LEADING ARTICLE

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Communication of Medical Product Risk

How Effective is Effective Enough?

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Abstract

Ever-increasing attention is being paid worldwide to the safety of medical products, and the risks associated with their use. The integral role of risk communication in overall risk management is demonstrated by several recent market withdrawals of drugs, in which a perceived incapability of healthcare systems to manage well-characterised, avoidable risks was a significant factor.

With advances in clinical pharmacology, pharmacogenomics and pharmacoepidemiology expanding our knowledge of medical products, effective delivery of the latest safety-related information to health professionals and consumers becomes even more imperative. In this regard, it is important to evaluate whether current modes of risk communication lead to desired changes in relevant behaviours such as prescribing or drug monitoring, particularly in context with which achieved level of effectiveness is deemed acceptable. This is crucial, as there have been product-specific risk communication efforts that achieved a fair degree of success, yet were not seen as effective enough to prevent market withdrawal of the medical product in question.

In the service of improving public health through enhanced risk communication, it is essential to critically assess current methods, both as to results achieved (or not), and whether each method is applicable to the various types of risks associated with medical product use. Furthermore, just as combining methods may well improve overall risk communication, there are societal and psychological factors that must be considered in attempting to maximise effectiveness. However, in assessing risk communication effectiveness, the particular benefit-risk relationship of any individual medical product must also be part of the evaluative process.

1. Historical Perspective

In recent years, there has been heightened concern about the safe use of such marketed medical products as prescription and non-prescription drugs, biological agents and medical devices. As a result, the methods by which the relative benefit-risk relationship of medical products are assessed, monitored and acted upon have come under close scrutiny. Given the prominence of the US FDA's position in innovative medical product risk management, an historical perspective on the FDA's national and

cooperative international initiatives regarding this critical public health issue is valuable.

In 1998, under then Commissioner Dr Jane Henney, a Task Force was established to assess the system for managing risks associated with the use of FDA-approved medical products, with particular focus on the role of the FDA. The resulting May 1999 Report to the FDA Commissioner, 'Managing the Risks from Medical Product Use: Creating a Risk Management Framework',[1] was a landmark document that established the FDA's philosophy in this respect. In combination with international safety-related initiatives under auspices of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, such as the Efficacy (E) Guideline E2A ('Clinical Safety Data Management: Definitions and Standards for Expedited Reporting')[2] and the Council For International Organizations Of Medical Sciences (CIOMS), such as CIOMS IV ('Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals'),[3] the Task Force Report provided a framework for the FDA's ongoing programmes and initiatives for the safe use of medical products that has both national and global applicability.

The Task Force recognised that evaluation of medical product risk management entailed its assessment in the entire healthcare delivery system, and thus examined all FDA risk-management activities in this context.[1] Adapting a federal proposed risk-management model for specific health hazards,[4] the Task Force assessed the FDA's role in both the premarketing and postmarketing phases.

Seeing the need for a new systems framework for risk management, the Task Force posited that better risk understanding combined with greater system integration would result in more effective risk interventions.

The Task Force assigned medical product risks to four general categories: (i) *known side effects* (from which most injuries and deaths result, an appreciable number of which are avoidable[5]); (ii) *medication/medical device errors* (also preventable); (iii) *product defects* (uncommon in the US); and (iv) *remaining uncertainties*. Regarding the FDA's role in risk management, it was found that safety-based drug withdrawal rates had remained essentially unchanged over decades, unexpected serious adverse events leading to labelling changes were occurring less frequently than before, and postmarketing surveillance/risk assessment was performing as intended. Discovery of adverse events in the premarketing phase was recognised as limited by several known factors inherent to the process, and that changes would increase costs and slow availability of new agents.

Most of the Task Force recommendations focused on ways to further improve risk management within the existing FDA structure (e.g. heightening surveillance of products new to the market). Options to address known limitations of pre-marketing study (e.g. large simple trials) were suggested, while other recommendations included enrichment of the FDA's role and responsibilities in risk communication.

The Task Force made it clear that the responsibility for risk management of medical products used in the US does not rest solely with the FDA, but rather is shared by the Agency with industry, health professionals, patients, other federal groups, healthcare delivery systems and professional organisations.[1]

This position is reflected in the FDA's responsibilities and actions under the Prescription Drug User Fee Amendments of 2002 (Public Law 102-571) [commonly referred to as 'PDUFA III'], which was signed June 12, 2002. In exchange for receipt of user fees under PDUFA III, the FDA agreed to specific performance goals, including the drafting of industry guidance on risk-management activities. As announced, the FDA plans to finalise three guidance documents for industry by September 30, 2004.[6]

To meet this goal, the FDA drafted and released for comment three concept papers outlining the Agency's preliminary thinking on 'Premarketing Risk Assessment', 'Risk Management Programs', and 'Risk Assessment of Observational Data: Good

Pharmacovigilance Practices and Pharmacoepidemiologic Assessment';[7] this was followed by a public workshop on April 9–11, 2003, to present the FDA's thoughts and solicit input from stakeholder groups regarding these critical topics.[6,7]

That these initiatives emphasise the integral role of risk communication in overall medical product risk management is no surprise, as the FDA (Honig, Phillips and Woodcock[8]) in 2000 stated "market withdrawals of terfenadine, astemizole, mebefradil, bromphenac, and cisapride resulted, in part, from the health care system's inability to manage the known and preventable risks associated with these products".

