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An Analysis of Vigimed, a Global E-Mail System for the Exchange of Pharmacovigilance Information

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Abstract

Background and aim: The Internet provides novel ways for communication and data exchange between national regulators. One innovation was the introduction of Vigimed, an e-mail discussion forum for national pharmacovigilance centres (NPCs). We reviewed a sample of Vigimed messages to learn more about this new tool and about the problems encountered in everyday pharmacovigilance and how these are handled.

Methods: We analysed the contents of 100 subsequent questions and the corresponding responses as stored in the Vigimed datafile.

Results: To the 100 questions circulated through Vigimed, 575 answers were received; mean number of answers per question 6, range 0–20. Fifty-five (77%) of the 71 collaborating countries and 88 (43%) of the 204 individuals who had access in the study period had submitted at least one question or answer. These countries were in all parts of the world and in various phases of development. A total of 38% of the questions concerned the regulatory status of a drug; 30% safety issues; 13% regulatory actions under consideration; and 10% drug use-related problems (more than one category possible). Of the questions, 89% concerned established drugs; 11% were classified as new. A total of 90% of the questions concerned specific active substances or drug groups. Of the drugs, 73% were classified as 'orthodox' and 9% as herbal; 4% were vaccines and 4% excipients. Emerging drug groups (anatomical therapeutic chemical codes) were NSAIDs and analgesics (M01, N02), antibacterials (J01), antiobesity drugs (A08), psychotropic drugs (N05) and antihistamines (R06).

Discussion: NPCs operate in a restricted environment and there is little published information about the daily practices and experiences at NPCs. Our study concerned a sample in a limited period in time. In the meantime, the use of Vigimed has greatly expanded. The data in the Vigimed records are subjected to confidentiality in regard to the identities of countries, staff members, drug products and pharmaceutical companies, which limits the presentation of data in a publication. For information about the actions taken to manage the matters and problems raised in Vigimed it would have been necessary to contact the NPCs and acquire follow-up data.

Conclusions: The Vigimed e-mail discussion group was rapidly incorporated into the routines at NPCs in many countries around the world. When two or more persons per country have access, participation increases. The matters raised predominantly refer to regulatory policy, safety concerns and drug use-related problems, and mainly concern established drugs. The latter emphasises the need for persistent monitoring of all drugs. New safety concerns are often sensitive and uncertain; the timely and efficient communication of such suspicions benefits from an environment of confidentiality. The Vigimed records give a unique view of real-life pharmacovigilance, of the matters addressed, the problems encountered, the data needed and the ways in which NPCs help each other. Such information can help make pharmacovigilance more efficient and effective.

Background

In brief, routine pharmacovigilance is, from the regulatory perspective, concerned with the detection of adverse effects, drug interactions and other drug-related problems and with restricting drug-related risks through regulatory interventions. The registration conditions may need to be changed regarding, for example, the instructions for use, indications and warnings and the information in the approved product information. Little is documented about the daily practices and experiences of pharmacovigilance specialists, both at drug regulatory agencies and national pharmacovigilance centres (NPCs). We lack information about the drugs involved, adverse events and other problems, and how matters are handled and solved. Only when major findings require immediate and drastic measures, such as suspension or termination of a marketing license, is this information overtly communicated to the medical-pharmaceutical community and the media. Many data sheet changes, on the other hand, take place without further notice.

The importance of pharmacovigilance is now widely recognised and there is also increased interest in the improvement of procedures and practices and in further development of the underlying science. In this context, a better understanding of the processes involved in current pharmacovigilance would be helpful.[1]

The WHO set up its International Drug Monitoring Programme following the thalidomide disaster, and since 1978 the Programme has been carried out by the Uppsala Monitoring Centre (UMC) in Sweden. One of the channels used by the UMC and national NPCs for communication and risk management is their e-mail discussion group Vigimed.[2,3]

About Vigimed

Vigimed is a worldwide e-mail discussion group maintained by the UMC. It has been in place since 1997, uses e-mail and related technology, and aims to improve and accelerate the sharing between its users of information regarding drug-related problems to aid problem solving and decision making. Vigimed allows rapid exchange of information and opinions on drug safety matters between NPCs around the world as well as the UMC. Membership is restricted to persons connected to NPCs or drug regulatory agencies in participating countries, including 'associate member countries'. Some of the UMC and WHO-headquarters staff are also on the list of Vigimed members. At the time of the study, there were 71 countries collaborating in the Vigimed system (see table I). In each country, one or more persons have access to Vigimed. It is the only e-mail discussion group connecting all NPCs participating in the international pharmacovigilance programme. The e-mail messages mostly concern announcements or questions and the subsequent answers. The message flow is not moderated; in other words, there is no manual filter between the submission of a message and the distribution to list members.

