Chapter

Introductory Chapter: Pharmacovigilance

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1. Introduction

Consuming a drug is equivalent to consume a risk. It is only when the benefit associated with the drugs are more than the risk, that the consumption of a drug is justified. Thus, it is benefit versus risk ratio of the drug which decides whether a drug is to be taken or not. The next question is how to measure risks and how to measure the benefits. Due to individualization of drugs to patients, it is the clinical judgment of the physician to identify what will benefit the patient. At the same time, risk associated with the drug can be ascertained by observations related to pharmacovigilance. The studies related to pharmacovigilance indicate what are the possible risks associated with the drug. Even drug can be associated with possible adverse reactions, intended or unintended. The only exception to this generality is the case of drug which is given in case of deficiency of specific components like vitamins or minerals. It is the study of possible adverse reactions of drugs which constitutes the essential content of Pharmacovigilance. This takes us to the definition of Pharmacovigilance.

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. [1] Spontaneous reporting of adverse events and adverse drug reactions is the commonest method utilized for generating safety data.

Major aims of pharmacovigilance are as follows:

- Early detection of hitherto unknown adverse reactions and interactions.
- Identification of risk factors and possible mechanisms underlying adverse reactions.
- Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation.

Safety of patient is the most important when it comes about medicines. Various types of medicines are used since ancient ages and various rules and regulation were formed in modern era. If we look back in early twentieth century, the safety of patient was discussed first time when Biologics Control Act, 1902 was passed by USA [2, 3]. After that in 1962, USA promulgated a law stating that it is the manufacturer's responsibility to prove safety and efficacy of the drug before getting marketing authorization. In 1963, a committee on Safety of drugs was established in UK. In 1964, a system of "Yellow Cards" was established in UK to trace reporting safety of drugs by all users of drugs [4]. By 1964–1965, National Adverse Drugs Reaction reporting systems was initiated in countries like UK, Australia, New Zealand, Canada, West Germany and Sweden.

Year	Legislation/Act/Law/Event
1902	**Biologics Control Act** [2, 3] Passed in 1902 by USA because many deaths were reported due to diphtheria vaccines tainted with tetanus.
1906	**Pure Food and Drug Act** [5] Passed by US Congress, for preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes. The bill was passed after significant public pressure which resulted from a novel by the journalist Upton Sinclair which exposed unhealthy practices of the meat industry in Chicago.
1937	**Sulfanilamide Elixir** [6] used to treat streptococcal infections, which had been used without any issues in powder and tablet form. A mass poisoning of 105 patients treated with an untested medication spurred Congress to empower the US Food and Drug Administration to monitor drug safety.
1938	**Federal Food, Drug and Cosmetics Act** [7] As a result of sulfanilamide elixir incident, the Federal Food, Drugs and Cosmetics Act was passed, the statute that today remains the basis for FDA regulation.
1949	**Council for International Organizations of medical sciences (CIOMS)** [8] Established jointly by WHO and UNESCO with the objective to facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary.
1961	**Thalidomide tragedy** [9, 10] Thalidomide first entered the German market as an over-the-counter remedy in 1957. A German newspaper soon reported 161 babies were adversely affected by thalidomide, leading the makers of the drug—who had ignored reports of the birth defects associated with the it—to finally stop distribution within Germany. Other countries followed suit and, by March of 1962, the drug was banned in most countries where it was previously sold.
1962	**Kefauver-Harris** [11] This amendment was passed in the US Congress as a response to thalidomide tragedy. This law required evidence of drug efficacy and safety before marketing.
1964	**Yellow Card Scheme** [4] Again in the wake of thalidomide tragedy the Yellow Card Scheme (UK) was established for collecting information on suspected adverse drug reaction (ADRs) of medicine to provide an early warning of possible hazards.
1967	**WHO resolution** Resolution 20.51 laid basis for the international system of monitoring ADR.
1968	**Medicines Act** [12] Established by UK to govern the control of medicines for human and veterinary, including manufacturing and supply.
1973	**Pharmacovigilance System** [13] French Pharmacovigilance system implemented.
1982	**Benoxaprofen** [14] Was removed from the market in the UK and USA after being linked to 3500 side effects and 61 deaths. Showing that despite progress and efforts to prevent disasters, these can still occur and great care is needed to ensure patient safety.
1990	**CIOMS – 1** [15] CIOMS–1: International reporting of Adverse Drug Reactions, released.
1991	**European Rapid Alert System** Was signed into force to felicitate early exchange of information concerning possible safety hazards relating to marketing medicinal products. Reducing delay in acting on safety signals such as the case in Sulfanilamide elixir in 1937
1995	**European Medicines Agency** Established to harmonize the work of existing national medicine regulatory bodies.
2001	**EU Clinical Trial directives** [16] Issued in April 2001 and approved and implemented in May 2004.Introduced more robust measures on the safe conduct of clinical trials. Volume 9A introduced to standardize post marketing PV systems in Europe.
2009	**Black Triangle** [17] MHRA Black Triangle scheme to report all suspected adverse drug reaction to designated drugs.

