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WHO international drug surveillance programme

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Abstract

The WHO International Drug Monitoring Programme, which started about 40 years ago, aims in timely detection of rare but serious adverse drug reactions (ADRs) not revealed during the clinical trials. As more new drugs came into market, the Programme has expanded further since there is an increased need of drug safety surveillance, termed pharmacovigilance.[1] By the end of period, Uppsala Monitoring Center (UMC, previously WHO Collaborating Center for International Drug Monitoring) maintains nearly 3.87 million case reports in its international database.[2] Besides maintaining these case reports, various other activities are also undertaken by UMC to meet the basic objective of coordinating the worldwide drug safety efforts. The international center established under WHO serves to maintain the international database and serve the national centers that are members of WHO Programme.

Key-Words: WHO, Case reports, Database, Center, Pharmacovigilance.

Introduction

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality.[3] According to WHO, Adverse Drug Reaction is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. All medicine-related problems can be classified in one basic system, taking into account their characteristics and distinctions.[4] ADR reporting programs encourage ADR surveillance, promote the reporting of ADRs and stimulate the education of health professionals regarding potential ADRs. Spontaneous reporting program, a common method of drug surveillance is capable of recognizing ADRs in the daily medical practice, even though underreporting and absence of information on number of people actually exposed to the drug are its disadvantages.[5]The WHO Global Drug Monitoring Programme was set up in 1968 when about 10 countries from Australia, Europe and North America agreed to pool their reports which they have maintained in their respective national monitoring centers, in a WHO-initiated international drug monitoring project in Geneva. Thereafter, in 1978, the Programme and the overall operational responsibilities were transferred to Sweden with the establishment of WHO Collaborating Center for International Drug Monitoring in Uppsala, Sweden.[6]

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According to the Programme, each member country appoints a national center and is responsible for collection and evaluation of all the spontaneous reports which are suspected of ADRs sent by the health professionals.[7] Currently 84 countries are contributing to the WHO international database and therefore, are full members whereas 23 countries have applied for the membership and are associate members of the Programme. National Centers then submits the report in a clearly defined WHO format to UMC on regular intervals. These reports are then technically evaluated to provide for an opinion on the correctness of the diagnosis and causality, or if more data should be requested. The data is then screened four times a year, using Bayesian Confidence Propagation Neural Network (BCPNN) signal detection methodology for new and serious reactions. The Medical Dictionary for Regulatory Activities (MedDRA) is more commonly being used throughout the world, and the ICH (International Conference on Harmonisation) E2B format, which is a guideline for the transmission format for the information to be included on an adverse reaction case report.[8]

However, common problems with reporting which might pose a threat to *the* basic UMC objective of drug safety include:

- Delays in reporting
- Backlogs
- E-mails and mail don't reach the UMC/NC
- Not unique ID-numbers
- New drug names/ADR terms

- Misspelled drug names/ADR terms
- Language barriers
- Different interpretations of reporting standards

The Alliance approach in the area of drug safety, has a greater focus on safety in the systems of drug provision (including prescription and dispensing) and other systematic issues relating to safe drug provision, such as fraudulent drugs.[9] Thus the visions and goals of UMC are: [10]

- To prevent harm to humans from the effects of medicines
- Promote rational drug therapy by collecting, analyzing and evaluating all the reports received from different national centers
- To gather and share objective intelligence and opinion in the field of drug safety through open and transparent means of communication
- Never miss a signal' is a goal for the member countries in the WHO Programme.
- Facilitate the pharmacovigilance of member countries by the provision of information and tools
- Encourage the growth of pharmacovigilance activities around the world, in particular the establishment of new national centers
- Encourage existing national centers and other stakeholders in the field:
    - to contribute actively to the global vision of the WHO Programme
    - to use and share available information openly and transparently
    - to sponsor and support others in their pharmacovigilance activities
    - to exploit fully the resources of *the* UMC
- Stimulate the development of coherent, harmonized systems worldwide for pharmacovigilance, through education, training, promoting and participating in international forums, the promotion of best practice and the publication of guidelines
- Maintain and develop useful products, services and tools in pursuit of the vision and goals of the WHO Programme.

