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Survey of the spontaneous adverse drug reaction reporting schemes in fifteen countries

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Introduction

The objective of this paper is to present an historical overview of the international experience of adverse drug reaction monitoring over the last 25 years since the thalidomide episode which was the initial trigger for the establishment of national systems of post-marketing surveillance. It is hoped that those seeking such historical data will find the survey of considerable archival value; but there are in addition general conclusions of considerable importance that can be drawn from the material presented.

Methodology

A questionnaire was sent to the Heads of the Drug Regulatory Authorities of Australia, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Japan, Netherlands, New Zealand, Norway, Sweden, United Kingdom, and United States of America. All authorities approached responded and completed the questionnaire as completely as they were able.

Adverse reaction data

The questionnaire sought information on whether the countries had a spontaneous adverse reaction reporting system, in which year the system was initiated, and the number of reports made to the reporting system in each year since its inception. The origin of reports made to the national centre and whether these were from hospital doctors, general practitioners, pharmacists, the pharmaceutical industry and others including consumer reporting was specifically sought.

The overall percentage of the total adverse reaction reports relating to a fatal adverse reaction was also obtained.

In addition the identity of the ten drugs most frequently associated with adverse reaction reports was sought for the years 1982, 1981, 1980, 1975, 1970 and 1965, i.e. the last 3 complete years of reporting and 5 yearly for the previous period.

Population data and numbers of registered medical practitioners

The population of the country and number of registered medical practitioners were also sought in the questionnaire. Data on the number of practising physicians were also obtained from an international survey of medical manpower in the ten European Economic Community countries by Brearley (1984) and for the Scandinavian countries for Nordisk Lakemedelsstatistik (1978–80).

The regulatory authorities were encouraged to make any specific comments about their adverse reaction reporting system and the features that rendered them somewhat unique.

Prescription data

Surveys on prescription data usage have been made for the United Kingdom, Germany, France and Italy by Abel-Smith & Grandjeat (1979) and O'Brien (1984) using IMS data. For the Scandinavian countries Denmark, Finland, Iceland, Norway and Sweden data were available in Nordisk Lakemedelsstatistik (1978–80). Comparable data for Australia had been published by Keith (1983) and from the paper by Burkholder (1979) data for the United States could be obtained.

A simple parameter of prescription drug usage could be obtained from each of these sources namely the number of prescription drugs per capita per annum; where possible two such points for different years were obtained.

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Results

The material supplied was such that its presentation and the observation based upon it fall naturally into two subsections. The first broadly covers the general demography of the adverse reaction registers in the fifteen countries which participated in the survey. The second relates to the various national experiences with specific drug substances.

Demography

Commencement of national adverse reaction reporting schemes In the 5 year period commencing 1961–65, Australia, West Germany, Italy, New Zealand, Netherlands, Sweden, United Kingdom and the United States initiated National Adverse Drug Reaction Reporting Schemes. During the succeeding 5 year period 1966–70 Denmark, Finland, Ireland, Japan, and Norway set up Adverse Drug Reaction reporting schemes. France and Belgium both initiated their national reporting schemes in 1976.

Special features of certain systems Certain drug regulatory authorities drew to our attention features of their national systems which they considered rendered them unique in one aspect or another.

West Germany The Bundesgesundheitsamt (BGA) is responsible by law for the central collection of ADRs, evaluation and, if needed, executive measures. The manufacturers are obliged by law to report to the Federal Health Office and by the statutes of their association to report to the Medicines Commission of the German Medical Profession. This is due to the fact that the Medicines Commission of the German Medical Profession started their system of spontaneous ADR monitoring before the drug law of 1976 made it obligatory to the Federal Health Office to collect and evaluate ADRs. This situation led to the situation that doctors became used to report to their Medicines Commission and not to the Federal Health Office. Therefore, the Medicines Commission maintains the system of spontaneous ADR monitoring both for the medical profession and the drug industry. Reports from patients are also accepted. These reports are passed on to the BGA for enforcement purposes.

Italy A voluntary system of ADR reporting was introduced in 1960 but in 1980 it was made compulsory for pharmaceutical companies to report ADR on products that they were marketing in Italy. The annual figures in Table 1 therefore only cover the period since these changes.

Japan In Japan 1001 hospitals including university hospitals, national hospitals and municipal hospitals have been designated as monitoring hospitals. The figure for registered medical practitioners in Japan is therefore meaningless and only those 65 000 doctors working in the designated monitoring hospitals are quoted since they alone are involved in the post-marketing surveillance schemes.

New Zealand In New Zealand in 1977 a system of intensive monitoring of certain drugs was introduced. The drugs being intensively monitored contributed 239 ADR reports in 1977, and 283, 202, 85, 102, 138 respectively in 1978, 1979, 1980, 1981 and 1982. The drugs intensively monitored figured in the ten drugs most frequently associated with ADR reports as follows: valproate and nifedipine in 1982, perhexilene, valproate, nifedipine and cimetidine in 1981, and perhexilene, cimetidine and the β-adrenergic receptor blocking drugs metoprolol, atenolol, acebutolol and labetalol in 1980. The high representation of β-adrenoceptor blockers in New Zealand's yearly lists of drugs most frequently reported to cause ADR is probably an artefact of their special monitoring system.

The United Kingdom In the United Kingdom new chemical entities and certain novel dosage forms are marked with an inverted triangle (▼) in the British National Formulary, ABPI Data Sheet Compendia and Monthly Index of Medical Specialities (MIMS) to alert doctors to report *any* ADR that might conceivably be related to the New Chemical Entity (NCE). For other products doctors are only requested to report serious or life threatening ADR. Pharmaceutical companies also conduct their own post-marketing surveillance studies and adverse reactions observed are subsequently reported to the regulatory authority. Such reports are however kept distinct from the spontaneous reports so that bias is not introduced.