Year	Legislation/Act/Law/Event
2012	**Good Pharmacovigilance Practice (GvPs)** [18] Release of this replaced volume 9A. It expanded and clarifies the PV responsibility of marker authorization holders. Regularly updated and made available for public consultation.
2014	**New Clinical Trial Regulation** [19] Signed into force to replace the 2001 EU-CTD. Standardized implementation across member states.

Table 1.
Roadmap of current pharmacovigilance system.

In 1962, International Center for monitoring of Adverse Drug Reaction by WHO was established in Geneva, which was later shifted to Uppsala in Sweden and this is the beginning of pharmacovigilance. From then, the WHO-supported Uppsala monitoring Centre has spearheaded many activities of pharmacovigilance all over the world (**Table 1**).

2. Current methods in pharmacovigilance

Pharmacovigilance is branch of pharmacoepidemiology but is restricted to the study, on an epidemiological scale, of drug events or adverse reactions.

Here 'events' means, recorded happenings during a period of drug monitoring in the patients notes, it may be due to the disease for which the drug is being given, some other intercurrent disease or infection, an adverse reaction to the drug being monitored or the activity of a drug being given concomitantly.

2.1 Hypothesis: generating methods

2.1.1 Spontaneous ADR reporting

Healthcare professionals are provided with forms upon which they can notify a authority of any suspected ADRs that they detect. The form is filled by healthcare professionals with direct interaction to patient after knowing the required information directly from patients. Even the consumers can directly report with the help of form.

This system remains helpful to obtain the safety information of drug throughout the lifecycle of the drug or the length of stay of the drug in the market. Spontaneous reporting has led to the identification and verification of many unexpected and serious adverse drug reaction.

2.1.2 Prescription event monitoring

This method provides the 'exposure data' showing which patients have been exposed to the drug being monitored. Strength of this method is that it provides the number of reports and the number of patients exposed both being collected over a precisely known period of time or observations.

2.1.3 Other hypothesis: generating methods

In some cases, data being collected for general public health surveillance, such as cause of death files, cancer registries and birth defect registries are used to identify patterns of events that might be associated with medication use.

2.2 Hypothesis: testing methods

2.2.1 Case-control studies

In this study, case is compared with controls susceptible to the disease but free of it. Here the exposure rate of case is compared with exposure rate in the controls. Special attention is needed in case definition so that the cases truly represent the specific outcome of interest (e.g. Stevens-Johnson syndrome and not all cases of rash).

2.2.2 Crossover design

Very useful design for the evaluation of events with onset shortly after treatment initiated. Here cases are identified not controls. A drug association is evaluated through comparing frequency of exposure at the time of the event with frequency of exposure at a different time for the same individuals. This design is less subject to bias than case–control studies because individuals serve as their own controls.

