Communicating a balanced picture of prescription drug risks and benefits is one of pharmaceutical manufacturers’ most important duties. The failure to adequately communicate prescription medications’ risks is a common basis for regulatory enforcement against and legal liability for prescription drug manufacturers. Healthcare professionals’ primary source of information about a prescription drug in the US is its prescribing information (PI), or “labeling.” The labeling may include a Medication Guide or Patient Prescribing Information that is intended to explain the drug’s risks to the patient.

During a prescription drug’s lifecycle, new safety information frequently emerges that may affect its benefit:risk profile in some patients and require changes in the product labeling. One mechanism used by pharmaceutical sponsors to promptly communicate new drug information to US prescribers is the “Dear Health Care Provider” (DHCP) letter. These letters may be initiated by the manufacturer or distributed at the request of the Food and Drug Administration (FDA). The US regulations describing the types of DHCP letters and the process to be used for disseminating them are found in 21 CFR §200.5.1

There are three types of DHCP letters: The Important Drug Warning Letter is used to convey important new and serious risk information about a drug; the Important Prescribing Information Letter conveys important changes made to the PI not related to serious risks (e.g., substantive changes to the Indications and Usage section intended to improve outcomes); and the Important Correction of Drug Information Letter, which serves to correct false or misleading messages in advertising or promotional labeling.2 For all such letters, manufacturers should work in tandem with the appropriate FDA review division to ensure the letter clearly and accurately describes the issue and the prescriber action required to address it.3 (For Important Correction of Drug Information letters, FDA’s Office of Prescription Drug Promotion (OPDP) is typically the contact for pharmaceutical manufacturers).
In the EU, similar communications are referred to as Direct Healthcare Professional Communications (DHPC) and are described in the European Medicines Agency’s (EMA) Guideline on Good Pharmacovigilance Practices (GVPs).  

Enhancing the Effectiveness of Dear Health Care Provider Letters

The effectiveness of US DHPC drug warning letters in changing prescribing behaviors has been studied. In the 1990s, the drug cisapride was the subject of five US DHPC letters prior to the manufacturer's final letter announcing the cessation of cisapride marketing. The first three DHPC letters informed prescribers of potentially life-threatening cardiac arrhythmias associated with QT prolongation when cisapride was taken concomitantly with a drug that inhibited the cytochrome P450 (CYP) 3A4 enzyme system. The availability of third-party payor and managed care organization (MCO) databases has enabled retrospective reviews of cisapride prescriptions to determine whether the issued DHPC letters had the intended effect of limiting co-administration of cisapride with the CYP 3A4 inhibitors listed in the warnings.

Collectively, the analyses conducted on different databases indicated the DHPC letters did not consistently have the expected effect of attenuating prescriptions of cisapride with a contraindicated drug, either for prescriptions filled on the same day or within a defined timeframe.

The first two cisapride DHPC letters were issued in 1995: the first in response to the addition of a boxed warning about drugs contraindicated with cisapride; the second an expansion of the boxed warning to include more contraindicated drugs. These letters had no discernible impact on reducing the number of patients receiving cisapride prescriptions or the number of patients receiving prescriptions for cisapride and a contraindicated drug. In fact, in one analysis, the number of new and total prescriptions of cisapride increased significantly after the first DHPC letter. After the second 1995 DHPC letter, the growth of new prescriptions fell, but total prescriptions continued to increase.

It is noteworthy that the 1995 cisapride boxed warnings and DHPC letters were not widely publicized and antedated the online postings of safety warnings and labeling changes on the FDA website. The 1998 DHPC letter that further expanded the boxed warning to include other specific drugs and drug classes was more widely distributed and publicized via an FDA press release, the Internet and the media. The 1998 letter appeared be more effective in changing prescription patterns, but the level of effectiveness varied by the prescription database examined.

Weatherby’s analysis of a large New England health insurer found that the 1998 letter was followed by a 66% decrease in same-day prescriptions of cisapride with a contraindicated drug as well as a noticeable but smaller decrease during a wider time window. However, Smalley’s review of a large managed care organization, consortium of health management organizations and a state Medicaid program found no material effect on contraindicated cisapride use following the 1998 DHPC letter and the regulatory action surrounding the letter.

EU Letters

A recent European study reviewed characteristics of Direct Healthcare Professional Communications that were likely to influence the communications’ impact. Among the factors that appeared to increase effectiveness was declining drug use prior to issuance of a DHPC. Declining use of a specific drug prior to DHPC issuance may be a signal that the drug is at an advanced lifecycle state when alternatives are available in the marketplace. Thus, the issuance of a DHPC will further accelerate the decline in that drug’s use.

