Senate Special Committee on Aging

Hearing on

Protecting Seniors from Medication Labeling Mistakes

December 11, 2013

Oral Statement for the Record
Submitted by the

Testimony by

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Good afternoon Chairman Nelson, Ranking Member Collins, and distinguished members of the Special Aging Committee.

I also want to thank Senator Gillibrand for her leadership on this issue.

My name is Gerald McEvoy, and I serve as Assistant Vice President of Drug Information for the American Society of Health-System Pharmacists and as Editor in Chief for our federally recognized professional drug information compendium and consumer medication information database.

ASHP is the national professional society representing over 42,000 pharmacists and technicians who practice in hospitals and health systems.

ASHP has a nearly 40-year history of providing patients with meaningful information about medications and provides the only trusted and objective compendium-based database of CMI published by a not-for-profit professional and scientific society in the US. Our patient medication information is provided electronically free of charge to consumers through the National Library of Medicine and our own safemedication.com website.

I am here today to provide ASHP's perspective on the issue of patient medication information. For more than a decade, I have been involved with efforts to simplify, and make more meaningful, patient medication information. It is critical that patients receive the necessary information along with their prescription that explains directions for taking the medication, potential side effects, critical warnings and precautions, and the potential for drug to drug interactions. Given the number of medications a typical senior citizen takes, this information is especially critical to the health and well-being of our nations' seniors.

In response to a 2008 Citizen Petition and other events, FDA proposed achieving this goal by putting manufacturers in charge of authoring the patient information for each of their products, and based solely on their own FDA-approved professional label. Although we agree with the goal of streamlining and enhancing the usefulness of patient medication information, we strongly disagree with FDA's plan. The FDA approach fails to ensure patients will receive timely, accurate, consistent, and impartial information.

Under their proposal, FDA would replace the existing system with manufacturer authored information. More than 800 manufacturers would be charged with authoring patient medication information without any central editorial oversight. FDA estimates that under their proposal approximately 22,000–25,000 individual documents initially would need to be created.

First, we are concerned that FDA's proposal to allow manufacturers to develop their own PMI will result in inconsistent information across tens-of-thousands of drug products, creating confusion for patients and their caregivers. There is no mechanism to ensure PMI for identical products would be identical or that similar information would be included in every relevant medication within a drug class.

For example, Zocor's professional label first included a warning about the increased risk of myopathy in patients of Chinese decent in early 2010, yet almost 4 years later the labeling for some generic products still does not include this critical risk information. If a patient is switched from an innovator product to a generic or from one generic to another, what safeguards would be in place to ensure the information is consistent, regardless of whose product the patient is taking?

Second, we have concerns with the timeliness in which this information would be updated for all related products. FDA's proposal to tie medication information to the product label is troubling due to the lag times we currently see with respect to changes in professional labeling. Information that is critical to safe, effective medication use must be made available to the patient as soon as it's known.

For example, when Viagra was approved in 1998, the professional label included an appropriate warning that it should not be taken with a nitrate product – a potentially fatal interaction. And yet, almost 15 years later we found that 29 of the 30 nitrate products still did not include the same complete class-wide contraindication about Viagra and other ED products on their professional labels.

Additional examples are included in my written testimony.

Third, the FDA maintains they lack the resources to review and approve each manufacturer's patient medication information for every product it makes. FDA

claims approval is unnecessary because manufacturers will base their patient information off of the PDA-approved professional label. Yet, as I described, this claim clearly is not valid.

Given these concerns, ASHP continues to urge the FDA to consider alternative models. ASHP believes that PMI developed by a single entity is the best pathway to ensure that timely, accurate prescription medication information gets into the hands of patients to ensure safe, effective medication use.

We strongly support Senator Gillibrand's Cody Miller Initiative for Safer Prescriptions Act, which would permit the Secretary of HHS to pursue this alternative pathway.

Again thank you for inviting me to testify today, and I am happy to address your questions.

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Testimony Overview

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Additional examples of inconsistencies and inadequacies of professional labeling as the sole source of information for manufacturer-authored patient medication information are provided below and in Appendix A.

Third, the FDA maintains they lack the resources to review and approve each manufacturer's patient medication information for every product it makes. FDA claims approval is unnecessary because manufacturers will base their patient information off of the PDA-approved professional label. Yet, as I described, this claim clearly is not valid.

Given these concerns, ASHP continues to urge the FDA to consider alternative models. ASHP believes that PMI developed by a single entity is the best pathway to ensure that timely, accurate prescription medication information gets into the hands of patients to ensure safe, effective medication use.

We strongly support Senator Gillibrand's Cody Miller Initiative for Safer Prescriptions Act, which would permit the Secretary of HHS to pursue this alternative pathway.

Introduction

FDA has proposed replacing the current system of independent drug information publisher-authored consumer medication information (CMI) with one of self-regulated, manufacturer-authored patient medication information (PMI). Under this proposal, more than 800 disparate manufacturers would independently develop and publish PMI employing a self-regulated model that includes no central editorial oversight. The content and format of each manufacturer-authored PMI document would not be subject to review by FDA to ensure compliance with agency-developed PMI standards or consistency with PMI for the same or similar medications prior to distribution to patients and their caregivers. In addition, FDA has proposed that printed PMI content be subject to an arbitrarily selected one-page limit regardless of medication risk or complexity. And finally, FDA has proposed that the content of the manufacturer-authored PMI will be limited to information in the respective manufacturer's own professional labeling, regardless of how inaccurate, out-of-date, or inconsistent that labeling may be.

Reasons for FDA embarking on this path include:

- Findings from 2001 and 2008 FDA-commissioned assessments of the current system of CMI to meet usefulness standards established by the Department of Health and Human Services (DHHS) 1996 *Action Plan for the Provision of Useful Prescription Medication Information* (the Action Plan, Keystone Guidelines) and subsequent 2006 FDA interpretive guidance
- 2008 Citizen Petition Requesting FDA Action on a "One Document Solution" for all Pharmacy-based Communications
- 2009 Recommendations of FDA's Risk Communication Advisory Committee (RCAC) that the agency adopt a single standard document for communicating essential information about prescription drugs, which would replace CMI, patient package inserts (PPIs), and Medication Guides (MedGuides)
- 2009 FDA public workshop on providing effective information to consumers about prescription drug risks and benefits
- Failure of Medication Guides and the impetus that their inclusion as a potential element of risk communication and mitigation strategies (REMS) provided for evaluating alternative approaches to communicating risk and benefit information about prescription medications to consumers
- Perceived benefit to consumers of providing more concise CMI

By its own admission, FDA has no evidence concerning the optimal length of PMI.[1] And while a recent pilot study survey found that patients reported one-page CMI as useful,[2] FDA never established through adequate research the essential level of information required by patients for safe and effective use of their medications prior to this study, and the agency's current research agenda is not designed to establish this. Thus, FDA is headed down a path that risks providing patients with inadequate information concerning the safety and optimal use of their medications. As practical matter, once one age is filled with information that is deemed important to patients, what do you do when equally important new information about the drug emerges?

Yet, more troubling than the length requirement is FDA's proposal to put drug manufacturers in charge of authoring their own patient information. FDA has never shown that the current system of CMI authorship by manufacturer-independent private publishers is not working. Instead, it only has been able to show that substantial downstream alteration of both the content and format of CMI by pharmacies or their information system vendors resulted in the provision at the point of dispensing of substandard CMI. And yet, rather than attempting to correct the real problem of downstream CMI alteration, FDA has neglected to consider fully a well-established editorial process that has exceeded the standards the Agency set for useful consumer medication information. In fact, had patients received the CMI intended for distribution by the authoring drug information publishers, it would have exceeded greatly the Agency's goals. Instead, FDA is focused on addressing concerns with authorship quality that simply do not exist. (See Appendix B and Appendix C.)

[1] Discussion guide. Expert workshop on Designing Pilot Programs to Distribute Patient Medication Information. Engelberg Center for Healthcare Reform at Brookings. February 2011. (http://www.brookings.edu/~/media/events/2011/2/23%20pmi%20pilots/discussion%20guide.pdf)

[2] Catalina Health releases results of patient information quality improvement initiative. Press release. April 9, 2013. (http://www.catalinamarketing.com/news-events/press-releases/details.php?id=335)

Another key premise of FDA's proposed model also is not valid. The Agency has argued that because it will limit the content of manufacturer-authored PMI to each company's FDA- approved professional label for their products, there is no need for the Agency to review and approve PMI. However, FDA's failure to ensure the accuracy, consistency, and timeliness of professional labeling it approves will result in a transfer of the same inadequacies that plague professional labeling. These problems will be described in more detail later in this testimony.

Inappropriate use of medications by patients is known to have extensive and sometimes severe human and economic consequences. Empowering the patient with knowledge to optimize medication therapy is a goal of all medication education and counseling efforts. Without this knowledge, the patient cannot form an effective partnership with healthcare professionals to manage their medication therapy. ASHP and other drug information publishers such as First DataBank (FDB Health) and Wolters Kluwer, independent consumer advocacy groups such as Consumers Union (CU), and government agencies such as the National Library of Medicine (NLM) have a history of providing accurate, high-quality prescription medication information to consumers.

Making well-informed healthcare decisions, including decisions about medications, can be difficult for consumers. A variety of factors may influence consumer decisions about medications, including information they receive from trusted healthcare providers (e.g., physicians, pharmacists) and from their health benefit managers; direct-to-consumer advertising; advice from family, friends, and internet contacts (e.g., chat rooms, blogs); advisories from the government (e.g., FDA); and information obtained independently (e.g., from medication information resources such as those that are Web-accessible). Contributing to this difficulty is the sheer magnitude of information and uncertainties about its quality and trustworthiness—factors that can greatly influence difficulties in understanding safe and effective medication use, including off-label uses, and the level of evidence concerning their benefits and risks.

For several decades, the principal source of objective, unbiased CMI in the US has been drug information publishers, whose independence from the influence of pharmaceutical manufacturers and consistently applied editorial standards have resulted in objective, timely information for patients about their drugs. These publishers have a record of developing CMI that meets the usefulness standards of the Department of Health and Human Services Action Plan for the Provision of Useful Prescription Medication Information (the Action Plan, Keystone Guidelines) and subsequent 2006 FDA interpretive Guidance. This information most typically is obtained by patients at the point of dispensing from pharmacies, whose downstream policies ultimately control what the patient actually receives. Unfortunately, because of this downstream control by pharmacies or their informations system vendors, the intended content and format of what the patient receives often is substandard, with changes such as poorly readable typography and wholesale deletion of entire sections of safety information depriving patients of the high-quality information intended by drug information publishers.

Dispelling the Myths about Drug Information Publisher Authored Consumer Medication Information (CMI)

The FDA frequently cites two studies that raise concern about the consumer medication information that currently is provided to patients. However, as set out below, both of these studies failed to look at the information that was actually prepared by the private publishers. Any concerns about usefulness are most likely attributable to alterations of the information that are made downstream such as

wholesale safety content deletion before the information is provided to the patient. That is the issue the FDA should be focusing on fixing.

ASHP has submitted to the Agency's docket two detailed analyses of FDA's contracted assessments of CMI—the 2001 study published by Svarstad (principal investigator) and the 2008 study published by Kimberlin and Winterstein (principal investigators).[3,4]

ASHP has consistently pointed out methodological problems with the study designs, particularly the inclusion of a substantial proportion of specific criteria for determining usefulness that were not supportable from FDA-approved labeling and/or the Action Plan. For example, only about 50–65% of the criteria used in the 2001 Svarstad study could be directly attributed to professional labeling and were explicitly required by the Action Plan as part of ASHP's analysis; that means that up to half of the criteria used to assess the consumer medication information of private publishers fell outside FDA's standards. (See Appendix B.) At a June 17, 2004 meeting that was convened by FDA with the assistance of the National Council on Patient Information and Education (NCPIE), both Dr. Svarstad and FDA acknowledged such methodological problems and agreed that a Guidance should be developed to ensure a fairer, more objective evaluation that was consistent with the language and intent of the original Action Plan. While the Guidance was finally published in 2006, the 2008 study design repeated the flaws of the original study, most notably failure to evaluate the source CMI from the publishers themselves and the inclusion of assessment criteria that fell outside the standards established by the Action Plan and Guidance. Thus, with the 2008 study, ASHP's analysis (see Appendix C) found that only about 70% of subcriteria could be supported by the 2006 Guidance and manufacturer's professional labeling.

Even with these subcriteria problems, Kimberlin and Wintestein found that the versions of CMI authored by FDB and Wolters Kluwer (the principal publishers of CMI accessed at the point of dispensing in community pharmacies) that were **least** altered downstream by pharmacies or their information system vendors actually greatly exceeded the usefulness threshold by over 20 percentage points. The magnitude of this downstream alteration of FDB's CMI for the same metformin leaflet was described to range from 760 words for a leaflet obtained from one chain pharmacy versus 2457 words for the same leaflet obtained from another chain pharmacy; the latter leaflet exceeded the usefulness threshold by 28 percentage points. In the shorter leaflet, the warnings section had been eliminated as well as sections on brand names, precautions, drug interactions, overdose, missed dose, and storage. Similar findings of downstream alteration of Wolters Kluwers' CMI by pharmacies or their information system vendors also were reported. When the subcriteria falling outside FDA's standards for useful CMI as defined by the Action Plan and 2006 Guidance were excluded from the 2008 analysis, the CMI performed even better. (See Appendix C.)

The inaccurate selection of subcriteria, methodological flaws, and inappropriate timing and communication of standards for the development of useful CMI all contributed to an inaccurate assessment of medication information available to consumers in 2008. In addition, the 2008 Final Report did not establish the root cause of subcriteria adherence issues, since the study did not perform a separate evaluation of the original content provided by the source publisher versus the content

[3] Docket No. FDA-2005D-0169 as part of ASHP comments on the Draft Guidance on Useful Written Consumer Medication Information (CMI). Gary C. Stein for ASHP. July 25, 2005.

[4] Docket No. FDA-2008-S-0627 as part of ASHP comments on Expert and Consumer Evaluation of Consumer Medication Information–2008. Justine Coffey for ASHP. May 29, 2009.

distributed downstream at the point of dispensing. Therefore, conclusions that can be drawn from the 2008 Final Report are incomplete and often presented in a misleading way, since FDA did not address important study design flaws and associated concerns raised by ASHP relating to the earlier 2001 evaluation. Even without this separate evaluation of the original content, there was a strong indication in the 2008 evaluation that problems noted in the Final Report reside at the point of distribution, rather than with the content provided by the CMI source publishers. Thus, FDA has started to create a new model of self-regulated, manufacturer-authored PMI without clear justification.

Inadequacies of FDA-approved Labeling as Sole-source Documents for Creating PMI

As discussed, under the FDA proposal, manufacturers would author their own patient medication information and the content would be based on the FDA-approved professional label.

The Government Accountability Office (GAO), health policy and epidemiology researchers, medical informatics researchers (including natural language processing [NLP] of DailyMed labeling files), and others have identified important inadequacies in FDA-approved professional labeling, including outdated, inaccurate, and inconsistent information as well as missing critically important safety information. (See Appendix slide set) Yet despite important evidence of the inadequacies of FDA-approved professional labeling, the Agency continues to recommend that it be the sole source of information to be used by manufacturers in a self-regulated environment to create PMI.

FDA recently acknowledged substantial deficiencies in its approved labeling when it issued a request for proposal for the private sector to convert a substantial backlog of outdated labeling into the format the Agency implemented in 2006.[5] However, even if FDA somehow could update and correct all existing professional labeling, a daunting task, it still couldn't ensure consistency for patient medication information from one product to another when over 800 manufacturers would be independently authoring PMI with no central editorial oversight. Even by its own estimates, only 15% of professional labeling is in the current form for both content and format, commonly referred to as the physician labeling rule (PLR) format, despite implementation of PLR almost a decade ago.[6] Only 10% of generic drugs are in the current PLR format, which is particularly troubling since 80% of prescriptions are currently filled with generic drugs.

Notably, Dr. John Jenkins, Director of FDA's Office of New Drugs for CDER in 2008, acknowledged the problems the Agency had in maintaining fully accurate and up-to-date labeling. He noted that many labels are out-of-date and in many cases contain incorrect information.[7]

[5] FDA Request for Proposal (RFP) No. FDA-SOL-13-1113769 entitled "Prescription Drug Labeling Improvement and Enhancement Initiative." Issued July 10, 2013. (https://www.fbo.gov/index?s=opportunity&mode=form&id=f34a5dae448324a0df299ae69ea12f6a&tab=core&_cview=1)

[6] Food and Drug Administration. Center for Drug Evaluation and Research; prescription drug labeling improvement and enhancement initiative; request for comments and information. 21 CFR Parts 201, 314, and 601. [Docket No. FDA-2013-N-0059] Fed Regist. 2013; 78:8446-8.