Rate of reporting of adverse reactions Two methods of expressing the rate of adverse drug reaction (ADR) reporting were adopted. In Table 1 the number of adverse reactions year by year is given in absolute terms for each country. In each country there is a steady increase in the annual number of reports. In Table 2 the rate of reporting is expressed as rate of ADR reporting per million of the population p.a. using the maximum number of reports received in any

Table 1 Annual input of adverse drug reaction reports into national adverse reactions register for 15 countries

Year	*Australia*	*Belgium*	*Denmark*	*Finland*	*France*	*Germany**	*Ireland*	*Italy*	*Japan***	*Netherlands*	*New Zealand*	*Norway*	*Sweden*	*UK*	*USA*
1964		–	–	–	–	230	–	–	–	376	–	–	–	1,415	NA
1965		–	–	–	–	400	–	–	–	366	441	–	155	3,987	NA
1966		–	–	63	–	200	–	–	3	NA	386	–	576	2,386	NA
1967	7188	–	–	24	–	280	43	–	44	390	453	–	598	3,503	NA
1968		–	728	10	–	300	105	–	595	1,018	366	–	657	3,486	NA
1969		–	721	19	–	700	132	–	293	1,119	425	–	1,103	4,306	NA
1970		–	470	34	–	600	187	–	200	799	422	196	1,303	3,562	NA
1971		–	414	125	–	830	206	–	338	333	963	331	1,376	2,881	19,629
1972		–	632	236	24	780	247	–	271	811	601	445	1,236	3,638	12,837
1973	1638	–	547	269	43	800	404	–	360	563	445	438	1,388	3,619	10,761
1974	1458	–	985	310	68	1577	387	–	285	462	557	565	1,367	4,818	9,709
1975	2669	–	1,128	676	603	3283	702	–	336	527	599	583	1,992	5,052	10.756
1976	1870	175	1,162	530	746	2116	477	–	416	441	476	487	1,712	6,490	12,012
1977	1792	350	2,185	670	1,395	2960	525	–	456	400	1160	528	2,002	11,255	12,459
1978	2408	300	1,922	726	2,753	2865	515	–	530	658	976	543	2,225	11,873	11,259
1979	2686	655	2,062	651	3,370	2334	474	–	712	1,912	863	909	2,409	10.880	12,046
1980	2503	396	1,784	546	3,811	2926	518	–	669	740	714	670	2,342	10,179	11,571
1981	2164	582	1,833	459	4,037	3287	634	287	816	850	787	681	2,310	12,357	11,529
1982	2760	492	2,087	611	4,198	3267	540	359	822	900	909	678	2,785	14,701	25,932
1983	3715	667 to Oct 83	NA	NA	NA	4516	NA	238 Oct 83	NA	1,150	NA	786	NA	12,689	33,314

NA Not available.
– No monitoring system.
* German adverse reaction monitoring was until 1978 the responsibility of Drug Commission of the German Congress (now Society) of Internal Medicine.
** Japanese spontaneous adverse reaction system is entirely hospital based.

Table 2 Frequency of adverse reaction reporting in 15 countries expressed as ADR reports $\times 10^{-6}$ of population p.a.

	Population in millions	*Date of commencement of spontaneous reporting scheme*	*Number of ADR reports in national register*	*Maximum number of ADR reports in any single year*	*Average rate of ADR reporting (ADR reports $\times 10^{-6}$ population p.a.)*	*Maximum rate of ADR reporting (ADR reports $\times 10^{-6}$ population p.a.)*
Denmark	5.12	1968	19,962	2,087	260.0	407.6
New Zealand	3.03	1965	11,543	1,160	211.8	383.2
Sweden	8.32	1965	25,207	2,785	98.0	334.7
United Kingdom	56.00	1964	130,000	14,701	122.2	262.5
Australia	14.93	1964	32,971	3,715	116.2	248.8
Norway	4.10	1970	8,981	909	156.4	221.7
Ireland	3.44	1967	6,725	702	122.2	204.1
Finland	4.81	1966	5,959	726	72.8	150.9
United States	226.54	1961	170,000*	33,314	62.5	147.0
Netherlands	14.29	1963	13,000	1,912	47.8	133.8
France	54.09	1976	21,598	4,198	23.5	77.6
Germany	61.66	1962**	34,000	4,516	25.0	73.3
Belgium	9.85	1976	3,617	655	52.4	66.5
Japan	117.88	1967***	7,146	822	3.8	6.9
Italy	56.24	1980****	884	359	5.23	6.3

* Figure for total reports in US adverse Reactions Register is from 1971 onwards.

** Spontaneous reporting of Adverse Drug Reactions was to the 'Drug Commission of the German Congress (now Society) of Internal Medicine but since 1978 has been to the Bundesgesundheitsamtes BGA in Berlin.

*** The ADR monitoring system in Japan is entirely hospital based and is conducted in specified hospitals.

**** A spontaneous reporting system existed in Italy from 1963 but adequate reports only appeared after 1980 when it was made compulsary for pharmaceutical companies to report adverse reactions observed on their products.

single year. Maximum rates of over 200 ADR reports 10^{-6} of the population p.a. were noted in Australia, Denmark, Ireland, New Zealand, Norway, Sweden, United Kingdom.

Maximum rates of reporting below 150 ADR reports $\times 10^{-6}$ p.a. were achieved in Belgium, Finland, France, Germany, Italy, Japan, Netherlands and the United States. (The lower reporting rate in Japan is to some extent due to the fact that ADR reports are only accepted from a selected hospital population).

An alternative method of expressing national ADR reporting rates is to express this as number of ADR reports p.a. $\times 10^{-3}$ medical practitioners (see Table 3). Using this method national reporting rates of over 100 ADR reports p.a. $\times 10^{-3}$ medical practitioners were achieved in Denmark, Ireland, New Zealand, Sweden and the United Kingdom in 1982.

It is pertinent to note that apart from the United Kingdom, which has a population of 56 million, all the other countries with a rate of ADR reporting of over 200 reports $\times 10^{-6}$ p.a. have populations of less than 15 million. The same point is equally apparent if the rate of reporting is expressed as ADR reports $\times 10^{-3}$ medical practitioners p.a. where again, apart from the United Kingdom, those countries where ADR reporting rate exceeded 100 reports $\times 10^{-3}$ medical practitioners p.a. had populations smaller than 10 million. The value of any spontaneous ADR reporting system on a national basis depends firstly on a high level of alertness and participation from its medical profession, but secondly, it is a necessity that there is a population of adequate size exposed to individual drugs to enable an ADR of low incidence to be detected. The United Kingdom is unique in having a high rate of reporting from a large population.

Source of ADR reports Most countries were able to break down the source of their adverse reaction reports into groups comprising hospital doctors, general practitioners, pharmaceutical industry or others (Table 4).