Present activities

1) Maintenance of international database: *the* VIGIBASE

The general work of the WHO Programme for International Drug Monitoring is supported by a database of individual case safety reports (ICSRs) reported globally. It is a computerized pharmacovigilance system, in which information is recorded in a structured, hierarchical form to allow for easy and flexible retrieval and analysis of the data. The data provided by the National Centers that are part of WHO drug monitoring Programme is stored in a relational database management system (RDMS), Mimer 8.2, which is ODBC (Open Database Connectivity) compatible and uses SQL for database communication. Member countries have centralized or decentralized reporting systems within their regulatory authorities or separate from them; they may rely on spontaneous reporting only. Earlier the WHO database was called INTDIS (International Drug Information System) and started in 1978.[11]

The model of the WHO database was designed in mid 90s based on the elements proposed in the CIOMS (Council for International Organizations of Medical Sciences) 1a document, which formed the basis for the ICH E2B format in the ICSR exchange. CIOMS has attempted to provide definitions and basic requirements for proper use of ADR terms. The work has concentrated on terms liable to be misinterpreted and those used for serious and frequently reported ADRs.[12] Now the process of receiving case reports from member countries is completely modified and rebuilt.[13] The structure and the basic elements of vigibase is explained in **Fig 1**. All reports submitted will be available in electronic format and are searchable even though they need not meet the UMC's standards for E2B format. Further, national centers can be able to upload and submit their reports directly into vigibase database along with some other information like reporting period, comments to UMC etc. All this is done through an upload interface. It would seem attractive to have a common, internationally accepted form for ADR reporting that could be put to immediate use in the field. The generic reporting form would give guidance as to what data items are important to collect.[14]

Search results in vigibase can be obtained by online search by the customers, or by request to UMC staff, or through ADRespherics i.e. by sending a request for a knowledge detection or data mining run. *the* UMC offers three different ADRespherics services developed after working on pilot-testing with major pharmaceutical companies. These services – Cumulus, Stratus and Nimbus – can be used separately, combined or commissioned sequentially. Instructions for coding individual items in the reports and technical specifications for submitting reports by computerized media are distributed to all national centers. For transfer of data to vigibase, national centers may use e-mails, CDs or diskettes or can use FTP (File Transfer Protocol) for electronic transfer of data and for national centers using vigibase online (now called Vigiflow) for

ADR reporting the data may be submitted automatically.[10, 11] For data to be stored in vigibase, it is subjected to technical evaluation using extensive quality-control procedure consisting of:

- Syntax check
- Inter-field coherence check
- Check for duplication of reports
- Check of drug names and adverse reaction terms.

Drug names and adverse reaction terms that are not found in the terminologies and all unrecognized codes were identified and corrected before entering into the database. Vigibase uses following terminologies:

WHO Drug Dictionary Enhanced (WHO-DDE)

WHO-Drug Dictionary is a comprehensive desk reference for giving information on variety of medicinal products. It is used as a reference source by pharmaceutical companies, clinical trial organizations and drug regulatory authorities for identifying drug names in spontaneous ADR reporting and clinical trials.[15] The recent collaboration with IMS Health will provide for inclusion of data from different countries, more data per country and also provides for fast and frequent updates. The dictionary provides proprietary and non-proprietary names of medicinal products used in different countries, together with all active ingredients. The WHO Drug Dictionary Enhanced, which contains the WHO's ATC classification is updated on a quarterly basis.[16] Different types of changes can be made in dictionary, namely change in drug code, deletion of medicinal product, change in drug names, changes in ATC codes. Most of the entries are prescription-only products. WHO-DD contains different files for identification of products namely the medicinal product file which contain the name of the product, generic or brand name; pharmaceutical product file containing more than one dosage form or more than one type of the same dosage form; therapeutic group and the active ingredient file. The products can be identified by a system, either by using a Medicinal Product ID which contain the information like product name, market authorization holder, country, strength, dosage forms etc or by Drug Record Numbers which allows a hierarchical grouping of drugs by their ingredients.

