February 13, 2008

Centers for Medicare and Medicaid Services
200 Independence Ave., S.W.
Washington, D.C. 20201

RE: Formal Request for Change to Part B Compendia List – DrugDex®

Pursuant to 42 U.S.C. 1395x(t) and 42 C.F.R. 414.930 ("Compendia for determination of medically-accepted indications for off-label uses of drugs and biologicals in an anti-cancer chemotherapeutic regimen"), Thomson Micromedex hereby requests that its DrugDex® compendia be included by CMS in the list of compendia appropriate for identifying medically accepted indications for drugs for purposes of Medicare Parts A and B.

In support of this request, we provide the following information:

I. Full Name and Contact Information of Requestor:

Richard Klasco, M.D.
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II. Full Identification of the Compendium:

Name: The DrugDex® System

Publisher: Thomson Micromedex (a business unit of Thomson Healthcare which is a division of Thomson Corporation)

Edition: N/A (continuously updated online; every 3 months on CD-ROM)

Date of Publication: Continuous

III. Complete Written Copy of Compendium:

DrugDex® can be accessed by an online subscription or by CD-ROM. A complete copy of DrugDex® can be accessed online at thomsonhc.com. A username and password will be sent under a separate cover. The online subscription to DrugDex® is updated continuously. The CD-ROM version is updated every three months.

IV. Specific Action Requested:

Thomson Micromedex requests that CMS exercise its authority pursuant to 42 USC 1395x(t) and the process set forth in 42 CFR 414.930 to include the DrugDex® compendia on the list of compendia appropriate for identifying medically accepted indications for drugs for purposes of Medicare Parts A and B.

V. Supporting Information:

A. General Background:

The Thomson Corporation is a leading global provider of integrated information solutions for both business and professional customers. Thomson provides "must-have" information, utilizing technologies and applications that help our customers to make better, faster decisions. Thomson is organized into five segments: Legal, Financial, Tax & Accounting, Scientific, and Healthcare. The Healthcare segment “Thomson Healthcare” includes several strategic business units including the Thomson Healthcare business known as Micromedex.

The Micromedex business delivers information solutions into three markets: hospitals, corporate (including managed care organizations), and international. This business has over 9,600 customers worldwide in more than 92 countries and utilizes an international network of 43 distributors. Thomson Healthcare utilizes its Micromedex business to create, market and deliver clinical evidence-based products including DrugDex® and DrugPoints®. Located primarily in Denver, Colorado, Thomson Micromedex employs over 100 people whose primary role is to develop proprietary content in accordance with documented editorial policies and procedures. These editorial policies and procedures, discussed below and attached as Attachments A - D, ensure that Thomson Micromedex’ evidence-based drug content remains unbiased and supports appropriate drug therapy.

DrugDex® was first developed over 30 years ago. It contains comprehensive evidence-based drug information including detailed information on dosing, pharmacokinetics, adverse effects, FDA-approved and off-label uses, comparative efficacy, and other critical information on the appropriate use of drugs. The information is referenced to the underlying studies and intended to provide the healthcare professional with both broad and in-depth review of all aspects of prescription drugs. DrugPoints® was initially developed approximately ten years ago and has been greatly enhanced during the last two years. DrugPoints® contains summary drug information aimed at the point of care clinician and is derived from the same core drug information as DrugDex. DrugPoints® provides evidence-based information delivered in a concise format to enhance readability and ease of quickly finding needed information. Sections

include dosing, adverse effects, FDA-approved and off-label indications, interactions, toxicology, and pharmacokinetics.

While DrugPoints® can be acquired as a stand alone product; it is automatically included with the DrugDex® product and provides a summarized version of the DrugDex® content. This summary view of the evidence-based data provides a "quick check" of drug information with the full depth of DrugDex® information linked to the summary for a more detailed review when needed.

DrugDex® is cited in federal statute as a compendia to be referenced for purposes of conducting drug utilization review (DUR) under the Medicaid program and determining whether, for purposes of the Medicaid program, a proposed use of a drug should be considered a "medically accepted indication" notwithstanding the absence of FDA approval for the proposed use (commonly referred to as an "off-label" use). (*See* 42 U.S.C. 1396r-8(k)(6); 42 U.S.C. 1396r-8(g)(1)). DrugPoints®, as the successor publication to USP DI, is also listed as compendia in this same statutory subsection. DrugPoints®, as the successor publication to USP DI, is also listed in 42 U.S.C. 1395x(t) as a reference compendia for making a similar determination as to whether a proposed off-label use constitutes a "medically accepted indication" for purposes of the Medicare Part B program. DrugDex® is not listed under this latter statutory section.

B. Attainment of MedCAC Criteria:

In 2006, the Medicare Evidence Development and Coverage Advisory Committee identified a number of characteristics that it felt were desirable for compendia. These criteria are listed below followed in each case by an explanation of how DrugDex® relates to the identified criterion.

1. Extensive Breadth of Listings:

DrugDex® contains the most extensive breadth of listed uses of any available product. Currently, DrugDex® lists over 2200 evidence-based, unbiased drug monographs, 500 drug consults and is fully referenced. DrugDex® provides advanced search capabilities such as searching by adverse effect, indication, therapeutic class, imprint code as well as full text searching.

2. Quick Throughput from Application for Inclusion to Listing:

Thomson Micromedex' editorial workflow relies on over 100 full-time editorial staff members, including physicians, clinical pharmacists, nurses, other allied health professionals, and medical librarians. This staff follows a multiple step process to create and review the content of Thomson Micromedex products. Our editorial staff, under the direction of the Chief Medical Officer, is trained in the identification of relevant literature and critical literature evaluation techniques. These techniques, in combination with clinical judgment, are employed throughout the process of creating and revising content.

