VigiBase, the WHO Global ICSR Database System: Basic Facts

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The main aim of the WHO International Drug Monitoring Programme, started in 1968, is to identify the earliest possible pharmacovigilance signals. The program now has more than 80 member countries from all parts of the world contributing individual case safety reports (ICSRs) to the WHO Global ICSR Database System, VigiBase.

VigiBase is maintained and developed on behalf of WHO by the Uppsala Monitoring Centre (UMC), situated in Uppsala, Sweden. The database system includes the ICH E2B compatible ICSR database, the WHO Drug Dictionaries (WHO-DD and -DDE), and the medical terminologies WHO Adverse Reaction Terminology (WHO-ART), International Classification of Diseases (ICD), and the Medical Dictionary for Regulatory Activities (MedDRA).

Apart from data management and quality assurance tools, the VigiBase system includes a web-based reporting tool, an automated signal detection process using advanced data mining, and search facilities, available to the member countries and, on request, to other stakeholders.

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INTRODUCTION

The WHO International Drug Monitoring Programme started in 1968, with 10 countries pooling data from their existing national spontaneous adverse reaction reporting systems. The aim of the program was to prevent drug disasters like the devastating fetal malformations caused by thalidomide in the early 1960s.

The rationale for bringing spontaneous reports into one international database was to enable the earliest possible detection of drug-related problems, and one of the primary tasks at the outset of the WHO program was to develop an international signaling system.

In 1978, the scientific and technical responsibility for the program was transferred from WHO in Geneva to a WHO Collaborating Centre in Uppsala, Sweden, set up specifically for this purpose. The center is a self-funding, non-profit foundation, now known under its field name, the Uppsala Monitoring Centre (UMC).

The UMC is responsible for development of the international system on the basis of a two-way flow of information on suspected adverse reactions to medicines, in collaboration with the national centers participating in the WHO program. The main tasks of the UMC are to:

- collect and analyse reports of adverse drug reactions from worldwide members of the WHO Drug Monitoring Programme and to issue international signals of drug safety concerns arising from the data;
- actively support and provide training both for aspirant countries in establishing their own national drug safety surveillance systems, and for current members in maintaining and developing their systems;
- develop the science of *pharmacovigilance* (drug safety surveillance), in theory, methodology, practice and research; and
- communicate the drug safety message throughout the world, to all stakeholders.

The WHO global individual case safety report (ICSR) database system, VigiBase, now holds more than 3,800,000 ICSRs contributed by the national centers (as of March 2007). VigiBase is used directly by the national centers and is accessed indirectly by other regulatory bodies, the pharmaceutical industry, and academia through data requests to the UMC.

CONTRIBUTORS

More than 80 countries participate in the WHO program, and another 17 countries are associate members, not yet actively contributing data

F I G U R E   1

Countries participating in the WHO International Drug Monitoring Programme, December 2006.

□ Associate member
■ Member

(see Figure 1 for a map, and Table 1 for the regional distribution of member countries as of December 2006).

As shown in Table 2, a majority of the ICSRs in VigiBase are received from Europe and North America, including 9 of the original 10 WHO program members on the top 15 list. Thailand and Cuba are examples of newer members contributing large numbers of reports. If country population is taken into consideration, some countries with smaller populations have a more prominent role, such as New Zealand, Ireland, Switzerland, and the Nordic/Scandinavian countries (see Table 3).

The ICSRs in VigiBase come from both regulatory and voluntary sources, depending on the national pharmacovigilance system. Some national centers accept reports only from medical practitioners; others accept reports from a wider spectrum of health professionals. Some national centers include reports from pharmaceutical companies in the information submitted to the collaborating center; other national centers do not. An overview of the different reporting sources in the International Conference on Harmonization (ICH) regions and the non-ICH countries is shown in Figure 2.