WHO-adverse reaction terminology (WHO-ART)

This terminology is used worldwide to serve as a basis of coding adverse reaction terms. The format of terminology is flexible enough so that new entries can be added without altering its structure and losing previous relationships. Besides in English, it is also available in 6 other languages- French, Spanish, German, Italian and Portuguese. It has a hierarchical structure beginning with body system/organ level, within which there are grouping terms (general or high level). The frequently used 'Preferred terms' provide for precise identification of medical terms and the commonly used verbatim terms like 'Included terms' help to point to the closest preferred term. Besides being flexible, the maintenance of terminology is dynamic due to its overall robustness. 'Critical terms' are also included to give an indication of serious disease state including death. System Organ Class is a set of terms included in WHOART which are not related directly to effect of drug. A methodology for clustering WHO-ART formally defined terms using semantic distance is documented.[17] WHOART is either available in paper print or computer files as a copy of the database. A comparision of terminologies, namely MedDRa and WHOART revealed that both are compatible.[18] WHO-ART to MedDRA mapping will enable users of WHO-ART to map their ADR reports to MedDRA.

ICD (International Classification of Diseases) codes for identification of indication for the use of drug(s), cause of death and predisposing factors.

2) Knowledge detection/data mining: signal detection and analysis

Data mining is defined as the search for relationships and global patterns that exists in large database but are hidden among vast amounts of data.[19] WHO has defined signal as 'Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Signal detection compromises of: selection of adverse event association of possible interest (the preliminary assessment) and a follow up of how the signal develops.[20] Data mining should be considered as a term for the application of tool(s) to analyze large amount of data in a transparent and unbiased fashion.

All data mining approaches to signal detection (proportional reporting ratio, PRRs, reporting odd ratio, ROR etc.) have in common that they look for disproportionalities in data i.e., a relationship or pattern standing out from the database background experience.[21] The advantages of this approach are:

- No external data needed
- They may be expected to counteract some of the biases related to variable reporting.

The only disadvantage is that, as the background data changes for all drugs in the data set, so does the expectedness for the drug-ADR combination in question. Moreover, there also some pitfalls and

limitations that have been discussed in the use of data mining techniques.[19, 22]

When the new data has been processed and entered into database, a BCPNN scan is run to generate statistical measurement for each drug-ADR combination.[23] The resulting data are presented in 2 steps:

- The resulting Combination database: The Combinations database is a table listing summarized data for all combinations of suspected drugs and ADRs that have been recorded in case reports received by the UMC.
- An Association database is generated by selecting those combinations that pass a preset threshold which is lower 95% confidence limit of the information component (IC-2SD).[24]

A line listing of all drug-ADR combinations reported over the last quarter is produced by the UMC Signal team and sent to NCs in form of table. The Combinations database table includes the Information Component (IC) value.[25] All associations are followed automatically for 2 years, the data being checked at 6-month intervals. The Association database is sent to expert review panel for evaluation and before entering in the database it is checked against standard reference sources like PDR, Martindale etc.

Bayesian confidence propagation neural network (BCPNN)

BCPNN methodology was designed to identify statistically significant disproportionalities in a large data set, with high performance, to allow for automated screening of all combination of drugs and adverse reaction in vigibase. For any individual report in the database, there is certain probability that a specific ADR is listed on it-the *prior probability*. If that case report has a specific drug on it, the probability of the ADR now being present is different-the *posterior probability.* If the posterior probability is higher than the prior probability, then presence of drug on the report has enhanced the chance of the ADR being present.[26] The dependencies are selected using a disproprtionality called *Information Component* (IC).

$$IC = \log_2 [P(x,y)/P(x)P(y)]$$

The IC value is based on:

- the total number of case reports with drug X (Cx) and its probability P(x)
- the total number of case reports with adverse reaction term Y (Cy) and its probability P(y)
- the number of case reports with the specific drug-ADR combination (Cxy) and their probability P(x,y).