[7] US House of Representatives Committee on Oversight and Government Reform. Majority Staff Report. "FDA Career Staff Objected to Agency Preemption Policies." October 2008.

> "[It is] a false assumption that the FDA approved labeling is fully accurate and up-to-date….we know that many current approved drug labels are out of date and in many cases contain incorrect information." Dr. Jenkins 2008

There also will be substantial editorial control challenges in global content revision and updating with the tens-of-thousands of proposed PMI documents and extreme difficulty in maintaining content consistency and currency from product to product with the same drug, among medications in the same drug class, and throughout the database. For example, changes associated with all affected drugs/products (e.g., for drug interactions, drug class effects) most likely would be updated over a period of many months, or even years, given the number of manufacturers affected by the changes in content information.

For example, when Viagra was approved in 1998, a specific warning was included on the professional label regarding a potential fatal drug interaction if Viagra is taken with a nitrate product. Yet, many of the nitrate labels still do not provide adequate warning about the contraindication against use with Viagra, Cialis, and other phosphodiesterase inhibitors. In fact, an ASHP review of the professional labels in 2011 found that 29 of the 30 nitroglycerin products failed to properly warn about the contraindication. And only one piece of FDA-approved nitroglycerin patient labeling posted in the Agency's electronic labeling repository even mentioned this risk. Many wonder how that is possible, but the FDA has no process in place to automatically update labels across a class of drugs as appropriate at the same time. That is a major advantage of using a single, independent author.

A 2012 GAO report found that FDA failed to ensure that antibiotic labels are updated on a timely basis. More than 3.5 years after FDA contacted manufacturers, the Agency had not yet confirmed whether critical information on the effectiveness of antibiotics was up-to-date in 70% (146 out of 210) of labels.

Likewise, a study on black box warning (BBW) information (Panagioutou), the strongest medication-related safety warnings, found the time lag for appearance of drug class BBWs within individual medications labels in the class ranged from 2 months to 14 years (median 5.5 years). In a more extensive analysis, almost 600 labels in DailyMed (the official repository for FDA-approved labels) that should have had BBWs were missing them. In another study (Duke et al), natural language processing of labels from DailyMed found that safety information for the same drug available from multiple manufacturers often differed. (See Appendix A for these examples.) For safety information that applies class-wide to medications within a given drug class, a single centrally controlled authoring model could ensure that the labels for all members of the drug class and their generic equivalents would get updated simultaneously.

As another example, Zocor professional labeling first included a warning about the increased risk of myopathy in patients of Chinese decent in early 2010, yet almost 4 years later the labeling for some generic products still does not include this critical risk information. (See Appendix A.) If a patient is switched from an innovator product to a generic or from one generic to another (a common practice with senior prescriptions), what safeguards would be in place to ensure that the information a patient receives is consistent regardless of whose product the patient is taking?

Problems with interacting drug pairs are common examples of professional labeling inconsistencies. As noted in the Viagra–nitrate example above, the interaction and associated warning often appears only in the professional label of one of the interacting drugs. As a result, patients may not be aware of the interaction depending on the sequence in which they get their prescriptions filled for the 2 drugs under

FDA's PMI model. By comparison, a single centrally controlled authoring model could ensure that the labels for both drugs and their generic equivalents would get updated at the same time.

Because of the important inadequacies of FDA-approved professional labeling and the Agency's model that depends solely on the manufacturer's label as the source for PMI content development, ASHP strongly opposes the current proposal for self-regulated, manufacturer-authorship and instead supports a central authorship model.

Even if the Agency were to permit use of the reference listed drug's (RLD) patient medication information, the substantial lag times and inconsistencies already observed for adoption by generic manufacturers of changes from the RLD professional labeling and the anticipated exacerbation of delays and inconsistencies that will result when generic manufacturers are permitted to independently revise their own safety information would remain with FDA's model. Further, differences that exist for drug interaction warnings between drug labels and safety information differences that exist for medications within a drug class also would remain with FDA's approach. As a result, patients will be confused and possibly deprived of potentially life-saving information if FDA's rather than ASHP's model were followed.

Recommended Alternative Path for PMI Development and Maintenance

ASHP fully supports FDA's goal of adopting a single document that is standardized and simplified with respect to content and format and that provides clear, accessible, and actionable information. Further, ASHP recommends that FDA's one-page limit be replaced by the optimal model defined through adequate patient-centered research to establish the best level and presentation of information as a first step to ensure that PMI will optimally promote safe and effective use of medications by patients and oversight by their caregivers.

At the core of ASHP's recommendation is full consideration by FDA of an alternative model of a single centrally controlled authoring model. ASHP believes that there is compelling evidence that such a model, if structured and administered properly, could avoid all of the issues associated with FDA's manufacturer-authored model, particularly those resulting from nearly 1000 authors operating without central editorial control and relying solely on problematic professional labeling as the source material.

Thus, we propose an alternative model for providing patients with the essential information needed for safe and effective use of their prescription medications. Elements of this PMI development model include:

- Single-source authorship by an independent scientifically based organization with experience in evaluating patient medication information and expertise suitable to develop PMI that is accurate, consistent, and timely, and updated as needed
- Compliance with FDA-established and enforced, evidence- and consensus-based standards for optimal PMI content and format
- Creation and maintenance of a central repository of XML-structured PMI at the National Library of Medicine that is readily accessible in the public domain and available for integration and distribution by information system vendors into pharmacy and other workflow environments and for alternative patient-centered access and applications

- Proposed new language in the National Association of Boards of Pharmacy's (NABP's) model state pharmacy act and rules reinforcing requirements for distribution to patients of unaltered PMI that meets FDA's content and format standards and exploration of other means such as endorsement and/or adoption by standards development organizations of FDA's PMI content and format standards to minimize downstream data alterations

Combined, the components of this alternative model for PMI can ensure that patients consistently receive the essential information about their prescription medications that is:

- Patient-centered
- Accurate
- Balanced
- Comprehensible
- Consistent
- Credible, trusted
- Up-to-date
- Evidence- and standards-based
- Accessible

As proposed by Senator Gillibrand in the Cody Miller Initiative for Safer Prescriptions Act, such an alternative model can be achieved by requiring the Secretary of HHS to promulgate regulations regarding the authorship, content, format, and dissemination of PMI aimed at ensuring that patients receive consistent and high-quality information about prescriptions medications and are aware of the potential risks and benefits in a consistent, accurate, and timely fashion.

Under this proposal, PMI would be scientifically accurate and based on professional labeling approved by the Secretary and authoritative, peer-reviewed literature and would be subject to new FDA standards for timely updates as new drugs and information becomes available. The regulations would ensure that common information is applied consistently and simultaneously across similar drug products and classes of medications to avoid patient confusion and harm and would require that a process, including consumer testing, be developed to assess periodically the quality and effectiveness of PMI to ensure that it promotes patient understanding and safe and effective medication use.

The scientifically based authoring organization should have experience in evaluating PMI and demonstrated expertise in:

- reviewing drug data
- researching appropriate clinical sources to identify the information needed to promote patient understanding and the safe and effective use of medications
- authoring in form and content that is high-quality, credible, accurate, balanced, consistent, up-to-date, and evidence- and standards-based and that is designed to ensure accessibility and comprehension by the general public

FDA would develop performance and quality metrics to ensure that the authoring organization monitors the marketplace to ensure PMI is promptly available for new drugs, has procedures in place to address relevant new information in a timely fashion, and is subject to FDA evidence-based standards for PMI content and format.

Appendix A

Examples of Inaccurate, Inconsistent, and Out-of-Date Professional Labeling – the Foundation for Patient Medication Information Under the FDA Proposal

FDA Admits Problems with Accuracy and Currency of Professional Labels

- “[It is] a false assumption that the FDA approved labeling is fully accurate and up-to-date….we know that many current approved drug labels are out of date and in many cases contain incorrect information”.

  - Dr. John Jenkins, Director, Office of New Drugs in the FDA Center for Drug Evaluation and Research (CDER)

  UNITED STATES HOUSE OF REPRESENTATIVES COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM MAJORITY STAFF REPORT, OCTOBER 2008 “FDA CAREER STAFF OBJECTED TO AGENCY PREEMPTION POLICIES”

January 2012 GAO Report – "FDA Needs to Do More to Ensure that Drug Labels Contain Up-to-Date Information

GAO
U.S. Government Accountability Office

What GAO Found

FDA has not taken sufficient steps to ensure that antibiotic labels contain up-to-date breakpoints. FDA designates certain drugs as "reference-listed drugs" and the sponsors of these drugs play an important role in ensuring the accuracy of drug labels. Reference-listed drugs are approved drug products to which generic versions are compared. As of November 2011, FDA had not yet confirmed whether the breakpoints on the majority of reference-listed antibiotics labels were up to date. FDA contacted sponsors of 210 antibiotics in early 2008 to remind sponsors of the importance of maintaining their labels and requested that they assess whether the breakpoints on their drugs' labels were up to date. Sponsors were asked to submit evidence to FDA showing that the breakpoints were either current or needed revision. As of November 2011, over 3.5 years after FDA contacted sponsors, the agency had not yet confirmed whether the breakpoints on the labels of 70 percent, or 146 of the 210 antibiotics, were up to date. FDA has not ensured that sponsors have fulfilled the responsibilities outlined

Authors with Marketing Interests Will Not Likely Be Objective

- “Companies rarely press for meaningful risk information or additional warnings. And they always oppose black box warnings. Much of the discussion of what goes in the label centers around the sponsors wish to promote the drug fully and to not be handicapped by risk information that would have to be conveyed in ads.”

  - CDER Comments - Redline of June 6, 2003 FDA Draft on Preemption

UNITED STATES HOUSE OF REPRESENTATIVES COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM MAJORITY STAFF REPORT, OCTOBER 2008 “FDA CAREER STAFF OBJECTED TO AGENCY PREEMPTION POLICIES”

Black Box Warnings – Late or Never Inconsistencies within Drug Classes

J Gen Intern Med. 2011 Jun;26(6):603-10. Epub 2011 Feb 1.

Different black box warning labeling for same-class drugs.

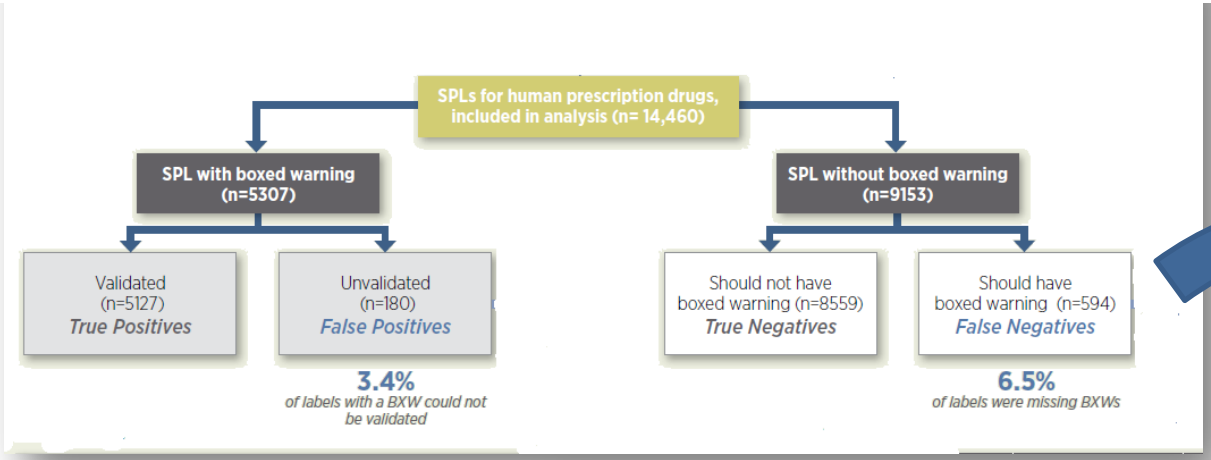
Panagiotou OA, Contopoulos-Ioannidis DG, Papanikolaou PN, Ntzani EE, Ioannidis JP.
Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece.

"Black box warnings…the strongest medication-related safety warnings that can be placed in a drug's labeling information…

…15 black box warnings not present on all the labels of drugs in the same class…a considerable time-lag in black box warning acquisition in 8 categories, ranging from 2 months to 14 years…

…drugs [withdrawn from the market] tended not to have a black box warning before their withdrawal, and the reason for their withdrawal rarely became a black box warning for other drugs in the same category."

Boxed Warnings Comprehensive Review



DRUG	Number of SPLs	BXW Issue
Acetaminophen-containing oral drugs	242	Liver injury, especially with doses exceeding 4,000 mg in 24 hours
Beta blockers	62	Exacerbation of angina following abrupt cessation
NSAIDs	45	Cardiovascular risk (thrombotic events, myocardial infarction, stroke) and gastrointestinal risk (e.g., bleeding, ulceration, perforation)
Estrogen-containing oral contraceptives	29	Risk of cardiovascular side effects with cigarette smoking
ACE inhibitor/ARB and combinations	26	Fetal risk
Thyroid drugs	12	Risk of toxicity when used for anorectic effects/weight loss
Metformin-containing drugs	11	Lactic acidosis
Methylphenidate-containing drugs	9	Abuse potential
Triamterene and hydrochlorothiazide drugs	9	Hyperkalemia
Antidepressants	6	Suicidality in children and young adults
Other	143	Various

Triptans and Rebound Headaches

Original Rebound/Medication Overuse Headache **Precaution added to Glaxo Smith Kline Treximet® label as of *11/2011*** - triggering the following Triptan labeling changes:

*Endo FROVA (frovatriptan succinate) "Patient Information" Medication Overuse Headache Information added **10/2013***

What are the possible side effects of FROVA?

Medication overuse headache. Some people who use too many FROVA tablets may have worse headaches (medication overuse headache). If your headaches get worse, your doctor may decide to stop your treatment with FROVA.

*Glaxo Smith Kline AMERGE (naratriptan hydrochloride patient information Medication Overuse Headache Information added **3/2012***

How should I take AMERGE?

- Some people who take too many AMERGE tablets may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with AMERGE.

Depakote Patient vs. Professional Label

Abbott Depakote professional labeling boxed ***warning in place in 2001*** ***"LIFE THREATENING ADVERSE REACTIONS"***

Abbott Depakote FDA Labeling ***NO NOTICE OF POTENTIALLY FATAL IMPACT ON LIVER AND PANCREAS NOTED UNTIL 2011***

WARNING: LIFE THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of two years are at considerably higher risk of fatal hepatotoxicity. Monitor patients closely, and perform liver function tests prior to therapy and at frequent intervals thereafter (5.1)
- Teratogenicity, including neural tube defects (5.2)
- Pancreatitis, including fatal hemorrhagic cases (5.3)

FDA-APPROVED PATIENT LABELING

Important Information for Women Who Could Become Pregnant About the Use of DEPAKOTE, DEPAKOTE ER, DEPAKOTE Sprinkle Capsules, and DEPAKENE.

Please read this leaflet carefully before you take any of this medication. This leaflet provides a summary of important information about taking this medication to women who could become pregnant. If you have any questions or concerns, or want more information about this medication, contact your doctor or pharmacist.

Information For Women Who Could Become Pregnant

You can only obtain this medication by prescription from your doctor. The decision to use this medicine should be made by you and your doctor based on your health needs and medical condition.

Before starting this medicine, you should know that using this medicine during pregnancy causes an increased chance of birth defects in your baby. These birth defects may include spina bifida and other defects where the spinal canal does not close normally. These defects usually occur in 1 to 2 out of every 1000 babies born in the United States. Studies show that for babies born to epileptic women who took valproate in the first 12 weeks of pregnancy, these defects occur in 1 to 2 out of every 100 babies.

Use of valproate during pregnancy also increases the chance of other birth defects such as of the heart, bones, and other parts of the body. Studies suggest that other medicines used to treat your condition may be less likely to cause these defects.

Information For Women Who Are Planning to Get Pregnant

Women using valproate who plan to get pregnant should discuss their treatment options with their doctor.

Information For Women Who Become Pregnant

If you become pregnant while taking valproate, you should contact your doctor immediately.

Other Important Information

- You should take your medicine exactly as prescribed by your doctor to get the most benefit from your medicine and reduce the risk of side effects.
- If you have taken more than the prescribed dose, contact your hospital emergency room or local poison center immediately.
- Your medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

From Independent Patient Education Monograph for Divalproex as of ***2001***

Serious, even fatal, liver problems have occurred in patients using this drug. Children using this drug who are under the age of 2 years are at higher risk...Additionally, severe (even fatal) pancreatitis (pancreas inflammation) has occurred during use of this medication...This drug may cause birth defects. Consult your doctor about the use of this medication during pregnancy.