In Australia, Belgium, Denmark, France, Japan and Sweden ADR reports by hospital doctors formed the largest single category of input into their national ADR registers. On the other hand in Ireland, Netherlands, New Zealand, and the United Kingdom reports of ADR emanating from general practitioners formed the largest input. In Germany, Italy, and the United States 70.0, 82.7 and 76.0% respectively of ADR reports made to the National ADR register were supplied by the pharmaceutical industry.

In the miscellaneous category of other sources of ADR reports dentists were cited by Australia, Belgium, Denmark, Ireland, Netherlands, New Zealand, the United Kingdom and the United States as sources of reports. Pharmacists were given as sources of ADR reports by Australia, Belgium, France, Germany, Ireland, New Zealand and the United States. Japan would accept ADR reports from hospital based pharmacists only. On the other hand, pharmacists were excluded from supplying of ADR reports

Table 3 Frequency of adverse reaction reporting expressed as number of ADR reports $\times 10^{-3}$ practitioners p.a. in 15 countries

	Number of prescribing doctors		*Number of ADR reports made in 1982*	*Number of ADR reports Pa/1000 medical practitioners based on official statistics*
	Official figures	*Questionnaire figures for 1983*		
Australia	33,000	30,500	2,760	83.6
Belgium	26,000	23,000	492	18.9
Denmark	11,143	12,000	2,087	187.2
Finland	7,641	10,050	611	80.0
France	143,000	143,769	4,198	29.4
Germany	178,000	135,800	3,267	18.4
Ireland	5,000	6,000	540	108.0
Italy	200,000	—	359	1.8
Japan	—	65,000*	822	12.6
Netherlands	28,000	26,987	900	32.1
New Zealand	—	6,426	909	141.4
Norway	7813	8981	672	86.1
Sweden	16,650	18,000	2,785	167.3
United Kingdom	90,000	—	14,701	163.3
United States	450,000	300,000 treating patients	25,932	57.6

* Number of doctors practising in monitoring hospitals and involved in post-marketing surveillance.

Table 4 Source of ADR reports received by national adverse drug reaction registers

	Australia	*Belgium*	*Denmark*	*Finland*	*France*	*Germany*	*Ireland*	*Italy*	*Japan*	*Netherlands*	*New Zealand*	*Sweden*	*United Kingdom*	*USA*
Year of commencement of ADR reporting system	1964	1976	1967	1966	1976	1962	1967	1980	1967	1963	1965	1965	1964	1961
Total number of reports on National Register	32,971	3,617	19,962	5,959	21,598	34,000	6,725	884	7,146	13,000	11,543	25,207	130,000	170,000
Source of reports														
Hospital doctors	48.1%	66.0%	49.8%	49.0%	71.0%	15.0%	20.8%	7.0%	98.8%	40.0%	26–42%	75.0%	18.9%	7.0%
General practitioners	31.1%	12.0%	45.6%	49.0%	14.0%	15.0%	44.6%	10.3%	0.2%	60.8%	55–68%	25.0%	60.3%	
Pharmaceutical industry	9.5%	–	–	–	–	70.0%	–	82.7%	–	–	–	–	20.8%	76.0%
Others	–	19.0%	4.6%	2.0%	15.0%	– under	34.6	–	1.0%	1.0%	2–6%	–	–	17.0%
% reports relating to a fatal event	1.7%	?	2.7%	2.5%	4.3%	5.0%	2.5%	0.4%	2.4%	4.0%	2.1–7.1%	2.0–3.9%	3.5%	Approx. 10%

to the National ADR registers in Denmark, Finland, Netherlands, Sweden and the United Kingdom. ADR reports direct from patients were stated to be entered into the National ADR registers in West Germany and the United States. Figures for the percentage contribution of ADR reports from patients were not given for West Germany but were said to be less than 1.0% in the U.S.A.

An analysis of the nature of adverse drug reactions made spontaneously on yellow cards in the United Kingdom in the years 1972–80 indicated that some 60% of adverse reactions received during this period were sent by general practitioners who during this period had used the yellow card system on two or more occasions. However only 8% of these reported reactions referred to a serious or fatal event.

The adverse drug reaction reports submitted during the same period by hospital doctors amounted to approximately 27% of the input but these reports contained a much higher percentage of serious and fatal adverse reactions (see Table 5).

Severity of ADR reports Only the simplest assessment of the nature of adverse reaction reports was sought in the questionnaire namely the percentage of ADR reports to the national register that referred to a fatal outcome.

Italy had only 0.4% of ADR reports in its National Register relating to a fatal outcome, in the United States the fatality figure was high, given as approximately 10.0%. In all other countries the percentage of the ADR reports that referred to a fatality averaged 2.5%.

Rate and source of ADR reports and prescribing habits Comparable prescribing data for different countries was difficult to obtain and only a crude figure based on the number of prescription items per caput per annum could be obtained for most countries.

Table 6 shows that in general there exists an inverse relationship between the number of ADR reports per million of the population per annum and the national number of prescription items per caput per annum. The correlation is more obvious if the contribution to the input of ADR reports from the medical profession alone is taken into account. Those countries with an average prescription drug usage of 10.0 drugs per caput p.a. or more, had ADR reporting rates of less than 150 ADR reports $\times 10^{-6}$ population p.a. Those countries using less than an average of 9.0 prescription drugs per annum had ADR reporting rates of over 150 ADR reports $\times 10^{-6}$ population p.a. It is unlikely that the higher rate

Table 5 Origin of spontaneous ADR reports on yellow cards: 1972–80, with the percentage of serious or fatal reactions for each group in brackets