Thanks to complete storage of all messages in the Vigimed system, it can also be used as a unique

Table I. Vigimed member countries divided into continents and EU members (countries that were EU members at the time of the study)

Region (group)	Country
Europe (EU)	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, UK
Europe (non-EU)	Bulgaria, Croatia, Iceland, Macedonia, Norway, Romania, Russia, Serbia and Montenegro, Switzerland, Turkey, Ukraine
North America	USA, Canada
South America	Argentina, Brazil, Chile, Costa Rica, Cuba, Guatemala, Mexico, Netherlands Antilles, Peru, Uruguay, Venezuela
Asia	Armenia, Bahrain, China, India, Indonesia, Iran, Israel, Japan, Korea, Malaysia, Oman, Pakistan, Philippines, Singapore, Sri Lanka, Thailand, Vietnam
Oceania	Australia, New Zealand, Fiji
Africa	Ghana, Morocco, South Africa, Tanzania, Tunisia, Zimbabwe

source of information regarding factual daily practice of governmental pharmacovigilance and the procedures and discussions in problem solving and decision making.

We looked at the data in the Vigimed message log, available at the UMC, in an attempt to increase our understanding of what the issues in practical pharmacovigilance are and which problems are encountered (the drugs, the adverse reactions or other experiences). In addition, we looked (in a quantitative way) into how the Vigimed system is being used, the numbers and characteristics of the countries that ask questions, communicate problems and give answers.

Our intention was to examine the flow of information in the discussion group, without affecting the normal flow or the integrity in the group. In the information from the UMC to Vigimed users, it is explained that "You might consider starting a discussion on a topical subject. Vigimed is a closed list with the intention that members may feel confident to share preliminary findings, suspicions and opinions with other pharmacovigilance professionals, knowing that such information will not be given to other parties, the public or to media without the consent of the originator". Because of this guarantee of confidentiality, our possibilities for the presentation of the study findings were restricted.

Materials and Methods

At the time of the investigation, Vigimed had been in operation for about 5 years; for practical reasons (limited time for this project), this study focused on 100 messages to Vigimed in the period April 2001 to May 2003. All questions and the subsequent answers were retrieved for further examination. Announcements without further questions or comments were not included in the study. Such announcements were mainly made by the UMC and mostly contained information about various activities of the WHO Programme.

The questions were summarised, categorised and counted; in addition, the answers were summarised and counted. The time interval of responding was also analysed. We looked at the contributions of NPCs as well as individual persons.

The UMC keeps a record of all persons who have access to the e-mail group; this list is distributed via Vigimed on an annual basis. Consequently, members submitting messages are in principle aware of whom they are communicating with. Only listed members can technically submit messages to and view messages on the system; members can also give colleagues access or distribute messages. Guidelines for Vigimed members are available on the UMC website (http://www.who-umc.org).

The membership list also made it possible to determine how many of the individuals in the various countries had been active. To be classified as an active participant, a person should at least have asked one question or given one answer during the chosen time period. An analysis was also made as to whether the number of access persons a country had influenced the number of questions and answers that the country produced.

The messages were classified according to the content of the question, as shown in table II. The distinction between these categories may not always be sharp because in practice such problems may have aspects of more than one category. A message

Table II. Subject categories of Vigimed questions. An e-mail message can deal with more than one category

No.	Category	Example(s)	% of total messages
1a	Safety problem – ADR	New ADR, signal generation, evaluation, interactions	29
1b	Safety problem	Overdose problem, dependence	1
2a	Drug use-related problem	Data sheet text, administration problem	6
2b	Drug use-related problem	Inappropriate use, dependence	4
3	Regulatory status	Prescription only, available over the counter	38
4a	Regulatory action under consideration (moderate)	Data sheet change	2
4b	Regulatory action under consideration (serious)	Suspension or withdrawal of licence	11
5	Other	Acceptance of case reports from pharmacists	10

ADR = adverse drug reaction.

can deal with more than one of the defined categories.

If a question concerned a specific active substance or drug group, a further classification was made concerning 'age', type and anatomical therapeutic chemical (ATC) code of the drug. A drug was considered 'new' when the interval between the introduction of the drug (i.e. when the drug was approved for the very first time in any country that is a Vigimed member) and the date when the message was issued was ≤6 years, and 'established' when the interval was ≥7 years.[4]

Results

We analysed 100 questions that were put forward to the Vigimed group (follow-up questions not included) and the 575 answers that were given to these questions. Most of the questions had less then ten answers (80%), whereas a few questions received ≥20 answers. Six questions did not receive any reply at all.

Most of the questions (81%) received the first response within <7 days. Twelve percent of the answers were received on the same day that the question was asked, 50% of the answers within 1 week (but not on the same day) and 32% within 1 month (but not in the first week).

