INTRODUCTION TO PHARMACOVIGILANCE CONCEPTS AND GENERAL FRAMEWORK

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Pharmacovigilance (Drug Safety)

- Pharmakon (=drug) and vigilare (=keep watch).

Discipline and activities relating to the **detection, assessment, understanding and prevention & management effects** or any other drug-related problem

(WHO, 2002)

Pharmacovigilance. Aims

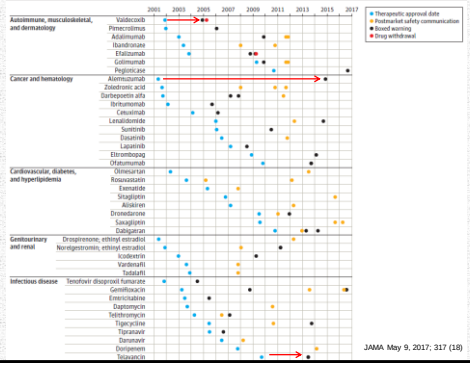
- **Early detection** of unknown safety problems
- Identification of **risk factors**
- **Quantification** of risks
- **Preventing** patients from being affected unnecessarily

Rational and Safe Use of Medicines, WHO

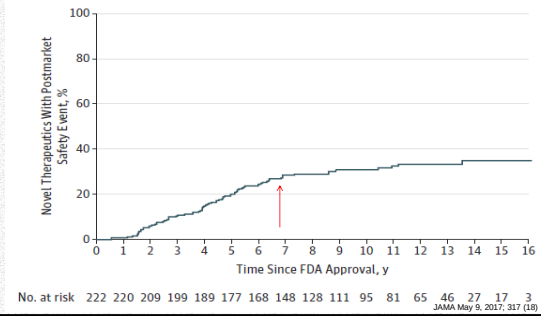
Why is Pharmacovigilance Important?

- Adverse Drug Reactions are among the top ten causes of mortality (Lazarou J. et al., 1998)
- The percentage of hospital admissions due to drug related events in some countries is about or more than 10% (Bhalla et al, 2003; Imbs et al, 1999)
- Drug related morbidity and mortality expenses exceeded US$ 177.4 billion in the USA in 2000 (Ernst & Grizzle, 2001)

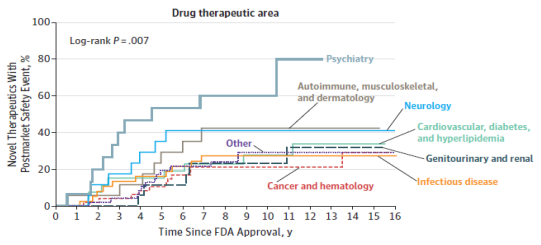
Timeline of Novel Therapeutics Approved by the US FDA, 2001-2010, That Experienced **Postmarket Safety Events**, Grouped by Therapeutic Area



Proportion of **Novel Therapeutics** Approved by the US Food and Drug Administration (FDA) from 2001 through 2010 affected by any Postmarket Safety Event as of February 2017



Proportion of Novel Therapeutics Approved by the US Food and Drug Administration (FDA) From 2001 Through 2010 Affected by Any Postmarket Safety Event by Therapeutic Area



JAMA May 9, 2017; 317 (18)

Phases of Drug Development

STUDIES IN VITRO AND IN VIVO ANIMAL TESTING •SHORT TERM •LONG TERM Questions answered in this phase • Is the substance biologically active? • Is it safe?	**PHASE I** Who? Healthy volunteers, small number Why? Safety, biological effects, pharmacokinetics profile, dosage range, duration of action and drug interactions By Whom? Clinical Pharmacologists **PHASE II** Who? Selected patients (up to 300 patients) Why? Therapeutic efficacy, dose range, kinetics, metabolism By Whom? Clinical pharmacologists, clinical investigators **PHASE III** Who? Large sample of selected patients (500-3000 patients) Why? Safety and efficacy By Whom? Clinical pharmacologists, clinical investigators and pharmacoepidemiologists	**PHASE IV** Who? Patients given drug for therapy Why? Adverse reactions-labeling changes, patterns of drug utilization, additional indications discovered, pricing negotiations, marketing By Whom? Pharmacoepidemiologists and all physicians Areas: Pharmacovigilance Pharmacoeconomics
1-5 years (μ=2.6 yr)	2-10 years (μ=5.6 yr)	Variable
Preclinical	*Clinical*	*Postmarketing Surveillance*