If the risks associated with the use of a particular medical product are indeed well-characterised and avoidable, then effective communication of those risks to health professionals is an international public health imperative. In 2002, van Grootheest and Edwards, perceiving 'Dear Doctor' letters and Summary of Product Characteristics (SPC) warnings/contraindications to be ineffective in ensuring prescribing behaviour is consistent with labelling, suggested four possible remedial strategies: (i) clinician education; (ii) improvements in available drug information; (iii) enhancements in communication, and (iv) health professional freedom coupled with responsibility regarding off-label use.[9] Similarly, in 2003 the FDA advocated an approach to maximise and assess the effect of risk communications in which the importance of patterns of practice and modes of learning are considered.[10] Both papers called for further research.[9,10]

Optimal use of the available worldwide literature is an important aspect of such research. In evaluating studies, thoughtful consideration of the method(s) used to communicate medical product risk, and the standard by which 'effectiveness' of that communication is determined, is crucial. Results and conclusions drawn from individual case studies of risk communication on the same drug can vary significantly based on these factors, with concomitant impact on future methodology selection. In addition, possibly advantageous synergistic usage of multiple approaches might be overlooked.

Three common methods used for risk communication will be examined here:

- Labelling changes and large-scale notification to health professionals: *are they effective, and what is the standard for effectiveness?*
- Interventions to improve medication use by health professionals: *do they actually result in modified behaviour?*
- Educational efforts regarding medical product risk: *do they make any difference?*

2. Labelling Changes and Large-Scale Notification to Health Professionals

Medical product use entails disparate categories of risk (e.g. teratogenicity vs drug-drug interactions), yet assessment of risk communication methods and effectiveness has frequently been performed and conclusions generalised without considering these important distinctions. Such differentiation will be made here.

2.1 Drug-Drug Interactions

2.1.1 Terfenadine

Terfenadine is a non-sedating histamine H_1 receptor antagonist that was FDA-approved for relief of allergic rhinitis symptoms in 1985.[11] Subsequently, it was confirmed that the metabolism of terfenadine could be blocked by drugs inhibiting hepatic enzyme metabolising system cytochrome P450 (CYP) 3A4,[11,12] and that resultant accumulation of the unmetabolised parent drug lead to serious cardiac abnormalities, including QT prolongation[11,12] and torsade de pointes, a potentially life-threatening ventricular arrhythmia.[13]

As a result, in July 1992 changes were made to terfenadine labelling, including elevation of previous warning statements against its use with concomitant ketoconazole or macrolide antibiotics, or in hepatically impaired patients, to contraindications within a boxed warning.[14] The labelling changes

were announced in a joint FDA-sponsor press release, followed by a 'Dear Doctor' letter distributed to 613 328 health professionals. While a drop-off in the frequency of cases involving serious cardiovascular events in association with terfenadine reported to the FDA had been observed since 1992, a study was established to further evaluate the effect of the actions taken.[14]

Using paid pharmacy claims from two state Medicaid and one health maintenance organisation (HMO) databases from 1988 to 1994, filling of terfenadine prescriptions within 2 days of those filled for either ketoconazole or erythromycin was examined by Burkhart et al.[14] Fast and significant declines in filling co-prescriptions of either ketoconazole or erythromycin corresponding to the 1992 publicity were found, and the rates stayed relatively constant after 1992; concomitant ketoconazole/erythromycin use with terfenadine fell by at least 80%.

These findings were consistent with two other studies using similar methods to evaluate the impact of actions taken. Using a large health insurer database, Thompson and Oster reported an 84% decline in same-day dispensing of terfenadine and contraindicated drugs, and a 57% decline in overlapping use.[15] Utilising a pharmacy claims database comprised of several HMOs, Carlson and Morris found the erythromycin co-prescription rate decreased by 47% over a 2-year period, with the first notable decline 18 months after initial regulatory action, and the largest at approximately 24 months.[16] Both groups noted that despite substantial declines after regulatory action, concurrent use of terfenadine and contraindicated drugs continued.[15,16]

Using a different approach, Cavuto, Woosley and Sale presented 50 pharmacies in the Washington, DC area with simultaneous prescriptions for terfenadine and erythromycin to see if they would be filled.[17] 32% (16 of 50) of the pharmacies filled both prescriptions without comment; 96% (48 of 50) of the pharmacies used computer programs designed for drug interaction prevention, but these were ineffective in 29% (14 of 48) of pharmacies so equipped.

