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# What is Drug Safety?
## Celebrating 20 Years of the *Drug Safety* Journal

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The year is 1986 and drug safety stands at a crossroads. The term 'pharmacovigilance' is not yet used outside of France and the WHO Programme for International Drug Monitoring, which was set up in 1968, consists of a membership of 27 mainly 'developed' countries. The WHO Programme has been the major force in global drug safety monitoring and significant national efforts are being made in the member countries, are debated at annual WHO meetings, and contribute to slow but significant scientific developments. Harmonisation, i.e. mutual recognition and understanding of different approaches, is very much sought after and often leads to agreed standards and definitions.

Until 1986, spontaneous reports of suspected adverse drug reactions had been the major source of information used as the basis for regulatory actions, but logic and much experience indicated that there were many problems in using these data. Emphasis was placed on individual case causality, as defined by largely clinical experts, perhaps with the use of various assessment algorithms to aid the process. Other pieces of information were gathered and collated by these experts to semi-quantify the process and to add collateral information of use in decision making. Approaches such as the Michel Auriche and Claudio Naranjo Bayesian logic approaches and Bengt-Erik Wiholm's 'puzzle method' were ingenious and effective. However, several questions were being raised in the wake of high-profile decisions in drug safety and over other ways of tackling drug safety.

One key problem was the issue of the denominator: how to quantify the number of exposed patients. Only in the intensive-monitoring programmes introduced by Professor Garth McQueen in 1978 in New Zealand and then Professor Bill Inman in the UK in 1981, were exposed patients routinely recorded for selected medicines outside the hospital setting. In hospitals, the task was easier and had already been tackled by Professor Herschel Jick in Boston, Massachusetts, USA, in 1967.[1]

In specific situations, reporting rates were being used. One example of an important analysis with considerable public health importance was the report by Rossi et al.[2] on the relative reporting rates of gastrointestinal bleeding with a variety of NSAIDs.

The NSAIDs were rightly considered very important in drug safety at the time: there were many agents in the class, they were very widely used for a non-life-threatening indication and, most importantly, were known to cause life-threatening bleeding in a significant number of patients. Many observational studies involving this group of drugs were conducted in the mid-1980s enabling the construction of tables comparing the rates of gastrointestinal bleeding associated with them. Comparisons were very similar in different studies and this led to the acceptance of pharmacoepidemiology as an important development in drug safety, at least for relatively common events, solving as it does both the problem of the denominator and to some extent under-reporting (providing retrospective recording of an event was both accurate and complete).

A particular NSAID, benoxaprofen, caused a stir in drug safety in another way. This drug was found to cause lethal hepatotoxicity and the elderly were found to be particularly at risk. It also caused a severe photosensitisation reaction that persisted even after the drug was stopped. Benoxaprofen was widely marketed around the world and its withdrawal in the UK led to much controversy, not least because it continued to be available in the US for

sometime after the UK withdrawal. Moreover, Australia and New Zealand had never registered the drug because the information about a high level of photosensitization was already clear from premarketing data. This and some other events led to the US FDA requiring all US market authorisation holders to report to the FDA any events reported to a company from whatever jurisdiction they occurred in around the world.

It is fair to say that this requirement heralded the greatest change in international drug safety monitoring since the WHO Programme commenced. The Council of Organisations of Medical Sciences (CIOMS) working groups on drug safety produced their first monograph on international reporting of adverse drug reactions directed principally at the pharmaceutical industry. Many other important reports have resulted since then and have subsequently found their way into the regulatory framework of the US, the European Union and Japan via the work of the International Conference on Harmonisation. Also at around this time the International Society of Pharmacoepidemiology and the European Society of Pharmacovigilance (later the International Society) were initiated.

It was into this environment that the journal *Drug Safety* was born.

The journal was launched in January 1986 as *Medical Toxicology: An International Journal of Clinical Toxicology and Adverse Drug Reaction Experiences* with James P. Duffy as the Editor. Published by Adis Press Ltd, a privately owned NZ-based medical publisher, the journal's aim was to be the 'professional journal of practical toxicology'. I believed that this was just the journal for me! As Director of the New Zealand National Toxicology Group, I was involved in all aspects of postmarketing drug and chemical safety from regulatory issues through to deliberate poisoning and therapeutic malpractice, together with laboratory and clinical research. The first issue lead with 'Why Medical Toxicology' by Susan Pond et al.[3] Another good paper in the first volume was 'Techniques of Postmarketing Surveillance', which was an overview of the area by Jeff Carson and Brian Strom.[4] A small country like New Zealand has many advantages, not the least is the need to be, or at least to try to be, a renaissance person (or organisation) with very broad interests and the journal started with that ideal. I think this was correct at the time since the distinction between professional work on, and interest in, chemical poisoning, drug overdoses and adverse drug reactions overlapped considerably. I think this breadth of coverage was attractive to an emerging professional discipline, which may still be recognised today as clinical toxicology.