Kaitlin KI, et al. J Clin Pharmacol 1987;27:542-548; Young FE, et al. JAMA1988; 259:2267-2270

Preclinical	Phase 1	Phase 2	Phase 3		Postmarketing
Safety & Biological Activity	Safety & Dosage	Safety & Efficacy	Safety & Efficacy	APPROVAL	Safety Surveillance
SAFETY CONCERNS					

Limitations of Clinical Trials

- Trial population
  - Size (small ~ 3,000 subjects)
  - Representativeness of trial population vs. real world population
  - Trial population vs. real world or treated population (CT: narrowly defined study population: age groups, comorbidities, concomitant medications)
- Indications for use
  - Proposed indication for use
    - Patients at complex disease stages often not enrolled
- Duration of trial
  - Typical chronic use (years) vs. trial (several weeks to months)
- Frequency of ADRs
  - Uncommon ADRSs are difficult to detect

FDA, 2018; Ann Intern Med. 2010;153:600-606.

Sample Size

Statistical Power

Frequency (AE)	95%	90%	80%	63%
1/100	300	231	161	100
1/500	1500	1152	805	500
1/1000	3000	2303	1,610	1000
1/5000	15,000	11,513	8,048	5000
1/10,000	30,000	23,026	16,095	10,000
1/50,000	150,000	115,130	80,472	50,000

Probability of detecting an unintended drug effect if it really occurs in the population under study.

Sackett DL, 1986. In: Inman WHW, Monitoring for drug safety 1986: 471-483.

Ideally, a medication should be prescribed to:

- The **right patient**,
- With the **right disease**,
- With the **right medication**,
- In the **proper dosage and intervals**,
- And for the **appropriate length of time**

Pharmacovigilance & Drug Utilization

- It is not always the product that determines drug safety but **how it is used**
- There is a high risk of misuse of drugs
  - Disease
  - Population
  - Drug
  - Health care system
- More than 50% of ADRs are preventable

Public Health Programs and Pharmacovigilance

- Incidence and prevalence of the disease
- Morbidity and mortality rates
- Number of patients treated
- Number of drug units delivered

What about **the risk / effectiveness** of drugs used?

IMPORTANT DEFINITIONS IN PHARMACOVIGILANCE

Side Effects

- Any **unintended outcome (negative or positive effects)** that seems to be associated with treatment.
- This term is often used in **patient information** and other contexts.
- Unintended effect occurring at normal dose related to the pharmacological properties?

Adverse Effect

A **negative or harmful patient outcome** that seems to be associated with treatment, including there being no effect at all

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/. Accessed May 2018

Adverse Event

- Any **unfavorable and unintended sign** (including an abnormal laboratory finding, for example), **symptom, or disease temporally associated with the use of a medicinal product, but not necessarily causally related**
- Unexpected medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and where **not necessarily have a casa relationship with the treatment.**

ICH E2A Guideline: 'Clinical Data Management: Definition and the Standards for Expedited Reporting', FDA guidance,

Adverse Event

Severity (Intensity)	Seriousness	Expectedness	Listedness	Causality
• Mild • Moderate • Severe	• Serious • Non-serious	• Expected • Unexpected	• Listed • No listed	• Related • No related (unrelated)
		Reference Safety Information of IB (Development), Label (Marketed)	*Label*	

Adverse Drug Reaction (ADR)

- A harmful effect suspected to be **caused by a drug**
- A response to a drug which is **noxious and unintended**, and which occurs at **doses normally used in man** for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function (WHO, 1972)

Standard Categories of Frequency	
Very common	≥ 1/10 [≥ 10%]
Common	≥ 1/100 to < 1/10 [≥ 1% and < 10%]
Uncommon	≥ 1/1000 to < 1/100 [≥ 0.1% and < 1%]
Rare	≥ 1/10,000 to < 1/1000 [≥ 0.01% and < 0.1%]
Very rare	< 1/10,000 [< 0.01%]
Frequency not known*	Cannot be estimated from the available data

* Summary of Product Characteristics (SmPC)/QRD guidelines recommends language "Not known", CDS recommends language "Frequency not known".