When IC is positive for drug-ADR association, this implies drug-ADR pair is more strongly associated than expected compared to c_x and c_y, and reverse applies to negative IC values. IC values close to zero present independence between drug and ADR- that is, prior and posterior probabilities are same. For every drug-ADR combination, we determine an interval estimate of the IC as a measure of certainty of the value of IC. Every 3 months IC and its confidence interval are calculated for all drug-ADR pairs. Combinations, where the lower 95% CI>0, are highlighted for clinical review. Moreover, a number of possible subsidiary selection algorithms are added as a second filtering step before potential signals were sent to the UMC expert panel for clinical review.[27] The steps involved in the processing of data signals for entry into vigibase is explained in **Fig 2**.

BCPNN is a neural network where learning and inference are done using Bayes' Law. The term neural network is used to describe a wide range of different computational architecture and is made up of many simple processors (units), where each unit has a small amount of local memory. Recently a method for anlaysis of complex quantitative associations using credibility interval estimate is proposed.[28] The BCPNN methodology have been further extended for analyzing isolating patterns for both rofecoxib and celecoxib, to improve data quality, especially the detection of duplicate reports and its use in the 2 million patient-record IMS Disease Analyzer.[29]

One of the advantage of using BCPNN is that it can search for patterns of associations between fields that are not determined *a priori:* it can find novel complex relationships. The BCPNN can manage large data-sets, is robust in handling very incomplete data, and may be used within data-sets filled with complex dependencies to find patterns of information. The performance of the BCPNN methodology to find new ADR signals has been evaluated.[30] Two important applications that the UMC is developing based on BCPNN are syndrome detection and identification of possible drug interactions.

However a recent study indicates that the total number of signals detected by IC-2SD is lower than other methods, namely proportional reporting ratio (PRRs) and reporting odd ratio (ROR) but proportion of serious signals detected by IC is higher than the two.[31] Further, in comparision with IC-2SD, these methods are highly sensitive but had a rather lower specificity.[32]

3) Causality assessment

No common standard for the detailed assessment of causal relationship between the drug and ADR has been internationally agreed. A number of complicated

and comprehensive algorithms for causality assessment have been proposed[33, 34], but these algorithms have been found to decrease variability among ratings produced by different individuals. A performance comparision of the decisional algorithms in assessing the causality of the ADR has been documented.[35] *the* UMC has proposed a practical tool for assessment of case reports that is basically a combined assessment taking into account the clinical-pharmacological aspects of case history and the quality of documentation of observation. The terminology used for causality assessment is given in Table 1.

4) Communications and publications

The UMC has an important role to play as a communication center- providing and disseminating information on drug safety at the service of drug regulatory agencies, pharmaceutical industry, national centers, researchers and other groups in need of drug safety information. Around 225 requests per year are received for special database searches and investigations. Access for non-member parties is subjected to some confidentiality restrictions agreed by Programme members. Use of information released is subject to a Caveat Document to explain its proper use.

The Erice Declaration, and the work arising from it, set out not only the practical demands of effective communication, but also the principles and practices essential for ethical communication in pharmacovigilance: openness, transparency and universality were amongst these.[35] Ethical effective, modern communication practices ensure:

a) Pateints understand their treatment and any possible ADRs occurring during treatment.
b) Secrecy and suspicion are avoided.
c) All health care professionals are informed of recent drug safety issues.
d) More focus on improved patient care and public health.

In cooperation with WHO, *the* UMC provides drug safety information in the *WHO Pharmaceutical newsletter*, giving wider distribution of information to member countries either electronically or printed. Six issues are generally published annually.

The UMC co-operates with Adis International in journal *Reaction Weekly* to provide additional information in 'Adverse reaction Case Report' in the journal.