In January 1997, the primary active metabolite of terfenadine, fexofenadine, having been approved as a separate drug and assessed as providing comparable beneficial effects without apparent risk of the parent drug's cardiotoxicity, the FDA announced its aim to withdraw approval of terfenadine-containing products.[18]

In its Talk Paper, the FDA noted: "Since the serious cardiac risks of terfenadine were identified, several educational campaigns have been launched by the drug's sponsor and FDA to inform health care providers and patients about the dangers of these drug interactions. These have included FDA warning statements, labelling changes and 'Dear Doctor' letters. Although these efforts have reduced inappropriate prescribing and dispensing of terfenadine with other drugs, such events have not been, and almost certainly cannot be, eliminated".[18]

2.1.2 Cisapride

Cisapride was approved in the US for nocturnal heartburn in adults with gastro-oesophageal reflux disease[19] in 1993.[20] Subsequently, because of risk of serious cardiac arrhythmias (including ventricular tachycardia and torsade de pointes), its indication was revised to recommend use when response to lifestyle modifications or other drugs was inadequate.[19,20] In June 1998, regulatory actions were taken including strengthening label warnings with new cardiac risk information (e.g. contraindication with drugs known to prolong QT interval or in patients with disorders that may predispose to arrhythmias on cisapride), and recommending use of other heartburn therapies before cisapride.[19,20]

To assess for effects of the 1998 regulatory actions, which also included manufacturer distribution of a 'Dear Doctor' letter[19] to 800 000 health professionals (physicians, pharmacists) and drug-alert database vendors, and FDA distribution of a Talk Paper (both the Talk Paper and 'Dear Doctor' letter were posted on the MedWatch website, and the MedWatch Partner organisations directly notified),

prescription data from three sites (managed care organisation; group of three HMOs; state Medicaid programme) for a 1-year period before and after the notification was analysed by Smalley et al.[21] Contraindicated cisapride use, as defined, included concomitant usage of cisapride and another drug labelled as contraindicated (either specifically named [CYP3A4-inhibiting drugs such as erythromycin], or with QT interval-prolonging properties [e.g. antipsychotics]), or a documented medical condition labelled as contraindicated preceding cisapride dispensing. In all three cohorts, a 2% decrease in contraindicated use after notification, with minor (1–3%) reductions in new users, was found. Not surprisingly, it was concluded that FDA regulatory action demonstrated no material change in contraindicated use of cisapride, and that more effective methods to communicate new drug safety information, and change practice based on such information, were needed.[21]

Weatherby et al. evaluated the impact of an earlier 1995 cisapride 'Dear Doctor' letter and the 1998 letter via health insurer plan data covering a 4.4-year period before and after the notifications.[22] In this case, contraindicated cisapride use was defined solely as concomitant use with contraindicated medications specifically denoted in the letters. In 1995, 450 000 US physicians received two 'Dear Doctor' letters about specific contraindicated medications, with no FDA website posting of the letters. While the 1995 letters had no perceived impact on prescribing, there was a 66% decline in same-day dispensing after the 1998 letter and concomitant actions, with most co-dispensing having come from the same pharmacy.

In addressing the different findings between the Smalley et al.[21] study and theirs, Weatherby and colleagues noted that the earlier study had examined overall cisapride use (with all drugs denoted [specified and implicated] as contraindicated in the 'Dear Doctor' letters, and all contraindicated medical conditions), while they had evaluated cisapride use solely with drugs specifically denoted as contraindicated in the letters.[22]

Weatherby and colleagues saw the respective study aims as different, with Smalley et al.[21] having evaluated the difference between cisapride prescribing and desired standard of care, while they evaluated conditions under which safety notifications impact prescribing.[22] Unlike the earlier study, Weatherby et al. reported that the intended 'Dear Doctor' letter effect was accomplished, but just to a degree, and only when the notification and labelling change were coupled with publicity and direct interventions by the FDA and the manufacturer.[22]

That two groups investigating risk notification effect on prescribing practice for the same drug came to different conclusions demonstrates the necessity to pinpoint precisely what is being assessed.

Cisapride co-prescribing/co-dispensing was evaluated further by Jones et al.,[23] who found a 3.4% overlap of cisapride with at least one specifically contraindicated drug after the drug warnings started, with a high proportion of all overlapping pairs by same physician for same patient (50%) and same pharmacies for same patients (89%).

Similarly, De Bruin et al.[24] reported that after notification to health professionals in The Netherlands (including one 'Dear Doctor' letter and communication via medical/pharmaceutical journals and textbooks), 3.1% of patients used one or more potentially interacting agent(s) [CYP3A4-inhibiting drugs specifically noted in labelling]. Approximately 50% received clarithromycin, while for all other potentially interacting drugs the prevalence of cisapride concomitant use was less than 0.6%. The authors perceived the prescription of fewer potentially interacting agents as resulting either from warnings or automated pharmacy systems designed to catch interactions, but the overriding reason why warnings did not appear to be effective in lessening days-at-risk or numbers of co-prescriptions was the large increase in concomitant clarithromycin prescribing. This increase was seen as likely to be due to overlapping indications, namely cisapride for

dyspepsia and reflux oesophagitis, and clarithromycin a first-line antibiotic in *Helicobacter pylori* treatment;[25] communication targeting clarithromycin/fluconazole use was seen as a potential way to further decrease risk.[24]