CIOMS III/V convention and the European Commission document "A Guideline on Summary of Product Characteristics" dated September 2009. https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/. Accessed May 2018

Serious Adverse Experience, Event or Reaction

- Results in any of these outcomes:
  - **Death**
  - **Life-threatening** adverse experience
  - Inpatient **hospitalization** –new or prolonged
  - Persistent/significant **disability/incapacity**
  - **Congenital birth defect**
  - Other serious: based upon appropriate **medical judgment**, they may jeopardize the patient and require intervention to prevent a serious outcome

  Note: Seriousness is different to **severity**, which refers to the **intensity** of the event (e.g. severe headache)

Federal Register -Code of Federal Regulations. 21 CFR 314.80 (a), FDA 2018

Unexpected Adverse Reaction

- Not consistent with applicable product information or characteristics of drug

Exercise

- Relate each case with each definition using the list distributed during the session

Cases	Relate w/correct answer
1) Female patient who experienced increased of hepatic enzymes after one week on an antifungal medication	a) Adverse event
2) This is a 35 year-old male, soccer player, who complained of myalgias and was on antihypertensive drugs and lipid lowering medications	b) Expected adverse drug reaction
3) This is a 49 year-old female patient exposed to insulin who experienced headache, dizziness and syncope and recovered after drinking a glass of orange juice	c) Adverse drug reaction

1) c , 2) a , 3) b

Benefit, Benefit/Risk

- Benefit:
  - Positive therapeutic effects of treatment in an individual
  - Positive health, social or psychological effects of treatment from the patient's perspective.
- Benefit-risk: Description of both positive and negative effects of a medicine and the likelihood of their occurrence, as far as they are known, as perceived by an individual.
  - B/R represents a critical information that health professionals and patients need to make wise therapeutic decisions. The perspectives of professionals and patients on the issues may differ.

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/. Accessed May 2018

Effectiveness, Effectiveness/Risk, Efficacy

- Effectiveness: A measure of the chances or odds (probability) of a medicine working positively as expected for patients.
  - Measure of the effect of a drug in the "real world"
- Effectiveness-risk: A comparison of the statistical chances (probability) of a medicine working as expected and/or causing harm.
- Efficacy: A measure of the extent to which a chemical substance or medicine works positively under laboratory conditions and in a selected group of patients.

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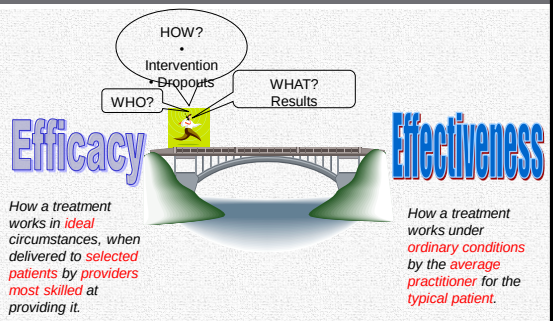
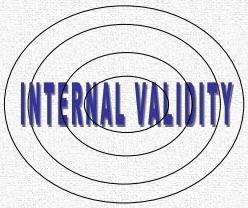


Efficacy: Randomized Controlled Clinical Trials

- Rigorous inclusion and exclusion criteria:
  - Limited to certain study population
  - Limited to a spectrum of a disease
  - Limited to certain number of comorbid conditions
  - Limited to certain number of medications



Effectiveness

- Heterogeneous group of patients:
  - Age
  - Gender
  - SES
- Co-morbid conditions
- Multiple treatments (pharmacologic and non pharmacologic treatments)
- Variation of patient adherence to treatment
- Variation of medical practice and compliance to guidelines
- Variation of medical knowledge among patients
- Access to care (HCS), type of care
- Costs

EXTERNAL VALIDITY

Harm, Hazard and Risk

- Harm: The damage, injury or impairment that is or might be caused by a medicine, including death.
- Hazard: The intrinsic chemical or biological characteristics of a medicine or its use that have the potential to cause harm.
- Risk: The statistical probability of harm being caused.

