

Integrated Case Management to Improve the Quality of Spontaneous Adverse Drug Reaction Reports ^{HS}

Incompleteness of adverse drug reaction reports seriously limits the ability to assess the reaction. Improving the quality of case report data is sure to improve the value of spontaneous reports. This paper proposes one method to improve the quality of data submitted with ADR reports.

Manufacturers and distributors of pharmaceutical products are required by both U.S. and international regulations to document spontaneously reported adverse drug reactions (ADRs) that they receive about their marketed products. Regulations and regulatory guidances provide case-processing directions and instructions for submission of individual case safety reports for serious and unexpected ADRs, and aggregate reports of all ADRs reported over defined time periods. The systems for spontaneous reports of ADRs were developed in the 1960s¹ and are currently recognized as the foundation of postmarketing surveillance of drug safety.^{2,3}

In 2009, the U.S. Food and Drug Administration (FDA) received 580,904 spontaneous reports from healthcare providers (HCPs) and consumers, submitted from both U.S. and foreign reporters.⁴ The spontaneous reporting system is a critical component of the early warning system for unknown and rare ADRs.⁵ Other objectives include identification of risk factors associated with known ADRs, as well as information regarding increased frequency and/or severity for known ADRs.⁶

Despite the acceptance of spontaneous reports as a critical and crucial method for the postapproval assessment of ADRs and increases in the number of reports received, serious limitations, including both underreporting and inadequate quality of data, have been associated with the reports. This article suggests one method to optimize the quality of data obtained for the suspected ADR from the reporter during the initial and subsequent contacts with the reporter.

Spontaneous Reports of Suspected ADRs

From 2000 through the third quarter of 2009, the number of spontaneous reports submitted to FDA increased by 118% (from 266,866 to 580,904). Reports from HCPs, primarily physicians, have decreased from a high of 74% of all reports for which the type of reporter was known in 2003 to a low of 54% in 2007, 2008, and 2009. Meanwhile, reports from consumers increased progressively from a low of 21% of known sources in 2002 to 46% in 2007, 2008, and 2009 (see Table 1).⁴

Reports from Physicians and Other HCPs

Physicians are more likely to report suspected ADRs for serious, unknown ADRs for new drugs (81%); serious, unknown reactions for established drugs (73%); and serious, known reactions for established drugs (65%).⁵

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Table 1 Number of ADR Reports by Type of Reporter

Year	Total HCPs N (%)	Consumers* N (%)	Total ADRs Reported
2000	98,075 (68)	46,249 (32)	144,324
2001	108,736 (73)	39,517 (27)	148,253
2002	113,095 (79)	30,282 (21)	143,377
2003	138,595 (74)	48,352 (26)	186,947
2004	159,122 (68)	74,644 (32)	233,766
2005	171,722 (62)	105,308 (38)	277,030
2006	184,783 (59)	127,475 (41)	312,258
2007	202,686 (54)	174,216 (46)	376,902
2008	269,765 (54)	226,647 (46)	496,412
2009	317,884 (54)	272,989 (46)	590,873

Note: Table adapted from the U.S. Food and Drug Administration. Reporting by healthcare providers (HCPs) and consumers, by year.⁴

*Consumer refers to any reporter who is not documented in the report as a healthcare provider.

In one study, unlabeled ADRs represented 63% of reported reactions for a drug in the first year of postmarketing, with the percentage declining to 56%, 45%, and 37% in years 2, 3, and 4 of postmarketing, respectively.⁷ In another study, 45% of spontaneous ADR reports from physicians were classified as serious,⁸ while 68% of the reports from a physician sample were classified as serious in another study.⁹

In the U.S., the number of expedited 15-day reports submitted to FDA from 2000 to 2009 for serious, unexpected ADRs has increased 248%.