3. Causality assessment in pharmacovigilance

While reporting any adverse reaction, it is necessary to establish causal relation between the suspected drug and the observed effect. It is also possible that one of the diseases processes, interaction of the drug on disease process or even lack of effect of a drug exacerbating the disease process may be involved in the observed effect.

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probably/ likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Table 2.
WHO-UMC system proposed by World Health Organization.

Questions	Yes	No	Do not know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	−1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was re-administered?	+2	−1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	−1	+2	0
Did the reaction reappear when a placebo was given?	−1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+	0	0

Scoring for Naranjo algorithm: >9 = definite ADR; 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful ADR.

Table 3.
Naranjo ADR probability scale—items and score.

The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC) [20], and the Naranjo Probability Scale [21] are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology (**Tables 2** and **3**).

4. Signal detection

As per World Health Organization, signal of adverse drug reaction is: "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" [22].

A signal is therefore very tentative in nature; the first expression that something might be wrong with a medicinal product, or a hint given by new information which might support or explain a medicinal product–adverse reaction relationship already known [23].

Usually, more than a single report is required for signal detection (SD), depending on the seriousness of the event and the quality of the information. Once a signal is detected, one can then analyze and confirm it. In detecting signals from large ADR databases, however, one has to use a procedure that is sensitive (low false negativity) and specific (high true positivity) for the purpose [24, 25].

Different methods are being developed till today for the detection of signal. In that statistical method is very useful and very under estimated method. Such method is data mining approach, in which important and useful information are automatically and continuously extracted from large amounts of data, it is a form of exploratory data analysis and a key component of the knowledge discovery process. This approach seems particularly valuable and can be used on any large data set.

Data mining approach is divided into mainly two parts: frequentist and Bayesian methods.

Method	Advantage	Limitations	Regulatory Agencies using the method
Frequentist methods			
Proportional reporting ratio (PRR)	Easily applicable and interpretable, more sensitive compared to Bayesian method	Cannot be calculated for all drug-event combinations, low specificity	EMA (EudraVigilance), Italian Regulatory Agency
Reporting odd ratio (ROR)	Easily applicable and interpretable, more sensitive compared to Bayesian method	Odd ration cannot be calculated if denominator is zero	Lareb (Netherlands)
Bayesian methods			
Multi-item Gamma Poisson Shrinker	Always applicable, more specific as compared to frequentist methods	Relatively non transparent for people non familiar with Bayesian statistics, lower sensitivity	FDA (AERS)
Bayesian Confidence Propagation Neural Network (BCPNN)	Always applicable, more specific as compared to frequentist methods	Relatively non transparent for people non familiar with Bayesian statistics, lower sensitivity	UMC (WHO-VigiBase)

Table 4.
Data mining methods.

4.1 Frequentist method

They are particularly appealing and therefore widely used due to the fact that they are relatively easy to understand, interpret and compute as they are based on the same principles of calculation using the 2 × 2 table.

Proportional reporting ratio (PRR), Reporting odd ratio (ROR), chi-square ratio, 95% confidence interval of PRR and observed to expected ratio are calculated.

4.2 Bayesian method

Bayesian methods interpret the concept of probability as the degree to which a person believes a proposition. Bayesian inference starts with a pre-existing subjective personal assessment of the unknown parameter and the probability distribution (called prior distribution).

The signal metric or signal score in BCPNN is the information component (IC) (**Table 4**).

5. Pharmacovigilance and ICH regulations

So far, pharmacovigilance-related topics entered the ICH process in two waves. The first wave resulted in adoption of the ICH Topic ICH-E2A in 1994 with an extension to this work in the form of E2B and E2C, finalized between 1996 and 1997. The second wave started in 2002 with three further ICH topics, E2D, E2C Addendum and E2E, finalized between 2003 and 2004 (**Figure 1**).