Inconsistent Package Inserts

There are potentially fatal low blood pressure reactions when nitrate heart drugs are combined with erectile dysfunction drugs. This interaction was first noted in approved Viagra labeling in 1998. <u>As of February 2011, product labeling from 29 of 30 nitroglycerin products did not provide adequate information regarding this interaction</u>

from Nitroglycerin Transdermal Patch labeling – Alvogen, Inc.

Missing ED drug contraindication

<u>Feb. 2011</u>

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

from Viagra (sildenafil) labeling – Pfizer ***<u>Nov. 1998</u>***

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

Mixed Messages
A 12-yr lag for a Contraindication

DIABETA (glyburide) tablet
[sanofi-aventis U.S. LLC]

An increased incidence of elevated liver enzymes was observed in patients receiving glyburide concomitantly with bosentan. Therefore this combination should not be used. (See CONTRAINDICATIONS.)

DIABETA® (glyburide) – *"Don't take with bosentan"* - labeling updated 2/2009

Who should not take Tracleer?

Do not take Tracleer if you:

- take one of these medicines:
  - —cyclosporine A used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants
  - —glyburide used for diabetes

TRACLEER® (bosentan) - *"Don't take with glyburide"* – original labeling 11/2001

Q14. Can I take GLUCOVANCE with other medications?

Remind your doctor that you are taking GLUCOVANCE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOVANCE may interfere with the way some drugs work and some drugs may interfere with the action of GLUCOVANCE.

GLUCOVANCE® (glyburide + metformin) - "……."

**** NO bosentan warning* until 10/2013 labeling update***

Same Drug, Different Warnings

ZOCOR (simvastatin) tablet, film coated
[Merck Sharp & Dohme Corp.] **as of 3/2010**

2 DOSAGE AND ADMINISTRATION

2.5 Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy, caution should be used when treating Chinese patients with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. *[See Warnings and Precautions (5.1).]*

People of Chinese descent shouldn't take this medication…

SIMVASTATIN (simvastatin) tablet
[Cobalt Laboratories Inc.] **as of 12/2013**

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage range is 5-80 mg/day. In patients with CHD or at high risk of CHD, simvastatin tablets can be started simultaneously with diet. The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter.

…but you wouldn't know it from this label

Inconsistent Safety Labeling for Bioequivalent Medications

Duke J et al. *Pharmacoepimiol Drug Saf.* 2012 Oct 8

- Bioequivalent medications required by FDA to have identical safety information
- 2011 Supreme Court ruling (PLIVA vs Mensing) that warning labels of brand drug and generics must be same
- Analysis of labels on DailyMed showed:
  - 68% of multi-manufacturer drugs had discrepancies in safety information
  - 78% of generic manufacturers produced labels differing from brand
- “Achieving true harmonization across all versions of a drug is a tremendous challenge”
- Resultant confusion of patients receiving PMI based on different label for same drug

Consumers Do NOT Trust Information from Drug Manufacturers

Deloitte 2011 Survey of Health Care Consumers in the United States

The most trusted sources of information about treatment effectiveness and costs are doctors and hospitals;
manufacturers, employers, insurers, and government agencies are less trusted.

For information on the most effective and safe treatments for a certain health condition, consumers continue to trust academic medical centers (47%) and medical associations (45%) most, and **trust manufacturers (10%) least**

Consumer Group Weighs In

Consumer Reports' testimony

October 12, 2010:

Doris Peter, Consumer Reports Health Rating Center

- **Panelist at Brookings Institute's FDA- sponsored PMI Proceedings: *Ensuring Access to Effective Patient Medication Information***

"First I wanted to reiterate that we feel that to ensure objective PMI that patients can trust, that the content really has to be generated by a third party and not by the manufacturers, and that the PMI really has to include information about quantitative information about benefits and risks, not unlike what Doctors Schwartz and Woloshin have published in their drug facts box."

July 25, 2005

Appendix B

Division of Dockets Management
(HFA– 305)
Food and Drug Administration,
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Docket No. 2005D– 0169

To Whom It May Concern:

The American Society of Health-System Pharmacists (ASHP) is pleased to respond to the Food and Drug Administration's (FDA's) May 26, 2005, request for comments on its "Draft Guidance on Useful Written Consumer Medication Information (CMI)." ASHP is the 30,000-member national professional and scientific association that represents pharmacists who practice in hospitals, health maintenance organizations, long-term-care facilities, and other components of health systems.

ASHP believes that the mission of pharmacists is to help people make the best use of medicines. Assisting pharmacists in fulfilling this mission is ASHP's primary objective. Components of the Society's efforts in assisting pharmacists in this regard include position and guidance documents for best practices such as those on pharmacist-assisted patient education and counseling (first published in 1975), extensive publishing activities with a strong focus on professional and patient drug information, and educational programs. ASHP has long held that private sector publishers, including professional associations, must play an important role in the creation and dissemination of useful medication information.

As a private-sector publisher, ASHP represents the perspective of a scientific, nonprofit publisher of evidence-based drug information. We have published *AHFS Drug Information* (originally called the *American Hospital Formulary Service*) since 1959. The authority of *AHFS Drug Information* includes federal recognition through legislation and regulation as an "official" compendium for information on medically accepted uses of drugs. As a well-respected publisher of evidence-based drug information, ASHP also has applied this expertise for almost 30 years in publishing high-quality drug information for consumers.

With the release in 1978 of the first edition of the "Medication Teaching Manual: A Guide for Patient Counseling," ASHP became one of the first private-sector organizations to publish medication monographs intended for educating patients. This manual was developed by an advisory committee that ASHP formed cooperatively with the American Hospital Association (AHA) and US Department of Health, Education, and Welfare's

(now DHHS) Bureau of Health Education. ASHP is a past recipient of an award of excellence for consumer education materials from FDA and the National Coalition for Consumer Education (NCCE).

ASHP also was one of the first (perhaps the first) publishers to address the guidelines of DHHS's 1996 Action Plan for the Provision of Useful Prescription Medicine Information ("Keystone guidelines"). ASHP's quick response to the Action Plan resulted in a major revision and reformatting in 1997–1998 of its "Medication Teaching Manual" and associated consumer medication information (CMI) resources. Therefore, ASHP has been interpreting and implementing the Action Plan for nearly a decade.

A variety of products and services currently are created from ASHP's master database of CMI (MedMaster database), including its MedTeach software used by healthcare professionals to provide customized patient monographs, the National Library of Medicine's MedlinePlus consumer website, the Consumers Union's Consumer Reports Medical Guide website, and others. The MedMaster database also serves as the basis for ASHP's widely acclaimed safemedication.com consumer website. In fact, ASHP's monographs often have been used as models of useful CMI, including by Dr. Bonnie L. Svarstad[1] (Principal Investigator of FDA's 2001 Evaluation of Written Prescription Information Provided in Community Pharmacies).

In large part, it was ASHP's criticism of FDA's 2001 assessment by Dr. Svarstad that led to FDA's development of the proposed Guidance. Beginning with public comments in July 2002 and July 2003 and continuing with stakeholder meetings organized by the National Coalition of Patient Information and Education (NCPIE) that included FDA, ASHP has pointed out methodological problems with the study design, particularly the inclusion of a substantial proportion of specific criteria for determining usefulness that were not supportable from FDA-approved labeling and/or the Action Plan. In fact, only about 50–65% of the criteria used in the Svarstad study could be directly attributed to labeling and were explicitly required by the Action Plan as part of ASHP's analysis (attached). At the June 17, 2004 meeting that was convened by FDA with the assistance of NCPIE, both Dr. Svarstad and FDA acknowledged such methodological problems and agreed that a Guidance should be developed to ensure a fairer, more objective evaluation in 2007 that was in better keeping with the language and intent of the original Action Plan.

While the proposed Guidance is an initial step in this direction, we are not convinced that it offers substantial practical advice beyond the Action Plan itself. In fact, in several key ways, we find that the Guidance actually exceeds the language and intent of the Action Plan and would create new burdens for publishers that were not previously embodied in the Guidelines. As previously noted, ASHP monographs often have been used as models for useful CMI and have not been the focus of recent criticism by FDA or others. Despite

[1] Svarstad BL (University of Wisconsin-Madison School of Pharmacy, Madison, WI) : Personal communication and request for permission to distribute ASHP MedTeach reprints; 2004 Jun 10. Svarstad BL: Comments (personal observations); FDA/CMI Criteria Committee Meeting, Rockville, MD; 2004 Jun 17.

this, however, substantial resources likely would need to be devoted even by ASHP if the proposed FDA Guidance were to be adopted.

In particular, ASHP is concerned with FDA's language about the inclusion of *all* precautions to meet criterion 4 of useful CMI. This exceeds the language of the Action Plan, which is limited only to "applicable" precautions, with additional language stating that precautions "are encouraged in serious situations." Rather than attempting to define "applicable" and "serious," FDA took the disingenuous approach of simply defaulting to "all." ASHP sees no basis in the Action Plan for FDA's current interpretation stated in the proposed Guidance (line 263). If finalized, this new standard would greatly raise the bar and require considerable resources for ASHP to ensure compliance, something that likely could not be accomplished in time for FDA's next scheduled evaluation of written CMI. ASHP previously proposed in discussions with FDA that in the absence of precise definitions for such qualitative terms, that the Agency establish an acceptable minimum threshold for useful CMI. This would be consistent with the Action Plan's intent which states that "components of useful information are meant to set a floor" and will allow for "some flexibility in content."

Some specific points that we have identified are as follows:

Lines 20-22 – Variety of CMI

> The introduction to the guidance states that "CMI is written information about prescription drugs developed by organizations or individuals other than a drug's manufacturer that is intended for distribution to consumers at the time of drug dispensing." ASHP recommends that mail-order pharmacies be included in the mix of outpatient pharmacies that are included in the 2007 evaluation, since a growing number of such prescriptions are now dispensed from such settings.
>
> In addition, FDA should recognize that consumers may also access this type of information at times other than when receiving the prescription or refills such as via Internet sites or directly accessible computer programs. While not included in the scope of the Action Plan nor in the proposed Guidance from FDA, future independent research on the usefulness of such information by appropriate groups (e.g., AHRQ) is encouraged since consumers increasingly are accessing information independently via the Internet, and very few standards for health information in general currently are being applied. The National Library of Medicine and other organizations currently are working on standards for health information on the Internet, and FDA is encouraged to participate in these efforts as the preferred mechanism for assessing the nature of such information. ASHP is not recommending any additional formal action by FDA at this time, only that it participate as appropriate with such developing efforts.

Line 114 – Svasrstad study findings and conclusions

FDA should discontinue specific reference to the 50% average *usefulness* included in Dr. Svastad's original study. As described earlier, both the principal investigator (Dr. Svarstad) and FDA have acknowledged that the specific criteria employed in this study exceeded the requirements for determining usefulness as outlined in the Action Plan. The Action Plan clearly states and this proposed Guidance acknowledges that the minimum standard for establishing compliance is the FDA-approved labeling, yet many criteria included in the 2001 evaluation had no basis in labeling but instead merely represented the opinions of a clinical consultant, the investigators, and panelists. While such criteria may in some cases represent good information to share with consumers, they should not have been used to establish minimum criteria for determining usefulness in the 2001 evaluation of compliance of CMI with the Action Plan.

Line 127-129 – Minimum characteristics

FDA considers meeting the criteria and components of the Action Plan as the "minimum" appropriate characteristics of useful CMI. However, guidance is silent regarding efforts by publishers aimed at exceeding these minimum characteristics. For example, could exceeding the minimum standard count positively in the overall assessment of usefulness (e.g., an "exceeds" or some similar determination)?

Lines 144-147 -- Approved professional labeling/package insert (PI)

FDA states (also in lines 333-34) that the FDA-approved professional labeling must serve as the source document for the information in CMI. Otherwise, the information will not be considered "useful." There often is valuable patient or consumer information available from the manufacturer's website or by phone contact with the manufacturer. Additionally, important information from other references often is useful to describe a drug's mechanism of action and disease state information. The professional labeling may serve as a good baseline, but additional information will provide more comprehensive information for the layperson without a background in the disease state.

In some cases, more recent well-substantiated evidence actually may refute information that continues to appear in labeling. Inclusion of such information may be in the consumer's best interest in weighing the risks and benefits of therapy. For example, warnings about cardiac risk in the labeling of sulfonylurea antidiabetic agents are based in large part on old, controversial University Group Diabetes Program (UGDP) data, which more recent United Kingdom Prospective Diabetes (UKPD) data could not confirm. Therefore, FDA's Guidance should allow inclusion of information outside labeling that attempts to provide a balance and it should not negatively score against the evaluation of usefulness. Likewise, acknowledging the widely recognized (e.g., by the American Heart Association and American Diabetes Association) benefits of beta-blockers in diabetics despite only

precautionary information appearing in labeling represents another example of not negatively scoring CMI in the interest of providing balance to the consumer.

Footnote (8) for these lines and the original Action Plan state that customized CMI can contain patient-specific information that is not included in the FDA-approved labeling. However, new in FDA's Guidance is the recommendation that the source of such information be included in the actual CMI. It seems impractical to include such referencing in the information intended for use by consumers, and complying with such a change in interpretation of the Action Plan at this late date would place considerable burden on publishers that could jeopardize any possibility of meeting the 2007 goals. Maintaining documentation as archival records rather than actually including such documentation in CMI intended for consumer use has long been the publishing standard for CMI developed both by the public and private sectors.

FDA also states that the most recent labeling must be reflected in CMI. Not even FDA's own websites nor those of the manufacturers routinely reflect the most recent labeling. In addition, there always will be some lagtime between publication of revised labeling and incorporation in any derived document, including CMI. In addition, publishers like manufacturers and FDA typically prioritize revisions based on the importance and seriousness of any labeling changes. For example, certain proposed revisions in manufacturer labeling can be submitted to FDA as infrequently as annually. Therefore, some reasonable alternative time frame should be acknowledged as should the modifier "readily accessible" for the aforementioned reasons.

Lines 181-3 – Drug names

The proposed Guidance and the Action Plan require the phonetic spelling (pronunciation) of a drug's established name, which has long been interpreted to mean generic (nonproprietary) name. "The USP Dictionary of USAN and International Drug Names" provides pronunciation for official US titles. While FDA *recommends* in the proposed Guidance that pronunciations also be included for brand names, there is no official pronunciation for these names, and contacting each manufacturer to establish such pronunciations would be impractical. In addition, some drugs literally have hundreds of brand names, adding greatly to the impracticality of this recommendation. It was never the intent of the Action Plan that either all brand names or their pronunciations be included in CMI.

Currently, USAN and USP serve as the source of established names in the US. Footnote 9 states that the Action Plan was incorrect in its interpretation that not all drugs have established names. It has been ASHP's experience that the established name for some drugs is not always apparent. Therefore, what authoritative source should publishers reference when there is no apparent established "compendial" (i.e., USP or USAN) name? Also, can USP's pharmacy equivalent names (PENs) be considered established, convenient names when referring to certain common

combinations such as co-trimoxazole (assuming the individual components are also described)?

Line 185 – FDA-approved indications

It has long been ASHP's position that consumers should be provided information both on labeled as well as off-label uses. The compromise reached as part of the Action Plan development process was that off-label uses could be included in customizable CMI. Since most currently available CMI is derived electronically, customizability is increasingly likely. Therefore, it is important that FDA establish that a piece of CMI obtained in the 2007 evaluation that includes off-label information be verified as *not* being customizable before being rated negatively for including such content.

Likewise, it also is important that the FDA requirement for *all* labeled uses be limited *only* to CMI that is *not* customizable since one of the consumer benefits of customizability is to provide information that is individualized to a specific patient with a specific disease. For example, there is no reason to list breast cancer in customizable megestrol CMI for patients who are receiving the drug for cachexia, another labeled use. Likewise, in customizable CMI, there is no reason to inform women who are receiving estrogens that the drugs also are labeled for use in prostate cancer.

For customizable CMI, this same rationale should also apply to other irrelevant information (e.g., contraindications, warnings, precautions, cautions) that only applies to Uses for which the drug has *not* been prescribed in the specific patient.

Lines 189-92 – How to monitor for improvement

This section exceeds the definitions for useful information included in the Action Plan and therefore should be deleted. There is no mention under the Components of Useful Information in the Action Plan that information for monitoring the effectiveness of therapy should be included in CMI. While such information may be useful to provide to the patient, it likely would be impractical to do so in the context of CMI, even when it can be customized.

The goals of therapy vary depending on the patient and specific disease being treated. These goals usually are established by the healthcare provider and communicated to the patient and often are not even known to the dispenser of CMI.

Even if it were practical to include such information, and ASHP believes that it is not, to add such information at this late date to existing CMI would represent a substantial burden to CMI publishers and likely could not be accomplished in time for the 2007 evaluation.