Although VigiBase is primarily intended to be a spontaneous adverse drug reaction (ADR) report system, the database includes cases with a varying degree of suspicion, both on the level of the initial reporter, and on the causality ascertainment made by the national center. Case reports from studies or special monitoring are also included, when provided to the UMC. These categories are flagged so that they can be distinguished from other report categories.

THE DATA

THE DATABASES

VigiBase is a relational database management system (RDMS) that is ODBC (open database connectivity) compatible and uses SQL for the database communication. The RDMS resides on a server that is accessible through client-server applications, ODBC, and Internet applications (using standard web browsers as the interface).

The main databases in VigiBase, apart from the ICSR database, include medicinal products, the WHO Drug Dictionary (WHO-DD), and medical terminology classifications WHO-ART,

T A B L E   1

Regional Distribution of Member Countries in the WHO International Drug Monitoring Programme		
Region	**Full Members**	**Associate Members**
Africa	9	9
Asia/Pacific	24	8
Europe	33	
North America	2	
Latin America/Caribbean	11	2

ICD, and MedDRA. These linked databases are described in the section Controlled Vocabulary and Classifications.

VigiBase is updated with incoming ICSRs on a continuous basis. National centers are recommended to send reports at least quarterly; most national centers adhere to these guidelines, and several report more frequently.

FORMAT AND DATA EXCHANGE

The current data model of VigiBase was designed in the mid-1990s based on the data elements proposed in the Council for International Organization of Medical Sciences (CIOMS) 1a document, which formed the basis for the ICH E2B format for ICSR exchange. Being E2B compatible, VigiBase allows for processing of incoming data in the E2B format. Currently, E2B format ICSRs are received from 25 countries in the ICH regions.

The issues of missing data, together with underreporting, are well-recognized problems for pharmacovigilance in general (1–3), but the fact that busy health professionals do not fill in all the expected data fields does not invalidate their concerns (but can make them more difficult to interpret). So although VigiBase, like any E2B database system, allows for the transmission and storage of a large amount of data for each individual case, there are few reports that have even the key data elements filled in, not to mention all possible data fields. This problem is not solved by an extensive format and has to be considered at each analysis step.

The UMC has, in collaboration with the Swiss authority Swissmedic, developed a web-based reporting tool, VigiFlow. This tool allows a streamlined flow of information, both ways, from the original notifier via regional centers and the national pharmacovigilance center to VigiBase. The data are stored directly in the database, removing the need for extraction and transfer between different database systems. This reporting tool is available to all national centers; currently there are 15 users.

A third option, for countries that do not yet produce an E2B format output or use the web-based reporting tool, is to send ICSRs to the

TABLE 2

Top 15 Contributors to Vigibase 2000–2005, by Number of Reports (Rounded Off to Nearest 1,000)		
Country	No. Reports	Start Year
United States	954,000	1968
UK	116,000	1968
Canada	65,000	1968
Germany	64,000	1968
Australia	60,000	1968
Thailand	56,000	1984
Netherlands	45,000	1968
Spain	40,000	1984
France	40,000	1986
New Zealand	17,000	1968
Sweden	16,000	1968
Italy	12,000	1975
Switzerland	11,000	1991
Ireland	10,000	1968
Cuba	9,000	1994

Start Year is the year in which the country joined the WHO International Drug Monitoring Programme.

TABLE 3

Top 15 Contributors to Vigibase 2000–2005, by Average Number of Reports Per Million Inhabitants Per Year	
Country	Reports/ Million Inhabitants
New Zealand	718
United States	538
Australia	494
Netherlands	454
Ireland	420
Canada	331
UK	320
Sweden	300
Denmark	249
Switzerland	245
Norway	178
Spain	163
Finland	159
Thailand	141
Cuba	135