Uppsala Reports is informal, informative magazine which gives general information about the developments within the WHO Global Monitoring Programme and is available on the UMC homepage (www.who-umc.org) as well as provided to about 3000 recipients.

Flexible on-line retrieval Programme is made available by which users can perform standardized searches by themselves called **Vigibase Online** (now termed **Vigiflow**). *the* UMC has been collaborating with the Swiss medicines agency, Swissmedic (IKS), on the challenge of improving ADR reporting. Vigiflow is designed on top of E2BXML format, with E2B compatible look-up table. To ensure that system is in validated state, the tool is maintained according to GxP standards. The basic signaling process involved in vigiflow is explained in Fig 3.

The WHO-DDE and other terminologies are integral part of the tool. The advantages vigiflow are:

- No access to any un-authorized user.
- Streamlined on-line reporting of ADRs by the physician.
- Assessment is done by both regional center (called First Level Assessment) and also by national centers (called Final Assessment).
- After completion, report can be entered directly into vigibase and can be searchable online and has built-in statistics.
- Multilingual, cost-effective and timesaving.

the UMC is maintaining an e-mail discussion group exclusively among the member countries called **Vigimed,** which allows for rapid exchange of information around the world on drug safety issues and to make general request for information related to specific cases.

A great number of publications are produced from UMC, both technical, which are intended for the national centers participating in the WHO Programme, and publications for wider audience with an interest in the field.

5) Training and education

Training and capacity building in pharmacovigilance are required for staff working at peripheral health facilities because adverse reactions are not well understood and, in many countries are seldom detected and reported. Monitoring is often neglected or absent, and staff therefore need to be made aware that ADR monitoring is a part of good professional practice. The identification of ADRs, the completion of reporting forms and procedures for patient referral all need to be taught. Clinical teaching in the diagnosis of adverse reactions is essential.[37]

The UMC has organizing training courses to foster education and communication in pharmacovigilance

and has discussed several methods to build awareness in pharmacovigilance.[38] Since 1993, *the* UMC offers every second year 2-week training course in adverse reactions and their monitoring. In February 2007, a pharmacovigilance training course was organized for Francophone countries. This year UMC's biennial course 'Pharmacovigilance- the study of ADRs' took place in May 2007 with international students from 30 countries. There is a great need for much more attention to drug safety issues in medical and pharmacy training at undergraduate and postgraduate levels. Members of the UMC team frequently take part in regional or national pharmacovigilance training courses in different parts of the world. A number of courses are also available via the UMC website. Members of the UMC team have provided communication skills training in a number of countries, and the Programme for the Uppsala course always includes this important topic. Crisis Management is a recent addition to the range of subjects taught.

Every year representatives of national centers are invited to a meeting arranged jointly by WHO and one of the participating countries. At these meetings, technical issues are discussed, both in relation to how to improve the global drug monitoring and concerning individual drug safety problems. These meeting are important for establishment and maintenance of personal relationships contributing to good communications among the member countries.[39]

6) Monitoring of herbal medicines

Herbal Medicinal Products poses a risk when are contaminated (e.g. with heavy metals) or adulterated (e.g. with prescription drugs).[40] The field of herbal safety monitoring is still in its state of infancy as the yield of information from spoantaneous adverse drug reactions reporting schemes was even poorer for this sector than for other medicines.[41] The UMC has published two new guides on herbals: Guidelines for Herbal ATC Classification and Herbal ATC Index.[42] The UMC has established a project with the aim of attaining global standardization for herbal medicines. The scope is to standardize information about herbal medicines, including their scientific names and therapeutic implications, which can vary widely between countries. The structure of the ATC system, developed for classification of orthodox medicines, has been used as a basis for the Herbal ATC structure. In the WHO database there are presently 16,154 suspected herbal case reports. The products that are included in the WHO Herbal Dictionary contain only substances of natural origin. The UMC group is collaborating with the Department of Botany, Uppsala University and the Royal Botanical Gardens at Kew in the UK, and with several other international experts. The UMC has developed nomenclature system based on scientific binomial names, optionally with author and plant part used.[43]

