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Assessing the Impact of Drug Safety Signals from the WHO Database Presented in 'SIGNAL'

Results from a Questionnaire of National Pharmacovigilance Centres

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Abstract

Introduction: A major task for *the* Uppsala Monitoring Centre (UMC) is to detect early signals of suspected adverse drug reactions (ADRs) in the WHO Database. The database currently contains over 2.8 million spontaneously reported ADR case reports continuously collected by National Pharmacovigilance Centres in countries participating in the WHO Programme for International Drug Monitoring. The database is scanned every quarter and drug-ADR combinations are filtered out using different selection criteria intended to catch potential international drug safety signals at an early stage. Summary case data are reviewed by experts on *the* UMC's review panel and the signals are presented to the Programme members in the restricted circulation document entitled 'SIGNAL'.

Objective: The aim of the study was to investigate: (i) how the signals presented in 'SIGNAL' are used; (ii) if they reach the right target group; (iii) if they are of interest and relevance to the recipients; (iv) if they are timely and; (v) if they make any difference. We were also interested in knowing the view of member countries regarding the definition of what a signal is.

Methods: A questionnaire was sent out to 71 countries participating in the WHO Programme. The recipients were asked to state what actions were taken for 26 different signal headings included in three issues of 'SIGNAL' sent out during 2001 and to rate how useful they considered these topics to be.

Results: Responses were received from 45 countries (63%). The Centres' average ratings of relevance, importance and usefulness on a scale 1–10 of the selected 26 signals were all above the expected average rating 5.5. The content of 'SIGNAL' in general was seen as always or often useful in 63.5% of the respondents. In 2001, 17 countries took actions on at least one signal. Actions were rarely taken without considering the signal from *the* UMC. All responding centres agreed on the WHO definition of a signal, but there were differences in the interpretation of what constitutes a signal.

Conclusion: The 'SIGNAL' publication is timely, plays an important role and has a direct impact on drug safety issues handled by members of the WHO Programme for International Drug Monitoring.

Background

A major task for *the* Uppsala Monitoring Centre (UMC) is to detect early signals of suspected adverse drug reactions (ADRs) in the WHO Database. The database currently contains over 2.8 million spontaneously reported ADR case reports continuously collected by National Pharmacovigilance Centres in countries participating in the WHO Programme for International Drug Monitoring. Every quarter the database is scanned and drug-ADR combinations are filtered out using different selection criteria intended to catch potential international drug safety signals at an early stage.[1,2] Summary case data are reviewed by experts in *the* UMC's review panel and signals are presented to the Programme members in the restricted circulation document entitled 'SIGNAL'.

In 1996 *the* UMC published the results from a study investigating the impact and credibility of the WHO adverse reaction signals.[3] The aim with this new study was to again investigate how the signals presented in SIGNAL are used, if they reach the right target group, if they are of interest and relevance to the recipients, if they are timely and if they make any difference, and to see if there were any changes from the results of the 1996 study. We were also interested in knowing the member countries view of what a signal is.

Methods

To investigate what impact 'SIGNAL' has, a questionnaire was sent out to 74 persons in the 66 member countries and five associate member countries. The recipients were asked to state what actions were taken generally upon receipt of 'SIGNAL' and specifically what actions had been taken for 26 different signal topics included in the three issues of 'SIGNAL' sent out during 2001. They were also asked to rate the topics on how useful, interesting and relevant they considered them to be.

Results

Responses were received from 45 (61%) persons in 45 (63%) countries. Responding countries had an average time as Programme members of 13.7 years (range 0–34, median 10) and there was no difference to the non-responders average time as Programme members (13.9 years; range 0–34, median 10).

Target Audience

The number of persons working in pharmacovigilance was 1–5 persons in 29 centres; 6–10 in five centres; 11–20 in seven centres and 21 or more in four centres. When asked how many of the staff read 'SIGNAL' regularly the answers were 1–5 persons in 32 centres; 6–10 in four centres; 11–20 in three centres and 21 or more in one centre. Five centres said none of their staff read 'SIGNAL' regularly.