Sources of reports in VigiBase from ICH and non-ICH countries. JP, Japan
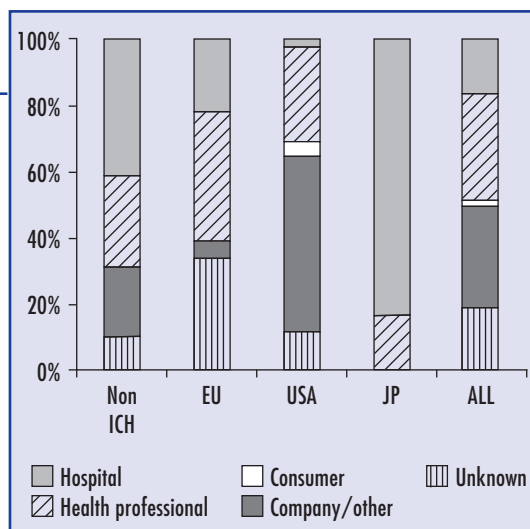
UMC as ASCII text files, in the old WHO format, which is a subset of the E2B format.

CONTROLLED VOCABULARY AND CLASSIFICATIONS

VigiBase includes free text fields, for example, for patient disease background information and descriptions of the adverse reactions. However, most fields are linked to controlled vocabularies (lookup tables) that contain predefined, allowed values, expressed as formatted text or codes. When linked to a field in a database table, the lookup table ensures that a value entered in that field matches an existing value in the lookup table. Lookup tables also allow for translations of values into different languages, as well as short and long text versions for each value stored.

At the start of the WHO program in 1968, hierarchical classifications for coding adverse reactions (WHO-ART) and drugs (WHO-DD) were created, with the purpose of aiding data input and analysis. By linking the recorded case safety data to the corresponding classification, the data can be aggregated and analyzed at different levels of precision.

Medical and drug product classifications also serve as controlled vocabularies for data entry in that any term or code value in an ICSR is checked against the corresponding values in the classification.

Medical Terminology. National centers may use either WHO-ART or MedDRA terms or codes when reporting to VigiBase. Both allow for groupings and aggregation of data on different levels, from broad system-organ classes to individual signs and symptoms. The main difference between WHO-ART and MedDRA is the number of terms included. WHO-ART has around 2,000 preferred terms and 3,000 lower level terms; MedDRA also has one more grouping level: high-level grouping terms (HLGT). On the preferred and included term levels, WHO-ART is a subset of MedDRA.

Until now, MedDRA terms in incoming reports have been mapped to the corresponding WHO-ART terms by UMC staff; all ICSRs have been coded in WHO-ART only, and database output has been provided according to the WHO-ART hierarchy. However, since the database system is not restricted to the use of only one medical terminology, the UMC has decided to fully implement MedDRA into VigiBase and to run WHO-ART and MedDRA in parallel. An obvious advantage in doing this is that there is flexibility both on the input and output sides; those who so wish can continue using WHO-ART, whereas MedDRA reports will not have to be recoded. Also, the impact of the different classifications on signal detection can be researched using live data.

To facilitate migration between the different coding systems, the UMC and the MedDRA Maintenance and Support Services Organization have jointly developed a WHO-ART–MedDRA term-code translation on the WHO-ART preferred term level, which is available from 2007 to users with a license for either classification.

Medical terminologies are also used for the coding of indication for drug use. VigiBase accepts WHO International Classification of Diseases (ICD) or MedDRA codes for this data element.

Drug Classification. The WHO Drug Dictionary is an integral part of VigiBase. All medicinal products mentioned in ICSRs provided to VigiBase are linked to the WHO-DD classification. This applies both to drugs reported as "suspected" of having caused the adverse reaction, and those reported as "concomitant" or "interacting."

In the past, data entry in WHO-DD was mostly

driven by what was reported in ICSRs: Incoming reports were matched against the WHO-DD information, and any medicinal product not included would be manually entered into WHO-DD by UMC staff. In addition, newly registered drugs posted on the FDA and European Agency for the Evaluation of Medicinal Products (EMEA) websites were regularly included, as well as drug product entries requested by WHO-DD users.

