators. Oversight is by named accountable officers and by regulatory inspection. The company's commercial interest and its safety duty point in opposite directions often enough that the system's design, independent reporting lines, audit, inspection, assumes the tension and engineers around it.

4.10 National programmes related to pharmacovigilance

National programmes are the state run form of the same work. PvPI is India's, described in section 4.4; its cousins include the FDA's MedWatch reporting programme feeding the FAERS database in the United States, and the Yellow Card scheme of the MHRA in the United Kingdom, the oldest national scheme of all, founded in 1964 directly after thalidomide. National programmes set reporting rules for their jurisdictions, run public and professional awareness, publish safety communications, and carry the country's cases into the WHO programme. Around the core drug programme sit allied schemes the syllabus touches through Unit 5, notably **vaccine safety surveillance** under the immunization programme, and specialized vigilance for medical devices, blood products and other product classes, collectively the vigilances, each with its own reporting form and centre but one shared logic.

4.11 Roles and responsibilities in pharmacovigilance

The system's duties distribute by position. **Healthcare professionals** detect and report: their case reports are the raw material, and no database substitutes for the clinician who connects a rash to a prescription. **Hospitals and their pharmacovigilance centres** collect, complete, assess and forward reports, and feed learning back to prescribers. **Industry** processes its products' cases worldwide, maintains databases, detects signals and reports to regulators on fixed clocks. **National centres and programmes** validate and pool national data, analyse, communicate and represent the country internationally. **Regulators** evaluate the assembled evidence and act: label changes, restricted indications, Dear Healthcare Professional letters, suspension or withdrawal. **The WHO programme and UMC** pool the world, standardize the language and return global analyses. **Patients and the public**, the newest recognized reporters, contribute reports directly in many systems including PvPI, and are the audience every communication finally serves. Pharmacovigilance works when each role trusts the next with its reports; it fails, characteristically, by silence at the first step.

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THE PHARMACOVIGILANCE CYCLE

  DETECT --> reports of suspected reactions are gathered
      |
      v
  ASSESS --> causality, seriousness, expectedness are judged
      |
      v
  UNDERSTAND --> patterns across cases: who, how often, why
      |
      v
  PREVENT --> warnings, labels, restrictions, education
      |
      +------> outcomes feed back into detection
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