5.1 Key points addressed in the ICH-E2A

- Definitions for AE and ADR in the pre-authorization phase [26]
- Criteria for serious AE/ADR

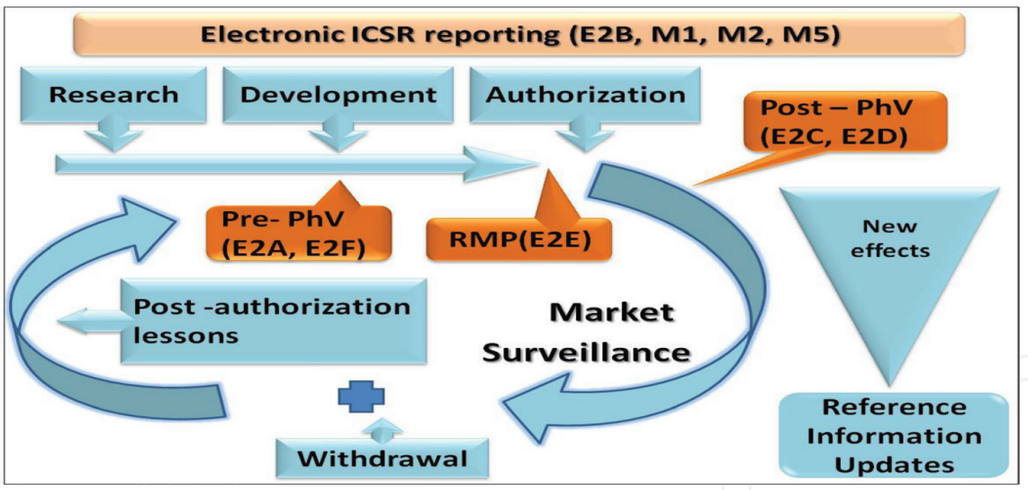

Figure 1.
Pharmacovigilance and ICH.

- Expectedness of an AE/ADR based on clinical observation and its documentation in the applicable product information
- Causality assessment as good case practice for AE/ADR cases from clinical trials
- Implied possible causality for spontaneously reported ADR cases
- Standards for expedited reporting from clinical trials
- Definition of minimum case report information for report submission to authorities
- Follow-up reporting
- Unblinding procedures for serious ADRs
- Reporting of emerging information on post-study ADRs
- Reporting requirement for active comparator

5.2 Key points addressed in the ICH-E2D

- Definitions for AE and ADR in the post-authorization phase [27]
- Criteria for serious AE/ADR in accordance with ICH-E2A
- Expectedness of an AE/ADR based on clinical observation and its documentation in the authorized product information; explanations regarding class effects
- Differentiation between sources of unsolicited and solicited reports
- Explanation on stimulated (but unsolicited) reporting
- Standards for expedited reporting in post-authorization phase

- Definition of minimum case report information for report submission to authorities with explanations
- Follow-up reporting
- Lack of efficacy reporting needs
- Guidance on ADR narratives
- Guidance on ADR case assessment
- Management of cases of exposure during pregnancy
- Explanation on reporting responsibility of marketing authorization holder despite any contractual relationship in place

5.3 Key points addressed in the ICH-E2B(M)

- Description of all data elements of ADR case reports: title and content of each data field [28]
- Technical specifications such as field length and field value for each of the data fields and the related additional technical data fields
- List of abbreviations for units
- List of units for time intervals
- List of routes of administration

5.4 Key points addressed in the ICH-E2C

- Inclusion of all product presentations in one PSUR [29]
- Concept of international birthdates of a product, determining the data lock points of PSURs
- Provision to submit a set of PSURs, each covering subsequent 6 months, to facilitate PSUR submission according to local frequency
- Description of all data sources to be covered in a PSUR
- Inclusion of worldwide information on marketing authorization status and regulatory safety-related action, ADR and exposure data
- Use of company core safety information (CCSI) as reference and concept of unlistedness of an ADR (i.e. unlisted in comparison to the CCSI versus unexpected in comparison with locally authorized product information)
- Presentation of individual case history
- Formats of ADR line listings and summary tabulations
- Presentation of exposure data