Doxorubicin —hazard→ Cardiotoxicity —harm→ Cardioversion

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DRUG UTILIZATION AND PHARMACOVIGILANCE

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Some Uses of Drug Utilization in Pharmacovigilance

- Estimation of drug exposure:
  - Overall population
  - By subpopulations
  - By demographic characteristics & other determinants
- As denominator for calculating rates of reported ADRs (reporting rates)
- Assessing effectiveness of risk minimisation measures

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Examining product risk in context. Market withdrawal of zomepirac as a case study. Ross-Degnan D1, Soumerai SB, Fortess EE, Gurwitz JH.

- To examine changes in the prescribing of analgesics after the market entry and subsequent withdrawal of zomepirac sodium, a nonsteroidal anti-inflammatory drug (NSAID), following repeated reports of zomepirac-related deaths.
- Natural quasiexperiment used to conduct **time-series analyses** to compare prescribing in two cohorts of primary care physicians from July 1980 through September 1983.
- Study physicians provided outpatient pharmaceutical care to patients enrolled in the New Jersey Medicaid program. We identified 260 primary care physicians who provided 10 or more prescriptions for zomepirac (zomepirac prescribers) and 308 who provided 10 or more prescriptions for NSAIDs other than zomepirac (other-NSAID prescribers) in Medicaid during the study period. Outcomes: Monthly rates of prescribing for zomepirac and several categories of substitute analgesics among Medicaid patients seen by study physicians.
- Zomepirac accounted for a stable 11.0% of analgesic prescribing among the zomepirac-prescriber cohort; label changes and manufacturer product-risk warnings 11 months before the product's withdrawal from the market had no impact on use. After market entry, zomepirac prescribers reduced use of other NSAIDs and propoxyphene (hydrochloride or napsylate) in comparison with other-NSAID prescribers (-8.1% and -2.8% of total analgesic prescribing, respectively; P < .001). After the product's withdrawal from the market, zomepirac prescribers showed significant increases in relative prescribing of other NSAIDs (+6.8%; P < .001), propoxyphene (+2.1%; P < .05), and analgesics containing barbiturates (+2.7%; P < .001).
- The sudden withdrawal of zomepirac from the market resulted in substitutions not only of other NSAIDs, but also of alternative analgesics that carry risks of habituation and adverse effects.

JAMA. 1993 Oct 27;270(16):1937-42.

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Drug Utilization in Pharmacovigilance

(e.g. assessing effectiveness of risk minimisation measures)

Table 1.—Prescriptions for Study Analgesics per 100 Medicaid Recipients in Practice by Provider Specialty, July 1980 Through November 1981

Physician Group	Physicians, No.	Study Analgesics: Zomepirac Sodium	Other NSAIDs*	Analgesic With Opioids†	Analgesic With Barbiturates	All Study Analgesics
General practice	477	5.1	39.2	34.4	8.8	87.5
Internal medicine	468	5.5	73.7	55.3	12.9	147.4
Family practice	236	3.7	45.3	33.0	8.2	90.2
All Primary Care Physicians	**1183**	4.9	49.0	37.1	9.7	**100.7**
Dentistry, oral surgery	140	3.3	4.9	81.8	4.2	**94.2**
Pediatrics	121	0.2	2.7	4.9	0.7	**8.5**
General surgery	122	3.1	36.1	33.3	8.4	**80.9**
Obstetrics, gynecology	106	1.3	9.8	21.7	5.7	**38.5**
Other specialty	287	3.1	29.8	42.8	7.0	**82.7**
All Non–Primary Care Physicians	**776**	1.5	13.1	24.5	4.0	**43.1**

*NSAID indicates nonsteroidal anti-inflammatory drug.
†Analgesic products containing propoxyphene (hydrochloride or napsylate), pentazocine, meperidine hydrochloride, or codeine.

