HAND DELIVERED – FINAL VERSION

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Food and Drug Administration,
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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(ASHP) is pleased to respond to the Food and Drug Administration's (FDA's) May 26, 2005, request for comments on its "Draft Guidance on Useful Written Consumer Medication Information (CMI)."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

2005D-0169 C7

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