The type of serious safety issue described in the communication also influenced drug prescribing following a DHPC. While all DHPCs describe a safety issue, the issues that are associated with more serious outcomes such as death or disability were shown to have a greater impact in reducing use of the relevant drug. In the EU, DHPCs about drugs that were designated to be prescribed by a specialist had less impact in changing prescribing behavior than those sent for drugs that could be prescribed by generalists. This may be due to the fact that specialists able to prescribe these more complex medications tend to use more risky treatment options for their medically complicated
patients and frequently have additional resources for patient monitoring that can better enable safe use of a drug following issuance of a DHPC.\textsuperscript{21} EMA’s addition of a fixed template for DHPCs to its pharmacovigilance guidelines appeared to enhance the impact of DHPCs, ostensibly due the greater understandability of the message.\textsuperscript{22}

**Themes**

In reviewing the publications generated from these retrospective analyses, as well as others that have examined the effectiveness of DHCP letters more generally, some themes emerge that may affect the effectiveness of DHCP letters, particularly those written as Important Drug Warnings:

1. DHCP letters appear to be more effective when they are disseminated with greater surrounding publicity—including notification on the FDA website\textsuperscript{23,24}—and when followed up by direct intervention at the pharmacy level.\textsuperscript{25}

2. The important role of pharmacists should not be overlooked by pharmaceutical manufacturers when disseminating DHCP letters. Pharmacists can identify potentially dangerous drug combinations for patients who receive multiple-refill prescriptions without direct physician involvement or for patients who have multiple physicians writing prescriptions for them.\textsuperscript{26} Despite the importance of the pharmacist, in a 2008 survey of more than 2,000 licensed pharmacists, 18% reported never having received a DHCP letter.\textsuperscript{27}

3. When the DHCP letter is intended to warn about drug-drug interactions, the use of specific drug names is more effective in decreasing co-administration than the use of drug class names or characterizations such as “certain drugs.”\textsuperscript{28}

4. The content, organization and formatting of a DHCP letter can favorably affect prescriber comprehension of the message and prescriber behavior.\textsuperscript{29}

5. Recommendations based on a study of DHCP letters rated by physicians include:
   a. Place the most important information early and prominently.
   b. Eliminate or reduce non-critical information.
   c. Keep the letter as brief as possible without compromising clarity.
   d. Clearly indicate what risk information and recommendations are new.
   e. Note the consequences of non-compliance with the new warning early and prominently in the letter (e.g., provide explicit information on possible adverse effects).
   f. Use special formatting (such as headers, bolding, etc.) to draw attention to key information.\textsuperscript{30}

6. Individual intervention letters from hospitals or a state-level drug utilization reviewers sent to prescribers who have been identified as prescribing inappropriately can be effective in altering practice.\textsuperscript{31}

**DHCP Letters on Promotional Websites**

While DHCP letters are not promotional, the FDA review division working with the manufacturer may consult with OPDP or ask the manufacturer to seek advisory comments from OPDP regarding the letter’s clarity. For full transparency, manufacturers frequently post DHCP letters on the Health Care Professional section of the respective product website. A prominent banner should be added to the splash page of the website directing the user to the DHCP letter and other accompanying important labeling changes such as the addition of a boxed warning or a Medication Guide.

Practically, it may take several days to weeks to change the Important Safety Message that is integrated into the entire website, depending on the website’s complexity, but links to the approved labeling and Medication Guide generally can be added to the site as soon as the new labeling is available. Similarly, the addition of a banner announcing a new warning or a banner announcing and linking to a DHCP letter usually can be accomplished promptly. If the new warnings significantly conflict with the product website’s content, it may be advisable to take the website down until it can be revised, posting the current labeling and DHCP letter.

Pharmaceutical manufacturers or their sales representatives may be tempted to use a competitor’s DHCP letter or other drug safety notice to imply superior safety of their own
drug. FDA cautions that comparative claims must be based on substantial evidence or substantial clinical experience which, for a drug comparison, is a head-to-head trial(s). To imply a competitive advantage from emerging safety data would likely be considered false or misleading by the agency.32

Additional information about DHCP letters can be found in FDA’s 2010 draft Guidance for Industry Dear Health Care Provider Letters: Improving Communication of Important Safety Information33 and the 2012 draft Guidance: Drug Safety Information–FDA’s Communication to the Public.34

References

2. Ibid.
10. Ibid.
12. Ibid.
13. Ibid.
19. Ibid.
20. Ibid.
21. Ibid.
22. Ibid.
30. Ibid.

About the Author

Mary Sullivan is an executive director of regulatory affairs at Boehringer Ingelheim Pharmaceuticals, Inc. She leads the Advertising and Promotion Compliance group within the Regulatory Affairs department. Before coming to Boehringer Ingelheim, Sullivan worked at Abbott Laboratories and Takeda Pharmaceuticals as a regulatory reviewer of advertising and promotion. While at Abbott, she also held positions in Clinical Research and in International Medical Affairs. Sullivan has a B.S. degree from Purdue University in Nutrition Science, a Masters of Public Health from the University of Alabama and has completed a graduate certificate in Regulatory Quality and Compliance from Purdue’s School of Pharmacy. She can be reached at mary.sullivan@boehringer-ingelheim.com.

© 2013 by the Regulatory Affairs Professionals Society. All rights reserved.