However, through a collaboration with IMS Health, the UMC has extended the number of products in WHO-DD considerably over the last couple of years. The March 1, 2006, version incorporated all IMS product data from 69 countries, in addition to previously held data from the countries submitting ICSRs to WHO.

The extended version, WHO Drug Dictionary Enhanced (WHO-DDE), March 1, 2007, contained:

- 1,095,000 medicinal product records (products with a given name, ingredients, form, strength, and market authorization holder in a given country; including records with one or more of these data ele-

ments recorded as "unspecified" to allow for data entry at different levels of specificity)
- 185,000 unique medicinal product names
- 33,000 unique combinations of ingredients
- 9,800 unique ingredient names (and an additional 9,000 synonyms)

Table 4 shows the different numbers of medicinal product records by country for those countries with the highest number of products in WHO-DD.

The majority of WHO-DD entries refer to prescription-only medicines, but many over-the-counter or pharmacist-dispensed products are also included. Vaccines, biotech and blood products, diagnostics, and contrast media are also covered to some extent.

The WHO-DD also incorporates herbal medicinal products with a unique new classification system based on the anatomical-therapeutic-chemical (ATC) classification, and which links to internationally accepted botanical names and synonyms (assigned in collaboration with the Royal Botanical Gardens, Kew, UK). This is an im-

Medicinal Product Records in WHO-DD, March 1, 2006, for the Top 15 Countries			
Country	Medicinal Product Records	Product Names	Combination of Ingredients
United States	72,700	9,100	3,800
Puerto Rico	51,900	3,600	1,600
India	40,800	14,500	2,100
Germany	37,400	10,700	5,200
Japan	36,500	15,600	3,600
China	29,000	4,100	1,500
Taiwan, Province of China	24,100	7,700	1,700
UK	24,100	7,400	3,300
Thailand	23,700	7,600	1,600
Pakistan	21,000	6,400	1,300
Russian Federation	20,500	3,800	1,600
Republic of Korea	20,500	7,800	1,800
Netherlands	20,100	3,400	1,900
Brazil	17,100	5,500	1,600
Indonesia	17,000	5,500	1,800
The second and third columns are unique product names and unique combinations of ingredients.			

TABLE 4

portant development, considering the increased use of herbals and traditional medicines all over the world, and therefore the increased need for safety monitoring of these products.

Thanks to its hierarchical structure, the WHO-DD allows for data aggregation on the following levels of precision:

- ATC level, denoting the main indication for which a medicinal product is used; the ATC is in itself a hierarchy, with five levels
- generic (ingredient or combination of ingredients) level
- active or inactive moiety level
- pharmaceutical product level (combination of ingredients, form, and strength)
- medicinal product name level
- medicinal product level (referring to the named product marketed and sold in a particular country, with a particular ingredient, form, and strength)

Each drug record is assigned a unique identifier on the medicinal product level and a three-level hierarchical code, which groups products based on their active ingredients, base or salt of ingredient, and product name (the WHO Drug Record Number System). The first level of this identifier is sometimes referred to as the pharmaceutical product, virtual product, or clinical product. In addition, all drugs with the same ingredients are allocated the same preferred name.

Since 1968, the following main data elements have been recorded for each drug product: product name, name source and source version, company, country, active ingredients, CAS numbers, and therapeutic indication according to the ATC classification.

In connection with the implementation of the new, extended version of the WHO database system, the drug database was also extended, so that much more detailed information on medicinal products could be captured. The database model and the nomenclature used for the data elements are based on the European Committee for Standardization (CEN) PreStandard prEN 12610 Health Informatics—Identification of Medicinal Products.

For the purpose of international pharma-

covigilance, it is unrealistic, and certainly not cost effective, to populate the "ideal" data set provided for by the new drug database format. Therefore, the additional level of detail currently used consists of a limited number of data elements such as form and strength.