Respondents were asked whether 'SIGNAL' was routinely circulated outside the centre to specified recipients. Fifteen respondents said that 'SIGNAL' was routinely circulated to the following recipients: 'regional centres' (9 centres); 'regulatory authorities' (6); 'practising healthcare professionals' (1); 'research healthcare professionals' (3); and 'other' (6). No Centres circulated 'SIGNAL' to the 'pharmaceutical industry' or to 'consumer associations and patient organisations'. 'Other' was specified as advisory committees, sentinel hospitals and drug information centres. It should be noted that many National Centres are also regulatory authorities.

Interest, Relevance and Usefulness

The answers to the question 'How often do you find the contents of 'SIGNAL' useful?' are shown in table I. The table also includes the number of centres finding responses from industry on signals concerning their drugs useful or of interest. When centres were asked if they want to have comments from

Table I. Number (%) of centres responding to the questions: (A) How often do you find the contents of SIGNAL useful? and (B) How often do you think that industry responses are useful or of interest?

Answer	Question A	Question B
Always	6 (13.5)	4 (10)
Often	22 (50)	9 (20)
Sometimes	13 (29.5)	23 (52)
Seldom	3 (7)	7 (16)
Never	0 (0)	1 (2)

Table II. Average ratings of relevance, importance and usefulness on a scale of 1–10 of 26 signals in 2001

	No. of centres	Average score	Lowest score	Highest score
Relevance	32	6.79	5.63	8.03
Importance	34	6.77	4.63	7.91
Usefulness	34	6.44	4.21	7.81

industry included in 'SIGNAL', 34 centres said 'yes' and eight centres answered 'no'.

Centres were asked to rate the relevance, importance and usefulness, on a scale from 1–10, of the 26 signal headings presented in three issues of SIGNAL during 2001. The results are showed in table II.

Taking Action

To the question 'What do you do when you receive SIGNAL?' several alternatives could be chosen. Twenty-four respondents answered 'file it'; 41 'read it'; 24 'distribute it to colleagues'; 13 'include as reference in literature database' and 18 stated to 'consider follow-up or taking regulatory action'.

Table III lists the number of centres that took action in relation to the 26 signal topics presented in the three issues of SIGNAL distributed during 2001.

Table IV lists what actions were taken in 2001 and 2002 and for how many of the 26 signal topics discussed in SIGNAL in 2001. The responses are divided by actions taken (i) due to the WHO signal alone; (ii) after taking the WHO signal and other information into account; or (iii) without considering the WHO signal, i.e. the action had been taken anyway.

What is a Signal?

Forty-three centres said 'yes' when asked if the WHO definition is in line with their centre's definition of a signal. None of the centres answered 'no'. When asked how well the contents of SIGNAL corresponds to the WHO definition of a signal, 20 centres said 'very well' and 23 thought 'reasonably well'.

Since a drug-ADR signal according to the WHO definition should be 'unknown or incompletely documented previously' we were interested in knowing when a drug-ADR would be considered 'known' by the centres. The results are shown in table V.

Discussion

In the publication 'SIGNAL' concerns regarding potential international drug safety problems discovered from quarterly analysis of data in the WHO Database are raised and discussed. The topics are varying levels of suspicions with the primary intention of informing, at an early stage, national regulatory authorities in countries participating in the WHO Programme. The results from this questionnaire show that 'SIGNAL' is regularly read by the intended target audience although internal circulation of the document could be improved at many centres; 45% of the recipients say they do not distribute 'SIGNAL' to their colleagues.

Sixty-seven percent of the National Centres do not share the information with anyone outside their centre. This may be due to the fact that the signals are considered early and the information immature but it is also apparent from the responses that the meaning of 'SIGNAL' being a restricted publication is not clear to everyone. 'Restricted' used here means that *the* UMC cannot distribute signals to anyone other than the members of the Programme and to recipients approved by them. However, while having the responsibility for any effects it may have, Programme members have the right to use and share the information in 'SIGNAL' in any way they feel is appropriate.