5.5 Key points addressed in the ICH-E2E

- Elements for the safety specification as summary of identified risks, risks potentially arising from populations and situations that have not yet been adequately studied and potential other risks [30]

- Format of a pharmacovigilance plan based on the safety specification

- Within the pharmacovigilance plan, the description of routine pharmacovigilance as minimum and inclusion of a safety action plan for specific issues/missing information as needed

- Format of safety action plan, with the description of rationale for action and timetable for evaluation and reporting ('milestones')

- Possible synchronization of timetable with regulatory timetable for post-authorization assessment, such as PSUR assessment or marketing authorization renewal assessment

- Principles for design and conduct pharmacoepidemiological studies of non-experimental design with references to international guidelines

- Overview of methods for data collection to investigate the known or unknown risks and references

6. Pharmacovigilance in pediatric population

Pediatric population is defined as age between 0 and 18 years of age. Since many ages, pediatrician deals with limited available medicines specifically made for children. The reason behind limited availability of medicines is lack of clinical trials in this age group. Pediatricians are left with no choice other than prescribing it as "off-label" basis as these medicines have not been adequately tested and or formulated and authorized for use in appropriate pediatric age group. So these health care providers should be aware of risk involved in prescribing and administering such drugs to children [1].

Risk of adverse reactions increases with "off-label" use of drugs and so regulatory authorities play an important role in reminding health care providers to report adverse drug reactions and process of pediatric pharmacovigilance [31]. Specific problems associated with pediatric population are lack of clinical trials, under or over dosage, lack of pharmacokinetics and dose-finding studies; drug induced growth and developmental disorders as well as delayed ADRs [31].

Various stakeholders that play a role in pharmacovigilance are health professionals, parents, pharmaceutical industry, patient organizations, national healthcare systems, etc.

Different regulatory guidance's available for pediatric pharmacovigilance are but not limited to:

ICHE2E

EMEA: Guideline on conduct of pharmacovigilance for medicines used by the pediatric population.

EMEA: Guideline on conduct of pharmacovigilance for vaccines.

Points to be considered for future in pediatric pharmacovigilance are [32]:

- Pediatric population should be taken into account during all phases of pharmacovigilance cycle
- Encourage ADR reporting
- Expanding definition of ADR to include off-label, misuse, error.
- Risk management plans
- Signal detecting systems
- Additional monitoring system

7. The future

The drugs can viewed, in general terms, like any other commodity. Patients will be able to choose what is best for them on the basis of information they are given. Drugs with relatively less benefit or more risk will find an appropriate market level. We believe this involves the public understanding more about benefit and risk, more suitable information coming from regulators and industry regarding benefit and risk of drugs, health professionals being able to interpret information for singular situations and the law and media playing a more constructive role in the whole process. The situation is undoubtedly more complicated than this, and the issues of communications in a crisis involving safety issues with a drug not only affect the situation but have a more general impact. These high profiles issues deserve special attention as does the impact of new communications media and sources.

Pharmacovigilance benefits everybody. The patients are protected from unsafe drugs, doctors and pharmaceutical industry keep their reputations intact and drug regulators receive pertinent data that helps them to take regulatory decisions.

It is expected that with the involvement of all related stakeholders, Pharmacovigilance program will help in reducing the cost of damages caused by drugs to minimal level. It will also try to prevent drug-related damages if appropriate care is taken by physicians on the basis of feedback from the pharmacovigilance program.