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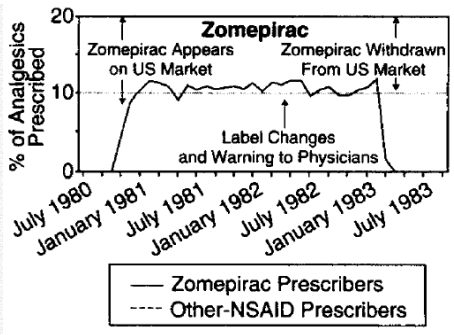
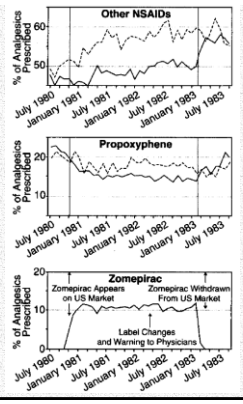




Changes in Analgesic Preference Following Release of Zomepirac and Its Market Withdrawal Among Prescribers of Zomepirac and Prescribers of Other NSAIDs*

	Study Analgesic Category, Proportional Share of Use (SE)†				
	Zomepirac Sodium	Other NSAIDs	Propoxyphene‡	Other Opioids	Barbiturates
Use at beginning of study period (June 1980)	0.000	0.475 (0.0061)	0.210 (0.0042)	0.206 (0.0040)	0.109 (0.003)
Monthly trend in use (July 1980–September 1983)	<0.001§	0.002‖ (0.0003)	<0.001	−0.002‖ (0.0002)	<0.001
Changes in average monthly use among prescribers of other NSAIDs					
While zomepirac on market	<0.001	0.058‖ (0.0087)	−0.027‖ (0.0061)	−0.013¶ (0.0058)	−0.018‖ (0.0045)
Following withdrawal	<0.001	−0.029¶ (0.0010)	0.008 (0.0069)	0.033‖ (0.0066)	−0.018# (0.0051)
Difference between prescribers of zomepirac and prescribers of other NSAIDs					
While zomepirac on market	0.110‖ (0.001)	−0.081‖ (0.0047)	−0.028‖ (0.0033)	−0.002 (0.0031)	0.001 (0.0024)
Following withdrawal	−0.110‖ (0.003)	0.068‖ (0.0118)	0.021¶ (0.0062)	−0.005 (0.0078)	0.027‖ (0.0061)

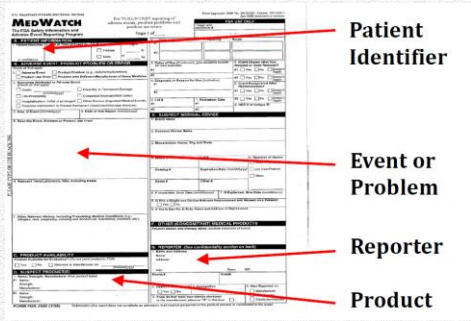
*NSAID indicates nonsteroidal anti-inflammatory drug.
†Based on time-series regression models.
‡Propoxyphene hydrochloride or propoxyphene napsylate.
§SEs not reported for proportions <0.001.
‖P<.001.
¶P<.05.
#P<.01.

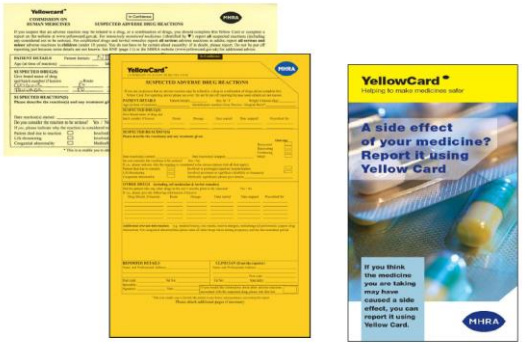
Pharmacovigilance Reporting Systems (Postmarketing/Safety Surveillance, Spontaneous Reporting Systems

The core **data-generating system** of pharmacovigilance, relying on healthcare professionals and patients to **identify and report any suspected adverse effects from medicines** to **their local or national pharmacovigilance center or to the manufacturer**.