None of the recipients of the questionnaire said they regularly approach the manufacturers of the concerned medicines and similar results were obtained in the 1996 study. Since *the* UMC wants to encourage openness and promote discussions, in 1998 we asked the centres if they would agree to allowing *the* UMC share information in the WHO

Table III. Number of centres taking action[a] on 26 topics discussed in 'SIGNAL' in 2001

Signal heading	Action taken		For action taken in year 2001–2002 the WHO signal		
	before 2001	in 2001 or 2002	lead alone to action	contributed together with other information	was not considered
Severe headache following artemether	2	2	2	2	2
Abacavir-Stevens Johnson syndrome and erythema multiforme	2	5	3	3	1
Atorvastatin-cataract	1	3	2	3	0
Topiramate-glaucoma	1	9	2	7	2
Loratadine-glaucoma	1	4	2	2	0
Abacavir-adult respiratory distress syndrome	2	4	3	2	1
Hepatic reactions with HMG-CoA reductase inhibitors in the WHO database	4	11	3	8	4
Celecoxib and myocardial infarction	2	13	2	9	5
Atorvastatin and optic ischaemic neuropathy	1	4	4	2	0
Orlistat, thyroxine and thyroid function	1	4	4	1	0
Skin striae induced by DT, DTP and DTP-HIB vaccines	0	4	1	3	2
Rofecoxib reported with Stevens Johnson syndrome and epidermal necrolysis	1	7	4	3	1
Clomipramine with cardiac failure and cardiomyopathy	0	3	2	2	0
Clopidogrel, glomerulonephritis and nephrotic syndrome	0	5	3	3	0
COX-2 inhibitors-medicine ineffective or therapeutic response decreased	0	8	3	6	0
Dactinomycin-Stevens Johnson syndrome	0	4	3	2	0
Amantadine-Stevens Johnson syndrome	0	4	3	2	0
Raloxifene-breast disorders	1	5	4	2	1
Raloxifene-vaginal haemorrhage	1	5	3	3	1
Fluoxetine, paroxetine-labour premature	0	5	3	3	0
Loratadine-lactation puerperal decreased	0	4	3	2	0
COX-2 inhibitors-post-menopausal bleeding	0	5	2	4	0
SSRI-neonatal withdrawal syndrome	2	5	2	4	2
Olanzapine and QTc prolongation	0	8	3	6	1
Ginkgo biloba-cerebral haemorrhage	4	6	3	4	4
Amiodarone-disseminated intravascular coagulation	1	3	3	1	1

a Action was defined as: 'check national data' or 'discuss in ADR committee' or 'initiate a study' or 'contact manufacturer' or 'notify doctors/pharmacists/healthcare providers' or 'publish in national drug information bulletin' or 'inform general public/mass media' or 'change labelling' or 'other'.

COX-2 = cyclo-oxygenase 2; **DT** = diphtheria, tetanus; **DTP** = diphtheria, tetanus and pertussis; **HIB** = *Haemophilus influenza* type B; **QTc** = corrected QT interval; **SSRI** = selective serotonin reuptake inhibitor.

Database with the international pharmaceutical companies identified as uniquely responsible for the concerned drugs. As 98% of the responses (42 centres) were affirmative, *the* UMC, during the last 2 years, has invited industry to comment on the signals presented in 'SIGNAL'. Industry comments are indeed appreciated by a majority of the centres demonstrated by the fact that 34 of 42 respondents want to continue to have them included while only eight do not. Furthermore, 36 of 44 respondents say that industry comments are useful 'always', 'often' or 'sometimes' and only eight say that they 'seldom'

Table IV. Number of centres that took actions in 2001 or 2002 on the topics discussed in 'SIGNAL' in 2001 and how many of the signals were acted upon. The responses are divided by actions taken: (A) due to the WHO signal alone; (B) after taking the WHO signal but also other information into account; or (C) without considering the WHO signal, i.e. the action had been taken anyway

Action	Reason for taking the action (no. of signals)								
	A			B			C		
	1	2–5	>5	1	2–5	>5	1	2–5	>5
Check national data	3	3	8	3	5	8	3	3	5
Discuss in ADR committee	1	9	3	2	10	4	3	2	3
Initiate a study	1	2	0	0	1	0	0	1	0
Contact manufacturer	2	1	1	2	2	1	6	2	0
Notify doctors/pharmacists/ healthcare providers	1	2	4	1	4	3	4	4	0
Publish in national drug information bulletin	1	5	2	3	3	4	3	2	2
Inform general public/mass media	1	0	1	1	0	1	2	1	1
Change labelling	1	0	3	2	4	1	4	2	2
Other[a]	0	0	0	0	0	0	1	1	0

a 'Other' was specified as 'suspension' and 'discussions with European Agency for the Evaluation of Medicinal Products'.