Line 199 – Contraindications

The FDA guidance states that "all" contraindications must be included in the CMI. This may be appropriate, but some contraindications only apply as signals for the prescriber. Patients are not always involved in prescribing or assessing if they have a certain disease state, so they only appear as, “tell your doctor if you have….”

In keeping with the Action Plan, the proposed Guidance should explicitly acknowledge that a contraindication need not be listed under a specific “Contraindications” heading nor are absolute terms such as “contraindicated” or “do not use” necessary in describing a contraindication in CMI. Instead, “providing directions regarding what to do if a contraindication applies” or a general statement such as “tell your health care professional before taking this medicine if any of these apply to you” should be more explicitly described in the Guidance as acceptable language defined by the Action Plan.

In addition, because the Action Plan does not explicitly state that *all* contraindications must be included in useful CMI, FDA should not expect that such information would be included in time for the 2007 evaluation at this late date. Instead, some future date (e.g., to coincide with Healthy People 2010) should be set for inclusion of *all* patient-relevant contraindications if it subsequently is determined by the consensus of experts that inclusion of *“all”* is an appropriate future course.

Line 219 – CMI as a stand-alone document

The statement that CMI must be a stand-alone document requires clarification. It is hoped that FDA did not intend this to include information typically found on the prescription vial (e.g., the prescribers directions for use, auxilliary labels)? This would seem impractical and unnecessarily duplicative and therefore should not be required. In addition, it is not known whether software vendors/pharmacies can satisfy this requirement, as it is impossible to know what dosage form, strength, or frequency of administration the doctor will prescribe. This information would have to be added at the point of dispensing.

This wording is problematic for other reasons since both current and potentially future FDA developments may make stand-alone CMI that addresses everything in one place impractical. For example, FDA’s own handling of the antidepressants Medication Guide was that it be a separate document and not incorporated even verbatim into existing CMI. That view is changing, but it certainly was not the original solution. This language also does not acknowledge current and future technologic developments where embedded hypertext links are far better solutions than stand-alone documents since they are more likely to ensure currency of the associated information and often represent more efficient and effective means of communicating such associated but distinct information.

Lines 224-7 – Detailed instructions on how to administer

This information contradicts what is described in lines 219-22, where it states that CMI should be considered a stand-alone document. Therefore, the language of lines 219-22 should be modified to acknowledge this exception.

Line 240 – Missed dose

The guidance states that information about what patients can do if they miss a scheduled dose must be in the CMI if it is in the PI. If missed dose information is not in the PI, does that mean it cannot be included in the CMI? We suspect that many CMI publishers include such information in at least general terms even when it is not present in professional labeling. We consider this information to be important to patients. Additionally, missed dose information is not in most professional labeling; it is often only in patient information or web-based FAQ information.

Line 261 -- Boxed warnings

Why does the proposed Guidance describe the "Black Box Warnings" with other Warnings/Precautions? While the proposed Guidance does indicate that a relevant boxed warning must be prominently displayed, the Action Plan lists boxed warnings as the second item in its “components of information” section, right after the drug name. The first four items were listed discretely in the Action Plan and were identified to be always written in that order.

Line 263 – Precautions

The proposed Guidance states that the CMI must “include *all* information stated in the PI regarding what precautions the patient should take while using the drug.” As described in the earlier introductory discussion of ASHP comments, the requirement in the proposed Guidance is too stringent relative to what is described in the Action Plan. This incorrect interpretation by FDA of the intent of the Action Plan must be corrected.

Lines 276-278 -- Behavioral instructions not in professional labeling

Why were behavioral instructions not specified in the professional labeling identified by FDA as representing examples of circumstances that sometimes should be specified in CMI? This appears to be an attempt by FDA to establish as a standard for inclusion of additional information beyond labeling that is not part of the intent of the minimum requirement for usefulness included in the Action Plan. However, the proposed Guidance seems to be silent on the possible inclusion of other risk information in a CMI that may be well documented in the literature but that does not yet appear in labeling.

Lines 284-7 – Risks to the fetus or infant

It is understandable that the risks for pregnancy, labor, or breast feeding be communicated to the patient. It is not clear, however, why the statement "It is not known if the medicine will affect your baby" is suggested. There may be further information available to the clinician that could be used to evaluate continued use of the drug in the patient. It is better to say "if you become pregnant while taking this medication, contact your doctor" rather than have the patient arbitrarily discontinue the medication because she is informed that "there is no information available."

Lines 297-299 – Adverse drug reactions

Although FDA has attempted to further define which adverse effects should be included in CMI, they have failed to explicitly define the qualitative term "common" in quantitative terms. At the June 17, 2004 FDA/CMI Criteria Meeting at FDA, a representative from the agency stated that such qualitative terms are in fact defined quantitatively. ASHP is not aware of such definitions and FDA never followed through by advising attendees of these definitions. Without defining this term, application of this criterion in measuring usefulness of CMI will remain subjective. For example, the 5–9 most frequently occurring adverse reactions are not necessarily "common."

Line 349 – Level of understanding

The proposed Guidance states that the CMI "should be written in wording that is understandable" and suggests using a validated readability instrument. It is notable that the 6th to 8th grade levels are only *suggested reading levels*, which is consistent with the Action Plan. However, this adds little to what will be considered acceptable in meeting the criteria for evaluating usefulness in the 2007 evaluation. FDA should include specific examples of validated readability instruments that it considers acceptable, and be prepared to accept for the 2007 assessment any reading level that can be interpreted as meeting the Action Plan guidance, where 6th through 8th are merely listed as preferable not required.

Lines 391-404 – Suggested order of CMI components

FDA should defer to the Action Plan for the order of CMI components since the proposed Guidance, which only offers a suggestion, adds little to interpretation of the Plan. In addition, the Action Plan was worded as it currently is to allow intended flexibility, while still requiring that certain elements always be included in a given order but not defined headings.

For more than 60 years, ASHP has helped pharmacists and pharmacy technicians who practice in hospitals and health systems improve medication use and enhance patient safety, and we appreciate the opportunity to present comments on this important patient care issue. We believe that the FDA, as it finalizes its guidance for useful CMI, should work with organizations such as ours in order to create a more effective document than the one issued for comment. Feel free to contact me if you have any questions regarding our comments. I can be reached by telephone at 301-664-8702, or by e-mail at gstein@ashp.org.

Sincerely,

Gary C. Stein
Director of Federal Regulatory Affairs

Analysis of Criteria from the December 21, 2001 Final Report to the US DHHS and FDA: Evaluation of Written Prescription Information Provided in Community Pharmacies, 2001. Svastad BL (Principal Investigator).

Table 5. Percent of leaflets with partial or full adherence to sub-criteria: ATENOLOL (n= 344)

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicitly required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Keystone Criteria &/or Labeling	Comments
1. Drug names and indications for use						
1.1 generic name: atenolol	1.2	95.9	X			
1.2 phonetic spelling of generic name	0	49.1	X			
1.3 brand names: Tenormin	0.6	4.4	X			Reason for low adherence here is likely the result of suppression of information by the end-user (e.g., pharmacy suppressed brand name because patient received a generic equivalent). See atorvastatin by comparison where there is no generic equivalent and the criterion adherence is 99%.
1.4 drug class :beta-blocker or beta-adrenergic blocking agent	3.8	79.1			X	Pharmacologic class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI.
1.5 treat hypertension (or high blood pressure)	0.6	89.2	X			
1.6 treat angina (or chest pain)	0.6	86	X			
1.7 treat definite or suspected myocardial infarction (or heart attack)	0.9	50.9	X			
2. Contraindications and what to do before using drug						**Note that half of the actual Contraindications from the PI are not included in the criteria. This shows the difficulty in establishing precise minimum-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.**
Tell PR or PH if you have:						

2.1 certain heart problems (or: heart failure, very slow heartbeat)	4.9	45.6	X			N.B.: "Overt cardiac failure" is a contraindication; therefore, criterion for this *specific* contraindication (i.e., do not take rather than just tell PR or PH if you have) is missing. The Keystone guidelines do provide latitude on whether contraindications should be treated as true (absolute) contraindications (i.e., do not take) or as strongly worded precautions (i.e., contact PR or PH). Therefore, any analysis of CMIs should recognize this latitude in measuring criteria adherence. Cardiogenic shock and complete heart block also are missing; whether these would be clinically relevant to advise a patient about reflects the subjectivity inherent in applying the Keystone guidelines. In atorvastatin, the approach was different. There, a distinction between "do not take" and "tell PR or PH" was made; this inconsistency in approach among the studied drugs compromises the objective evaluation of CMIs.
2.2 asthma or emphysema	2.9	32	X			
2.3 diabetes	3.5	32	X			N.B.: There is evidence of cardiovascular benefit of beta-blockers in diabetics; both ADA and AHA recognize this in various guidelines. Just an example of the complexity in balancing risk-benefit statements.
2.4 overactive thyroid	2.9	31.7	X			
2.5 poor circulation	2.9	0.3	X			
Tell PR or PH if you are:						
2.6 pregnant or may become pregnant; can cause harm to baby	15.4	75.6	X			
2.7 nursing or breast-feeding	1.2	79.9	X			

3. Specific directions about how to use, monitor, and get most benefit						
3.1 It is important to take this medicine regularly to get the most benefit	1.7	0.9		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take."
3.2 To help you remember, take it the same time(s) each day	9	28.5			X	Ditto. PI does not specify; take as prescribed by HC provider.
3.3 If you miss a dose, take it as soon as you remember	2.6	83.4	X			
3.4 Skip missed dose if next scheduled dose is less than 8 hours away	35.5	50.3			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., so that a specific time could be included); not evidence based.
3.5 Do not take two doses at same time (or: do not double up)	0	84.6	X			
3.6 May take with or without food	1.2	50.9			X	PI does not specify
3.7 Store at room temperature, away from excess heat and moisture	58.4	27.3		X		PI does not mention moisture but does mention protecting from light. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
4. Specific precautions and how to avoid harm while using it						**N.B.: PI contains additional precautionary information (e.g., risk of heart failure, concomitant use with prostaglandin synthase inhibitors), which was not addressed by criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.**
4.1 Tell PR or PH if you take any other medications, especially:	0.9	86.2	X			
4.2 calcium channel blockers such as verapamil and diltiazem	6.4	19.5	X			

4.3 other blood pressure medicines such as clonidine	20.3	6.7		X		Only clonidine, Ca-channel blockers (which are covered in 4.2), and catecholamine-depleting agents (e.g., reserpine) are listed, but precaution should be specific like PI not just "other blood pressure medicines." These drugs have uses other than hypertension and the interactions described are not necessarily limited to hypertensive patients.
4.4 over-the-counter cold products or decongestants	0.6	79.7			X	PI does not specify.
4.5 Do not stop suddenly; gradual dose reduction may be needed	60.8	35.8	X			
4.6 May cause serious reaction to allergy shots; tell PR before shots	0	0		X	?	PI does not specify per se. PI does state that "patients with a history of *anaphylactic reaction* (emphasis added) to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic," but this does not precisely support the criterion.
4.7 May worsen allergic reaction to foods, medicines, or stings; tell PR as soon as possible so it can be treated	0	0.3		*X*	?	Ditto. Not precisely supported by labeling. Criteria 4.6 and 4.7 are based on extrapolation of the same statement in PI. Separation into 2 criteria exacerbates the consequence of criteria non-adherence.
4.8 Before surgery, tell PR or dentist you are taking this medicine	0.6	84.9	X			
4.9 May affect blood sugar or cover up signs of low blood sugar	0.3	49.4	X			

Table 5. Percent of leaflets with partial or full adherence to sub-criteria: ATENOLOL (n= 344)						
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicitly required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Keystone Criteria &/or Labeling**	**Comments**
5. Symptoms of serious or frequent adverse reactions and what to do						Note that what is considered "serious" or "occur frequently" is not defined by Keystone. Likewise, what is considered "reasonably associated with the use of the drug" is not defined by Keystone. For purposes of this analysis, if it was in PI, it generally was counted as required even though Keystone language permits great latitude of interpretation. In cases where it clearly was not a frequent or serious reaction (e.g., atenolol criterion 5.8), it was noted as optional/open to interpretation. The bottom line is that greater adherence would have occurred if the latitude intended by Keystone had been applied. Some expectations regarding causality, seriousness, and frequency need to be stated to objectify the measure of adverse effects.
Tell PR or PH as soon as possible if any of these occur:						
5.1 trouble breathing	1.7	73.3	X			
5.2 cold hands or feet	11	17.2	X			

5.3 slow heartbeat	6.4	20.6		X		N.B.: Fainting is not specified in PI. Although fainting could be a consequence of postural hypotension, why was it chosen when other possible consequences that actually are specified in PI (e.g., dizziness, vertigo, light-headedness)? Or was fainting listed as a sign of severe bradycardia? In either case, it is not from PI.
5.4 swelling of legs or ankles/feet	2	31.7		X		Were these added as examples of signs of CHF? PI does not specify.
Tell PR or PH if any of these do not go away or bother you:						
5.5 feeling dizzy	12.2	70.1	X			
5.6 feeling tired	21.5	62.2	X			
5.7 feeling depressed	3.5	22.1	X			
5.8 trouble having sex	0	0.3			X	Impotence is mentioned at end of adverse reactions discussion but it would be male-specific advice and was NOT reported as "frequent or serious." Therefore, it would EXCEED the Keystone guidelines. In addition, VA Cooperative Trial and other studies have failed to show a relationship between beta-blocker use and erectile dysfunction (see NHLBI's JNC 7 report).
5.9 trouble sleeping	0.6	0.9			X	PI does not specify.
6. General information and encouragement to ask questions						
6.1 Keep all medicines away from children	0.3	56.4			X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefaclor CMI.
6.2 Do not give this medicine to others	0.6	47.4	X			
6.3 Leaflet states that it does not include all uses, precautions, interactions, adverse reactions, or side effects	9.3	54.7	X			
6.4 Name of publisher	0.3	56.4	X			
6.5 Date of publication or most recent revision	0.6	47.4	X			

6.6 Ask PR or PH if any questions or concerns	9.3	54.7	X			Why was adherence so low? FDB, Medi-span, ASHP, and others include this a boiler-plate language. Likely that end-user (e.g., pharmacy) suppressed.
6.7 You may ask PH for longer leaflet written for professionals	0.6	0.6		X		Keystone criteria do not require mentioning that a "longer leaflet written for professionals" may be requested. Instead, Keystone merely states that consumers should "be encouraged to request additional information" (PI is given as an example). The emphasis in the Keystone guidelines is that consumers should be advised that additional information is available and that the health care professional can provide such information.
Criterion 7: Information is scientifically accurate, unbiased, up-to-date	**% partial**	**% full**	**Explicitly required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
7.1 information is neutral in content and tone	0.6	97.4	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses)	16	68.3		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities)	4.4	89.2	X			
7.4 no inaccurate or outdated claims about benefits of product	2.6	96.5	X			
7.5 no inaccurate or outdated claims about risks of product	4.9	93.3	X			
7.6 no other inaccurate or outdated information was found by this rater	1.5	83.1	X			
Criterion 8: Information is readily comprehensible and legible	**% partial**	**% full**	**Explicitly required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**

						Note that most of these criteria are open to interpretation, even those noted as explicit in this table, since Keystone states that "written information that is *generally* emphasis added) consistent with the language and format guidelines set out here and in Appendix G will be presumed to be understandable and readily comprehensible, and will satisfy the criterion for useful information absent evidence to the contrary." In addition, Keystone states that "legibility and readability cannot be reduced to a precise formula."
8.1 black box warning information printed in bold-face type or box	15.7	19		X		Keystone merely states that BBW info from PI be "prominently displayed," mentioning bold-face type and a box as "examples" of such not as required formats.
8.2 minimal use of italics or ornate typefaces that are hard to read	0.9	93.3	X			
8.3 upper and lower case lettering	0.6	96.2	X			
8.4 headings placed on separate lines (not on same line as text)	4.9	19.2		X	?	Not specified in Keystone guidelines but likely to increase readability. Therefore, adherence should be considered as exceeding criterion NOT a minimum threshold for meeting it.
8.5 bullets used to enhance readability	2	2.6		X	?	Ditto
8.6 information is well organized and easy to find	9.9	61.6	X			
*The following will be assessed by office staff:						

8.7 adequate space between lines (2.2 mm=partial; >2.2 mm=full) . . . . . *	10.8	2		X		Does not specify how much space between lines; 12-pt spaces "generally recommended" when 10-pt type is used. N.B.: With browser-based HTML applications, there is no control over such spacing.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . *	49.1	3.5		X		Keystone specifies 10 pt in its Format Guidelines (this is very explicitly stated); 12 pt is *generally* (emphasis added) recommended as the minimum size for older people. Therefore, 10-pt should be considered FULL adherence to the criterion and 12-pt as exceeding the minimum threshold for this criterion. N.B.: With browser-based HTML applications, the end-user controls the font size.
8.9 good ink-paper contrast . . . . . *	26.7	68.3	X			What was defined as full versus partial adherence? Keystone simply states that "black, dark blue, or brown ink on pale yellow or white paper provides the best contrast." Also, that uncoated paper should be used.