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/. Accessed May 2018

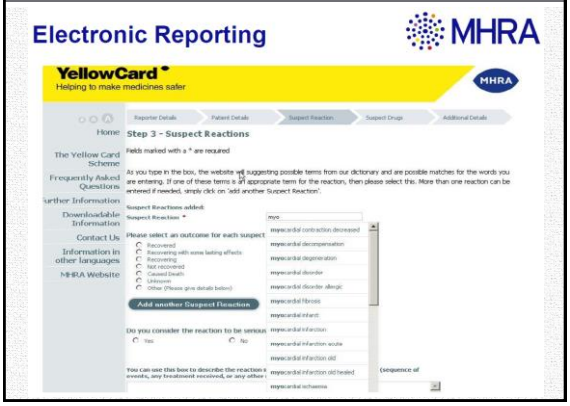
Reporting to MedWatch





Electronic Reporting

Electronic Reporting



Benefits of Spontaneous Reporting Systems

- Key in monitoring patient safety
- Particularly useful for new medications where clinical trials:
  - Exposed small numbers of people
  - Short duration
  - Unlikely to detect ADRs particularly those with frequency of <1/1500 or long latency
- Lack of experience in special patient groups such as pediatric population, elderly, pregnancy
- Important for chronic and long term use
- To detect drug-drug interactions, drug-food interactions

Severe Cutaneous Adverse Reactions (SCAR) in Oncology

Drug class	Drug	Pharmacology	References	Total (n)	Mortality	SJS	SJS/TEN	TEN
Alkylating agents	Treosulfan	Alkysufonates	[6]	1	1	0	0	1
	Chlorambucil	Mustard gas derivatives	[7, 8]	2	0	0	0	2
	Mechlorethamine (topical)	Nitrogen mustard	[9]	1	0	1	0	0
	Temozolomide	Hydrazines and triazines	[10]	1	0	0	1	0
	Procarbazine	Hydrazines and triazines	[11–13]	3	0	0	0	3
Plant alkaloids	Paclitaxel	Taxanes	[14]	1	0	1	0	0
	Docetaxel	Taxanes	[15–19]	5	2	3	0	2
	Etoposide	Podophyllotoxins	[20]	1	0	1	0	0
Anthracyclines	Doxorubicin		[21]	1	1	0	0	1
Antimetabolites	Methotrexate	Folic acid antagonists	[22–26]	5	2	2	0	3
	Cytarabine	Pyrimidine antagonist	[27, 28]	2	2	0	0	2
	Fludarabine	Adenosine deaminase inhibitor	[29]	1	1	1	0	0
	Gemcitabine	Pyrimidine antagonist	[30–32]	3	0	2	1	0
	Capecitabine	Pyrimidine antagonist	[33]	1	0	1	0	0
	Cladribine	Purine antagonist	[34, 35]	2	NA	1	0	1
	6-Mercaptopurine	Purine antagonist	[36]	1	NA	0	0	1
	TS-1 (tegafur-gimeracil-oteracil potassium)		[37, 38]	2	0	1	0	1
	Pemetrexed	Multitarget antifolate	[39, 40]	2	0	0	0	2
Antitumor antibiotics	Bleomycin		[41, 42]	2	1	0	0	2
	Peplomycin		[43]	1	0	1	0	0
	Mithramycin		[44, 45]	2	0	0	0	2
Miscellaneous	Lenalidomide		[46–48]	14	2	12	1	1
	Thalidomide		[49–53]	5	1	1	0	4
	Asparaginase		[54]	1	0	0	0	1
			Total	**60**	**13**	**28**	**3**	**29**

NA: not available.

Journal of Immunology Research 2018; 1-9

SAFETY SIGNALS

Safety Signal. Definition

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

CIOMS Working Group VIII, Geneva 2010

Types of Safety Signals

- Potential safety signals: identified from individual case analysis and formal epidemiological studies
- Statistical Safety Signals:
  - Principle: Drug–event pair is **reported more often than expected** relative to an independence model, based on the frequency of ICSRs on the reported drug and the frequency of ICSRs of a specific adverse event

Sources of Safety Data

- Pre-clinical studies
- Clinical studies (pre- and post-marketing)
- Postmarketing data/studies
  - Spontaneous adverse events
  - Epidemiological studies (e.g. PASS)
  - Data collected for other purposes
  - National statistics
  - Databases of prescription, EMR, insurance claims, and outcomes
  - Scientific Literature

Individual Case Safety Reports (ICSR)

- Reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more medicines.