	Single users	% *(Serious and fatal ADRs)*	*Multiple users*	% *(Serious and fatal ADRs)*
Junior hospital doctors	3,432	(32)	5,528	(26)
Consultants	1,090	(29)	3,672	(23)
General practitioners	5,362	(13)	30,352	(8)
Others	806	(19)	3,443	(15)
Sub total	10,690		42,995	

of drug usage is in fact associated with a true lower incidence of adverse reactions and therefore a safer use of drugs. In practice the converse is true that ADR are most likely to occur in patients receiving multiple therapy. It therefore would appear that it is more reasonable to explain this finding on the hypothesis that in countries where the medical profession in general is more aware of the possibility of drug induced disease fewer drugs per caput are prescribed. One must, however, be most careful in drawing conclusions that are too broad from these figures because even in countries with a relatively low prescription drug usage per caput per annum there has been a moderate but significant increase in prescription drug usage. For example in the United Kingdom in 1970 the number of prescriptions per caput p.a. was 5.5, in 1975 it was 6.2 and in 1980 was 6.7, for the same years the number of ADR reports was 3563, 5052, and 10179, respectively. However over the last 10–15 years the prescription drug usage per caput p.a. in the United Kingdom has consistently been comparatively low in international terms and the moderate increase seen over this period does not invalidate the hypothesis made earlier. There is also an inverse relationship between the number of pharmaceutical specialities on the national market and the rate of ADR reporting per million population per annum. The Scandinavian countries have the lowest national rates of drug usage per caput per annum, they also have the lowest numbers of pharmaceutical specialities on their national market and have with the British Commonwealth countries, Australia, New Zealand and the United Kingdom, the highest rates of ADR reporting $\times 10^{-6}$ population p.a.

Drugs most commonly reported to cause adverse drug reactions (ADRs)

The questionnaire sent to each country sought information on the 10 drugs which were most commonly reported to be associated with ADRs for the years 1982, 81, 80, 70 and 65. These lists are given in Tables 7 (a–f) for all the countries able to supply the data requested. Norway was unable to present the data in the format requested but supplied information on the therapeutic classes of drugs most frequently reported to cause adverse reactions, in that country in 1982 and 1981, respectively, non-steroidal anti-inflammatory drugs were implicated in 22 and 14% of ADR reports, cardiovascular drugs in 19 and 28%; analgesics in 6 and 7%; antibiotics in 5.5 and 4%, respectively.

Belgium produced a list of the 10 drugs most commonly reported to cause adverse reactions for the period 1976–83. In rank order these were triazolam, flunitrazepam, glafenine, piroxicam, troleandomycin, cimetidine, indomethacin, doxycycline, metoclopramide, and alclofenac; of these 10 drugs four were non-steroidal anti-inflammatory agents.

West Germany provided lists for 1982, 81, and 80 and produced a composite list for the years 1967–76. The 10 drugs most associated with ADR reports are given in rank order: ampicillin, dextran, amidotrizoic acid, digoxin, co-trimoxazole, ioglycamic acid, D-penicillamine, BCG vaccine, nitrofurantoin and spironolactone.

Italy produced lists of the 10 drugs most commonly attributed to cause ADR reports for the years 1982 and 81. In the cases of the other countries the 10 drugs most frequently reported to cause ADR are listed in Tables 7 (a–f).

Only New Zealand, Sweden and the United Kingdom were able to furnish data for the year 1965. The Netherlands and the United States did not supply data on the 10 drugs most commonly reported to cause ADRs. The problems of interpretation of these lists of drugs most frequently associated with ADR reports are considerable since the rate of ADR reporting on individual drugs may be influenced by a number of factors which introduce bias.

Availability of the drug Some drugs appear uniquely in the lists of 10 drugs most commonly

Table 6 Correlation between the prescription items per caput p.a., rate of ADR reports 10^{-6} population p.a. and a percentage of ADR reports in national adverse drug reaction register supplied by the medical profession

	Prescription items per caput p.a. (relevant year quoted in brackets)		*Rate of ADR reports 10^{-6} population p.a.*	*% ADR reports in register emanating from Medical Profession*	*Number of pharmaceutical products on market 1977/1978*
United States	16.6 (1979)***	—	147.0	7.0%	NA
Italy	11.3 (1982)*	21.0 (1973)**	7.3	17.3%	13 700
Germany	11.2 (1982)*	11.0 (1973)**	73.3	30.0%	15 000
France	10.0 (1982)*	10.5 (1973)**	77.6	85.0%	7 800
New Zealand	8.5 (1983)	—	383.2	94.0%	NA
Australia	7.7 (1981)†	7.5 (1978)	248.8	79.2%	NA
United Kingdom	6.5 (1982)*	6.3 (1973)**	262.5	79.2%	15 000
Denmark	6.5 (1980)‡	6.1 (1975)‡	407.6	95.4%	2100
Norway	—	5.8 (1975)‡	221.7	—	1870
Finland	5.1 (1980)‡	4.9 (1975)‡	150.9	98.0%	3700
Sweden	4.7 (1980)†	4.9 (1975)‡	334.7	97.2%	2700

* O'Brien (1984).
** Abel Smith & Grandjeat (1978).
*** Burkholder (1979).
† Keith (1983).
‡ Nordisk Lakemedelstatistik (1978'1980).

Table 7 The 10 drug substances, or combination of substances, most frequently reported to cause adverse drug reactions (ADR)
(a) 1982—in Australia, Denmark, Finland, France, Germany, Ireland, Italy, Japan, New Zealand, Sweden and the United Kingdom

Australia	*Denmark*	*Finland*	*France*	*Germany*	*Ireland*	*Italy*	*Japan*	*New Zealand*	*Sweden*	*United Kingdom*
Co-trimoxazole	Benoxaprofen	Nitrofurantoin	Glafenine	Cimetidine	Amiodarone	Probucol	Tiopronin	Co-trimoxazole	Piroxicam	Benoxaprofen
Amoxycillin	Fenbufen	Co-trimoxazole	Amiodarone	Diclofenac	Buprenophine	Piroxicam	Amoxicillin	Valproate	Zimeldine	Fenbufen
Sulindac	Pivampicillin	Penicillin	Triazolam	Benoxaprofen	Cimetidine	Ranitidine	Cephalexin	Nifedipine	Mumps + Measles + Rubella vaccine	Piroxicam
Methyldopa	Co-trimoxazole	Piroxicam	Cimetidine	Latamoxef	Indomethacin	Diclofenac	Mefenamic acid	Sulindac	Trimethoprim	Cimetidine
Naproxen	Carbamazepine	Doxycycline	Acetyl salicylic acid	Piracetam	Nalidixic acid	Cefotaxime	Meglumine	Metoprolol	Co-trimoxazole	Zomepirac
Cimetidine	Amiloride	Carbamazepine	Heparin	Cianidanol	Nifedipine	Zomepirac	Sulindac	Hydrochlorthiazide + Amiloride	Nitrofurantoin	Buprenorphine
Erythromycin	Hydrochlorthiazide	Ampicillin	Erythromycin	Dipyrone	Piroxicam	Diflunisal	Cefatrizine	Naproxen	Dextran	Diphtheria/tetanus vaccine
Metoprolol	Nomifensine	Trimethoprim	Nicoumalone	Buprenorphine	Salbutamol	Bendrofluthiazide	Piroxicam	Perhexiline	Metoprolol	Zimeldine hydrochloride
Indomethacin	Ibuprofen	Tolfenamic acid	Valproic acid	Piroxicam	Co-trimoxazole	Ticlopidine	Indomethacin	Cimetidine		Ethinyloestradiol/progestogen combination oral contraceptive
Carbamazepine	Indapamide	Pindolol	Amineptine	Contrast media	Zimeldine	Tegafur	Betamethasone	Labetalol		Mianserin

Table 7 (cont'd.)