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References

[1] WHO. Pharmacovigilance. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/ [Accessed: September 11, 2018]

[2] A Short History of the National Institutes of Health. Available from: https://history.nih.gov/exhibits/history/docs/page_03.html [Accessed: September 11, 2018]

[3] Bren L. The road to the biotech revolution: Highlights of 100 years of biologics regulation. FDA Consum. **40**:50-57

[4] Yellow Card Scheme—MHRA. Available from: https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/ [Accessed: September 11, 2018]

[5] Food and Drug Act of 1906. Encyclopedia.com. Available from: https://www.encyclopedia.com/history/united-states-and-canada/us-history/food-and-drug-act-1906 [Accessed: September 11, 2018]

[6] Akst J. The Elixir Tragedy, 1937 | The Scientist Magazine®. https://www.the-scientist.com/foundations/the-elixir-tragedy-1937-39231, [Accessed December 13, 2018]

[7] FDA Basics—How did the Federal Food, Drug, and Cosmetic Act Come About? Available from: https://www.fda.gov/aboutfda/transparency/basics/ucm214416.htm [Accessed: September 11, 2018]

[8] Our History—CIOMS. Available from: https://cioms.ch/history/ [Accessed: September 11, 2018]

[9] Kim JH, Scialli AR. Thalidomide: The tragedy of birth defects and the effective treatment of disease. Toxicological Sciences. 2011;**122**:1-6

[10] Thalidomide Embryopathy Report of a meeting of experts World Health Organization (WHO), Geneva, 2014. p. 1-26

[11] Greene JA, Podolsky SH. Reform, regulation, and pharmaceuticals—The Kefauver-Harris amendments at 50. The New England Journal of Medicine. 2012;**367**:1481-1483

[12] Medicines Act 1968, United Kingdom Legislative Body, London. 1968

[13] Welsch M, Alt M, Richard MH, Imbs JL. The French pharmacovigilance system: Structure and missions. Presse Médicale. 2000;**29**:102-106

[14] Lowe D. When Drug Launches Go Bad | In the Pipeline. https://blogs.sciencemag.org/pipeline/archives/2012/11/29/when_drug_launches_go_bad, (Accessed December 13, 2018)

[15] Pharmacovigilance—CIOMS. Available from: https://cioms.ch/pharmacovigilance/becoming-the-cioms-member-2/ [Accessed: September 11, 2018]

[16] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. Available from: https://www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf [Accessed: September 11, 2018]

[17] Black Triangle Scheme-new medicines and vaccines subject to EU-wide additional monitoring, London. 2009

[18] Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems, European Medicines Agency, London. 2012

[19] European Medicines Agency. Clinical Trials—Clinical Trial Regulation. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp [Accessed: September 11, 2018]

[20] World Health Organization. The use of the WHO-UMC system for standardized case causality assessment. Uppsala: The Uppsala Monitoring Centre. 2005:2-7

[21] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981;**30**:239-245

[22] UMC. Signal Detection. Available from: https://www.who-umc.org/research-scientific-development/signal-detection/ [Accessed: September 13, 2018]

[23] Mann RD, Andrews EB. PHARMACOVIGILANCE Second Edition, John Wiley and Sons, Ltd, West Sussex, Second., 2007

[24] Chakraborty BS. Pharmacovigilance: A data mining approach to signal detection. Indian Journal of Pharmacology. 2015;**47**:241-242

[25] Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. British Journal of Clinical Pharmacology. 2004;**57**:127-134

[26] International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: Clinical Safety Data Management: Definations and standards for expedited reporting (E2A). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Oct 1994

[27] International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: Post Approval safety data management: Definations and standards for expedited reporting (E2D). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Nov 2003

[28] International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: Implementation working group electronic transmission of individual case safety reports (ICSRs) questions and answers , E2B(R3). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2004

[29] International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: Periodic benefit-risk evaluation report (PBRER). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Dec 2012

[30] International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: Pharmacovigilance Planning (E2E). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Nov 2004

[31] Cristiana Scasserra EN. Pharmacovigilance in Pediatric Age: The

Role of Family Pediatricians-Medicines for Children Research Network (FP-MCRN), J. Pharmacovigil. 2015;**03**:1-6

[32] Raine JM. An agency of the European Union Pharmacovigilance in Paediatric Population The PRAC's perspective, London. 2014