In the study period, 55 (77%) of the 71 countries were 'active' members. Of the total of 204 individuals having access to Vigimed (UMC staff excluded), 88 persons (43%) had been active. Most member countries had between one and three individuals with Vigimed access. The analysis showed that there was a positive correlation between the number of access persons per country and the number of questions and answers per country.

On the whole, the countries active in Vigimed were found to be fairly heterogeneous with regard to phase of development and geographical location.

Most questions (90%) concerned either specific active substances, excipients or particular drug groups; the remainder dealt with other matters, e.g. the policy with regards to case reports from pharmacists, drug-price management or parallel import. Many questions concerned safety problems relating to adverse drug reactions (ADRs) [category 1a: 29%] and/or the regulatory status of drugs (category 3: 38%). Regulatory actions under consideration (categories 4a and 4b) were discussed in 2% and 11% of the Vigimed questions, respectively. Categories concerning regulatory questions (i.e. 3, 4a and 4b), as a group, were discussed in >50% of the questions. Just a few questions concerned drug-use-related problems, such as inappropriate use (category 2b: 4%), or administration problems (category 2a: 6%). Various other matters were included in the 'other subjects' category (category 5: 10%); for example, questions regarding parallel import, drug price management or unidentified products (see table II).

Some examples of questions can be found in the following bulleted list. The questions are summarised and edited taking into account limitations in space and confidentiality of the identities of individuals, countries and drugs.

- "What is the status of sibutramine in your country? Any ADRs related to disturbances of vision?"

- "The local press have reported that an article in the London *Times* was stating that 'mercury in vaccines could be the cause of a steep rise in neurological disorders and autism'. Therefore the following questions were raised: 'do vaccines still contain thiomersal in different countries?', 'which actions are taken on these products?' and 'what is WHO's stand in this issue?' "
- "The drug flutamide is being used in the treatment of hirsutism, alopecia and acne, although the drug has only been approved for the treatment of prostate cancer. Because of this inappropriate use, two deaths in younger women have been reported. What is flutamide approved for in other countries? Is it just for the treatment of prostatic cancer or also for hirsutism, alopecia and acne?"
- "Is Comfrey regulated in your country? Allowed for systemic and/or topical use?"
- "After receiving reports of seizures and cardiac failure with carboplatin, sometimes in combination with paclitaxel, we want to know if in some other country reports have been received of this drug causing these ADRs"
- "Do you accept ADR reports from pharmacists? If yes, since when?"

Most Vigimed questions concerned established drugs (89%); only 11% of the drugs were considered as new. The majority of problem drugs in the study were classified as 'orthodox' (73%), 9% as herbal, 4% as vaccine, 4% as excipient and 2% as biotechnology product. Seven percent of the questions concerned drug groups, instead of single agents, in particular cyclo-oxygenase 2 inhibitors, oral contraceptives, anorectics, antiretroviral drugs and growth hormones. Using the ATC classification, the categories A08 (anti-obesity preparations), J01 (antibacterials for systemic use), M01 (anti-inflammatory and antirheumatic products) and N02 (analgesics) were most frequently discussed.

The nature of the answers in Vigimed may differ from a simple "No, this substance is not allowed in our country" to extensive discussions and investigations. Most answers were clearly written, understandable and relevant. Most of the answers were clearly written and seemed to be relevant according to the authors of this article. In order to find out how satisfied Vigimed members themselves had been, it would have been necessary to do a further (questionnaire) investigation.

Discussion

In addition to the pre-registration assessment of new medicines, regulators have devoted more and more time in recent years to the evaluation of their safety after approval. The use of medicines can, directly or indirectly, lead to a wide variety of problems.[5] Compared with drug development and clinical trials, the theory and practice of the post-approval study of drugs are in an earlier phase of development. There is still a lot to be learned and improved.

Vigimed is a forum where colleagues may discuss problems. It is a complementary tool, in addition to other sources of information and activities at NPCs. Our review shows that Vigimed has been well received and has rapidly found a place in international pharmacovigilance routines.

In addition to assessing how it has been performing quantitatively in the past few years, our interest was to evaluate the nature of the matters discussed in order to increase our understanding of what pharmacovigilance is about in practice, to learn more about the problems that are encountered (the drugs, the ADRs and other possible experiences) and to get an idea of how such problems are dealt with.

It should be noted that the questions posted on Vigimed may have generated traffic not captured by this study. Although the Vigimed guidelines recommend that answers be posted on Vigimed, any member may respond directly to the inquirer without sharing the response with other Vigimed members. The extent of this 'extra-Vigimed' traffic has not been measured. This study covers information exchange at Vigimed for a limited period of time. Vigimed is used on a daily basis, new members are signing up to the discussion group regularly and new drug problems arise continuously; therefore, an analysis of the exchange of information made during a different time period may show a different result.