Conclusion

Pharmacovigilance programs are being established in many developing countries and more countries are becoming the member of the WHO-UMC Programme. Much information on drug safety is now collected and subject to expert analysis and review. However, drug induced morbidity are one of the major causes of hospital related admissions. Many improvements have been made, but the primary immediate need is for effective communications to health professionals. This will involve a more focused approach on finding the problems associated with drug use in community and measures to improve it. In near future, the provision of better information to health professionals and time to analyze them is the main challenging task. Only then patients can feel that they will receive rational treatment, will have less chance to experience ADRs and best chance of relevant experiences of ADRs being reported.

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Fig 1: **Structure of Vigibase**

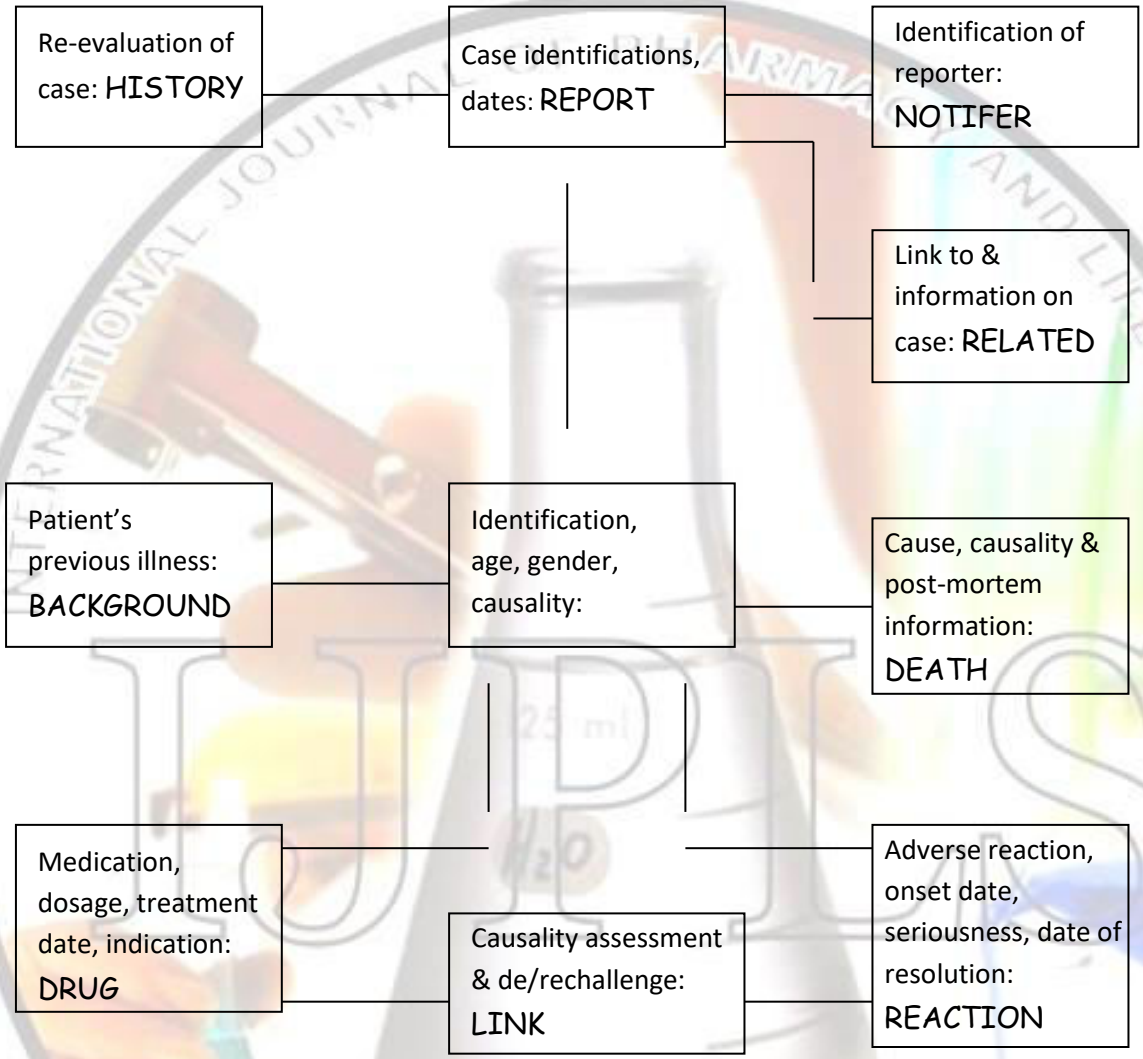

Fig. 2: Data Signalling Process

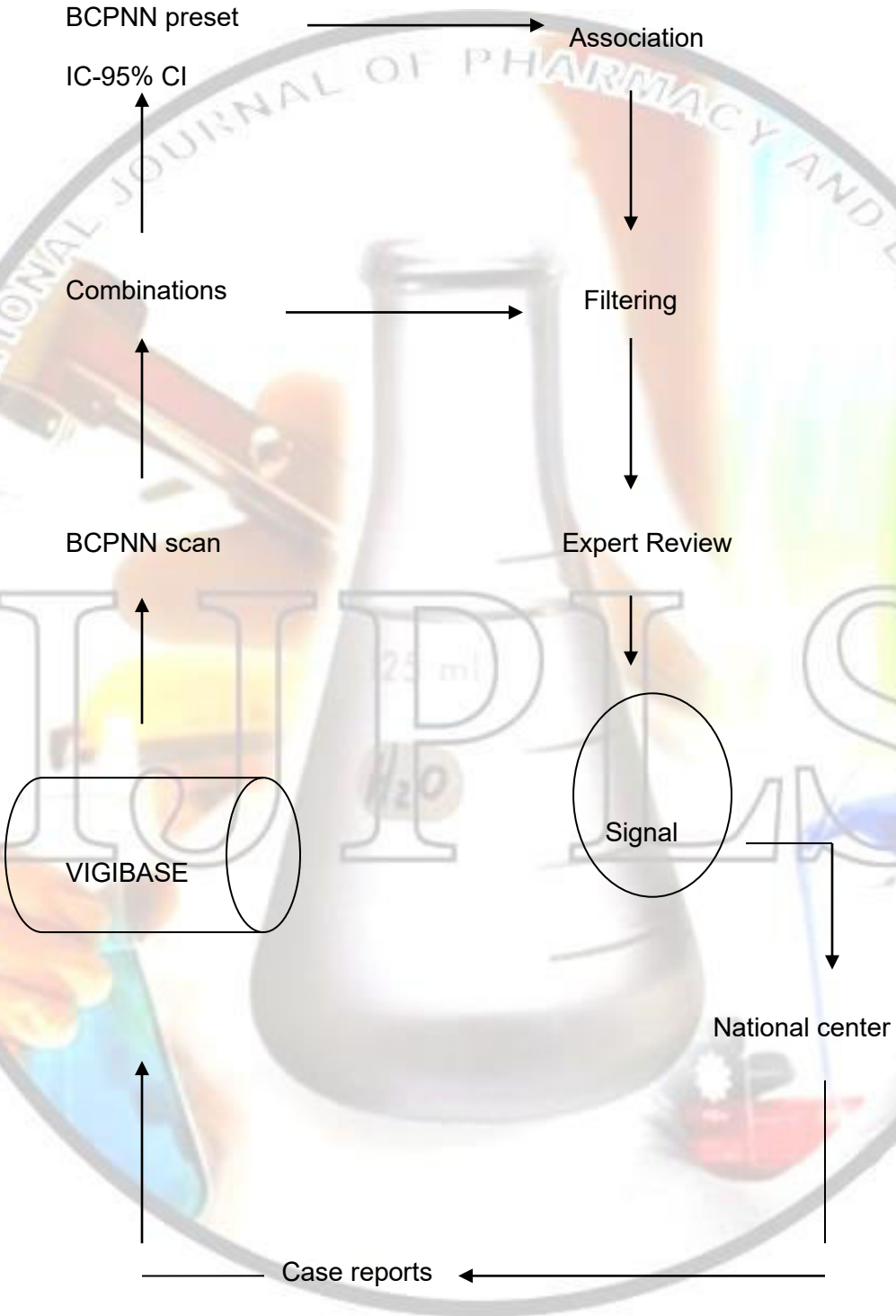

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Fig 3: Vigiflow: Route of ADR report