8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . *	2	14		X		Note that even this criterion is open to interpretation since Keystone states "*preferably*" at the 6-8th grade level. Further, Keystone states that the "information could also be available at higher reading levels." Unclear why 8th grade was chosen as full adherence; nothing in Keystone to support this interpretation. In the strictest sense, anything that is 6th grade or higher would FULLY meet the Keystone criteria as "preferable" not "minimal" standard. Finally, the presence of drug names and certain unavoidable medical condition descriptions (e.g., for clarity) in CMIs can skew these measures.

Table 6. Percent of leaflets with partial or full adherence to sub-criteria: GLYBURIDE (n= 341)						
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
1. Drug names and indications for use						
1.1 generic name: glyburide	17	79.5	X			
1.2 phonetic spelling of generic name	0	46.3	X			
1.3 common brand names: DiaBeta, Micronase, Glynase	0.9	3.8		X		Although Keystone specifies inclusion of trade names, it does not specify how many to include. Therefore, determinant for full compliance with this criterion is not defined by Keystone, i.e., open to interpretation. Reason for low adherence here is likely the result of suppression of information by the end-user (e.g., pharmacy suppressed because patient received a generic equivalent). See atorvastatin by comparison where there is no generic equivalent and the criterion adherence is 99%.
1.4 antidiabetic (or used to treat diabetes)	0	84.2	X			
1.5 sulfonylurea	0	47.2			X	Pharmacologic/chemical class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI other than in context of cross-sensitivity. Also note that additional weight has been added by having 2 separate criteria (1.4 & 1.5) for this same concept. In other drugs, there is a single criterion for this. Sulfonylurea and antidiabetic could have been combined.

1.6 used to lower blood sugar	3.2	27	X	?		Why such low adherence? Keystone does not require describing use in pharmacologic terms. While stating that it is used to lower blood sugar may be more meaningful to some patients, it actually overly simplifies the therapeutic rationale for using these drugs, i.e., the secondary outcomes are far more important than lowering blood sugar per se. Simply stating that it is used to teat diabetes (see 1.4) should fully meet the minimum threshold ("floor") for adherence to a statement about the drug's use.
1.7 used in patients whose diabetes cannot be controlled by diet	0.6	0.3		X		How detailed does indication have to be? I.e., is this overly specific? (N.B.: stating that it is used in addition [i.e., adjunctively] to diet would be more precise relative to the PI.)
1.8 used for non-insulin dependent (or Type 2) diabetes	0.6	1.5		X		Is this overly specific? E.g., will patient understand what "non-insulin dependent or type 2 diabetes" is? Can it be confusing since some type 2 diabetics will require insulin occasionally for correction of symptomatic or persistent hyperglycemia.
						Note that criteria 1.4 & 1.6-1.8 are all included in a SINGLE summary/overview statement of Indication and Usage in PI. Creating separate criteria for each adds to weight of nonadherence here.

2. Contraindications and what to do if applicable						**Note that Contraindication about ketoacidosis was omitted in criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.**
Tell PR or PH if you are:						
2.1 allergic to glyburide or other sulfonylureas	24.6	29.3		X		PI does not mention cross-sensitivity w/ other sulfonylureas. Why is criteria about glyburide allergy stated as telling PR or PH rather than as do not take? Another example of Keystone latitude.
2.2 pregnant or may become pregnant	0.6	81.8	X			
2.3 nursing or breast-feeding	0.3	79.2	X			
Other:						
2.4 use of other sulfonylurea drugs has been associated with serious heart problems. This risk may apply to use of glyburide	0.6	0.3		X		This warning in PI in based on old, controversial UGDP data; more recent UKPD could not confirm and there is broad-based controversy.
3. Specific directions about how to use, monitor, and get most benefit						
3.1 It is important to take this medicine regularly to get the most benefit	40.2	37.2		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take." Could be dangerous advice, i.e., patient would not take dose if they were hypoglycemic. Take as directed is more judicious advice.
3.2 To help you remember, take it at the same time(s) each day	30.2	42.8			X	Ditto. PI does not specify; take as prescribed by HC provider should be sufficient.

3.3 May take with or without food	30.5	54.5			X	PI recommends taking with food; therefore, criterion is incorrect.
3.4 If you miss a dose, take it as soon as possible	0.9	82.4	X			
3.5 Skip missed dose if next scheduled dose is less than 8 hours away	80.6	2.1			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., so that a specific time could be included); not evidence based.
3.6 Do not double up or take two doses at the same time	1.8	81.2	X			
3.7 Regular testing of blood glucose is important	1.2	49.9	X			
3.8 Important to follow proper diet and exercise program	28.7	54.3	X			
3.9 Store at room temperature, away from excess heat and moisture	40.5	41.3		X		PI does not mention moisture. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
4. Specific precautions and how to avoid harm while using it						**Note that PI contains additional precautionary information (e.g., risk of stress on glycemic control, possibility of primary or secondary treatment failure, advising patients of risk-benefits for glyburide versus other therapies, additional drug interactions), which were not addressed by criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.**
4.1 Tell PR or PH before taking any other medications, especially:	10.6	73.6	X			

4.2 aspirin products	0.3	26.1		X		PI does not specify ASA. Instead, it says salicylates and NSAIDs. Therefore, a more precise criterion would be to list "aspirin" as an example of one of these classes. Also, why was ONLY ASA specified, particularly since the classes are not mentioned?
4.3 anticoagulants (or blood thinners)	0.3	26.4	X	?		N.B.: Only applies to oral anticoagulants; modifier is missing in criterion.
4.4 azole antifungals (eg, fluconazole)	7	0.3			X	Only oral miconazole listed in PI.
4.5 beta blockers	0	26.7	X			
4.6 diuretics (water pills)	0	0.6	X			Diuretics and corticosteroids are only 2 of several classes of drugs specified in PI as causing hyperglycemia.
4.7 corticosteroids	0	0	X			Ditto.
4.8 MAO inhibitors	0.3	50.1	X			
4.9 May increase sensitivity to sun; reduce exposure to sun	5.3	84.2		X		PI merely states under Adverse Reactions that photosensitivity has been reported with sulfonylureas; there is no associated precautionary information (e.g., no specific precaution about avoiding sun exposure). Although this is good advice, it exceeds professional labeling, which should represent the threshold criterion for adherence.

Table 6. Percent of leaflets with partial or full adherence to sub-criteria: GLYBURIDE (n= 341)						
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
5. Symptoms of serious or frequent adverse reactions and what to do						
5.1 May cause low blood sugar or hypoglycemia	1.8	81.5	X			
5.2 To help prevent, do not miss meals or drink alcohol	68	23.5	X	?		Note that PI mentions other conditions (e.g., severe [whatever that means?] or prolonged exercise, concomitant use of other glucose-lowering drugs) that could exacerbate. How would CMI adherence have been measured if it included these 2 conditions rather than those chosen by the study?
5.3 Some symptoms of low blood sugar: fast heartbeat, sweating,						
tremors, headache, confusion, nervousness [list 3]	2.3	78.9		X		On what basis was listing 3 determined to meet full adherence to criterion? In addition, while PI states that patients should be advised of both the symptoms and treatment of hypoglycemia, none of these specific symptoms is given
5.4 Use quick-acting sugar to treat low blood sugar	10.6	33.4		X		PI states "oral glucose" not "quick-acting sugar." Would consumer even know what constitutes "quick-acting sugar"?
Tell PR or PH as soon as possible if any of the following occurs:						

5.5 allergic reaction: fever, chills, rash, trouble breathing [list 2]	30.5	32		X		Skin reactions are most common allergic reactions, occurring in 1.5% of patients. No incidence specified for other mentioned allergic reactions (i.e., angioedema, arthralgia, myalgia, vasculitis). Therefore, on what basis was listing 2 determined to meet full adherence to criterion and why were symptoms not specified in PI (fever, chills) included for minimum threshold ("floor") for full adherence? Instead, their mention should be deemed as exceeding the threshold. Finally, certain allergic reactions would require greater urgency than implied by this criterion.
5.6 dark urine, unusual bleeding/bruising, yellowing of eyes [list 2]	13.2	34.3		X		PI does not specify these symptoms; it only states that cholestatic jaundice and hepatitis may occur. It is silent on whether patient should be advised to monitor for possible development. Therefore, open to interpretation as to which symptoms should be mentioned.
Tell PR or PH if any of these do not go away or bother you:						
5.7 stomach discomfort, pain, fullness [list 1]	1.2	84.5	X			
5.8 diarrhea	11.7	32.8			X	
5.9 more frequent urination	16.4	0.3			X	
6. General information and encouragement to ask questions						
6.1 Keep all medicines away from children	0	34.6			X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefaclor CMI.
6.2 Do not give this medicine to others	0	18.8	X			
6.3 Leaflet states that it does not include all uses, precautions,						
interactions, adverse reactions, or side effects	1.8	42.8	X			
6.4 Name of publisher	0.6	50.7	X			
6.5 Date of publication or most recent revision	1.2	39.9	X			
6.6 Ask PR or PH if any questions or concerns	16.4	55.1	X			

6.7 You may ask PH for longer leaflet written for professionals	0.3	0		X		See atenolol 6.7
Criterion 7: Information is scientifically accurate, unbiased, up-to-date	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Keystone Criteria &/or Labeling**	**Comments**
7.1 information is neutral in content and tone	1.2	97.7	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses)	0.3	98.5		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities)	0.6	97.7	X			
7.4 no inaccurate or outdated claims about benefits of product	0.3	98.5	X			
7.5 no inaccurate or outdated claims about risks of product	1.5	91.5	X			
7.6 no other inaccurate or outdated information was found by this rater	7.9	89.1	X			
Criterion 8: Information is readily comprehensible and legible	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Keystone Criteria &/or Labeling**	**Comments**
						See introductory comment in Atenolol 8.
8.1 black box warning information printed in bold-face type or box	N/A	N/A				
8.2 minimal use of italics or ornate typefaces that are hard to read	10.6	85.3	X			See Atenolol.
8.3 upper and lower case lettering	16.7	76.8	X			See Atenolol.
8.4 headings placed on separate lines (not on same line as text)	1.5	18.8		X	?	See Atenolol.
8.5 bullets used to enhance readability	5.3	1.5		X	?	See Atenolol.
8.6 information is well organized and easy to find	38.1	51.6	X			See Atenolol.
The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	10.3	2.1		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . *	51.6	2.6		X		See Atenolol.
8.9 good ink-paper contrast . . . . . *	25.8	69.5	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . *	50.1	13.1		X		See Atenolol.
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
1. Drug names and indications for use						
1.1 generic name:atorvastatin	0	84.5	X			
1.2 phonetic spelling of generic name	0	54.2	X			
1.3 brand name: Lipitor	0	99.4	X			
1.4 drug class: HMG - CoA reductase inhibitors	0	50.1			X	Pharmacologic class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI. In addition, this would be meaningless to most consumers; even health professionals would have difficulty with this class descriptor versus "statin."

1.5 used to lower cholesterol levels	1.2	87.2	X			N.B.: PI describes 5 other indications, but these all involve cholesterol lowering.
1.6 used in persons whose cholesterol levels cannot be controlled with						
proper diet, exercise, and weight loss if overweight.	1.2	0.9		X		
						How detailed does indication have to be? I.e., is this overly specific? Also, PI "indications and Usage" section only specifies adjunct to diet not exercise & weight loss. (N.B.: stating that it is used in addition [i.e., adjunctively] to diet would be more precise relative to the PI.) N.B.: Exercise and weight reduction are mentioned under the PI "Precautions" section but not in the context of "Indications and Usage," which is the PI section serving as the basis for criterion 1.6.
2. Contraindications and what to do if applicable.						**Note that the Contraindication for active liver disease or unexplained persistent elevations of serum transaminases is missing.**
Do not take this medicine if you are:						
2.1 allergic to atorvastatin	12	3.5	X			N.B.: Uncharacteristically, PI not specify drug, only "any component of this medication."
2.2 pregnant or may become pregnant; can cause harm to baby	7	88.9	X			
2.3 nursing or breast-feeding	2.9	84.5	X			
Tell PR or PH if you:						
2.4 drink large amounts of alcohol	22.2	7.6	X			
2.5 have had liver disease	7.3	47.2	X			N.B.: Based on current evidence, Nix's NICE has questioned whether stations are hepatotoxic at all.
2.6 have had kidney disease	0.3	0			X	PI does not specify. Also, no need for dosage adjustment.

2.7 have had recent major surgery	14.6	37.3	X			N.B.: Why were major surgery and uncontrolled seizures chosen? PI also specifies severe acute infection; hypotension; trauma; and severe metabolic, endocrine, and electrolyte disorders). How would adherence to this criterion have been judged if any of these were specified in CMI instead? Seems like an instance where "list 2" or some other number would have been appropriate.
2.8 have uncontrolled seizures	0.3	30.6	X			Ditto.
3. Specific directions about how to use, monitor, and get most benefit						
3.1 It is important to take this medicine regularly to get the most benefit	8.7	0.3		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take."
3.2 To help you remember, take it at the same time(s) each day	2	54.5			X	Ditto. PI does not specify; take as prescribed by HC provider. Also, this could confuse patient if they were advised that they could take the drug at "any time of the day," which is what the PI states under Dosage & Administration.
3.3 May take with or without food	0	85.1	X			
3.4 If you miss a dose, take it as soon as possible	0	86	X			
3.5 Skip missed dose if next scheduled dose is less than 8 hours away	47.2	39.1			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., so that a specific time could be included); not evidence based.
3.6 Do not take two doses at the same time (or: double up)	0.3	84.8	X			
3.7 Cholesterol levels should be monitored on a regular basis	21	6.7	X			
3.8 Important to continue proper diet and exercise	40.5	34.7		X		PI only specifies diet not exercise.

3.9 Store at room temperature, away from excess heat and moisture	48.4	34.4		X		PI does not mention moisture. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
4. Specific precautions and how to avoid harm while using it						
4.1 Tell PR or PH before taking any other medications, especially:	0.9	84.8	X			
4.2 immunosuppressants, especially cyclosporine (Sandimmune)	0.9	23	X	?		Note that PI's handling of this is confusing. Cyclosporine is never given as an example of immunosuppressive drug; instead, both are described distinctly. Therefore, "especially cyclosporine" in the criterion is interpretive not explicit.
4.3 gemfibrozil (Lopid)	0.6	50.1	X			N.B.: PI does not specify gemfibrozil; instead, fibric acid derivatives as a class are specified.
4.4 erythromycin	0	26.5	X			
4.5 niacin (nicotinic acid)	0.3	26.2	X	?		N.B.: Only therapeutic doses not supplemental doses are specified in PI; could confuse patients since niacin is widely present in supplement form in many foods, vitamin supplements, etc.
4.6 azole antifungals (e.g. fluconazole, ketoconazole, or itraconazole)	12.8	37.9	X	?		How was adherence measured? PI only states class not specific antifungals within the class.
4.7 Do not eat grapefruit or drink grapefruit juice while using this drug	34.1	49.3			X	PI does not specify. Therefore, inclusion should be considered as exceeding threshold ("floor") for full criterion adherence.
4.8 Should have liver function tests before and after starting this						

medicine and on regular basis to check for harmful effects.	25.4	0.3	X	?		How was adherence to "on a regular basis" determined? PI states "periodically (e.g., semiannually)," which sounds less frequent than regularly and also less proscriptive.
Table 7. Percent of leaflets with partial or full adherence to sub-criteria: ATORVASTATIN (n= 343)						
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
5. Symptoms of serious or frequent adverse reactions and what to do						
Tell PR or PH as soon as possible if any of these occur:						
5.1 muscle pains or weakness, especially with fever	20.7	74.6	X			PI also mentions muscle tenderness. How would adherence to criterion have been measured if tenderness were listed instead of one of the other symptoms noted here?
5.2 unusual tiredness	2.6	23.3		X		Malaise, like fever, is described in PI in the context of muscle symptoms not as a symptom alone. I.e., it, like fever, should be a modifier in 5.1.
5.3 dark urine or yellowing of skin or eyes	64.1	20.1		?	X	According to PI, jaundice was reported in only one patient in clinical trials. Principal hepatic effect is on LFTs. NIH's NCEP does NOT caution against cholestatic effects, only effects on transaminases (I.e., LFTs).
5.4 skin rash	6.7	70.8	X			Rare reports of skin hypersensitivity.
Tell PR or PH if these do not go away or bother you:						N.B.: The only effects described in PI as "thought to be related to atorvastatin" were constipation, flatulence, dyspepsia, and abdominal pain. Criteria that follow are inconsistent with this.
5.5 constipation	0	33.2	X			