- 49-year old female patient
- Diagnosis: Bipolar Disorder
- Treatment: Antipsychotic medication started one year before the reported adverse events
- After stopping therapy, she developed "dizziness, can hardly walk and feet are going numb"
- Concomitant therapy: not provided
- Outcome: unknown

https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/. Accessed May 2018

Four Requirements for a Valid Case Report

- ✓Patient
- ✓Drug product
- ✓Adverse event
- ✓Reporter

FDA, 2018

Evaluation of Case Reports

- Adverse event occurrence in expected time
- Absence of symptoms prior to exposure
- Positive dechallenge or rechallenge
- Consistent with pharmacologic effects
- Consistent with known effects in the class
- Support from pre-clinical studies, clinical trials
- Absence of alternative explanations

FDA, 2018

Elements of an Informative Postmarketing Report

- Description of adverse event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

FDA, 2018

Exercise

- Read each case reports and classify them as:
  - Valid and non-valid case
  - Informative and non-informative case
  - Related or not related to the medication

Exercise

Case	Valid/NV, Informative/NI, Related/NR/Unk
Report from a caregiver related to an elderly patient who received unspecified medication and died	
Report from a nurse related to a 16 year-old male HIV patient who was on remission but developed disseminated candidiasis that required administration of fluconazole during 3 days and developed generalized rash	
Spontaneous report from a cardiologist related to an 85-year old female who was on propranolol for 24 h and developed renal failure	

1) nv,ni,unk; 2) v, l, r; 3) v,ni,unk

MEASURES IN PHARMACOVIGILANCE

Statistical Safety Signals

- Principle: Drug–event pair is **reported more often than expected** relative to an independence model, based on the frequency of ICSRs on the reported drug and the frequency of ICSRs of a specific adverse event
- Signals of Disproportionate Reporting (SDR)

Statistical Safety Signals

- Signals of disproportionate reporting (SDRs): Statistical associations between medicinal products and adverse events i.e. drug- event pairs.
- Proportional reporting ratio (PRR): Statistical method where an adverse event is reported relatively more frequently in association with this medicinal product than with other medicinal products

Proportional Reporting Ratio (PRR)

- Statistical method where an adverse event is reported relatively more frequently in association with this medicinal product P than with other medicinal products

	Adverse Event (R)	All Other Adverse Events	Total
Suspect Medicinal Product (P)	A	B	A+B
All other medicinal products	C	D	C+D
Total	A+C	B+D	N=A+B+C+D

95%CI $s = \sqrt{(1/A + 1/C - 1/(A+B) - 1/(C+D)}$

$PRR = \frac{A/(A+B)}{C/(C+D)}$

Example

- Proportion of individual cases of nausea involving medicinal product 'Trade Name' = 15% (e.g. 15 reports of nausea amongst a total of 100 reports reported with medicinal product 'Trade Name').
- Proportion of individual cases of nausea involving all other medicinal products in a database (but medicinal product 'Trade Name') = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 3 (0.15/0.05).

Example of AE Monitoring

Reaction SOC	Reaction PT	Metrics	PRR (-)	PRR	PRR (+)	New	Total
Blood and lymphatic system disorders							
	Agranulocytosis		0.14	0.44	1.35	1	3
	Anaemia		1.94	2.31	2.77	7	64
	Anaemia megaloblastic		1.05	7.56	54.51	1	1
	Aplasia pure red cell		2.44	4.42	8.00	1	10
	Bone marrow depression		2.09	3.07	4.52	5	17
	Granulocytopenia		0.42	1.32	4.09	1	2
	Haemolytic anaemia		1.19	2.15	3.89	1	9
	Histiocytosis haematophagic		0.88	3.53	14.18	1	2
	Hypoplastic anaemia		1.97	14.43	105.53	1	1
	Idiopathic thrombocytopenic purpura		0.08	0.56	3.98	1	1
	Leukocytosis		0.32	0.85	2.26	1	4
	Leukopenia		1.57	2.12	2.85	2	33

Example of Metrics from Eudravigilance

Metrics*	
A	3
A + B	2,430
A + C	254
A + B + C + D	163,417
CHI^2 (A)	0.1598
CHI^2 (B)	0.0002
CHI^2 (C)	0.0024
CHI^2 (D)	0.0000
CHI^2	0.1625
Expected A	3.7770
Expected B	2,426.2230
Expected C	250.2230
Expected D	160,736.7770
PRR (-)	0.26
PRR	0.79
PRR (+)	2.46