(b) 1981—in Australia, Denmark, Finland, France, Germany, Ireland, Italy, Japan, New Zealand, Sweden and the United Kingdom

Australia	*Denmark*	*Finland*	*France*	*Germany*	*Ireland*	*Italy*	*Japan*	*New Zealand*	*Sweden*	*United Kingdom*
Co-trimoxazole	Fenbufen	Nitrofurantoin	Glafenine	Cimetidine	Borax and honey	Atenolol	Cephalexin	Co-trimoxazole	Co-trimoxazole	Benoxaprofen
Naproxen	Pivampicillin	Co-trimoxazole	Aspirin	Diclofenac	Cimetidine	Piroxicam	Betamethasone	Valproate	Nitrofurantoin	Cimetidine
Amoxycillin	Nomifensine	Amoxycillin	Acenocoumoral	Dipyrone	Diphtheria and tetanus vaccine	Cephamandole	Ampicillin	Metoprolol	Trimethoprim	Piroxicam
Ampicillin	Benoxaprofen	Tolfenamic acid	Digoxin	Aspirin	Feprazone	Cefaclor	Indomethacin	Labetalol	Hydralazine	Fenbufen
Methyl-dopa	Carbamazepine	Sodium aurothiomalate	Cimetidine	Dextran	Metoclopramide	Cefotaxime	Co-trimoxazole	Cimetidine	Amoxycillin	Diphtheria/tetanus vaccine
Cimetidine	Co-trimoxazole	Carbamazepine	Amiodarone	Benoxaprofen	Metoprolol	Tegafur	Trichlormethiazide	Nifedipine	Cimetidine	Ethinyl oestradiol + progestogen
Metoprolol	Amiloride + hydrochlorthiazide	Trimethoprin	Co-trimoxazole	Flunitrazepam	Nifedipine	Indoprofen	Amoxycillin	Indomethacin	Phenoxymethyl-penicillin	Zomepirac
Timolol	Oral contraceptives combined	Indomethacin	Methyl-dopa	Piracetam	Piroxicam	Ritodrine	Mefenamic acid	Sulindac	Doxycycline	Diphtheria/tetanus pertussis vaccine (DTP)
Erythromycin	Oral contraceptives Sequential	Bromocriptine	Aurothiopropanol sulphate	Spironolactone	Triazolam	Bendrofluthiazide	Fluocinolone	Naproxen	Metoprolol	Nifedipine
Amiloride hydrochlorthiazide	Cimetidine	Ampicillin		Blood	Captopril	Captopril	Tegafur	Perhexilene		Co-trimoxazole
Indomethacin	Halothane									

Table 7 (cont'd.)

(c) 1980—in Australia, Denmark, Finland, France, Germany, Ireland, Japan, New Zealand, Sweden and the United Kingdom

Australia	*Denmark*	*Finland*	*France*	*Germany*	*Ireland*	*Japan*	*New Zealand*	*Sweden*	*United Kingdom*
Co-trimoxazole	Pivampicillin	Co-trimoxazole	Glafenine	Cimetidine	Aspirin	Co-trimoxazole	Co-trimoxazole	Nitrofurantoin	Fenbufen
Naproxen	Co-trimoxazole	Nitrofurantoin	Tienilic acid	Diclofenac	Cimetidine	Cephalexin	Diphtheria/tetanus vaccine	Co-trimoxazole	Piroxicam
Meglumine diatrizoate	Carbamazepine	Penicillin	Aspirin	Nomifensine	Droperidol	Betamethasone Valerate	Metoprolol	BCG vaccine	Cimetidine
Amoxycillin	Nomifensine	Amoxycillin	Heparin	Co-trimoxazole	Fenbufen	Amoxycillin	Atenolol	Hydralazine	Benoxaprofen
Metoprolol	Cimetidine	Doxycycline	Co-trimoxazole	Tromantidine	Ibuprofen	Cephazolin	Acebutolol	Nalidixic acid	Diphtheria/ tetanus vaccine
Ampicillin	Halothane	Metoprolol	Cimetidine	Nor-pseudoephedine	Indomethacin	Ampicillin	Perhexilene	Cimetidine	Feprazone
Amiloride + hydrochlorthiazide	Amiloride + hydrochlorthiazide	Ampicillin	Phenoperidine hydrochloride	Tilidate	Metoclopramide	Indocyanine green	Amoxycillin	Amoxycillin	Ethinyloestradiol + progestogen
Cimetidine	Oral contraceptives combined	Atenolol	Indomethacin	Streptokinase	Salbutamol	Fluocinolone acetate	Cimetidine	Diflunisal	Ketotifen
Methyl-dopa	Nitrofurantoin	Methyl-dopa	Digoxin	Bemetizide + triamterene	Triazolam	D-penicillamine	Labetalol	Phenoxymethyl-penicillin	Diphtheria/tetanus pertussis vaccine
Erythromycin	Maprotiline	Tolfenamic acid	Amiloride + hydrochlothiazole	Contrast media			Methyl-dopa		Intrauterine contraceptive device

Table 7 (cont'd.)