In order to overcome perceived limitations of computerised systems that generate so many drug interaction alerts of problematic importance users start to ignore all such warnings (including those with lethal potential), McMullin et al.[26] developed a Web-based system utilising patient-specific data for drug interaction signalling. In a retrospective study, significant decreases after system implementation were found in: (i) proportion of patients receiving a contraindicated drug with cisapride (9% to 3.1%); (ii) mean (SD) duration of contraindicated treatment (4.1 [3.8] vs 1.6 [1.4] days); and (iii) percentage of patients discharged on potentially hazardous drug combination (36.2% vs 7.7%).[26]

It is striking that three independent studies found essentially the same percentage (approximately 3%) of cisapride co-prescribing with contraindicated medications after notification[23,24] or implementation of a computerised alerting system.[26] Jones et al.[23] saw this result as indicative of a significant and preventable risk, while Cahill,[27] in commenting on their study, pointed out that 96.6% of cisapride prescriptions did not involve contraindicated co-prescription. At least two of the studies reported significant decreases in co-prescription of cisapride with contraindicated drugs after notification, and thus deemed communication to have been at least a qualified success,[22,24] but evaluation for impact on a desired standard of care was interpreted as demonstrating notification to have been an almost total failure.[21]

Cisapride was removed from the US market by the manufacturer as of July 2000;[28] the FDA noted that while labelling had been revised multiple times, in spite of "these risk management efforts, the firm decided in consultation with the Food and Drug Administration that continued general US prescription access to the drug poses unacceptable risks".[28]

2.2 Off-Label Use

2.2.1 Bromfenac Sodium

Bromfenac sodium is an NSAID that was approved for short-term (≤10 days) acute pain management[29,30] in 1997.[31] Due to cases of severe hepatitis and liver failure in patients on bromfenac for longer than 1 month without liver enzyme monitoring, the labelling was changed to include a boxed warning advising of the hepatotoxicity risk and emphasising the indicated duration of use.[29,30]

Risk communication regarding bromfenac was performed via a 'Dear Health Care Professional' letter[29] mailed to health professionals by the manufacturer, combined with posting of the letter and an FDA Talk Paper[30] on the MedWatch website and MedWatch Partners notification. In assessing the effect of risk communication, the FDA (Friedman et al.)[32] reported that labelling revision and provider notification reduced long-term prescriptions to 15% of total prescriptions, but use beyond 10 days was not eliminated.

Despite the risk communication measures taken, reports of severe injuries and death associated with long-term bromfenac use continued to be received by the company and the FDA, who agreed upon withdrawal from the market.[31] The decision to withdraw bromfenac from the market was based both on the availability of other therapies with a larger margin of safety[32] and the perceived impracticability of employing necessary restrictions to ensure use of bromfenac within the labelled timeframe.[31]

2.3 Recommended Blood Test Monitoring

2.3.1 Troglitazone

In January 1997, troglitazone was approved in the US for treatment of type II diabetes mellitus in patients inadequately controlled on insulin.[33] Within its first year of marketing, severe hepatotoxicity was recognised to occur – in consultation with the FDA, the manufacturer strengthened the label multi-

Table I. 'Dear Healthcare Professional' letters regarding troglitazone 1997–1999

October 1997
New warning information on 'idiosyncratic hepatocellular injury' ranging from mild transaminase elevations to death
Recommended liver function test (LFT) monitoring: serum transaminase levels within first 1–2 months, then every 3 months for first year, then periodically[35]
December 1997
Revised recommended LFT monitoring: liver enzymes and bilirubin at baseline, then every month for 6 months, then every 2 months until end of first year, then periodically[36]
July 1998
Importance of liver function monitoring emphasised
Revised recommended LFT monitoring
• patients with 'moderately elevated' alanine aminotransferase (ALT) levels (>1.5 × upper limit of normal) should not be started on drug
• ALT levels at baseline, then every month for 8 months, then every 2 months until end of first year, then periodically
• patients with 'moderately elevated' ALT levels (>1.5–2 × upper limit of normal) should have ALT retested within one week, then weekly until: (i) ALT returns to normal; or (ii) ALT rises to about 3 × upper limit of normal, at which time drug should be stopped[37]
June 1999
No longer indicated for use as 'initial single agent'
Revised recommended LFT monitoring
• Serum transaminase levels prior to initiating treatment, then monthly for first year, then quarterly[38]

ple times and recommended that liver function of patients on troglitazone be closely monitored.[34]

To keep the healthcare community apprised of new information, four 'Dear Healthcare Professional' letters were distributed between 1997 and 1999. These are summarised in table I.

In order to assess the effect of notification on health professional and patient behaviour, Graham et al.[39] studied liver function test (LFT) monitoring compliance via a large healthcare company database, with four assigned patient cohorts established in relation to serial FDA regulatory actions and LFT monitoring recommendations. Baseline liver function testing increased from 15% (cohort 1) to 44.6% (cohort 4), and follow-up LFT monitoring at 1 month went from an initial 3.8% to a final 33.4%; by 5 months, monthly monitoring fell to 13% in cohort 4, and the same patients were not usually tested each month. Overall, low levels of full adherence to monitoring recommendations were found, with only 18.4% of cohort 4 patients having both baseline and LFT testing at 1 month; by 3 months, less than 5% of any cohort's patients received all recommended LFT testing.[39]

At the same March 1999 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee in which results from this study were presented, the sponsor reported results from a February 1999 survey of physicians in the top nine deciles of troglitazone prescribers.[40] 96% reported awareness of the need for LFT monitoring, and that 97% of patients were baseline tested prior to starting troglitazone, with 82% having had monthly monitoring for the first 8 months, as per label.