QUALITY MANAGEMENT

As part of the processing into the WHO database, each incoming report is checked according to predefined quality criteria. Syntactic accuracy is obtained using controlled vocabularies (see above): entered values are compared and checked against reference classifications and lookup tables containing permissible data values.

Reports that contain rejected values are flagged and subsequently examined by UMC staff. After correction of the problem, the report is reprocessed. Missing data do not lead to a rejection, unless they involve one of the mandatory fields. Currently, these are reporting country, case ID, (at least one) medical term, and (at least one) drug.

Adverse reaction terms are checked against WHO-ART/MedDRA; drug names are checked against the WHO-DD; the values in those fields that are linked to a lookup table are checked against these. In addition to these checks, reports are also matched against a knowledge database that contains correct values for previously identified errors or synonyms to accepted values.

The main reason for rejection is due to the reporting of drug names that are not included in the WHO-DD. Many of these are misspellings or drug names recorded using a different nomenclature than that of the WHO-DD. These are corrected and, when applicable, entered into the knowledge database. In case of new, valid products, UMC staff make the necessary updates of the WHO-DD.

The web-based ADR reporting tool, VigiFlow, has undergone a GxP validation process, and all new database development projects adhere to good pharmaceutical practice (GxP) standards. To ensure good quality management, all UMC staff working with the VigiBase system receive continuous quality management training.

DOCUMENTATION GRADING

In the 1990s a documentation grading field was added to VigiBase. The grading information is used for statistical purposes and to identify problems related to missing or erroneous data in the reports received. It is also used to facilitate the identification of well-documented cases for the purpose of the initial clinical review, which is part of the signal detection process. The documentation grading is highlighted in the standard output from regular screenings of the database for easy filtering of reported drug–adverse reaction combinations with a high score.

The grading is a score generated for each report as the result of an algorithm including the following core fields (apart from the mandatory fields: reporting country, case ID, adverse reaction, and drug):

- Age and gender
- Onset of reaction and treatment dates
- Patient or reaction outcome
- Drug dosage
- Route of administration
- Indication for treatment

In connection with an upgrade of VigiBase, which started in 2007, an extended documentation grading system will be implemented. The underlying principle is based on a change in philosophy regarding ICSR processing rules: Instead of rejecting a report at the data entry point because of an error (which might be trivial), the report should be accepted but have good descriptors of the following quality parameters:

- Completeness
- Relevance
- Duplication
- Accuracy
- Consistency
- Precision

Thus, the new processing rules will include a greatly reduced number of "gate-stopping" logical checks; these will instead be incorporated into the grading system, storing information with each ICSR on its documentation quality. Apart from an improved processing speed, the documentation grading will allow flexible data retrieval, taking the quality dimension into consideration.

DATA RETRIEVAL AND ACCESS

The main database search tool, VigiSearch, is a web-based program that runs against the current database. It includes an interface for user-defined database queries and standard preformatted outputs, ranging from summary listings such as number of ICSRs by year, country, reaction, or drug (in various combinations) to CIOMS line listings, to the individual ICSR. VigiSearch also has integrated medical terminology and WHO-DD browsers for easy selection and aggregation of data.

In addition, a standard data mining output (Combinations Table) is currently produced four times per year using the UMC Bayesian Confidence Propagation Neural Network (BCPNN) data mining tool, VigiMine. VigiMine can also be used for ad hoc data mining runs. Currently it is only available to UMC staff, awaiting an integration into the VigiSearch interface.