In the U.S., the number of expedited 15-day reports submitted to FDA from 2000 to 2009 for serious, unexpected ADRs has increased 248% (from 94,931 to 330,476, respectively). Although the source of these 15-day reports is not reported separately for HCPs and consumers, it seems likely that the majority are submitted by physicians and other HCPs, such as pharmacists, nurses, and dentists.⁴

Reports from Consumers

Reports of suspected ADRs from consumers have been accepted by regulatory authorities in the U.S. since 1993, in Sweden since 1978, and in several other European countries since 2003.⁸ However, do these reports from consumers increase the number and quality of signals and/or lead to a more timely detection of ADRs, or do they simply add volume to the numbers of reports to be assessed?

A major concern regarding consumer ADR reports is the ability of the consumer to identify and describe the ADR, not to mention the quality of supporting data. One early study of consumer reports suggested that the reports are reliable and valid, and that consumers are able to differentiate between an adverse effect of a drug and other complaints or symptoms related to their diseases, although there was concern regarding the consumers' ability to associate the suspected adverse event with a suspected drug.¹⁰ In a later study, consumers were shown to have knowledge of ADR symptoms that is substantially accurate and related to the drug usage.¹¹

More recently, it has been suggested that reports from consumers differ from HCP reports because the suspected ADRs are not filtered by an HCP,

are considered less relevant by HCPs, are more difficult to communicate to an HCP, and are experienced during use for off-label indications.¹² A retrospective analysis of spontaneous ADRs reported over a three-year period showed that although consumers reported 11% of the total ADRs compared to 70% reported by physicians, approximately 45% of the reports of each group were classified as serious.⁸ A later study of reports between HCPs and patients showed differences in both seriousness and outcome, although similarity in most frequently reported ADRs and drugs.¹³ (The study showed that HCPs and patients evaluated seriousness and outcome differently, but the reports from both were similar for the ADR and the drugs related to the ADR.)

Studies in which consumers and HCPs were queried directly suggest that consumer reporting does contribute to the understanding of ADRs. Consumers and HCPs reported different categories of ADRs (e.g., nervous system and psychiatric disorders were reported by consumers and hepatobiliary and blood and lymphatic system disorders by physicians).⁸ Other studies suggested that consumers provided information on adverse changes in quality of life¹⁴ and reported ADRs because their HCPs had not listened to their concerns.¹³ Thus, although prospective studies of the value of spontaneous reports from consumers have not been conducted, evidence is mounting that consumer reports complement those received from HCPs, even though they may be more time-consuming to process.¹⁵

Data Quality

One major limitation of spontaneous reports often noted is the low quality of the data reported. Lack of detail and incompleteness of ADR reports seriously limit the ability to evaluate the association of the ADR and the drug. Consumers depend on personal notes or memory regarding the event, and do not have access to their medical records. For such incomplete reports,

follow-up with either the primary or secondary reporters is usually required in order to obtain the relevant case information. The nature and extent of follow-up activities are determined by the seriousness, rarity, and previously unknown vs. known status of ADRs.⁶

Improving the quality of case reports available for assessment by reducing the number of ADR reports with incomplete data is one obvious way to improve the value of spontaneous reports. With the increasing number of reports from consumers, the increasing number of serious ADRs reported, and the large majority of spontaneous ADRs reported to pharmaceutical manufacturers, there is an opportunity to develop systems to improve the quality of data before the case reports are analyzed internally or submitted to regulatory authorities.

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In the U.S., about 6% of spontaneous ADRs are reported directly to FDA, while approximately 94% are reported first to pharmaceutical manufacturers.⁴ An opportunity clearly exists for manufacturers to work with the reporters to provide high-quality data so that each individual case report can be appropriately assessed. This paper proposes one method to improve the quality of data submitted with ADR reports.

Receipt of the Initial Report

The majority of ADRs reported to manufacturers are received via telephone or e-mail. Careful attention to the initial contact between the reporter and the contact center agent is of paramount importance. Incoming telephone calls should be answered directly by qualified HCPs (HCP agents) who are knowledgeable about adverse events and

highly trained in telephone and interviewing skills. HCP reporters will communicate directly with HCP agents, who will readily understand the medical information being provided.

On the other hand, consumers may initiate reports with some degree of reluctance, and may be hesitant to share personal medical information. HCP agents must convey concern for the reporters and help them feel at ease. The HCP agents should establish a trusting relationship with the reporter by employing a conversational interview style so that the reporter is comfortable sharing information about the suspected ADR. Although electronically guided interview scripts may be helpful, reporters typically respond more favorably to a more relaxed, one-on-one conversational style, rather than being guided through a preformatted document.