ADR = adverse drug reaction.

or 'never' find these useful or of interest. That *the* UMC includes industry responses in 'SIGNAL' can possibly explain why centres see no reason in contacting the manufacturers themselves, and obviously, it is more time efficient for both national agencies and pharmaceutical companies to have the discussions co-ordinated centrally by *the* UMC.

In general, 'SIGNAL' was judged as 'always' useful by 14%, 'often' by 50% and 'sometimes' in a further 30% of the responding centres. The results are similar to the study published in 1996 where the responses were 'always' 16%, 'often'57% and 'sometimes' 24%. The centres' ratings of relevance, importance and usefulness on a scale from 1–10 of the selected 26 signals (table II) had a median rating of seven, and the average scores were all above the expected average rating of 5.5. This clearly shows that 'SIGNAL' is considered an important publica-

Table V. Number (%) of centres responding to the question: 'For the following scenarios, please indicate yes (known) or no (not known) whether you from your point of view would consider a drug-ADR association 'known'

Scenario	Yes	No
The reaction is listed as ADR in the prescription information for the drug in your country	37 (84)	7 (16)
The reaction is listed as ADR in the prescription information for the drug in your country but		
the reaction is *not* listed in the PDR	24 (63)	14 (37)
the reaction is *not* listed in Martindale	25 (66)	13 (34)
there are no published case reports on the drug-ADR association	24 (65)	13 (35)
The reaction is *not* listed as ADR in the prescription information for the drug in your country but		
the prescription information includes a warning that the drug group may cause the ADR (or refers to another drug for which the reaction is listed as ADR)	22 (52)	20 (48)
the reaction is listed in the PDR	25 (68)	12 (32)
the reaction is listed in Martindale	26 (70)	11 (30)
there are published case reports on the drug-ADR association	19 (51)	18 (49)
the reaction is listed for the drug in the prescription information in other countries	26 (67)	13 (33)
the reaction is listed for the drug in another source[a]	22 (63)	13 (37)

a Other sources mentioned were: Company Core Data Sheet, Meyler's Side Effects of Drugs, Vademecum International, Farmacotherapeutisch Kompas, Informatorium Medicamentorum and Davies' Textbook of Adverse Drug Reactions.

ADR = adverse drug reaction, **Martindale** = Martindale Extra Pharmacopoeia; **PDR** = Physicians Desk Reference.

tion that is relevant and of help to most of the recipients. However, although appreciated by the majority, there is a diverse view of what actions the signals should lead to. Some centres do not even consider follow-up or taking actions while others are prepared to change labelling. In 1996, nine National Centres reported having changed labelling in up to five cases per centre. In the current study, three centres stated that change of labelling occurred in more than five signals in 2001 due to the information provided by 'SIGNAL' alone. Considering the preliminary nature of signals from the WHO database, substantial regulatory actions based on UMC signals alone cannot normally be recommended. On the other hand, nor should there be no action at all.

It must be noted that the topics discussed in 'SIGNAL' are hypotheses based on often incomplete reports in the WHO Database. The signals are unconfirmed and, as already mentioned, primarily intended as an early warning about possible safety problems. In this light, *the* UMC encourages checking of national data, discussions in national or regional ADR committees, inclusion of 'SIGNAL' in literature reference databases and, when required, initiation of further studies. However, unless there are other data supporting the signal from *the* UMC we would advise against actions such as labelling changes, informing the general public/mass media or withdrawal of products from the market. *the* UMC's position is well summarised in the following comment from one of the centres: " *We find SIGNAL an important contribution tool to making decisions concerning drug safety. However, SIGNAL alone is not usually sufficient*".