In some instances, none of the standard tools provide sufficient flexibility; for example, not all database fields are searchable in VigiSearch. To cover all data retrieval needs, UMC staff are trained to perform ad hoc retrievals using SQL query statements and to produce outputs using report generators.
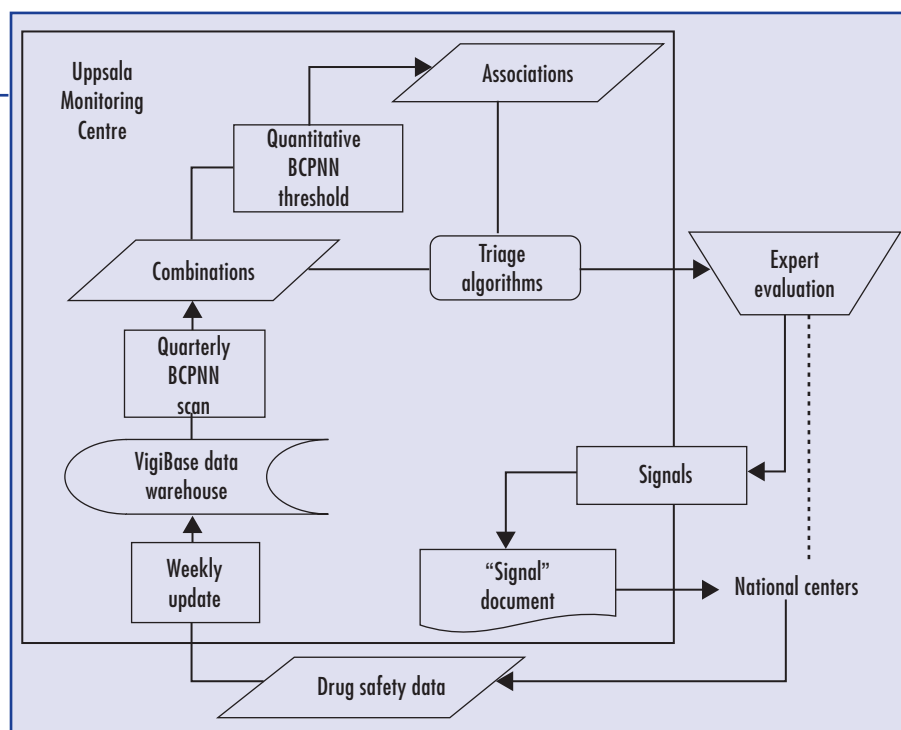
National centers have full access to the contents of VigiBase. They receive all regular data output from UMC and have passwords to the VigiSearch web program. Also, national centers can request ad hoc data retrieval, to be performed by UMC staff.

Other stakeholders can request database searches too; this service is available to any inquirer with a legitimate interest in pharmacovigilance data. To avoid misinterpretations and misuse of the data, each search result comes with a caveat document that contains guidelines for interpretation and data use.

The current standard ICSR display contains the detailed case information, except some free text fields and any confidential patient or reporter details. This latter information was previ-

ously not included at all in VigiBase, but the E2B format allows transmission of information that can be regarded as sensitive. The complete ICSR data may be released outside the WHO program members, but only by explicit permission from the data provider, and on a case-by-case basis.

SIGNAL DETECTION AND ANALYSIS

Since 1998, routine data mining of the WHO database has been carried out using a BCPNN. Like all quantitative signal detection tools, the BCPNN method aims to detect what is more frequently reported than expected relative to a background of other reports. It uses a Bayesian statistical approach and a measure of disproportionality, the Information Component, which is calculated as a logarithm of the observed/expected ratio. The method has been tested, and over a 7-year period nearly 50% of the identified drug-ADR associations were subsequently cited in the literature (4).

The data mining is an integral part of the UMC signal detection process, together with a triage procedure for additional filtering of data and manual expert clinical review undertaken by a group of more than 30 international experts (see Figure 3 for a schematic process overview).

The resulting signals are made available to all national centers and to pharmaceutical companies, for their own branded products. The UMC has made surveys of the usefulness and use of signals from the WHO database, which have confirmed that national centers find them both timely and valuable (5).

It must be pointed out that the WHO definition of *signal* does not include any statement or implication that a signal means that there is evidence of a causal relationship—the whole idea with the WHO monitoring program was to identify potential problems as early as possible. In doing so, there will always be some signals that can later be refuted or further explained, but, in waiting for final evidence, the duty of early warning cannot be fulfilled. However, it should be made quite clear that a WHO signal is merely a starting point, a hypothesis, and rarely has the level of evidence needed to be the sole source of restrictive regulatory action.