5.6 diarrhea	2.6	34.4		X		Causality not specified and no "p" value relative to placebo is listed.
5.7 headache	0.6	3.8			X	Causality not specified and no "p" value relative to placebo is listed. In fact, except at 20-mg dose, headache occurred more commonly with placebo.
5.8 nausea or heartburn	1.7	9.6		X		Causality not specified for nausea. Unclear why PI says that dyspepsia is thought to be related to atorvastatin when this effect occurred more frequently with placebo relative to all drug doses reported.
6. General information and encouragement to ask questions						
6.1 Keep all medicines away from children	1.5	33.8			X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefaclor CMI.
6.2 Do not give this medicine to others	0	17.5	X			
6.3 Leaflet states that it does not include all uses, precautions,						
interactions, adverse reactions, or side effects	9	42	X			
6.4 Name of publisher	0	54.2	X			
6.5 Date of publication or most recent revision	0.6	44.3	X			
6.6 Ask PR or PH if any questions or concerns	6.7	50.4	X			
6.7 You may ask PH for longer leaflet written for professionals	2.3	1.2		X		See Atenolol 6.7.
Criterion 7: Information is scientifically accurate, unbiased, up-to-date	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
7.1 information is neutral in content and tone	3.5	96.5	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses)	2.6	97.1		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or						
distributor (may compare chemical entities)	2.3	97.7	X			
7.4 no inaccurate or outdated claims about benefits of product	2	98	X			
7.5 no inaccurate or outdated claims about risks of product	2.9	97.1	X			
7.6 no other inaccurate or outdated information was found by this rate. .	1.5	97.4	X			
Criterion 8: Information is readily comprehensible and legible	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**

						See introductory comment in Atenolol 8.
8.1 black box warning information printed in bold-face type or box	N/A	N/A				
8.2 minimal use of italics or ornate typefaces that are hard to read	1.2	98.3	X			See Atenolol.
8.3 upper and lower case lettering	0.6	96.2	X			See Atenolol.
8.4 headings placed on separate lines (not on same line as text)	1.2	16.6		X	?	See Atenolol.
8.5 bullets used to enhance readability	2	2.6		X	?	See Atenolol.
8.6 information is well organized and easy to find	24.2	57.1	X			See Atenolol.
The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	13.1	3.2		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . . *	55.4	3.2		X		See Atenolol.
8.9 good ink-paper contrast . . . . . .*	23.3	71.7	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . . *	2.6	14.9		X		See Atenolol.
Table 8. Percent of leaflets with partial or full adherence to sub-criteria: NITROGLYCERIN (n=339)						
Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Keystone Criteria &/or Labeling**	**Comments**
1. Drug names and indications for use						**Note: Analysis of criteria for NTG is based on Keystone guidelines and Professional labeling. The "Xs" and "?s" that follow reflect this analysis. The dollar signs ($) indicate information that was NOT attributable to either of these sources but was found in the manufacturer's patient information (i.e., NitroQuick); these criteria would EXCEED the Keystone-defined "floor" for information that is deemed as sufficiently specific and comprehensive.**
1.1 generic name: nitroglycerin	12.1	71.1	X			
1.2 phonetic spelling of generic name	0.3	51.3	X			
1.3 common brand names: Nitrostat, NitroQuick, or Nitrotab	42.8	24.5		X		Although Keystone specifies inclusion of trade names, it does not specify how many to include. Therefore, determinant for full compliance with this criterion is not defined by Keystone, i.e., open to interpretation.

1.4 drug class: nitrates	1.5	47.2			X	Pharmacologic/chemical class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI other than in context of cross-sensitivity.
1.5 used to relieve or prevent symptoms of angina (chest pain)	4.7	82.6	X			
2. Contraindications and what to do if applicable						
Do not take this medicine if you:						
2.1 are allergic to nitroglycerin or other nitrates	29.8	10.6		X		PI does not mention cross-sensitivity w/ other nitrates.
Tell PR or PH if you:						
2.2 have other heart problems	0.6	27.4		X		Vague criterion relative to PI. Open to interpretation.
2.3 have severe anemia	2.7	26		X		This is a contraindication in PI.
2.4 have recent stroke or head injury	15.3	12.1			X	Not specified in PI; only increased intracranial pressure is specified.
2.5 have kidney disease	0.3	0.3			X	PI does not specify. In fact, PI explicitly states that there is no need for dosage adjustment.
2.6 have liver disease	1.8	0.6			X	PI does not specify. Also, no need for dosage adjustment.
2.7 are pregnant or may become pregnant	1.2	79.4	X			
2.8 are nursing or breast-feeding	1.5	79.4	$	X		Discrepancy in PIs. NitroQuick sublingual tablets PI states that the nursing precaution applies only to INTRAVENOUS nitroglycerin. NitroStat PI does not include this modification. Another example of inconsistencies in FDA-approved professional labeling for the same drug and dosage form.

3. Specific directions about how to use, monitor, and get most benefit						**Risk of tolerance (tachyphylaxis) is omitted from criteria. Why? This is relevant to the patient and it receives considerable attention in the PI. Possible cross-tolerance with other nitrates & nitrites to antianginal effects also omitted. Precaution to not use burning or tingling sensation as indicator of potency also omitted. Therefore, although Keystone provides great latitude in what precautionary information to include and omit, it is unclear why certain info was included while other was not and how criterion adherence for CMIs would have been judged if they had included ones for which there were no criteria versus those for which there were.**
3.1 Use one tablet at first sign of angina attack (chest pain)	2.4	86.1	X			
3.2 Put tablet under tongue and let it dissolve	0.9	91.7	$	X		N.B.: PI states under the tongue or in the buccal pouch; therefore, criterion is incomplete relative to PI.
3.3 Do not chew, crush, or swallow it	0.9	85.3	$	X		PI for sublingual tablets only specifies to not swallow the tablet; no info on crushing or chewing.
3.4 This usually brings relief in 1 to 5 minutes	8.6	38.9		X		PI for sublingual tablets does not specify. The only information relative to 5 minutes is that a second tablet should be taken if relief is not achieved with the first dose; this would not precisely support the criterion.
3.5 If no relief after 5 minutes, use a second tablet. If no relief after another 5 minutes, use a third tablet	1.2	84.6	X			

3.6 If no relief after three tablets in 15 minute period, call doctor						
and have someone take you to hospital emergency room	2.7	86.1	X			
3.7 May use one tablet 5 to 10 minutes before an expected attack	2.9	22.1	$	X		PI does not specify "one tablet."
3.8 Store in original glass screw-cap bottle, tightly capped	6.8	84.1	X			
3.9 Store at room temperature, away from excess heat and moisture	3.2	81.7	X			
4. Specific precautions and how to avoid harm while using it						**Precaution on use in patients with hypertrophic cardiomyopathy is missing.**
4.1 If possible, sit down when using this medicine. This may						
prevent falls due to dizziness	57.2	28.6	X			
4.2 May cause dizziness when standing up or getting out of bed;						
getting up slowly may help	10.9	68.1		X		PI merely states that severe hypotension may occur, particularly with upright position. No recommendation for avoiding.
4.3 If become dizzy while sitting, take several deep breaths and bend						
forward with your head between your knees	0	0.6			X	PI does not specify.
4.4 Dizziness may be more frequent if you have had alcohol. Limit						
amount of alcohol while using this medicine	49.3	41.6	X			
4.5 Tell PR or PH about any other medications, especially:	2.4	48.7		X		**Too general, i.e., no specific drugs mentioned in criterion 4.5. Also, precautions about phenothiazines and aspirin, which are in PI, are missing. Rationale for criteria on some but not other interacting drugs is unclear. How did this affect CMI criteria adherence determinations? Several other drug interactions were mentioned in Nitrostat but not other NTG PIs.**
4.6 high blood pressure medicines	0.3	25.4	X			

4.7 other heart medicines	0.3	0.6		X		The only other heart medicines mentioned in PI are other nitrates, beta-blockers, and calcium-channel blockers. Therefore, this criterion is too broad (nonspecific) as written.
4.8 sildenafil (Viagra); death can occur with combined use	31.9	32.7		X		Although this is in sildenafil PI, it is not in NitroQuick or NitroTab PIs; in fact, it is missing from most PIs for nitroglycerin. It is in Nitrostat. Such inconsistencies and serious content omissions in associated PIs are emblematic of problems that would occur if FDA were to regulate CMIs. It also is missing from the NitroQuick patient information.

Table 8. Percent of leaflets with partial or full adherence to sub-criteria: NITROGLYCERIN (n=339)

Criteria 1-6: Information is sufficiently specific and comprehensive	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
5. Symptoms of serious or frequent adverse reactions and what to do						
Tell PR or PH as soon as possible if any of these occur:						
5.1 bluish lips or finger nails	0.3	0			X	Not in PI
5.2 blurred vision	5.9	46	X			
5.3 drying of the mouth	0.3	31.3	X			

5.4 severe headache	15.6	15.6		X		Headache is common and is an indicator of pharmacologic effect. How will patients distinguish "severe" headache from common headache that is expected with the drug? Although the PI cautions that severe headache may result from excessive dosage, is it practical or clinically relevant to instruct patients to contact PR or PH "ASAP" if this occurs? NitroQuick patent information states that "sometimes, patients experience mild to severe headaches with their first few tablets. These side effects usually are not signs of other problems, but you should let your doctor know **if you have any concerns**." Therefore, this criterion also is more stringent than manufacturer's patient information.
5.5 shortness of breath, weakness, or fainting [list 1]	26	26		X		Shortness of breath ("dyspnea") only specified in Nitrostat PI; another example of FDA lapse in enforcing PI consistency. Why were these 3 effects singled out and why was "list 1" chosen? Rationale unclear. What if CMI had listed other effects instead (see 5.9)? Why should patient contact PR or PH "ASAP" for weakness?
Tell PR or PH if any of these do not go away or bother you:						
5.6 feeling dizzy or lightheaded	11.8	72.3	X			Related to 5.5 as sign of hypotension. Why a separate criterion?
5.7 fast pulse (or heartbeat)	12.1	72	X			Ditto.
5.8 flushing of face and neck	13.9	65.8	X			

5.9 nausea or vomiting	51.3	23		X		Why were these signs of marked sensitivity to hypotensive effects singled out? What if CMI had included others (e.g., excessive sweating, pallor) instead? Signs described in 5.5 are part of PI description of this effect. Therefore, why 2 criteria?
6. General information and encouragement to ask questions						
6.1 Keep all medicines away from children	1.5	31.9	$		X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefaclor CMI.
6.2 Do not give this medicine to others	0	16.8	X			
6.4 Leaflet states that it does not include all uses, precautions, interactions, adverse reactions, or side effects	1.8	46.9	X			
6.5 Name of publisher	0	54.9	X			
6.6 Date of publication or most recent revision	4.4	41.3	X			
6.7 Ask PR or PH if any questions or concerns	11.2	56	X			
6.8 You may ask PH for longer leaflet written for professionals	2.4	2.4		X		See Atenolol 6.7.
Criterion 7: Information is scientifically accurate, unbiased, up-to-date	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
7.1 information is neutral in content and tone	0.6	99.1	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses)	0	99.7		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities)	1.2	98.2	X			
7.4 no inaccurate or outdated claims about benefits of product	0	99.7	X			
7.5 no inaccurate or outdated claims about risks of product	0.3	97.9	X			
7.6 no other inaccurate or outdated information was found by this rater	0.3	98.8	X			
Criterion 8: Information is readily comprehensible and legible	**% partial**	**% full**	**Explicit required Keystone Criterion**	**Optional Keystone Criterion or Open to Interpretation**	**Not specified in Keystone Criteria &/or Labeling**	**Comments**
						See introductory comment in Atenolol 8.
8.1 black box warning information printed in bold-face type or box	N/A	N/A				
8.2 minimal use of italics or ornate typefaces that are hard to read	1.8	96.5	X			See Atenolol.
8.3 upper and lower case lettering	3.8	90.3	X			See Atenolol.
8.4 headings placed on separate lines (not on same line as text)	20.9	31.3		X	?	See Atenolol.
8.5 bullets used to enhance readability	2.4	5		X	?	See Atenolol.
8.6 information is well organized and easy to find	15.1	67.5	X			See Atenolol.

The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	10.9	3.2		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . . *	51	3.2		X		See Atenolol.
8.9 good ink-paper contrast . . . . . *	22.7	71.4	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . . *	54.4	45		X		See Atenolol.

Appendix C

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May 29, 2009

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-S-0627, Expert and Consumer Evaluation of Consumer Medication Information-2008

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit written comments pertaining to the *Expert and Consumer Evaluation of Consumer Medication Information-2008* (2008 Final Report). For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 35,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students. Pharmacists in hospitals and health systems are experts in medication use who serve on interdisciplinary patient-care teams. They work with physicians, nurses, and other health-care professionals to ensure that medicines are used safely and effectively.

ASHP promotes safe medication use by publishing federally recognized, evidence-based drug information. The Society publishes best practices guidance documents, participates in key national safety and quality initiatives, and has published consumer medication information (CMI) for over 30 years. Our CMI is widely accessed via the National Library of Medicine's MedlinePlus consumer Web site, ConsumerReportsHealth.org Web site, and ASHP's safemedication.com Web site. The Society integrates Medication Guide (MedGuide) and Black Box Warning safety information into its CMI, with hyper-links to the full text of the MedGuide embedded in the electronic CMI and URLs and patient access instructions included in the print versions.

ASHP was pleased to participate in the US Food and Drug Administration's (FDA's) Risk Communication Advisory Committee (Advisory Committee) Meeting held on February 26 and February 27, 2009, when the Society made an oral presentation to the Advisory Committee during the Open Public Hearing section of the meeting. ASHP

appreciates FDA's willingness to consider our recommendations as it decides on appropriate next steps to improve the communication of patient information regarding prescription drugs.

In the comments that follow, ASHP will address the following points regarding the 2008 Final Report by Kimberlin CL and Winterstein AG:

- The background surrounding the 2008 Final Report
- Issues associated with the Expert Panel and the development of the criteria and evaluation process for the 2008 Final Report
- Issues associated with subcriteria included in the Final Report
- The failure of the 2008 Final Report to accurately assess written CMI
- Next steps for CMI

Following its analysis, the Society will recommend:

- The continued enhancement of private-sector CMI through ongoing development and better communication of style and content guidelines.
- The establishment of a certification process for private-sector CMI publishers coordinated by a neutral party.
- The resolution of the downstream output issues at the point of dispensing that were identified in the study as areas of non-compliance by the pharmacy system vendors and their customers that do not reflect the format or quality of CMI provided by the publishers.
- That FDA conduct research to provide an evidence-based assessment of the actual effect of CMI on specific areas of consumer behavior related to safe and effective prescription medication use, adherence, and patient outcomes.

Careful examination of the original CMI issued by the private-sector publishers versus CMI that was provided at the point of service in retail pharmacies shows that most of the problems noted in the 2008 Final Report resulted from downstream failures in the delivery systems rather than from failures relating to the actual content. Unfortunately, the Advisory Committee did not adequately consider the important distinction between failures in content as originally created by private-sector publishers and systems failures in its downstream delivery to consumers. This is an important distinction that should have weighed heavily in the Advisory Committee's deliberations and subsequent recommendations.

ASHP requests that FDA reevaluate the recommendations of the Advisory Committee since they likely also were unaware of important methodologic limitations of the 2008 Final Report's findings at the time of their meeting on February 26 and 27, 2009. ASHP is greatly concerned that the timing of submission of critiques about the Final Report followed the Advisory Committee's actions in response to this study by over 3 months.

ASHP is particularly concerned since careful examination of the study's design finds important flaws relative to the standards for CMI established by the *Action Plan for the Provision of Useful Prescription Medicine Information* (Keystone Guidelines) and FDA's 2006 *Guidance: Useful Written Consumer Medication Information*. It is these standards, not the opinions of the expert panelists, which should have formed the basis of the findings of the study and the subsequent deliberations of the Advisory Committee. As a result, the recommendations of the Advisory Committee were not fully informed since the methodologic limitations of the 2008 CMI study were not made apparent to them at the time of their deliberations on February 26 and 27, 2009.

In fact, when questionable subcriteria that exceeded the official CMI standards were eliminated, ASHP found that the content of the private-sector CMI evaluated in the study actually exceeded the 95% goal for useful written information for patients. This calls into serious question the conclusions and recommendations of the Advisory Committee since they were not made aware of alternative views about the study findings. In addition, it shows that substantial effort was made and resources devoted by the private sector to ensure that their CMI met or exceeded the 95% goal

2008 Final Report - Background

In 1995, the Food and Drug Administration (FDA) proposed a regulation to set and assess specific goals regarding the distribution and quality of medication information provided to consumers. Specific goals of the regulation included a target that by the year 2000, 75% and by 2006, 95% of new prescriptions dispensed would include "useful" written information for patients. In 1997, Public Law 104-180 was enacted, establishing a voluntary private-sector process and adopting the goals and time frames of the 1995 proposed rule.