In March 2000, the FDA announced that the manufacturer had agreed to its request that troglitazone be removed from the market.[34] The agency reported this action was taken after review of available safety data on troglitazone and two comparable drugs (rosiglitazone and pioglitazone) demonstrated that troglitazone had greater relative liver toxicity, with the other two agents offering equivalent benefits to troglitazone with less risk of severe hepatotoxicity.

2.4 Teratogenicity

2.4.1 Acitretin

Acitretin and its parent compound, etretinate, are both used to treat severe keratinisation disorders[41] and are known teratogens;[42] their elimination half-lives are quite different (acitretin: 50 hours; etretinate: 100–175 days, with high fat accumulation).[43] In October 1989 acitretin was registered in The Netherlands with an initial recommended post-therapy contraception period (PTCP) of 2 months, and etretinate withdrawn from the Dutch market within two months.[41] However, in October 1990, health authorities of many countries (including The Netherlands) were notified that etretinate was found in the plasma of 17 of 30 acitretin users, and the PTCP was extended to 2 years.[41]

Warning of the PTCP change had to be rapidly communicated to multiple groups, the effectiveness of which Sturkenboom and colleagues[41] evaluated in the following way:

- Level 1: Company; health authorities; professional associations (semi-structured interviews)
- Level 2: Dermatologists; GPs; pharmacists (structured questionnaire)
- Level 3: Population at risk: exposed females aged 15–45 (questionnaires with both structured and open questions).

Effectiveness of communication was delineated as: (i) ways and extent dispensers tracked acitretin users and informed physicians, and physicians informed patients; and (ii) whether women at risk took necessary precautions, particularly adherence to the new recommended PTCP.

Direct mail penetration to health professionals was successful, with almost all receiving at least one letter (from health authorities, company ['Red Hand Envelope'] and/or professional association), and most more than one. The population at risk was informed through personal contact with a health professional and/or media (press, radio, TV). While 19% were informed by a dermatologist, 30% by a GP, and 39% by a pharmacist, 35% were never contacted by any health professional; as for media information, 45% read the notification in a newspaper (57% of regular readers could not recall message), and 60% followed the message on radio and TV (35% could not recall message).

As for action taken, 9% of women at risk (i.e., exposed during or within 2 years after acitretin treatment) did not use any contraceptive method. A high percentage of women stopped acitretin for reasons other than the alert; however, of those continuing treatment, the proportion was higher for those without desire for children, and 32% of women showed a negative influence of the alert on intention to become pregnant.[41]

The authors concluded that there was adequate dissemination from three main sources to health professionals, but despite use of a multi-media method to inform those at risk, the effect was moderate, with recall of the message 6–12 months after warning low. They deemed overall notification effectiveness to be poor because of insufficient personal communication with those at risk.[41]

3. Interventions to Improve Medication Use by Health Professionals

3.1 Information Provided to Health Professionals

A critical aspect of risk notification is the actual information that is provided. For example, in 1997, given postmarketing reports of epidural or spinal haematomas in association with the use of low molecular weight heparin (LMWH) and spinal/epidural anaesthesia or lumbar puncture, with subsequent neurological injury (including long-term/permanent paralysis), the FDA notified health professionals and patients via a Public Health Advisory.[44] Two months later, the transcript of the related February 1998 Anesthetic and Life Support Drugs Advisory Committee was posted on the FDA website.

In response to ongoing questions and concerns of the healthcare community, in May 1998 the FDA posted questions and answers regarding LMWHs/

heparinoids and spinal/epidural anaesthesia in which updated safety information was provided, including common clinical aspects, signs/symptoms of spinal/epidural haematoma in reports, factors to consider in performing procedures, and where to find further information.[45] Reaction from health professionals to this type of notification was most positive (communication to MedWatch).

In another branch of the FDA, the Center for Devices and Radiological Health (CDRH) has been issuing two types of notifications to communicate with medical device users regarding safety issues.[46] Safety Alerts are used when public health risk is perceived as being in the highest risk category (e.g. potential cross-contamination linked to haemodialysis treatment [1999][47]), while a Public Health Advisory is used when risk is perceived as not as high as the requisite for a Safety Alert (e.g. potential for injury from medical gas misconnections of cryogenic vessels [2001][48]).[46]

Recently, the CDRH has added a new form of notification to the existing programme, Web Notifications, in which safety information is posted on the CDRH website.[49] While Public Health Advisories and Safety Alerts are also posted there, Web Notifications are intended to supplement the other forms of notification by providing a mechanism for quick dissemination of device safety information of benefit to health professionals, but not deemed appropriate for other mechanisms. These may be used when available information is limited, changing, and/or the CDRH is unable to make specific recommendations, but timely provision to the healthcare community is desired. Web Notifications are updated upon availability of further information.[49]

Via these three levels of safety notification, the CDRH triages information of interest to medical device users based on the level of perceived public health risk, and seeks to keep the healthcare community as informed as possible of the latest developments.