(d) 1975—in Australia, Denmark, Finland, France, Ireland, Japan, New Zealand, Sweden and the United Kingdom

Australia	*Denmark*	*Finland*	*France*	*Ireland*	*Japan*	*New Zealand*	*Sweden*	*United Kingdom*
Co-trimoxazole	Co-trimoxazole	Practolol	Aspirin	Ampicillin	Ampicillin	Co-trimoxazole	Nitrofurantoin	Practolol
Ampicillin	Pivampicillin	Methyl-dopa	Bismuth	Aspirin	Betamethasone Valerate	Ampicillin	BCG vaccine	Prazosin
Methyl-dopa	Oral contraceptives combined	Nitrofurantoin	Nicoumalone	Dextropropoxyphene	Amoxycillin	Practolol	Practolol	Ethinyloestradiol + progestogen combined oral contraceptives
Amoxycillin	Indomethacin	Co-trimoxazole	Glafenine	Haloperidol	Fluocinolone	Frusemide	Sulphamethoxypridazine	Propranolol
Practolol	Gravigard (IUD)	Penicillin	Bucloxic acid	Lignocaine + noradrenaline	Sodium aurothiomalate	Indomethacin	Co-trimoxazole	Phenylbutazone
Propranolol	Ampicillin	Indomethacin	Ethyl biscoumacetate	Metoclopramide	Mefenamic acid	Methyl-dopa	Dextran	Co-trimoxazole
Indomethacin	Phenylbutazone	Mefenamic acid	Pethidine	Penicillin	Pentazocine	Minocycline	Ampicillin	Diphtheria/tetanus/ pertussis vaccine
Pindolol	Phenytoin	Carbamazepine	Phenindione	Practolol	Lincomycin	Prochlorperazine	Methyl-dopa	Oxprenolol
Digoxin	Clozapine	Phenformin	Sedarone (Noramidopyrine (Quinine (Caffeine (Pholcodine (Aconite	Co-trimoxazole	Cefalexin	Amoxycillin	Naproxen	Maprotiline
Diazepam	Practolol	Clozapine	Adalgur (Glafenine (Meprobamate (Colchicine		Indomethacin	Aspirin		Indomethacin

Table 7 (cont'd.)

(e) 1970—in Denmark, Finland, Ireland, Japan, Sweden and the United Kingdom

Denmark	*Finland*	*Ireland*	*Japan*	*New Zealand*	*Sweden*	*United Kingdom*
Oestrogen/progestogen oral contraceptives	Methyl-dopa	Ampicillin	Ampicillin	N/A	Norethisterone + mestranol	Ethinyloestradiol/progesterone oral contraceptives
Phenylbutazone	Co-trimoxazole	Aspirin	Suxamethonium bromide Suxamethonium chloride	N/A	Norgestrol + ethinyloestradiol	Mestranol containing oral contraceptives
Indomethacin	Nitrofurantoin	Oestrogen/progestogen oral contraceptives	Pentazocine	N/A	Nitrofurantoin	Co-trimoxazole
Phenytoin	Sulphanomides	Fluphenazine	Bleomycin	N/A	Ampicillin	Measles vaccine
Meglumine amidotrizoate	Dextran	Levo-dopa	Chloramphenicol	N/A	Lynoestrenol + ethinyloestradiol	Phenylbutazone
Oxyphenbutazone	Ampicillin	Methyl-dopa	Coralgil	N/A	Digitalis	Ampicillin
Nitrofurantoin	Indomethacin	Nitrofurantoin	Fluocinolone acetonide + neomycin	N/A	Sulphamethoxypyridazin	Pentazocine
Thiethylperazine	Pseudoephedrine	Pentazocine	Oxyphenbutazone	N/A	Methyl-dopa	Indomethacin
Phenoxymethylpenicillin	Tetracycline	Phenylbutazone	Alkylbenzyl ' trimethylammonium chloride	N/A	Oxyphenbutazone	Nalidixic acid
		Phenytoin	Neomycin	N/A	Acetazolamide	Methyl-dopa

Table 7 (cont'd.)
(f) 1965—in New Zealand, Sweden and the United Kingdom

New Zealand	*Sweden*	*United Kingdom*
Phenothiazines	Norethisterone + ethinyloestradiol oral contraceptives	Mestranol combination oral contraceptives
Phenylbutazone	Lynoestrenol + ethinyloestradiol oral contraceptives	Ethinyloestradiol combination oral contraceptives
Oxyphenbutazone	Norethisterone + mestranone oral contraceptives	Indomethacin
Penicillin	Oxyphenbutazone	Phenylbutazone
Tetracycline	Meglumine + sodium amidotriozoate	Nalidixic acid
Sulphonamides	Tiocarlide	Ampicillin
Thiazides	Indomethacin	Amitriptyline
Indomethacin	Phenacetin	Frusemide
Chloramphenicol	Nialamide	Methylodopa Diphtheria/tetanus/pertussis vaccine

associated with ADR reports and this is a matter in some cases of the uniqueness of availability e.g. glafenine and glafenine containing combination products which regularly appear as major sources of ADR reports in Belgium and France but in no other country. This is because the availability of this non-steroidal anti-inflammatory agent is limited to these two countries and the Netherlands (which did not provide lists of the drugs most frequently reported to cause ADRs).

Common usage Widely used drugs are likely to generate large numbers of adverse reaction reports, examples of this kind of drug substances are co-trimoxazole and cimetidine.

It is of considerable interest that co-trimoxazole was the single drug substance that most consistently appeared in the national lists of the 10 drugs most frequently associated with ADRs. In all the countries surveyed, with the exception of Italy, co-trimoxazole appeared in the list of the 10 drugs most frequently associated with ADR reports in at least one of the five years studied, i.e. 1982, 81, 80, 75 and 70. In Australia, Denmark, Finland, New Zealand and Sweden co-trimoxazole appeared in the top 10 drugs in either 4 or 5 of these 5 years. In Finland and Sweden in both 1982 and 1981 trimethoprim as a single substance also appeared in the lists of the 10 drugs most commonly associated with ADR.

Cimetidine's consistent appearance in the national lists of the 10 drugs most frequently reported to cause ADR is also a feature of the wide usage of the drug. Cimetidine appeared in the Australian, French, German, Irish, New Zealand and United Kingdom lists for 1982, 1981, and 1980; and in Denmark and Sweden for 1981 and 1980. Cimetidine is conspicuous by its absence from the lists of Finland and Japan. In Italy the most widely used H_2-receptor blocker is ranitidine which featured amongst the top 10 drugs in 1982 for that country.