There is 100% agreement among the respondents on the WHO definition of a signal, which is as follows: "*Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously*." Further notes says: "*A signal is an evaluated association which is considered important to investigate further*"; *"A signal may refer to new information on an already known association*"; and "*Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information*".[4] However, the interpretation of whether the material from *the* UMC constitutes a signal varies greatly between countries. Forty-three percent of the centres think that UMC signals correspond 'very well' to the WHO definition while 57% answer 'reasonably well'. Table V shows that there are also differences in the centres' view of which reference sources the adverse drug reaction needs to be listed in to consider it 'known'. Interestingly, seven centres do not consider a drug-ADR 'known' even if it is listed in the product information for the drug in their country although most centres (84%) do agree it would. However, this number decreases to around 66% if the same drug-ADR is not concurrently listed in the Physicians Desk Reference or Martindale Extra Pharmacopoeia or if there are no published case reports on the drug-ADR association. The results demonstrate the difficulty in providing international signals relevant to all Programme members. All countries have different amounts of knowledge and background data available; some have no experience at all of some of the concerned drugs as it is not registered in the country. But, as visible from the answers to this questionnaire, even if two centres have the same information available they may still judge differently whether a drug ADR report is a potential signal or not. With this in mind it is apparent that a signal to one recipient may not be a signal in another recipient's opinion although both agree on the definition. Naturally, the spread view of what constitutes a signal can to some extent explain the differences in actions taken by the National Centres on signals presented in 'SIGNAL'.

One aspect of 'SIGNAL' that was appreciated was the range, from very tentative but important signals with little information, to signals that provide additional information and more in-depth analyses. Seventy percent of the centres wanted 'both kinds' when asked about which of these types of signal analyses they prefer in 'SIGNAL'.

Although many centres state they do not regularly act on the topics in 'SIGNAL', all signals presented during 2001 lead alone or together with other information to actions; 17 countries took action on

at least one signal whereof three had acted on all 26 signal topics. Only rarely were actions taken without considering the signal from *the* UMC and in most cases the actions were taken in 2001 and 2002. This indicates that 'SIGNAL' is timely, plays an important role and has a direct impact on drug safety issues handled by National Centres.

However, compared with the previous study[3] it seems that a higher fraction of Programme members were taking actions on the 44 signals presented in 'SIGNAL' in 1994 than on the 26 signals presented in 2001. In the previous study, 8 of 37 (22%) questionnaire respondents in total reported having initiated a study; 22% contacted the manufacturer; 51% published signals in national bulletin and 24% changed labelling. The corresponding results from the current study were that three of a total of 45 (7%) responding centres initiated a study; 13% contacted manufacturer; 27% published signals in national bulletin and 17% changed labelling. However, it must be emphasised that the two questionnaires were not identical and it is therefore difficult to make exact comparisons. The response rate from countries was almost identical in this and the previous study, at just over 60%. The current questionnaire was more complex, and especially the questions concerning activity were perceived as difficult to fill in by some centres: 23 centres did not fill in anything when asked about actions taken but only two of these specifically pointed out that no actions had been taken. Nevertheless, there appears to be fewer centres acting on signals today than 5 years ago. There was no major difference between the two studies in the general appreciation of usefulness of 'SIGNAL', so one explanation could be that there is a now a greater awareness among the centres of the preliminary nature of *the* UMC signals making the authorities more conservative in taking action. Other possible reasons are that national agencies have fewer resources today than in 1996 leading to down prioritising of signals not originating from national data; or that the centres did not find the time to fill in the questionnaire. The limited response rates were disappointing but the apparent similarity between the expertise and experience of the responding and non-responding group of countries suggests that there may not be important biases. Further investigations are needed, perhaps with a narrower focus.

Conclusion

From the responses to the questionnaire used in this study we conclude that 'SIGNAL', which is a restricted document edited and produced by *the* UMC, is read regularly by the responding National Centres. The topics discussed in 'SIGNAL' are timely and judged as relevant, interesting and useful by its recipients. This study shows that 'SIGNAL' is contributing to the knowledge and drug safety activities of countries participating in the WHO Programme for International Drug Monitoring.

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