Further demonstration of the effect of risk information presentation comes from the evaluation of cisapride warnings to the health professional community by Weatherby et al.[50] Assessing the two 1995 and one 1998 'Dear Doctor' letters previously discussed[22] for their impact on cisapride and the co-dispensing of contraindicated medications (January 1995–May 2000), the 1998 letter (with heightened publicity) was associated with significant decline (58%) in concomitant dispensing with those drugs specifically denoted as contraindicated, but not those used to exemplify, or implied as members of, a drug class. Further, neither the 1995 letter, which was explicit as to contraindicated medications but less well-publicised, nor a 1999 letter stressing proscribed medical conditions, had a discernible effect on co-prescription;[50] Guo et al., studying cisapride prescriptions from July 1993–December 1998, found comparable results.[51]

Weatherby et al. saw their findings as indicative of the tantamount importance of wording to actual content in altering physician behaviour, and that the "key characteristics of a successful drug warning appear to be specificity, prominence, brevity, no reliance on secondary information, publicity, and in-person discussions".[50]

3.2 Other Interventions to Improve Medication Use

Improving decision-making by physicians, in particular prescribing practice, is a generally accepted goal, but how it is best achieved is not fully resolved. Soumerai and Avorn[52] have promoted a model of 'academic detailing', delineating such principles as determining motivations underlying use of a particular medical product, establishing credibility, involving opinion leaders, stimulating learner involvement, and repetition/reinforcement.

Manning and colleagues[53] provide an instructive example of an individual educational approach to altering prescribing practice, in which analysis of physician prescriptions and additional pertinent medical information was performed by clinical pharmacologists in order to pinpoint prescribing problems. One group of physicians then received

direct feedback addressing delineated prescribing problems via instructional packets, with a second sample of prescriptions amassed and analysed. Those physicians receiving educational feedback revised prescribing practices in line with recommendations in 30% of the cases, while those in a group that had no feedback changed only 3% of the time; furthermore, a stated intention to alter prescribing behaviour resulted in an actual change 50% of the time. The authors perceived that such individualised instruction in reaction to actual events in office practice is both a sensible and effective way by which physician performance can be improved.[53]

Similarly, in their literature review Anderson and Lexchin[54] found that printed material distribution by itself does not result in prescribing practice improvement, but quality of care can improve with specific education (entailing personal contact between expert and physician) and feedback (explicit recommendations for alterations in medication use). Based on a review of interventions to change provider behaviour, Grimshaw et al.[55] reported passive interventions are usually ineffective while most other strategies are situationally effective; however, no intervention was effective under all conditions. Instructional outreach (for prescribing) and reminders were reported as promising, with a greater likelihood of success in changing behaviour seen with multiple targeted interventions rather than individual strategies.

Further illustration of potential significant change in prescriber behaviour with use of 'academic detailing' comes from a study by May and colleagues,[56] in which Australian community physicians receiving regular continuing education visits on therapeutics, with an initial focus on minimising risk associated with prescribed NSAIDs (service area), were compared with physicians not receiving this service (comparison area). Using two different measures, May et al. found that there was marked difference in total reduction in NSAID usage (9% and 28%, respectively) between the comparison and service areas, while a 70% reduction in gastrointestinal (GI) disorder-related hospital admissions was seen over a 5-year period (since visits began) in the service area, without significant concomitant change in comparison area hospitalisation rates. The authors noted that education on NSAID prescribing apparently was a contributory factor in decreasing hospitalisations for GI adverse effects.[56]

Application of the multifaceted approach is shown in a case study by Roughead, Gilbert and Primrose of the effort to improve Australian physicians' use of flucloxacillin.[57] With data amassed over 10 years by the Australian Adverse Drug Reaction Advisory Committee (ADRAC) indicating an association between adverse hepatic reactions and flucloxacillin use, several actions were taken. In 1989/1990 an article was published in an Australian medical journal and two in the Australian Adverse Drug Reaction Bulletin. In December 1990, the Pharmaceutical Benefits Advisory Committee (PBAC) issued a warning statement and the Australian Approved Product Information was revised, denoting hepatitis as an adverse reaction. In 1991 the Australian Approved Product Information was revised again to include a warning statement.

As pharmacoepidemiological investigations of flucloxacillin users[58-60] provided an estimate of incidence of cholestatic hepatitis[58,59] and risk factors for developing jaundice,[60] the warning in the Schedule of Pharmaceutical Benefits August 1993 edition[61] and product information (December 1993) were both revised to emphasise patients at greatest risk. However, despite warnings in various objective informational sources, flucloxacillin dispensing continued to increase.