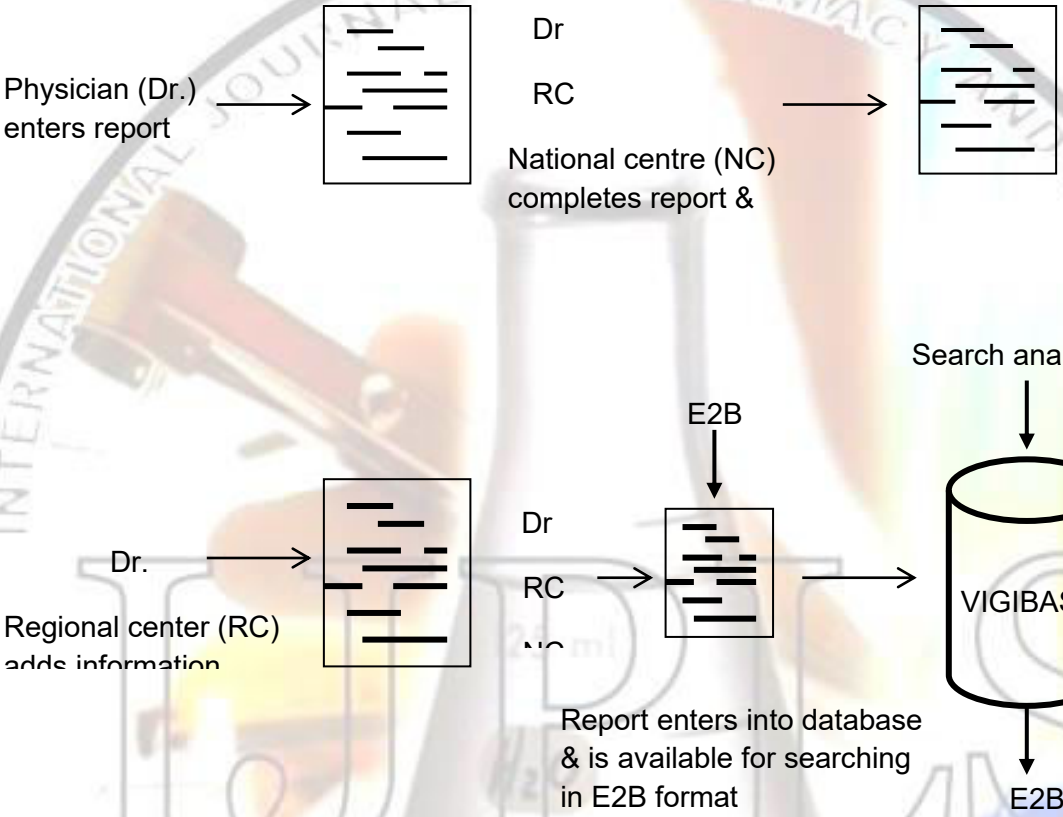

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Table 1: Causality assessment of suspected adverse reactions

CERTAIN

A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

PROBABLE/LIKELY

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge do not fulfil this definition.

POSSIBLE

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

UNLIKELY

A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

CONDITIONAL/UNCLASSIFIED

A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

UNASSESSIBLE/UNCLASSIFIABLE
A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.