The 2008 Final Report assessed whether the 2006 goal that 95% of people receiving new prescriptions should receive "useful" written patient information with their prescriptions was being met according to criteria that purportedly was contained in FDA's 2006 Guidance on Useful Written CMI. While the Final Report found that the majority of community pharmacies provided computer generated CMI, the length and format of the CMI and the percent of critical content items covered varied considerably from pharmacy to pharmacy. Careful examination of the original CMI issued by the private-sector publishers versus CMI that was provided at the point of service in retail pharmacies shows that most of the problems noted in the 2008 Final Report resulted from downstream failures in the delivery systems rather than from failures relating to the actual content. Unfortunately, the Advisory Committee did not adequately consider the important distinction between failures in content as originally created by private-sector publishers and systems failures in its downstream delivery to consumers. This is an important distinction that should have weighed heavily in the Advisory Committee's deliberations and subsequent recommendations.

The delay by the FDA in providing the final version of *Guidance: Useful Written CMI* until July 18, 2006 left very little time for content providers of CMI to review the standards and update databases that contain several thousand monographs. Additionally, it left almost no time to communicate with pharmacies and system providers the importance of having the most current format of information available for patients as well as the samples used for the study that was conducted during January – March 2008. Additionally, there were a number of areas originally addressed by the Keystone Guidelines that were not adequately addressed by the 2006 FDA Guidance document (e.g., definition and intent of the "usual dosing" wording, clarification of request for either brand or generic pronunciation) and were not clarified in a formal manner.

ASHP and others did make recommendations to FDA which, if followed, would have ensured that a fair and accurate assessment of CMI usefulness resulted from the current evaluation. In public comments to the FDA in July 2002 and July 2003, ASHP pointed out important study design flaws in the original 2001 evaluation conducted by Svarstad et al, focusing principally on the inclusion of substantial subcriteria for usefulness that were not supported by FDA-approved labeling and/or the Keystone Guidelines. In fact, only about 50−65% of criteria used in the Svarstad evaluation could be directly attributed to labeling and were explicitly required by the Keystone Guidelines. The evaluation criteria were never independently validated prior to their application, and the interpretive validity of many of the subcriteria relative to the Keystone Guidelines was questionable. At a June 2004 meeting convened by FDA, both Dr. Svarstad and FDA acknowledged these methodological problems. Therefore, it is especially concerning that similar design flaws concerning measurement subcriteria were in place in the 2008 Final Report by Drs. Kimberlin and Winterstein.

Issues Associated with Expert Panel and Evaluation Tool Development

The Expert Panel members who created the evaluation form as well as the members who conducted the evaluation were primarily clinicians with an academic background. This was apparent in the selection of a number of subcriteria that were included for monitoring parameters that are primarily the responsibility of the clinician and not information that would be known or could be easily accessed by the patient. Similarly, the inclusion of information from outside references and compendia such as Clinical Pharmacy Online, Micromedex, Drug Facts and Comparison, and AHFS Drug Information was not supported by the 2006 FDA Guidance or Keystone Guidelines which states CMI is to be based on the information in the most current FDA-approved version of the professional labeling or package insert.

Methodological issues associated with the 2001 study such as inclusion of substantial criteria for determining usefulness that were not supported by the Keystone Guidelines or FDA-approved labeling were not addressed, and therefore similar issues were repeated in the development of the criteria and evaluation process for the 2008 CMI study. The

criteria which were developed as the evaluation tool to assess the usefulness of CMI in the study period were not independently assessed prior to use in the review process. Review of these standards by individuals or professionals familiar with CMI development or by practicing pharmacists or the professional organizations that represent them would have enhanced the quality and focus of the criteria that were selected for evaluation to be consistent with the Keystone Guidelines and 2006 FDA Guidance as well as applicable to the consumer.

Assessment of reading levels remains a controversial issue and is affected by other variables in addition to the sentence length and the number of syllables per word as evaluated by the Flesh-Kincaid Level Index. Therefore, the method that was used in the 2008 Final Report to evaluate the reading level may not give a precise assessment of the actual reading level that would be required of the consumer. Because medical terms that may have been explained or defined in consumer language as well as the names of medications that would not require comprehension were not removed from assessment, the final score of a 9th grade reading level may reflect a higher reading estimate than would be required by the reader. A more accurate assessment would be to remove those terms and to evaluate only the content necessary for comprehension.

Issues Associated with Subcriteria Selection

The 2008 Final Report included a substantial number of subcriteria that were not defined by the recommendations included in the report titled *Action Plan for the Provision of Useful Prescription Medicine Information* (Keystone Guidelines) or FDA's July 2006 Guidance on Useful Written CMI (2006 FDA Guidance). Therefore, in 2008, CMI was evaluated using a higher standard than is required under existing guidelines. ASHP raised similar concerns about the 2001 assessment, which were presented in face-to-face meetings with the primary investigator and FDA personnel, and submitted a detailed analysis showing that only 50−65% of the subcriteria could be directly attributed to labeling and were explicitly required by the Keystone Guidelines.

Again, there was a high correlation between the subcriteria that were not supported by Keystone or the 2006 FDA Guidance and a low adherence percentage to the subcriteria found in the in the 2008 Final Report results for both medications. In the 2008 Final Report, only about 70% of the subcriteria could be supported by the 2006 FDA Guidance and were supported by the manufacturer's prescribing information. (See attached spreadsheets.) For example, the lower adherence to subcriteria from the Guidance, under *Criterion 1:Drug Name, Indications for Use, and How to Monitor for Improvement* (actually assessed and reported in the 2008 Final Report under Criterion 3), relative to the previous evaluation, was an indicator of the application of a standard that exceeded the Keystone Guidelines and the 2006 FDA Guidance. The FDA Guidance states: "Information regarding how to monitor the effectiveness of the treatment by correctly interpreting *physical reactions* to the medicine, if this is in the package inserts." Using lisinopril as an example, 47% of the subcriteria (8/17) contained specific advice about the

frequency and specific type of lab tests, none of which were related to *physical reactions* as specified in the 2006 FDA Guidance. While information on the frequency and specific type of lab tests may be useful to communicate to the patient, this information is not included in the standard established by the 2006 FDA Guidance. That is why less than 20% of CMI adhered to specific subcriteria on frequency of laboratory tests and actions to take. For clarity, it should be noted that the authors of the 2008 Final Report moved provision of such information from Criterion 1 (as specified in the 2006 FDA guidance) to Criterion 3 without explanation.

One of the dangers of providing such detailed information about the frequency of a specific type of lab test is that it could contradict instructions provided by the patient's clinician or accepted standards of care not reflected in labeling. An example of that occurred with subcriterion 3.14 for metformin which stated in the 2008 Final Report that HbA1c should be monitored at least every 6 months. This statement differs from FDA-approved labeling, which states under *Information for Patients* simply that HbA1c should be tested regularly and under *Dosage and Administration* information for prescribers states that it should be measured approximately every 3 months. Current standards of care described in the American Diabetes Association *Standards of Medical Care in Diabetes* state that HbA1c should be measured at least twice yearly in patients who are meeting treatment goals and at least quarterly in those whose therapy has changed or who are not meeting glycemic goals. Thus, not only does this subcriterion exceed the 2006 FDA Guidance standard of only providing information on interpreting physical *reactions* to therapy but it also could confuse patients.

Lower adherence to the subcriteria that addressed "Actions to take for serious side effects" under *Criteria 5) Symptoms of serious side effects and what to do* was also found to be related to the application or interpretation of a standard that exceeds the Keystone Guidelines and the 2006 FDA Guidance. The controversy in the Expert Panel was over the interpretation of the action(s) for the patient to take when a serious side effected occurred (i.e., whether the patient should contact their clinician versus not to take drug) which is why the adherence to the subcriteria with instructions to not take the drug is considerably lower than compliance with the subcriteria to contact their health care provider.

The direction provided by the 2006 FDA Guidance only includes "…..and What to Do" in the Criteria header so the standard to specifically instruct the patient not to take the medication was an interpretation by the Expert Panel. This discrepancy was noted in the 2008 Final Report as an example of a subcriterion with low inter-rater reliability and was to have been removed from the final total score. The FDA-approved metformin prescribing information or patient information does not clearly state to stop the medication when symptoms of hypoglycemia are noted (as the condition may actually be related to other medications or conditions unrelated to the metformin therapy). Additionally, the recommendation to stop therapy when symptoms associated with infection are noted as a severe side effect during lisinopril therapy is not noted in the

FDA-approved prescribing information for Zestril® or Prinivil®. Thus, these statements reflect the opinions of the Expert Panel, rather than the standards established by Keystone, the 2006 FDA Guidance, and FDA-approved labeling.

The listing of specific common effects as subcriteria under *Criteria 5) Symptoms of serious side effects and what to do* is not supported by the Keystone Guidelines or the 2006 FDA Guidance. The 2006 FDA Guidance only states to "include a list of the symptoms of the most frequently occurring (common) adverse reactions." While most of the subcriteria for both medications achieved high percentages of adherence to the standard, several of the subcriteria did not. This standard should have been stated as a broad listing of commonly reported side effects, rather than represented by identification of specific symptoms.

The decision by the Expert Panel to collect information about off-label uses is questionable since there is no evidence in the study methodology that the shoppers were obtaining CMI that was specifically customized to them. Although there is sufficient evidence and clinical support for the off-label use of both of the medications, the Keystone Guidelines and the 2006 FDA Guidance state that CMI should be limited to labeled uses, unless it is customized to specific patients. Even if the CMI were customized, the shopper script included in Appendix A of the study indicates that they only should have received information on labeled uses if the pharmacists had information about the specific diseases being treated. Therefore, it appears to be another instance where the Expert Panel interjected their own viewpoints, instead of developing the criteria based on the documents provided as the basis for the content and formatting of CMI. ASHP does support educating consumers and communicating specific information about off-label uses whenever possible and relevant to the specific patient: however, for the purpose of the assessment by the Expert Panel, the guidelines should have been adhered to.

Failure of the 2008 Study to Accurately Assess CMI

The inaccurate selection of subcriteria, methodological flaws, and inappropriate timing and communication of standards for the development of useful CMI all contributed to an inaccurate assessment of medication information available to consumers in 2008. In addition, the 2008 Final Report did not establish the root cause of subcriteria adherence issues, since the study did not perform a separate evaluation of the original content provided by the source publisher versus the content distributed downstream at the point of dispensing. Therefore, conclusions that can be drawn from the 2008 Final Report are incomplete, since FDA did not address important study design flaws and associated concerns raised by ASHP relating to the earlier 2001 evaluation. Even without this separate evaluation of the original content, there was a strong indication in the 2008 evaluation that problems noted in the Final Report reside at the point of distribution, rather than with the content provided by the CMI source publishers. For example, the 2008 Final Report showed the elimination of substantial content from the distributed

information at the point of service, thus demonstrating a failure to adopt best practices for formatting and legibility at the point of dispensing.

ASHP's own evaluation of First DataBank's CMI on metformin and lisinopril indicated that CMI on both medications when evaluated for content as issued originally by the publisher exceeded the 95% threshold for useful written information when the subcriteria that were not supported by the Keystone Guidelines or the 2006 FDA Guidance were eliminated. Therefore, ASHP seriously questions the conclusions about private-sector CMI that were drawn by the Advisory Committee at its February 26 and 27, 2009 meeting. ASHP recommends that FDA not follow the advice of this Committee to dismiss the usefulness of written information for consumers published by the private sector. Because of the substantial scope and economic consequences of following the Committee's advice about private-sector CMI, and because the advice is based on a flawed interpretation of the 2008 Final Report, FDA should provide a more accurate assessment of the findings of the Final Report and request new deliberations by its Advisory Committee. Alternatively, FDA should reject the Advisory Committee's recommendations because the principal basis was flawed.

Next Steps for CMI

Although the 2008 Final Report did not provide an accurate assessment of the distribution and quality of CMI currently available, there are a number of issues and areas noted in the study that could be targeted for improvement. Because the 2008 Final Report did identify many areas of strong compliance and excellence (e.g., number of patients receiving the document, scientific accuracy, identification of precautionary and serious side effect information), it is evident that the current system can be enhanced to provide the quality of medication information to consumers that was proposed in the 1995 regulation. It also is important to recognize that FDA never undertook a key recommendation of the 1996 Keystone Action Plan to actually validate the effectiveness of CMI on patient comprehension and retention of information; ASHP believes that measuring effects on patient behaviors and outcomes also are important.

ASHP presents the following topics for consideration by FDA as the agency improves the quality of consumer medication information:

1) Continued enhancement of private-sector CMI through ongoing development and better communication of style and content guidelines. These guidelines must be identical to those used for any follow-up assessments. Private-sector CMI publishers and other CMI experts must be involved in the process to resolve issues of ambiguity or in the establishment of new content or formats.

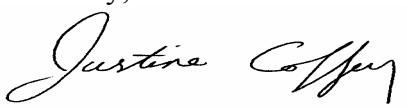
2) Establishment of a certification process for private-sector CMI publishers that would be coordinated by a neutral party.

3) Resolution of the downstream output issues at the point of dispensing that were identified in the study as areas of non-compliance by the pharmacy system vendors and their customers and do not reflect the format or quality of CMI provided by the publishers. Work with the National Association of Boards of Pharmacy to ensure inclusion of clear and strong wording in the Model State Pharmacy Act and Model Rules that results in routine provision to consumers of Keystone Guidelines- and 2006 FDA Guidance-compliant CMI at the point of service in pharmacies.

4) Conduct research to provide an evidence-based assessment of the actual effect of CMI on specific areas of consumer behavior related to safe and effective prescription medication use, adherence, and patient outcomes.

The Society appreciates this opportunity to present its written comments relating to the report. Given the complexity of the issue, and extent of our concerns, we would be pleased to meet with you to discuss these items further. I can be reached by telephone at 301-664-8702, or by e-mail at jcoffey@ashp.org.

Sincerely,



Justine Coffey, JD, LLM
Director, Federal Regulatory Affairs

	Lisinopril Analysis				
Adherence %	Criteria 1- 6: Information is sufficiently specific and comprehensive	In Keystone	In 2006 FDA guidance	In PI	Comments (PI = professional labeling, KAP = Keystone Action Plan, FDA 2006 = 2006 FDA Guidance Useful Written Consumer Medication Information [CMI])
	1. Drug names and indications for use				
97	1.1 Generic name (lisinopril)	Y	Y	Y	
85	1.2 Phonetic spelling of generic name (lyse-IN-oh-pril)	Y	N/Y	N	FDA claims that the KAP conatined an error concerning inclusion of pronunciation of established (generic) versus trade names. However, an "official" pronunciation standard only exists for generic names, i.e., the USP Dictionary of USAN and International Drug Names. The current research rightly assessed inclusion of generic name pronunciation.
39	1.3 Brand names (e.g., Prinivil®, Zestril®)	Y	Y	Y	
91	1.4 Drug class (ACE-I)	N	N	Y	
92	1.5 Indication: hypertension, congestive heart failure, acut e MI	Y	Y	Y	
45	1.6 Physical description of the drug or FDA imprint code i s mentioned	N	N	Y	Neither KAP nor FDA 2006 specify inclusion of this information in CMI.
84	1.7 Off-label use possibility is mentioned	N	N	N	Both KAP and FDA 2006 state that off label uses are only to be included if the information is customized for the individual patient. The methods of the study did not state whether the shoppers received customized CMI.
	2. Contraindications and what to do if applicable				
86	2.1 Angioedema history or history of similar symptoms	Y	Y	Y	
02	2.2 Angioedema can be fatal	Y	Y	Y	
90	2.3 Hypersensitivity to lisinopril or other ACE-I	Y	Y	Y	PI limits contraindication to patients with angioedema to other ACE-I not simply any hypersensitivity.

95	2.4 Pregnancy or planning to become pregnant	Y	Y	Y	Not listed as contraindication in PI - instead listed under Warnings
91	2.5 Teratogenic / can cause birth defects/ fetal harm	Y	Y	Y	Not listed as contraindication in PI - instead listed under Warnings
	3. Specific directions about how to use, monitor, and get most benefit				
91	3. 1 Administration: with or without food	Y	Y	Y	
38	3. 2 Usual Dosing	N	N	Y	KAP did not define what was meant by "usual dosing instructions." FDA 2006 clarified this by stating that CMI should simply refer patient to the prescription label for specific dosing instructions.
71	3. 3 Recommendation to follow individual dosing instructi ons	Y	Y	N/A	
59	3. 4 Personal dosing instructions are inserted in leaflet	N	N	N/A	FDA 2006 clarified this by stating that CMI should simply refer patient to the prescription label for specific dosing instructions.
76	3. 5 Missed dose – action to take: reasonable recommen dation	Y	N	N	FDA 2006 states to include this information only if it is stated in the PI.
71	3. 6 Overdose - action to take: contact poison control center or emergency services	Y	Y	N	FDA 2006 also lists contacting a doctor as an option.
32	3. 7 Phone number for poison control center provided	N	N	N	No mention in KAP or FDA 2006 of the need to actually list the phone number in CMI.
32	3. 8 Overdose symptoms	Y	Y	N	
70	3.9 Safety monitoring (general statement that monitoring i s needed)	N	N	N	No mention that such a statement be included in CMI.
71	3.10 Renal function monitoring	N	N	Y	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.