During the initial contact, data regarding the patient's demographics, medical history, and use of the suspected drug (indication for use, dosage, and treatment duration) should be obtained, along with a description of the suspected ADR and its outcome. Specific information regarding comorbidities and concomitant prescription and nonprescription medications should be obtained, if available. Consumers may not be able to provide all of the information required, so their permission should be obtained for any contact with their HCPs for additional details. Depending on the seriousness of the case, HCP reporters should be asked to provide medical records as necessary. In all cases, it is important to request permission to contact the reporter at a later date if necessary.

The necessity for follow-up can be minimized if the HCP agent obtains complete case information during the initial call. If further information is required, telephone follow-up by the same HCP agent with the appropriate healthcare providers is often effective in obtaining additional medical details, records, and insights required for case assessment, while providing continuity of case management. Where telephone follow-up is not possible

or unsuccessful, written follow-up requests using postal services should be employed. Use of certified or overnight postal delivery may be more effective than regular postal mail, since it provides a statement of urgency.

Integrated Case Management Through One Call Center

Reports of suspected ADRs from physicians, and more frequently from consumers, are often included within a medical inquiry (MI) or occasionally within a product quality complaint (PQC). In the author's experience in a contact center, 96 of 1,197 (8%) product information inquiries received in a 12-month period included a report of a suspected ADR. During the same time period, 46 of 1,196 (4%) PQC reports included a report of a suspected ADR. If these ADRs are not identified and reported, the number of ADRs reported may be significantly reduced and important ADRs unrecognized.

Reporters are not necessarily able to differentiate between an adverse event and a product complaint.

The ability to document and process ADRs, MIs, and PQCs within one call center using one integrated case management system has several potential advantages in terms of the following factors:

- *Quality of data.* The reported ADR is received and processed by an HCP agent trained to interview the reporter and obtain all available data for each ADR, PQC, and/or MI on the initial call. Reporters are not necessarily able to differentiate between an adverse event and a product complaint. A well-trained HCP agent can classify the event correctly. Information

gaps requiring follow-up can also be identified on the first call. Follow-up with either the reporter or secondary sources can be planned to minimize inconvenience to both HCPs and reporters.

- **Contact center staff.** A staff cross-trained to process ADRs, POCs, and MIs could maximize productivity and provide flexibility to meet the changing support needs during launch and maturation of products. For instance, following drug approval and during product launch, the number of inquiries and the number of reported ADRs are higher. The number decreases as the product becomes well known within the market. Mature products generate fewer MIs and ADRs. The staff could easily be reassigned from a mature product to a new product early in its lifecycle. One HCP agent takes responsibility for the entire case and communication with the reporter. Obtaining follow-up information and resolving outstanding consumer issues (e.g., addressing an inquiry or arranging product return) are handled efficiently. Furthermore, the variety and complexity of the work could lead to greater staff satisfaction. Increased productivity, flexibility, and staff satisfaction may decrease staffing costs.
- **Information technology.** Licensing, validation, maintenance, and support costs (both internal and external) could be reduced since only one multifunctional database would be required. Duplicate data entry into multiple electronic systems with the potential for data loss and/or error is eliminated.
- **Operations.** Complex and time-consuming processes required to reconcile ADRs, POCs, and MIs on a regular basis could be reduced since all are processed by the same group and captured in

the same database. Management and staff time to coordinate the functions of several different departments (e.g., Drug Safety, Quality Assurance, and Medical Drug Information) could be minimized with a potential reduction in costs.

- **Customer Service.** Each customer interacts with one HCP agent who represents the company and establishes the relationship with the customer. A supportive relationship may encourage the reporter to provide additional case information if it becomes available. There is no need to transfer calls, an inconvenience that may result in exasperated, uncooperative callers who provide incomplete information. In addition, call transfers increase the risk of the contact being disconnected and irretrievably lost.