Concern from the PBAC about flucloxacillin use for minor infections and associated unfavourable benefit-risk relationship led to restriction of use to serious staphylococcal infections (August 1994 Schedule of Pharmaceutical Benefits),[62] with an open letter to physicians and pharmacists advising of the change included inside the front page. A striking decline in flucloxacillin dispensing rates was seen.[57]

In addition, after the PBAC regulatory action, alternative therapies (cephalexin and erythromycin) for common skin infections were suggested, and changes in advertising of flucloxacillin and cephalexin occurred in relation to the time course of events. At the time of publication, dispensing of flucloxacillin was reportedly declining, while that of cephalexin was increasing. It was not known if flucloxacillin prescribing was less in those most at risk, or if treatment of serious staphylococcal infections was now being done with cephalexin, but no increase was seen in the rate of hospitalisations for soft tissue/skin infections despite the decrease in flucloxacillin use.

In discussing the notable decrease in flucloxacillin use in relation to various interventions, the authors saw this desired change as resulting from a combination of actions, rather than any individual event. Cautioning that evaluation by any one organisation of its intervention without consideration of other factors might lead to a false conclusion, in either very positive or negative directions, they noted that sustaining desired change entails coordination of activities and ensuring concordance of all disseminated messages.[57]

4. Educational Efforts Regarding Medical Product Risk

All educational outreach to health professionals regarding medical product safety need not be product-specific to be effective. In fact, with health professional adverse event/reaction reporting predominantly voluntary worldwide, efforts to inform the healthcare community of the public health importance of recognising, managing and reporting medical product-induced disease are imperative. The specification by Edwards and Hugman[63] of stimulation of increased rates of quality adverse event reporting as a significant issue needing to be addressed for improving communication of risk-benefit information provides support for this viewpoint.

Performed under an FDA contract, the Rhode Island Adverse Drug Reaction (ADR) Reporting Project was designed to increase physician reporting of suspected ADRs via sustained education utilising several forms.[64] Scott et al.[64] found that after 2 years, there was a >17-fold increase in Rhode Island direct reports to the FDA versus the yearly average prior to the project (overall the US rate remained essentially unchanged), with a similar trend for serious reports (1981–1985: 0.4% of total reports to the FDA were serious vs 3.6% in 1988); there were 31 reports on serious unlabelled reactions during 1988. Significant gains in knowledge and attitude toward the ADR reporting system occurred during the 3-year experience (familiarity with FDA ADR reporting programme increased from 55% to 85%; familiarity with FDA forms/guidelines for reporting increased from 39% to 69%).

Similarly, Schlienger and colleagues[65] reported that a programme in Switzerland in which 'academic detailing' was performed via clinical pharmacist participation in daily rounds, coupled with their solicitation of follow-up information from physicians and nurses and performance of chart review, resulted in improved adverse drug event (ADE) identification and reporting.

In another programme to stimulate physician ADE reporting carried out in Mississippi, health professional dissatisfaction about not knowing the disposition of ADE information they reported was addressed by a letter indicating what happened to the data they provided.[66] Juergens and colleagues[66] found both physician appreciation for such feedback and good reception to a newsletter summarising number/types of reports and involved drugs, the latter further enabling education about new drugs warranting careful observation. Use of posted notices and in-service teaching to maintain awareness of the significance of ADE surveillance and its concomitant effect on quality of care were successful.

Within the traditional continuing education paradigm, a novel conference on recognition and man-

agement of drug-induced disease utilising an underlying clinical therapeutic approach was developed in a cooperative effort between the FDA and Georgetown University Medical Center (Goldman, Lieberman and Kausal).[67] Using multiple formats (lectures, panels, small group case discussions with faculty facilitators), improved knowledge (both globally and by professional discipline) was demonstrated via pre-/post-testing, and the conference was very well received by attendees.

The success of the conference provided the basis for development of the first mail-out MedWatch Continuing Education (CE) Article, 'Clinical Therapeutics and the Recognition of Drug-Induced Disease'[68] as an important part of the MedWatch programme's outreach to health professionals (Goldman).[69] Certified for physician and pharmacist CE credit and distributed nationwide through the MedWatch Partners, 15 260 health professionals received CE credit, a 2.2% response rate. On assessment of the first 10 000 successfully completed exams (55% physicians; 37% pharmacists), 99% agreed that learning objectives were met and the article relevant to clinical practice; unexpected were the 150+ spontaneous comments of which the great majority were quite positive, including several expressing hope for continuation of the programme.

Given this response, and utilising what had been learned, a second MedWatch CE article, 'The Clinical Impact of Adverse Event Reporting',[70] was written as a direct continuation and covered other medical products (biologicals, medical devices, dietary supplements) in addition to drugs. Further CE articles (e.g. the third, 'Improving Patient Care by Reporting Problems with Medical Devices'[71]) followed in the same manner.[69]

5. Special Considerations in Risk Communication

While this paper focuses on communication to health professionals about risks associated with medical product use, an important aspect of overall risk management is effective communication between health professionals and patients. Alaszewski and Horlick-Jones[72] delineate social influences on responses to health risk information about which physicians should be aware:

- the extent to which the informational source is trusted;
- the relevance of the information to everyday life/decision-making;
- relation to other understood risks;
- concordance with prior knowledge/experience;
- difficulty/significance of choices/decisions.