It would however be unwise to dismiss high levels of reporting of adverse reactions of widely used drugs such as co-trimoxazole and cimetidine as being solely due to their wide usage. The association of any widely used drugs with consistently high levels of ADR reporting for more than 2 to 3 years after its launch on to the market merits careful scrutiny.

Media bias ADR reports may be generated by media exposure of an alleged problem with a particular drug substance. A clear example of this is triazolam (Halcion) which, following the published report of van der Kroef (1979) was given extensive media exposure particularly on Dutch television. These transmissions were also received by viewers in Belgium. As a consequence the Netherlands received 999 ADR reports relating to triazolam out of the total 1979 annual input of 1912 reports. Similarly in Belgium for the period 1976–83 triazolam was associated with more ADR reports than any other drug.

In the United Kingdom triple vaccine (diphtheria/tetanus/pertussis) has featured amongst the annual lists of the ten drugs most frequently associated with adverse reaction reports intermittently for 17 years; in several years diphtheria/tetanus vaccine has also figured in the U.K. lists. In no other country has triple vaccine figured in the list of the 10 drugs most commonly reported

to cause ADR in any year although diphtheria/tetanus featured in Ireland (1981) and New Zealand (1980). It is tempting to attribute this peculiarity of ADR reporting in the U.K. to the publicity which has surrounded pertussis vaccination in the United Kingdom.

Conspicuous by their absence from the lists of drugs which have been a major source of ADR is Debendox (Bendectin in the U.S.A.). In none of the countries participating in the survey did Debendox appear at any time amongst the 10 drugs most frequently reported to be associated with ADR. Yet this drug was subjected to 'Trial by Media' and was condemned by adverse publicity not by any Regulatory Authority, not one of which ever advanced a case against the product.

It therefore would appear that the media has the power to adversely affect a product in two ways—firstly to generate ADR reports relative to a particular problem in such a way as to cause bias and secondly to destroy a product without adequate evidence.

Monitoring bias Specific monitoring requirements can, of themselves, introduce bias. In New Zealand, for example, intensive monitoring schemes for certain drugs were introduced in 1977 and in 1980 six drugs in the list of 10 drugs most frequently associated with ADR had been subjected to such intensive monitoring; comparable figures for 1981 are four out of 10 and 1982 two out of 10.

Monitoring bias may therefore be a confounding factor when trying to assess relative safety between drugs of the same class, even when comparative prescription data are available.

National differences in susceptibility to ADR Nitrofurantoin has appeared consistently amongst the 10 drugs most frequently associated with ADR reports for the last 17 years in Sweden and for the last 12 years in Finland. An analysis of these reports for the U.K., Holland and Sweden by Penn & Griffin (1982) indicated that the reports differed qualitatively in the nature of the ADR reported as well as quantitatively. Nitrofurantoin did not appear in the national lists of 10 drugs most frequently associated with ADR other than in Denmark in 1980, Ireland 1970 and in West Germany in the composite list for 1970–76.

Clozapine appeared on the list of 10 drugs most frequently associated with ADR from Finland in 1975. In 1975 the Finnish National Board of Health received over a period of 2 months 18 reports of severe blood disorder, nine of them fatal (eight agranulocytosis, one leukaemia). Clozapine had been introduced on to the Finnish market 5 months earlier and the total number of patients exposed was between 1500–2000. Since the total number of cases of fatal agranulocytosis p.a. in Finland is between 5–12 the appearance of eight cases in 2000 patients was very alarming. The drug was withdrawn from the market. In three of these eight cases no drug other than clozapine had been given but in four cases amidopyrine had been taken. In summarizing the episode Idänpään-Heikkila *et al.* (1975) advanced three alternative hypotheses to account for the clustering of these cases. The alternatives proposed were an allergic or toxic reaction to the drug or an interaction with other substances not identified, or the patients involved may have had particular genetic characteristics.

Interpretation of international ADR data ADR reports supplied to the 15 national adverse reaction registers were collected in different ways and from different sources. In some countries the ADR reports are derived almost entirely from spontaneous reports from doctors and dentists, in others pharmacists also supply reports, and in two countries reports from patients are also accepted into the national adverse reaction registers. In several countries reports from the pharmaceutical industry formed the majority of reports supplied to the authorities.

The rate of spontaneous reporting of ADR reactions associated with individual drugs can be influenced by a number of factors not necessarily directly related to the safety of the product e.g. media bias, monitoring bias.

National differences in volume of usage of individual drugs varies and there are also national differences in the susceptibility to the toxicity of a drug which may vary qualitatively as well as quantitatively. National Drug Regulatory authorities should make their adverse drug reaction data available to each other, but should have regard to the heterogenicity of the data collected and realize that extrapolation of ADR data from one country to another may be unjustified. There is no justification for 'lumping' data reported to, or collected by the various international authorities into a single pool and regarding it as homogeneous. Any international analysis of the spontaneous ADR reports made to national regulatory authorities should keep the integrity of the national ADR register and where possible correlate the reports with the extent of the national drugs usage.

Adverse reaction reports to non-steroidal anti-inflammatory agents (NSAIs) form a very high percentage of the total input of ADR reports into the national ADR registers, for this reason

they were selected as an example of how international comparisons of disparate data might be made. The national authorities were asked to provide information as to the number of ADR reports that were received relating to NSAIs and what percentage of the total input of ADR reports these comprised. Data were also obtained on the number of prescriptions written for NSAIs and the percentage of total prescription drugs usage for NSAIs. In a situation where a therapeutic class of drugs presents no particular hazard then the percentage of ADR reports relating to that category when divided by the percentage of prescriptions for that category of drugs should be approximately 1.0. In Table 8 are shown the total numbers of ADR reports received by the United Kingdom's national register and the absolute number of reports relating to NSAIs by source of report.

In Table 9 are shown the percentage of prescriptions written for NSAIs in 1982 in Denmark, Finland, France, Germany, Italy, Norway, Sweden and the United Kingdom compared with the percentage of ADR reports relating to NSAIs from these countries for 1983, 1982 and 1981. The prescription usage of NSAIs as a percentage of total prescription usage varied from 9.2% in Finland to 2.8% in Germany.