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- **Manufacturers.** Manufacturers of approved prescription drug products, over-the-counter drug products, dietary supplements, and a variety of other medicinal products are required by law to document and investigate POCs. The investigation often involves product return from the complainant to the manufacturer. Certain adverse events (e.g., lack of drug effect) may result from a quality issue requiring documentation and investigation as a quality complaint. An integrated call center with staff well-trained in both POCs and ADRs can process such combination cases very efficiently for timely, appropri-

ate response and action by the manufacturer.

An integrated contact center has potential disadvantages. HCPs, such as pharmacists and nurses, are required to staff the contact center. The staff would require training across multiple functional areas rather than specializing in one area, and may need training to support multiple products in multiple therapeutic areas. The highly trained HCP staff may waste time performing tasks that do not require medical knowledge and training. Personnel costs may be higher for a call center staffed with HCPs rather than with non-HCPs. In addition, a database that is compliant with the *Code of Federal Regulations* (CFR) stipulations in 21 CFR Part 11 regarding management of electronic records and workflow, as well as having the capability to capture the information for ADRs, POCs, and MIs—each of which requires specialized data documentation and processing—would be required.

Conclusions/Summary

The value of the spontaneous reporting system for suspected ADRs is well-documented and fundamental to understanding the full safety profile of drugs following marketing introduction. Both HCPs and consumers contribute important safety information through their reports. Limitations of the system include the lack of information provided in initial reports and the inability to obtain follow-up information, both of which may limit the assessment of the individual case. A contact center staffed by trained HCPs using an integrated case management system may maximize the information provided by the reporter during the initial contact to improve the quality of the suspected ADR report.

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References

1. Waller PC. 2006. Making the most of spontaneous adverse drug reaction reporting. *Basic & Clinical Pharmacology & Toxicology* 98(3): 320–3.
2. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. 2009. Determinants of under-reporting of adverse drug reactions. *Drug Safety* 32(1): 19–31.
3. Nichols V, Theriault-Dube I, Touzin J, Delisle J, Lebel D, Bussieres J, Bailey B, Collin J. 2009. Risk perception and reasons for noncompliance in pharmacovigilance. *Drug Safety* 32(7): 579–90.
4. U.S. Department of Health and Human Services, Food & Drug Administration. Reports Received and Reports Entered into AERS by Year. Available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm. Accessed 14 Jun 2010.
5. Hasford J, Goettler M, Munter K-H, Muller-Oerlinghausen B. 2002. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. *Journal of Clinical Epidemiology* 55: 945–50.
6. U.S. Department of Health and Human Services, Food & Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. *Good Pharmacovigilance Practices and Pharmacoeconomic Assessment*. 2005.
7. Haramburu F, Begaud B, Moride Y. 1997. Temporal trends in spontaneous reporting of unlabelled adverse drug reactions. *British Journal of Clinical Pharmacology* 44: 299–301.
8. Aagaard L, Nielsen LH, Hansen EH. 2009. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. *Drug Safety* 32(11): 1067–974.
9. Gedde-Dahl A, Harg P, Stenberg-Nilsen H, Buajordet M, Granas AG, Horn AG. Characteristics and quality of adverse drug reaction reports by pharmacists in Norway. *Pharmacoepidemiology and Drug Safety* 16: 999–1005.
10. Mitchell AS, Henry DA, Sanson-Fisher R, O'Connell DL. 1988. Patients as a direct source of information on adverse drug reactions. *British Medical Journal* 297: 891–3.
11. DeWitt JE, Sorofman BA. 1999. A model for understanding patient attribution of adverse drug reaction symptoms. *Drug Information Journal* 33: 907–20.
12. van Grootheest K, de Graaf L, de Jong-van den Berg LTW. 2003. Consumer adverse drug reaction reporting. *Drug Safety* 26: 211–7.
13. de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K. 2008. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. *Drug Safety* 31(6): 515–24.
14. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. 2006. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *British Journal of Clinical Pharmacology* 63(2): 148–56.
15. Anton C, Cox AR, Ferner RE. 2009. Improving follow-up rates in spontaneous adverse drug reaction reporting. *Drug Safety* 32(12): 1135–40. **ACRP**

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