They note that improvement in risk communication entails building of trust, and awareness of both patients' access to varied/conflicting sources of risk information, and psychological factors impacting response to such information.[72]

In a similar vein, Gigerenzer and Edwards[73] note that physicians need to be aware of possible confusion in relaying medical statistics with health risk information. As an illustrative example, they report that a single event probability, such as the statement that there will be a 30% chance of rain tomorrow, can be interpreted by some people as:

- tomorrow it will rain in 30% of the area, or
- tomorrow rain will occur 30% of the time, or
- rain will occur on 30% of days like tomorrow,

but confusion can be reduced with good, simplified risk presentation/representation.[73]

Regarding health professionals themselves, information overload is having a major impact. As Aronson, Derry and Loke[74] point out, the overwhelming extent of published ADR literature makes keeping up-to-date on drug safety a daunting task for physicians. Based on their study, the authors reported that no one journal or collection of journals (not even what are termed 'pharmacotherapeutics' journals, e.g. those that cover clinical pharmacology, pharmacy or therapeutics) can be pinpointed as a recurrent source of ADR information. Noting that more systematic reviews (including those based on reviews of relatively large clinical trials) are of necessity, they perceive change in practitioner needs make it important for literature to be responsive to

an evidence-based paradigm in medicine. Through availability of better ADR data (both for rare, serious events and those which are more common), greater precision in risk quantification, and thus in clinical decision-making, can be achieved.[74]

6. Lessons Learned

Risk communication is a critical component of medical product risk management, particularly with respect to recognised and preventable risks, and can undoubtedly be improved through ongoing research and appropriate commitment of resources. Ascertaining which combinations of risk communication methods, disciplines and interventions will maximise safe use of medical products is of great international public health import.

Notwithstanding the need for further study, there are clearly lessons to be learned from our experience to date.

6.1 Labelling Changes and Large-Scale Notification

In choosing communication methods and assessing effectiveness of safety notifications, the major category or categories of perceived risk (e.g. drug-drug interactions/contraindications, teratogenicity, monitoring necessity [drug blood levels, LFTs], off-label use) with use of a particular medical product must also be part of the evaluative process. Behaviours associated with each category of risk may well differ, along with the communication methods optimally utilised – one size may NOT fit all, and there must be flexibility in choosing strategies. Further, it appears that using multiple modes of risk communication and providing as much publicity as possible may well heighten effectiveness of the overall effort.

By the same token, in assessing risk communication effectiveness, the desired results must be clearly stated at the outset. As seen by cases discussed earlier, a fair degree of achieved success in changing behaviours such as prescribing may not be seen as effective enough to prevent the withdrawal of a product from the market.

As medical products differ in their perceived benefit-risk relationship, based on such factors as the disease entity or population treated, availability of other products, or reversibility of the adverse event(s) in question, each case merits individualised assessment, rather than a formulaic, 'cookie-cutter' approach.

Understanding how health professionals use risk information is critical to improving communication methods, as is examination of varied information sources and related factors impacting on practitioner behaviour. In that realm, optimum use of promising new communication technologies (e.g. the Internet, computerised pharmacy systems) will continue to entail a global learning process. Lastly, information overload and increasing time demands on health professionals must be acknowledged and considered when planning and assessing risk communication interventions.

6.2 Information Provided

There is good evidence that risk information intended for health professionals should be as clinical and relevant to patient care as possible. In that vein, such FDA efforts as generating/disseminating questions and answers based on the latest safety information for a particular drug of concern and the CDRH's Web Notifications should be encouraged and modelled, as they are specifically targeted to the treating healthcare community.

6.3 Health Professional Education

Medical product safety/risk management education for health professionals should enhance general knowledge and application of pharmacotherapy, and of the impact individual patient factors can have on pharmacotherapy. In addition, educational efforts should inculcate greater awareness of medical product-induced disease, including its recognition, management and reporting. To foster receptivity by busy health professionals, medical product risk education

needs to be as clinically oriented as possible, and presented as such.

Risk education efforts need to occur at all levels of training and experience, for all health professional disciplines, from professional schools to training programmes to post-graduate continuing education. It is preferably based in clinical care settings (e.g. hospitals or clinics) to emphasise impact on patient care.

Such efforts must be ongoing, as 'one-shot' programmes are not nearly enough to foster desired change in practitioner behaviour. It is also apparent that there are no quick fixes in this regard, and that commitment of resources and partnerships/cooperation among stakeholders will be of necessity to maximise success of health professional educational efforts.

6.4 Risk Communication Principles

To optimise risk communication effectiveness, awareness of social/psychological factors that impact health risk information receipt and perception, clarity of presentation and minimisation of ambiguity/possible sources of confusion are all necessary. Furthermore, deserved trust in informational sources needs to be established via critical evaluation of these sources.

7. Conclusion

Do these examined risk communication modalities result in desired outcomes? Based on current knowledge and experience gained from efforts to maximise awareness of risk associated with medical product use and change associated behaviours through effective notification, education and intervention, an answer of "yes, but not in all circumstances, not every time, and not always to the ideal extent" appears reasonable.

The public health question that remains paramount is, how effective is effective enough? As a result, it is critical that new methods and novel combinations of techniques to communicate medical product risk continue to be sought and tested, so that occurrence of preventable adverse events and product use errors can be minimised, and patients protected, to the greatest degree possible.

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