The risk ratio =

$$\frac{\text{ADR reports to NSAIs as of total ADR reports}}{\text{Prescriptions for NSAIs as a \% age of total prescriptions.}}$$

This ratio of ADR reports to NSAI as % of total reports divided by the prescriptions for NSAIs as percentage of total prescription usage was Denmark 4.5, Finland 0.9, France 1.3, Germany 2.9, Italy 2.2, Norway 3.6, Sweden 2.7, United Kingdom 4.9. Apart from Finland where the usage figure for NSAIs was remarkably high, the contribution of NSAIs to the total input of ADR reports seems disproportionately high.

Can the existing ADR monitoring systems detect unsafe drugs? ADR reports may be generated in respect of drugs which present an intrinsic hazard in their own right. In this context it is important to ascertain whether or not the spontaneous adverse drug reaction systems in the individual countries were capable of detecting the hazard caused by these intrinsically dangerous drugs. The only way the systems could be tested in retrospect, using the data available, was to determine whether or not those drugs e.g. practolol, benoxaprofen, zomepirac, zimeldine, feprazone, fenclofenac, phenylbutazone or oxyphenbutazone which have been withdrawn from

Table 8 Number adverse reactions reports to non-steroidal anti-inflammatory drugs compared with total ADR reports for the period 1964–83 for the United Kingdom

Year	Total ADR reports	ADR reports relating to NSAIs		Others	ADR reports related to NSAI with a fatal outcome
		Yellow-card report	Industry report		
1964	1415	84	15	20	21
1965	3987	409	36	50	51
1966	2386	184	37	24	49
1967	3503	171	21	46	46
1968	3486	190	27	44	47
1969	4306	203	43	35	46
1970	3563	188	29	32	40
1971	2851	139	44	43	45
1972	3638	215	38	51	51
1973	3619	236	42	19	46
1974	4815	433	75	54	67
1975	5052	274	61	95	99
1976	6409	472	84	49	54
1977	11 255	1072	84	60	61
1978	11 873	1679	242	69	61
1979	10 881	1812	314	106	63
1980	10 179	2309	594	84	55
1981	12 357	4017	309	182	88
1982	14 701	3021	255	309	111
1983	12 689	3154	336	276	127

Table 9 The percentage of prescriptions written for NSAIs in various countries

Country	*Prescriptions for NSAIs as a percentage of total prescriptions for 1982*	*ADR reports on NSAIs as a percentage of total reports (%)*			*Number of NSAIs amongst the 10 drugs most commonly reported to produce ADR reports*	
		1983	*1982*	*1981*	*1982*	*1981*
Australia					3	2
Denmark*	4.4%	13.4	28.3	20.1	3	2
Finland*	9.2%	5.4	9.1	10.4	2	2
France**	4.8%	7.0	6.7	6.0	2	2
Germany**	2.8%	—	—	—	4	4
Italy**	6.2%	11.0	16.0	13.0	4	2
Norway	approximately 5.0%	NA	22.0	14.0	NA	
Sweden*	3.5%	—	—	—	1	0
United Kingdom**	5.2%	24.8	20.5	32.5	4	4

* Prescription data provided by Granat (1984)
** Prescription data derived from O'Brien (1984)

the market on grounds of safety featured regularly in the top 10 drugs causing ADR. (This leaves aside the question of whether these monitoring systems served an alerting or confirmatory role).

Practolol featured in the top 10 drugs reported to cause ADR in 1975 in Australia, Denmark, Finland, Ireland, New Zealand, Sweden and the United Kingdom (Norway was the only country included in the survey where the drug was marketed but not specifically mentioned as being a major source of ADR reports.

Benoxaprofen was consistently in the list of the 10 drugs most frequently associated with ADR in the United Kingdom 1982, 1981 and 1980 and in Denmark and Germany in 1982 and 1981. Benoxaprofen was also on the market in France and USA of the countries surveyed as well as Spain, Switzerland and South Africa.

Zimeldine was in the lists of 10 drugs most frequently associated with ADR reports in 1982 in Ireland, Sweden and the United Kingdom. Zimeldine was also on the market of West Germany, Netherlands and Belgium of the countries surveyed.

Zomepirac was in the lists of 10 drugs most frequently associated with ADR reports in Italy in 1982 and the United Kingdom for 1982 and 1981.

Feprazone was in the list of 10 drugs most frequently associated with ADR reports in the United Kingdom in 1980, and of the countries surveyed was also on the market in West Germany and France.

Indoprofen was in the list of 10 drugs most frequently associated with ADR reports in Italy in 1982, but was also on the market in Ireland, and West Germany of the countries surveyed.

Phenylbutazone and oxyphenbutazone are old drugs but appeared in the list of 10 drugs most frequently reported to cause ADR consistently throughout the 1965, 1970, and 1975 lists from Denmark, Ireland, Japan, New Zealand, Sweden and the United Kingdom.

Therefore, these systems have value although not perfect despite their limitations due to the undoubted under-reporting of ADRs in all countries and the inadequacies of individual reports in many instances, and lack of usage data to enable incidence of ADRs to be determined.

General conclusions

Adverse drug reactions (ADR) reports supplied to the 15 national adverse reaction registers were collected in different ways and from different sources. In some countries the ADR reports are derived almost entirely from spontaneous reports from doctors and dentists, in others pharmacists also supply reports, and in two countries reports from patients are also accepted into the national adverse reaction registers. In several countries reports from the pharmaceutical industry formed the majority of reports supplied to the authorities.

In all countries there is gross under-reporting of ADR, but the number of reports received each year by the national adverse reaction centres is increasing.

The rate of spontaneous reporting of ADR associated with individual drugs can be influenced by a number of factors not necessarily directly related to the safety of the product, e.g. media bias, monitoring bias.

National differences in volume of usage of individual drugs vary and there are also national differences in the susceptibility to the toxicity of a drug which may vary qualitatively as well as quantitatively.

National Drug Regulatory authorities should make their adverse drug reaction data available to each other, but should have regard to the heterogenicity of the data collected and realize that extrapolation of ADR data from one country to another may be unjustified.

There is no justification for 'lumping' data reported to, or collected by the various national regulatory authorities into a single pool and regarding it as homogeneous.

The rate of ADR reports $\times 10^{-6}$ population p.a. showed an inverse correlation with the number of drugs prescribed per caput p.a. The interpretation placed on this correlation is that the national awareness of the medical profession to the possibility of ADR results is greater in countries with more conservative prescribing habits than in those countries in which drugs are prescribed more liberally.

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