70	3.11 Potassium / electrolytes monitoring	N	N	Y	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.
54	3.12 CBC monitoring	N	N	Y	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.
13	3.13 Frequency of tests	N	N	N	KAP and FDA 2006 do not specify that patients be advised about the frequency of laboratory tests.
08	3.14 Action to take: ask about lab tests	N	N	N	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.
71	3.15 Effectiveness monitoring (general statement that monitoring is needed)	N	Y	N	
72	3.16 Blood pressure monitoring needed	N	N	Y	FDA 2006 only specifies that patients be advised about *physical reactions to the medicine* (not laboratory tests) that they should monitor for effectiveness. In addition, this would only apply to hypertension effectiveness.
18	3.17 Action to take: ask about blood pressure readings / tests or self-monitor	N	N	N	FDA 2006 only specifies that patients be advised about *physical reactions to the medicine* (not laboratory tests) that they should monitor for effectiveness. In addition, this would only apply to hypertension effectiveness.
	4. Specific precautions and how to avoid harm while using it				
76	4. 1 Drug-drug interactions: Diuretics	Y	Y	Y	
94	4. 2 Drug-drug interactions: Potassium supplements	Y	Y	Y	
86	4. 3 Action to take if patient is taking potassium supplements	Y	Y	Y	
95	4. 4 Drug-drug interactions: Salt substitutes	Y	Y	Y	

87	4. 5 Action to take if the patient is taking salt supplements	Y	Y	Y	
80	4. 6 Inform healthcare provider about all medications you take	Y	Y	N	
78	4. 7 Other: Aortic Stenosis/Hypertrophic cardiomyopathy/ heart problems	Y	Y	Y	
80	4. 8 Other precautions: Impaired Renal Function / renal a rtery stenosis	Y	Y	Y	
79	4. 9 Other precautions: Hyperkalemia / electrolyte proble ms	Y	Y	Y	
41	4.10 Other precautions: Leucopenia/neutropenia / bone m arrow disease	Y	Y	Y	
84	4.11 Other precautions: Upcoming surgery or anesthesia	Y	Y	Y	
91	4.12 Other precautions: Breast feeding	Y	Y	Y	
01*	4.13 Children < 6 years of age: Has not been tested	N	N	Y	KAP and FDA 2006 only state to describe specific risks in children.
47*	4.14 Children < 6 years of age: Should not be used / not r ecommended	N	N	Y	KAP and FDA 2006 only state to describe specific risks in children.
	5. Symptoms of serious or frequent adverse reactions and what to do				
93	5.1 Serious side effects: Angioedema	Y	Y	Y	
90	5.2 Serious side effects: Fainting	Y	Y	Y	
91	5.3 Serious side effects: Infection symptoms	Y	Y	Y	
03	5.4 Action to take for serious side effects: don't take drug	N	Y	Y	Only noted in PI for angioedema/fainting
80	5.5 Action to take for serious side effects: contact provider	N	Y	Y	Only noted in PI for angioedema/fainting
93	5.7 Common side effects: Headache	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.
96	5.8 Common side effects: Dizziness	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.

94	5.9 Common side effects: Cough	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.
86	5.10 Action: Tell doctor/pharmacist if side effects do not go away or bother you	N	Y	N	Only noted in FDA 2006 Criteria 5 section header as "what to do"
	6. General information and encouragement to ask questions				
64	6.1 Sharing medication: do not give this medicine to others	Y	Y	N/A	
67	6.2 Out of reach of children	N	N	N/A	Not included in KAP or FDA 2006
76	6.3 Storage directions	Y	Y	Y	
63	6.4 Name of publisher	Y	Y	N/A	
51	6.5 Date of publication / most recent revision / expiration date	Y	Y	N/A	
74	6.6 Ask doctor or pharmacist if you have any questions or concerns	Y	Y	N/A	
	7. Information is scientifically accurate, unbiased, up-to-date				
98	7.1 Information is neutral in content and tone	Y	Y	N/A	
97	7.2 No promotional messages about brand, manufacturer, or distributor	N	Y	N/A	
96	7.3 No inaccurate or outdated claims about benefits of the product	Y	Y	N/A	
99	7.4 No inaccurate or outdated claims about risks of product	Y	Y	N/A	
97	7.5 No other inaccurate or outdated information was found	Y	Y	N/A	
	8. Information is readily comprehensible and legible				
31	8.1 Short paragraphs with a single topic	Y	Y	N/A	
94	8.2 Limited use of medical / technical terms	N	Y	N/A	
03	8.3 Black box warning is printed in bold-face or box	Y	Y	N/A	
87	8.4 No ads or coupons for other products or non-pharmacy services	N	Y	N/A	Only noted in FDA 2006 as "to distinguish from any promotional material"

15	8.5 Space between lines ≥2.2 mm	N (Not speci	Y	N/A	
26	8.6 Adequate white space around text (≥.5 inch)	N (Not speci	N	N/A	
29	8.7 Font size ≥10 pt	Y	Y	N/A	
97	8.8 Good ink-paper contrast	Y	Y	N/A	
25	8.9 Fonts with Serifs	N	N	N/A	KAP indicates that this is controversial.
49	8.10 Line length ≤ 6”	Y - 40 Letter	Y	N/A	
99	8.11 Minimal use of italics or ornate typeface	Y	Y	N/A	
99	8.12 Upper and lower case lettering	Y	Y	N/A	
05	8.13 Bolded text used for emphasis	Y	Y	N/A	
22	8.14 Headings placed on separate lines	N	Y	N/A	
07	8.15 Bullets used to enhance readability	Y	Y	N/A	
10	8.16 Written at ≤8th grade level	Y	Y	N/A	

	Metformin Analysis				
Adherence %	Criteria 1- 6: Information is sufficiently specific and comprehensive	In Keyston	In 2006 FDA guidance	In PI	Comments (PI = professional labeling, KAP = Keystone Action Plan, FDA 2006 = 2006 FDA Guidance Useful Written Consumer Medication Information [CMI])
	1. Drug names and indications for use				
96	1.1 Generic name (metformin)	Y	Y	Y	
87	1.2 Phonetic spelling of generic name (met-FOR-min)	Y	N/Y	N	FDA claims that the KAP conatined an error concerning inclusion of pronunciation of established (generic) versus trade names. However, an "official" pronunciation standard only exists for generic names, i.e., the USP Dictionary of USAN and International Drug Names. The current research rightly assessed inclusion of generic name pronunciation.
37	1.3 Brand names (e.g., Fortamet™, Glucophage®, Glucophage® XR)	Y	Y	Y	
93	1.4 Indication: Diabetes, type 2	Y	Y	Y	
39	1.5 Physical description of the drug or FDA imprint code is mentioned	N	N	Y	Neither KAP or FDA 2006 specify inclusion of this information in CMI.
25*	1.6 Off-label use possibility is mentioned	N	N	N	Both KAP and FDA 2006 state that off label uses are only to be included if the information is customized for the individual patient. The methods of the study did not state whether the shoppers received customized CMI.
	2. Contraindications				
63	2.1 80 years or older and no test for kidney function	Y	Y	Y	Not listed as contraindication in PI - instead listed under Warnings
85	2.2 Renal or kidney disease	Y	Y	Y	

80	2.3 Liver problems	Y	Y	Y	Not listed as a contraindication in PI - instead listed under Warnings & Precautions as "generally be avoided in patients with clinical or laboratory evidence of hepatic disese"
80	2.4 Serious dehydration	Y	Y	Y	Not listed as a contraindication in PI - instead listed under Warnings to promptly withhold metformin until dehydration is resolved
40	2.5 X-ray/ contrast agent	Y	Y	Y	PI states to withhold metformin until approx 48 hours after proceedure completed and renal function is normal
81	2.6 Planned surgery	Y	Y	Y	Not listed as a contraindication in PI - instead listed under Precautions and only if surgery associated with restricted intake of food and liquids
81	2.7 Serious condition, such as heart attack, severe infectio n, or stroke	Y	Y	Y	PI does not specify stroke
84	2.8 Metabolic acidosis: acute or chronic	Y	Y	Y	Not certain patients would be aware of these disease states
79	2.9 Hypoxemia	Y	Y	Y	Not certain patients would be aware of these disease states
89	2.10 Hypersensitivity to metformin	Y	Y	Y	
	3. Specific directions about how to use, monitor, and get m ost benefit				
91	3.1 Administration: with meals	Y	Y	Y	
34	3.2 Usual Dosing (e.g., “the regular tablet is usually taken 1-3 times a day”)	N	N	Y	KAP did not define what was meant by "usual dosing instructions." FDA 2006 clarified this by stating that CMI should simply refer patient to the prescription label for specific dosing instructions.
90	3.3 Recommendation to follow individual dosing instruction s	Y	Y	N/A	

60	3.4 Personal dosing instructions are inserted in leaflet	N	N	N/A	FDA 2006 clarified this by stating that CMI should simply refer patient to the prescription label for specific dosing instructions.
75	3.5 Missed dose – action to take: reasonable recommendation	Y	Y	N	FDA 2006 states to include this information only if it is stated in the PI.
64	3.6 Overdose – action to take: contact poison center or emergency services	Y	Y	N	FDA 2006 also lists contacting a doctor as an option.
17	3.7 Phone number for poison control center provided	N	N	N	No mention in KAP or FDA 2006 of the need to actually list the phone number in CMI.
71	3.8 Safety monitoring (general statement that monitoring is needed)	N	N	Y	No mention in KAP or FDA 2006 that such a statement be included in CMI.
68	3.9 Renal function	N	N	Y	Although stated in PI under Information for Patients, KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.
01	3.10 Vitamin B12	N	N	Y	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring.
05	3.11 Frequency of tests (e.g., “renal function at initiation and annually”)	N	N	Y	KAP and FDA 2006 do not specify that patients be advised about specific laboratory tests that clinicians should perform for safety monitoring. PI section on Information for Patients does not specify advising patients of frequency
01	3.12 Action to take: ask about lab tests	N	N	N	KAP and FDA 2006 do not specify that patients be advised to ask about laboratory tests.
72	3.13 Effectiveness monitoring (general statement that monitoring needed)	N	Y	Y	
69	3.14 Glycosylated hemoglobin (HbA1c or A1c)	N	N	Y	FDA 2006 only specifies that patients be advised about *physical reactions to the medicine* (not laboratory tests) that they should monitor for effectiveness.

09	3.15 Monitoring schedule (e.g., “HbA1c at least every six months”)	N	N	N	FDA 2006 only specifies that patients be advised about *physical* reactions to the medicine (not laboratory tests) that they should monitor for effectiveness. In addition, the schedule listed here differs from what is in PI: Information for Patients section simply says "reguar testing" and that in prescriber Dosage and Administration section states intervals of about 3 months.
00	3.16 Action to take: Ask about lab tests	N	N	Y	KAP and FDA 2006 do not specify that patients be advised to ask about laboratory tests.
	4. Specific precautions and how to avoid harm while using it				
88	4.1 Lactic acidosis	Y	Y	Y	
78	4.2 Frequency of lactic acidosis (“rare” or numeric estimate)	N	N	Y	Keystone Action Plan allows flexibility in organizing adverse reactions by organ system, severity, **OR** frequency; therefore, frequency is not requirred. 2006 Guidance does not specify that patients be advised about frequencies of adverse effects. In addition, has health literacy research established whether terms like "rare" and "very low" or which numeric estimates are meaningful to patients?
78	4.3 Case fatality rate or statement that it can be fatal	Y	Y	Y	KAP and FDA 2006 simply state to describe any circumstance in which use of the medicine could be fatal not the case fatality rate.
88	4.4 Symptoms of lactic acidosis described (e.g., “tired, muscle/stomach pain, cold, dizzy, tachycardia”)	Y	Y	Y	
81	4.5 Actions to take: Contact provider immediately	N	Y	Y	Only noted in FDA 2006 Criteria 5 section header as "what to do"

33	4.6 Actions to take: Don't take medication	N	Y	Y	Only noted in FDA 2006 Criteria 5 section header as "what to do"
90	4.7 Alcohol use	Y	Y	Y	
88	4.8 Pregnancy	Y	Y	Y	
81	4.9 Action to take: Tell your doctor if you are pregnant or b reast feeding	Y	Y	Y	
69	4.10 Drug-drug interactions identified	Y	Y	Y	
71	4.11 Action to take: Inform provider about all medications y ou take	Y	Y	N	
02	4.12 Children under 10: Has not been tested in children un der 10	N	N	Y	KAP and FDA 2006 only state to describe specific risks in children.
40	4.13 Should not be used / is not recommended in children under 10	N	N	Y	KAP and FDA 2006 only state to describe specific risks in children.
	5. Symptoms of serious or frequent adverse reactions and what to do				
92	5.1 Serious side effects: Hypoglycemia or symptoms	Y	Y	Y	
70	5.2 Action to take: contact provider	N	Y	Y	Only noted in FDA 2006 Criteria 5 section header as "what to do"
18	5.3 Action to take: don't take drug	N	Y	Y	Only noted in FDA 2006 Criteria 5 section header as "what to do"
93	5.4 Common side effects: Diarrhea, Indigestion, Abdomina l Discomfort	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.
91	5.5 Common side effects: Nausea/Vomiting	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.
57	5.6 Common side effects: Flatulence	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.
53	5.7 Common side effects: Headache	Y	Y	Y	Open to interpretation concerning what to list. Neither the KAP nor the FDA 2006 define what is meant by most frequent or common adverse reactions.

87	5.8 Common side effects: Metallic taste in mouth	N	N	N*	Metallic taste in mouth is not specified in PI. Only taste disturbance ot taste disorder are mentioned.
81	5.9 Action to take: Tell your doctor or pharmacist if any of the common side effects do not go away or bother you	N	Y	N	Only noted in FDA 2006 Criteria 5 section header as "what to do"
	6. General information and encouragement to ask questions				
52	6.1 Sharing medication: do not give this medicine to others	Y	Y	N/A	
62	6.2 Out of reach of children	N	N	N/A	Not included in KAP or FDA 2006.
75	6.3 Storage directions	Y	Y	Y	
55	6.4 Name of publisher	Y	Y	N/A	
48	6.5 Date of publication / most recent revision / expiration date	Y	Y	N/A	
87	6.6 Ask doctor or pharmacist if you have any questions or concerns	Y	Y	N/A	
	7. Information is scientifically accurate, unbiased, up-to-date				
98	7.1 Information is neutral in content and tone	Y	Y	N/A	
98	7.2 No promotional messages about brand, manufacturer, or distributor	Y	Y	N/A	
98	7.3 No inaccurate or outdated claims about benefits of the product	Y	Y	N/A	
98	7.4 No inaccurate or outdated claims about risks of product	Y	Y	N/A	
97	7.5 No other inaccurate or outdated information was found	Y	Y	N/A	
	8. Information is readily comprehensible and legible				
14	8.1 Short paragraphs with a single topic	Y	Y	N/A	
93	8.2 Limited use of medical / technical terms	N	Y	N/A	
01	8.3 Black box warning is printed in bold-face or box	Y	Y	N/A	

91	8.4 No ads or coupons for other products or non-pharmacy services	N	Y	N/A	Only noted in FDA 2006 as "to distinguish from any promotional material"
15	8.5 Space between lines ≥2.2 mm	N (Not spe	Y	N/A	
26	8.6 Adequate white space around text (≥.5 inch)	N (Not spe	Y	N/A	
28	8.7 Font size ≥10 pt	Y	Y	N/A	
97	8.8 Good ink-paper contrast	Y	Y	N/A	
25	8.9 Fonts with Serifs	N	N	N/A	KAP indicates that this is controversial.
49	8.10 Line length ≤ 6”	N (40 lette	Y	N/A	
99	8.11 Minimal use of italics or ornate typeface	Y	Y	N/A	
99	8.12 Upper and lower case lettering	Y	Y	N/A	
06	8.13 Bolded text used for emphasis	Y	Y	N/A	
22	8.14 Headings placed on separate lines	N	Y	N/A	
07	8.15 Bullets used to enhance readability	Y	Y	N/A	
06	8.16 Written at ≤8th grade level	Y	Y	N/A	