A year after its launch, the new journal gained MEDLINE-indexing and acceptance on to Current Contents (the necessary first hurdle to getting an impact factor). The name was changed to *Medical Toxicology and Adverse Drug Experience* and a new editor, Roderick H. Sayce, took over. In this volume, there was an interesting paper on Reye's syndrome[5] by Mary Glen-Bott from the UK Committee on Safety of Medicines. In the final issue of the second volume, the journal published 'Improving Adverse Drug Reaction Monitoring'[6] by John McEwen from the Therapeutic Goods Association in Australia and I wrote an accompanying article called 'Adverse Drug Reactions Monitoring: The Practicalities'.[7] In these articles, there was little emphasis on pharmacoepidemiology, although we were all concerned that the drug use denominator data needed careful consideration as well as the clinical assessment of each report.

Four years after the journal's launch, the title was changed again to the current title *Drug Safety* with the byline 'An International Journal of Medical Toxicology and Drug Experience'. During this period, the journal remained eclectic and covered pre- and postmarketing safety, methodological issues, reviews of specific safety problems, management of poisoning and much more. However, as the title matured there began a slow change in focus from toxicology/poisoning and case reports to postmarketing surveillance, benefit-risk assessment and the safe use of drugs. There was a seminal article in the first issue under the *Drug Safety* name from M.N.G. Dukes on the importance of adverse reactions in drug regulation.[8] Later in the volume, the journal published an overview of 25 years of the UK Committee on Safety of Medicines.[9] Such important perspective articles have been a continuing feature of the journal. In this year, the publisher became Adis International Limited, which was a clear sign that the Adis group of journals had grow-

ing popularity among professionals involved in all aspects of drug therapy and pharmacology.

In 1991, the journal cover was overhauled, the byline was dropped and Stephen P. Coleman took over as Editor. From this time, benefit-risk assessment papers became a feature of the journal as did papers on methodological issues. Notable papers at this time include one by Hollenberg et al.[10] dealing with quality-of-life assessments, a paper by Naranjo and Lanctot[11] on further uses of the Bayesian approach to clinical case assessment and one of the early papers on the epidemiological method, 'Statistical Methods on Pharmacoepidemiology: Principles in Managing Error', by Samy Suissa.[12] In 1992, in addition to publishing case reports the journal began to consider original research. This move was not without controversy. For many, the clinical cases and reviews were the heart of the journal's interest. I felt, both then and now, that the review content is very valuable to readers as a convenient way of becoming updated in a particular field. The various Editors of the journal over the years should all be congratulated in their choice of review subjects, out of so many possible candidates, for their interest and topicality.

In 1993, to cope with increasing demand on page space, *Drug Safety* increased in frequency from 6 to 12 issues a year. In this year, Myles Stephens wrote on 'Marketing Aspects of Company-Sponsored Postmarketing Surveillance Studies',[13] and Wallander[14] published on the important topic of adverse drug reaction monitoring in clinical trials. Such articles deal with broad methodological issues and the effects of drug safety work on the ways drugs are developed for marketing. The next year, Cecilia Biriell and I wrote on 'Harmonisation in Pharmacovigilance',[15] a paper dealing with the various international developments in pharmacovigilance. This paper discussed the various definitions that were being created by different groups as well as new methodologies and approaches to drug safety. Differences in the latter were found to give different results, depending on their various strengths and weaknesses and indeed the definitions used in those methods. Then, as now, there is no single way to approach drug safety problems, yet there seems to be demand for global standardisation. The span of the journal's articles reflecting on methodological change and its impact has been most interesting, but we have still to come to the realisation that there is no future in the 'one size fits all' approach to drug safety: the challenges are simply too variable.

In 1994, the journal stopped considering studies and case reports for publication in order to focus completely on reviews. Two reasons for this change were the paucity of good quality studies submitted to the journal and the difficulties associated with dealing with a constant stream of case reports. The change also reflected the success of the review article content. An example of the ability of the journal editors to identify interesting topics for review was a solid paper in this year on the role of active metabolites in drug toxicity by Pirmohamed et al.[16] Each author of a review approaches the review task in a different way according to the material being reviewed. This is both a strength and weakness. Undoubtedly, the flexibility is essential to approach subjects as different as those covered by *Drug Safety*. On the other hand, there is a heavy burden on referees of papers to ensure that each review is both complete and unbiased. It is clear that, not only does the system work, but also there is a general and continual methodological improvement in reviews, undoubtedly helped by the Cochrane Foundation approach to reviews of medicines.