In the study period, two-thirds of the countries participating in the WHO programme for international pharmacovigilance used Vigimed. This frequent usage could be taken as a sign that Vigimed is needed and appreciated by the participating NPCs and that Vigimed is recognised as a positive extension of the tools for communication and problem solving.

The countries using Vigimed (asking as well as answering questions) are heterogeneous, in various phases of development and from all parts of the world. The contributions per country were higher if more persons per centre had access to Vigimed. A possible reason for non-activity of some members, on the other hand, may have been difficulty communicating in English. It is known that pharmacovigilance experts in some countries do not feel confident expressing themselves in English. Consequently, drug problems of concern in such countries may be under-represented in the present study.

The majority (approximately 70%) of the questions concerned the regulatory status of a drug and/or a safety problem, in particular ADRs. Most questions were of substantial public health importance. Although the category 'regulatory status' may sound somewhat administrative or bureaucratic, this was mostly not the case. Many of the questions that were classified into this category described problems that were serious, realistic and linked to drug safety matters. Many of the matters in the questions were preliminary, i.e. somewhere between suspicion and fact, between 'smoke and fire'. A few examples of questions were included in the Results section to illustrate this point.

As many as 90% of the questions raised in the Vigimed discussion group concerned established drugs, i.e. drugs that have already been on the market for ≥7 years. This finding is of interest in light of the relaxation of the legal obligations in the EU regarding pharmacovigilance to pharmaceutical companies 5 years after the approval of a medicine. Our study gives support to the view that pharmacovigilance is continuously needed for all products on the market and should not be restricted to new ones only.[4]

The review of the substances discussed by the e-mail group showed that a few therapeutic groups (ATC codes) predominated, notably NSAIDs/analgesics, antibacterials, anti-obesity drugs, psychotropic drugs, antihistamines and vaccines. Obviously, these groups contain drugs that are heavily used around the world and may therefore be more likely to attract the attention of Vigimed members. NSAIDs, in particular, seem to constitute a complex challenge to regulators; there is a great demand for these drugs in society, by patients, prescribers and companies alike, while their benefit/risk profile is often controversial. Most of the questions (73%) concerned orthodox drugs, 9% herbals and 4% vaccines. On the other hand, novel biotechnology products, such as mononuclear antibodies, received little attention in the study period.

Once a question had been raised, the answers came quickly and most of them were appropriate, relevant and useful. The answers often described the situation in the responding person's country and often also contained advice for how to carry on with the issue in the question. Several of the questions where forwarded by Vigimed members to experts in different areas in their country. Many of the questions were of a sensitive nature. The spontaneity of the asking and answering of these questions seems to have benefited much from Vigimed's guarantee of confidentiality. The presentation of the results of our study has been limited by this.

A distinctive pattern in problem raising and problem solving could be seen. In order to find out how satisfied Vigimed users are, what changes would likely improve the functioning and the use of the system, and to learn more about the details of the complex processes underlying problem solving and decision making, more active data collection and contacts with the NPCs, for example using questionnaires and interviews, would be needed.

Conclusions

The Vigimed e-mail discussion group has, since its introduction by the UMC, been generally incorporated in NPC routines and been found to fulfil a need. Many NPCs in countries around the world

promptly and efficiently help fellow centres. Increasing the number of access persons per country is likely to raise the numbers of responses and to improve the functioning of the system.

The Vigimed records give a unique view of real-life pharmacovigilance, detailing the matters addressed, the problems encountered, the data needed and the ways in which NPCs help each other. Such information can help to make pharmacovigilance more efficient and effective.

The matters raised in Vigimed predominantly referred to regulatory policy, safety concerns and drug use-related problems, in particular concerning NSAIDs/analgesics, antibacterials, anti-obesity drugs, psychotropic drugs, antihistamines and vaccines. Novel drugs such as monoclonal antibodies and other biopharmaceuticals received little attention. There was a striking predominance of established drugs (i.e. ≥7 years on the market), emphasising the persistent need for monitoring of all drugs well beyond the first 5 years of approval.

New safety concerns are often sensitive and uncertain; the timely and efficient communication of such suspicions benefits from an environment of confidence and confidentiality.

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References

1. Meyboom RH, Egberts AC, Gribnau FW, et al. Pharmacovigilance in perspective. Drug Saf 1999; 21 (6): 429-47
2. Olsson S. The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts. Drug Saf 1998; 19 (1): 1-10
3. Uppsala Monitoring Centre. WHO programme [online]. Available from URL: http://www.who-umc.org/ [Accessed 2007 Jun 1]
4. Meyboom RHB, Gribnau FWJ, Hekster YA, et al. Characteristics of topics in pharmacovigilance in The Netherlands. Clin Drug Invest 1996; 12 (4): 207-19
5. Meyboom RHB, Lindquist M, Egberts ACG. An ABC of drug-related problems. Drug Saf 2000; 22 (6): 415-23

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