	Adverse Event (R)	All Other Adverse Events	Total
Suspect Medicinal Product (P)	A	B	A+B
All other medicinal products	C	D	C+D
Total	A+C	B+D	N=A+B+C+D

EMA, Guideline on the use of statistical signal detection... 2006

Factors that can Impact the PRR

- Type of medicinal products included in the database
- Medical terminology(ies) applied
- Coding practices
- Date of the creation of the database
- Source of ICSRs (i.e. all unsolicited reports)

Note: Eudravigilance computes PRR using the entire database except interventional clinical trials

Chi-square (χ2) statistics

- Statistic used in disproportionality analyses as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

$$\chi^2 = (AD - BC)^2 (A + B + C + D) / [(A + B)(C + D)(A + C)(B + D)]$$

- Criteria used by Eudravigilance when the PRR is displayed with the χ2 statistic: PRR > 2, χ2 > 4; The number of individual cases greater or equal to 3.

Interpreting Statistical Safety Signals

- The usual threshold for a statistical safety signal =2.
  - It the threshold is too low = Many false positive signals
  - If the threshold is too high = Missing potential signals
- The absence of a SDR does not necessarily exclude the possibility of an association between the medicinal product and the adverse event.
- Additional analysis of PRR (e.g. by age and gender or combining multiple medical products of the same class) can be done

Interpretation of Statistical Safety Signals

- An increase in a SDR or other statistic, does not necessarily imply a **causal relationship** between the **administered medicinal product and the occurrence of the adverse event**

Therefore,

- ALL statistical safety signals should be medically assessed

Example of PRR from Eudravigilance Database

Reaction SOC	Reaction PT	Metrics	PRR (-)	PRR	PRR (+)	New	Total	New EEA	EEA	New Non EEA	Non EEA	New Fatal	Fatal
Blood and lymphatic system disorders													
	Agranulocytosis		0.14	0.44	1.35	1	3	0	2	1	1	0	0
	Anaemia		1.94	2.31	2.77	7	64	0	10	7	54	1	6
	Anaemia megaloblastic		1.05	7.56	54.51	1	1	0	0	1	1	0	0
	Aplasia pure red cell		2.44	4.42	8.00	1	10	0	3	1	7	0	1
	Bone marrow depression		2.09	3.07	4.52	5	17	0	2	5	14	0	2
	Granulocytopenia		0.42	1.32	4.09	1	2	0	1	1	1	0	1
	Haemolytic anaemia		1.19	2.14	3.69	1	9	1	3	0	6	0	2
	Histiocytosis haematophagic		0.88	3.53	14.18	1	2	0	0	1	2	0	1
	Hypoplastic anaemia		1.97	14.43	105.53	1	1	0	0	1	1	1	1
	Idiopathic thrombocytopenic purpura		0.08	0.56	3.96	1	1	0	0	1	1	0	0
	Leukocytosis		0.32	0.85	2.26	1	4	0	1	1	3	0	0
	Leukopenia		1.57	2.12	2.85	2	33	0	7	2	26	0	3
	Lymphadenopathy		0.81	1.62	3.24	1	6	0	1	1	6	0	0
	Macrocytosis		0.60	4.33	31.01	1	1	0	0	1	1	0	0
	Neutropenia		0.75	1.12	1.69	4	20	1	3	3	17	0	1
	Normochromic normocytic anaemia		0.32	1.30	5.19	2	2	2	2	0	0	0	0
	Pancytopenia		1.31	1.81	2.51	6	30	0	7	6	23	2	7
	Red blood cell abnormality		0.89	6.44	46.30	1	1	0	0	1	1	1	1
	Thrombocytopenia		0.60	0.88	1.28	5	23	1	7	4	16	0	5
	Thrombotic thrombocytopenic purpura		5.17	8.04	17.05	1	10	0	2	1	8	1	3
Cardiac disorders													

In Conclusion….

AE/ADR
Valid case
Serious vs. severe
Reporting rates
Threshold for PRR