In 1995, Kathy Fraser became the editor and in 1996, Rosie Stather took over. Rosie joined Adis in 1993 to work on the adverse drug reaction newsletter *Reactions Weekly* and she must be heartily congratulated for the last decade of successful development of the journal!

In volume 15, there is a paper from Bengt-Erik Wiholm, Carlos Martinez and myself on benefit-risk assessment.[17] This is worth mentioning only because the journal has published so many papers in this area, and at the time CIOMS was considering how such assessments might be given more objectivity. Our paper was simplistic, but it heralded others that adopted variations on similar basic philosophy. However, even now, reviews of the benefit and risk of drugs remain very variable in terms of how much of what is covered is fact, the strength of probabilities expressed, use of the author's own opinion, what information is missing and how conclusions are drawn. Comparisons between drugs are

then difficult to make and such comparisons are essential material for those who need to make therapeutic decisions. A major area for the future is the improvement in benefit-risk analysis.

At the end of 1997, the publisher of *Drug Safety,* Adis International Limited, became part of Wolters Kluwer, a Dutch-based multinational publisher. In 1998, once again original research went back on the menu and the journal entered the digital age and became available online via the World Wide Web. In mid 2000, the journal became more firmly online when it began to be hosted by the online content aggregator Ingenta. Finally, in 2005, the journal got its own independent website and e-toc became available. However, the most significant development in 2005 was the adoption of *Drug Safety* as the official journal of the International Society of Pharmacovigilance (ISoP). This development was made possible because the journal was again publishing original material. The balanced combination of good, topical reviews and such potential for an international membership to publish original material is a major benefit for any society. The web availability also has considerable benefits to ISoP's many members from the developing world who would not be able to afford a solely paper-based version.

In the new millennium, the journal has gathered even more strength. Its coverage of contemporary issues is extensive. The whole of volume 25, issue 6 dealt with the topic of signal detection, reporting on a symposium held by the Drug Safety Research Unit in which all aspects were discussed, including the place of automated methods. I was pleased to see that their place as an adjunct to, rather than replacing, human intelligence was made quite clear. In 2003, Hauben and Zhou[18] performed an exhaustive and balanced review of data mining, concluding that there was no preferred method, and again emphasising that "It is crucial to remember that automated methods do not replace the need for expert clinical case review and interpretation by drug safety professionals…". Data mining has been further discussed over the last few years, for example the White Paper by Almenoff et al.,[19] though I was disappointed to see that these authors asked for a "…publicly accessable global safety database…", when the WHO database already exists and can be accessed. I hope that those who want access will come forward and help strengthen its use rather than start another one! In the same edition as Hauben and Zhou,[18] we were reminded by Elliot Brown about pitfalls in the use of terminologies.[20] The conversion of free text into stored, computer-searchable words is an essential process, but it is very necessary to understand the importance of this conversion both on input and when searching databases. Many errors can creep in during the conversion processes, ultimately giving spurious results.

Other very important contemporary matters that have recently been discussed are: patients' understanding of risk (Berry et al.[21]), consumer reporting (van Grootheest[22]), medication errors (Chua et al.,[23] Hoffman et al.[24] and McCarter et al.[25]), pharmacovigilance of herbal drugs (Barnes[26]) and risks of counterfeit drugs (ten Ham[27]). Then we have discussion initiated over the very latest development: risk management (Segal et al.[28]), and the coverage of this will continue as I hope we will evaluate the success of such clearly needed strategic development.

Finally, I entitled this appreciation of 20 years of *Drug Safety* 'What is Drug Safety?' because I think there is considerable confusion in both the public and in the health professions about what we mean by this most basic term. In its emphasis on benefit-risk reviews, the journal has been magnificent in not letting go of a most important practical tenet, that of setting the whole risk profile of a drug against its effectiveness and bearing in mind the risks of the disease for which the drug is used. But setting that major point aside, there still seems to be much confusion as to the nature and level of risk the public (are they the same as patients?) will tolerate from drugs, not to mention the value of epidemiological information in guiding individual therapeutic decisions as well as issues surrounding therapeutic misadventure. These are challenges for the future.

The story of *Drug Safety* is one of considerable success. Under the guidance of several capable editors, the journal has covered the breadth and depth of drug safety matters faithfully over the years. Its origins reflect the intensely clinical aspects of drug safety, and the therapy reviews have maintained their great clinical value. On the other hand, the methodological and regulatory changes have also

been covered, together with pharmacoepidemiological and public health perspectives in a way that has given a balance to the journal's coverage of drug safety, which is unequalled.