To further improve the UMC's signal detection function, new tools for unsupervised pattern recognition using artificial intelligence have recently been added to identify new complex and subtle relationships in VigiBase (6). These new tools have already shown their practical useful-

ness in identifying possible duplicates in the database (7).

Another facility, which is used in further analysis and signal strengthening, is calculation of reporting rates using denominators from IMS Health's sales and prescription data, which cover a large number of countries in the world (2).

Spontaneous reports are also likely to provide much useful information in the future. However, there is also a wealth of information contained in health care databases, providing real-life numerators and denominators from the same data sets. In 2005, the UMC completed a pilot development in which the VigiMine tool was adapted to data mining of IMS health care databases. Further work in this new area is ongoing.

CONCLUSIONS

ADVANTAGES OF THE WHO DATABASE SYSTEM

The WHO individual case safety reporting system and its database VigiBase are built on ICSRs provided from more than 80 countries all over the world. As of March 2007, VigiBase contained 3,800,000 reports. The advantages of spontaneous reporting systems apply also to VigiBase: continuous data collection, low cost, and broad population coverage (at least in theory).

Although the data in VigiBase are more heterogeneous than in national pharmacovigilance databases, due to, for example, different medical practices and regulatory requirements, it does offer opportunities to make country comparisons and to identify and analyze differences between countries or regions.

The ICSRs are stored in an ICH E2B-compatible database, and all data from 1968 onward are in the same database, in the same format: legacy data from 1968 to 2002 were converted to the new format when the database structure was revised.

The VigiBase database system includes linked databases containing medical and drug classifications: WHO-ART/MedDRA, WHO ICD, and WHO-DD. These classifications enable structured data entry, retrieval, and analysis at different levels of precision and aggregation. Other data fields (apart from some free text fields) con-

tain codes linked to lookup tables providing controlled vocabularies, with the permitted code values and corresponding texts.

In addition to an overall quality management system, with GxP validation and quality training of staff, VigiBase has a quality system whereby each report is scored according to its level of documentation. This documentation grading system will be extended and to some extent will replace the logical checks (business rules) that so far have been applied in the report processing to identify and reject reports which do not meet the technical reporting requirements.

Standard database summary reports and retrieval facilities are available to all national centers, and other stakeholders have access to VigiBase data on request.

The aim when setting up the WHO Drug Monitoring Programme was to avoid drug disasters by pooling national data into a global database. Thus, an effective signal detection process applied to the VigiBase data is essential. Since the start of the program in 1968, quarterly summary reports have been reviewed by clinical experts, and their findings have been disseminated to the participating national centers. The regular production of a signal document started in the mid-1980s.

In 1998, the UMC implemented an automated signal detection method, using a BCPNN data mining approach. The current UMC signal detection process is built on a combination of automated screening using the BCPNN, further filtering by triage, and clinical assessment by a panel of international experts. More recent additions to the signal detection tools are extensions of the BCPNN system to be capable of unsupervised pattern recognition, and its application to other data sets, such as health care databases.

DISADVANTAGES

Since no chain is stronger than its weakest link, the WHO system suffers from the same weaknesses as those systems contributing to it. These include underreporting and missing data (although the latter is made transparent by the documentation grading and can be handled by the BCPNN). Also, the data in VigiBase are affect-

ed by various biases and contain heterogeneous information, but at least some factors can be analyzed by comparison of national differences.

In addition, the VigiBase system is dependent on national centers for timeliness, completeness, and quality of reports: the chances of UMC being able to directly influence these are less than in national reporting systems, due to the greater distance to the report originators and the fact that the WHO program to a large extent relies on the goodwill of the participating pharmacovigilance centers—although the countries, through membership in WHO, have undertaken to contribute to the WHO Drug Monitoring Programme.

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