I am proud to be one of the three longest-serving members of the Editorial Board, the others being Dr Glyn Volans and Professor Peter Chyka, and I congratulate *Drug Safety* for its excellence in serving the pharmacovigilance community around the world. I also apologise to the many authors of important papers that I have not quoted – my selection was completely selfish in order to underline some points! I am very much indebted to Rosie Stather for providing the internal history of *Drug Safety* as it has developed over the years and for her great work in the many other matters concerning the journal now and previously.

## References


1. Borda I, Jick H, Slone D, et al. Studies of drug usage in five Boston hospitals. JAMA 1967 Nov 6; 202 (6): 506-10
2. Rossi AC, Hsu JP, Faich GA. Ulcerogenicity of piroxicam: an analysis of spontaneously reported data. Br Med J (Clin Res Ed) 1987 Jan 17; 294 (6565): 147-50
3. Pond SM, Prescott LF, Goldfrank L. Why medical toxicology. Med Toxicol 1986; 1 (1): 1-2
4. Carson JL, Strom BL. Techniques in postmarketing surveillance: an overview. Med Toxicol 1986; 1 (4): 237-46
5. Glen-Bott M. Aspirin and Reye's syndrome: a reappraisal. Med Toxicol Adverse Drug Exp 1987; 2 (3): 161-5
6. McEwen J. Improving adverse drug reaction monitoring. Med Toxicol Adverse Drug Exp 1987; 2 (6): 398-404
7. Edwards IR. Adverse drug reaction monitoring: the practicalities. Med Toxicol Adverse Drug Exp 1987; 2 (6): 405-10
8. Dukes MNG. The importance of adverse reactions in drug regulation. Drug Saf 1990; 5 (1): 3-6
9. Bem JL, Wood SM, West L, et al. 25 Years of the Committee of Safety of Medicines: an international perspective of the benefits. Drug Saf 1990; 5 (3): 161-7
10. Hollenberg NK, Testa M, Williams GH. Quality of life as a therapeutic end-point: an analysis of therapeutic trials in hypertension. Drug Saf 1991; 6 (2): 83-93
11. Naranjo CA, Lanctot KL. Recent developments in computer-assisted diagnosis of putative adverse drug reactions. Drug Saf 1991; 6 (5): 315-22
12. Suissa S. Statistical methods in pharmacoepidemiology: principles in managing error. Drug Saf 1991; 6 (5): 381-9
13. Stephens MDB. Marketing aspects of company-sponsored postmarketing surveillance studies. Drug Saf 1993; 8 (1): 1-8
14. Wallander M-A. The way towards adverse event monitoring in clinical trials. Drug Saf 1993; 8 (5): 251-62
15. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994; 10 (2): 93-102
16. Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. Drug Saf 1994; 11 (2): 114-44
17. Edwards IR, Wiholm B-E, Martinez C. Concepts in risk-benefit assessment: a simple merit analysis of a medicine? Drug Saf 1996; 15 (1): 1-7
18. Hauben M, Zhou X. Quantitative methods in pharmacovigilance: focus on signal detection. Drug Saf 2003; 26 (3): 159-86
19. Almenoff J, Tonning JM, Gould AL, et al. Perspectives on the use of data mining in pharmacovigilance. Drug Saf 2005; 28 (11): 981-1007
20. Brown EG. Methods and pitfalls in searching drug safety databases utilising the medical dictionary for regulatory activities (MedDRA). Drug Saf 2003; 26 (3): 145-58
21. Berry DC, Raynor DK, Knapp PR, et al. Patient understanding of risk: impact of EU guidelines and other risk scales for consumer medicines information. Drug Saf 2003; 26: 1-11
22. van Grootheest K, de Graaf L, de Jong-van den Berg LTW. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? Drug Saf 2003; 26 (4): 211-7
23. Chua S-S, Wong ICK, Edmondson H, et al. A feasibility study for recording of dispensing errors and 'near misses' in four UK primary care pharmacies. Drug Saf 2003; 26 (11): 803-13
24. Hoffman J, Proulx S. Medication errors caused by confusion of drug names. Drug Saf 2003; 26 (7): 445-52.
25. McCarter TG, Centafont R, Daly F, et al. Reducing medication errors: a regional approach for hospitals. Drug Saf 2003; 26 (13): 937-50
26. Barnes J. Pharmacovigilance of herbal medicines: a UK perspective. Drug Saf 2003; 26 (12): 829-51
27. ten Ham M. Health risks of counterfeit pharmaceuticals. Drug Saf 2003; 26 (14): 991-7
28. Segal ES, Valette C, Oster L, et al. Management strategies in the postmarketing period: safety experience with the US and European Bosentan surveillance programmes. Drug Saf 2005; 28 (11): 971-80


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