The process for identifying topics for research are based on numerous inputs, including literature review, clinical judgment, regulatory standards, healthcare trends, FDA actions, editorial board suggestions, external requests, and policy changes emanating from professional health care societies. The evidence is reviewed and evaluated for appropriate statistical analysis and methodological rigor.

In addition, an internal panel of senior clinical staff reviews all new content. Certain topics may undergo additional review by an external editorial board, which consists of experts in their field of study and practice. Thomson Micromedex established an Oncology Advisory Board to assist in the review of off-label drug indications in oncology practice. These external board members provide additional input particularly when documentation is controversial or indeterminate or when evidence ratings for off-label indications are subject to significant change based on new documentation.

Our editorial workflow process results in a system that identifies potential new uses for drugs and biologicals -- as well as new information regarding previously-identified uses -- and subjects that information to a review process that is both extremely thorough and entirely evidence-based but also expeditious.

3. Detailed Description of the Evidence Reviewed for Every Individual Listing:

DrugDex® provides extensive detail regarding the information that has been reviewed for each and every listing. It contains comprehensive evidence-based drug information including detailed information on dosing, pharmacokinetics, adverse effects, FDA-approved and off-label uses, comparative efficacy, and other critical information on the appropriate use of drugs. The information is referenced to the underlying studies and intended to provide the healthcare professional with both broad and in-depth review of all aspects of prescription drugs.

To facilitate ease of use by practitioners, DrugDex® also provides information in a summary database through DrugPoints®.

4. Use of Pre-Specified Published Criteria for Weighing Evidence:

Thomson Micromedex employs an evidence-based approach to content creation. This approach is consistent with AHRQ and the U.S. Preventive Services Task Force Ratings of the quality of clinical evidence. These policies and procedures, coupled with detailed analysis of the evidence, support Thomson Micromedex' goal of providing products of the highest quality. Further, the DrugDex® system has fashioned its evidence based system of efficacy, strength of recommendation, and strength of evidence ratings on well known and accepted methodologies. This is discussed in greater detail below.

5. Use of Prescribed Published Process for Making Recommendations:

Thomson Micromedex rigorously adheres to its published editorial process in the review of all uses and assignment of all ratings. Our process for assigning ratings for various uses is discussed in full detail below.

6. Publicly Transparent Process for Evaluating Therapies:

Thomson Micromedex' process of evaluating therapies involves a continuous review of the medical literature as well as all the other steps delineated above and in our published editorial process.

7. Explicit "Not Recommended" Listing When Validated Evidence is Appropriate:

As discussed below, DrugDex® contains an explicit rating category entitled "not recommended".

8. Explicit Listing and Recommendations Regarding Therapies, Including Sequential Use or Combination in Relation to Other Therapies:

Sequential or combination therapies are included in DrugDex® (and DrugPoints®) as supported by validated research published in the primary literature. As an example, the DrugDex® monograph on bevacizumab provides explicit recommendations with regard to its use as one element of a combination chemotherapeutic regimen and it is a sequential use as first-line and second line therapy.[1]

9. Explicit "Equivocal" Listing When Validated Evidence is Equivocal:

Thomson Micromedex rating system is designed to provide information needed to assist clinicians and payers in assessing equivocal evidence on a particular use. As discussed in greater detail below, DrugDex® utilizes a Strength of Recommendation category of "recommended in some cases" (tests or treatments that may be useful, and are indicated in some but not most cases) and an Efficacy rating of "evidence is inconclusive" (evidence/expert opinion is conflicting but the weight of evidence argues against efficacy) as well as a Strength of Evidence rating that indicates the type of evidence to support the ratings. The evidence ratings used in DrugDex® include a middle tier rating that includes meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. By analyzing very granular information to make recommendations regarding Efficacy, Strength of Recommendation, and Strength of Evidence, clinicians and payers can assess the information provided to make reasonable determinations regarding appropriate treatment.

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[1] Excerpt: "Bevacizumab combined with 5-fluorouracil-based chemotherapy (bolus-IFL (irinotecan, 5-fluorouracil, leucovorin) and FOLFOX4 (5-fluorouracil, leucovorin, oxaliplatin)) is indicated for first-or second--line therapy in patients with metastatic colorectal cancer."

10. Process for Public Identification and Notification of Potential Conflicts of Interest of the Compendia's Parent and Sibling Organizations, Reviewers, and Committee Members, with an Established Procedure to Recognize Conflicts.

Thomson Micromedex has a carefully developed conflicts policy which entirely complies with this desired characteristic. Thomson Micromedex takes its role very seriously and has taken many steps to keep our editorial content development process separate from the influence of outside interests. Like other companies (for profit and not for profit) Thomson Micromedex utilizes conflict of interest policies to ensure that no inappropriate influence touches the editorial integrity of our products. The editorial team responsible for off-label content is operationally independent from editorial departments at other Thomson Healthcare businesses.

C. Approach to Grading of Evidence:

Evidence-based medicine is the foundation for the recommendations that appear in DrugDex®. The need for an evidence-based approach to medical practice is widely accepted. Using an evidence-based rating system brings additional rigor to the assessment of indications, and allows clinicians to make better informed treatment decisions. Many schemas have been devised for the classification of the key elements of evidence-based medicine (e.g., strength of evidence, strength of recommendations, etc.). Thomson Micromedex' classification is patterned after the widely accepted American College of Cardiology/American Heart Association and U.S. Preventive Services Task Force (USPSTF) guidelines.[2] In both systems, well-designed clinical studies are given greater weight and poorly designed studies and case reports are assigned lesser weight. Evidence-based medicine does not negate the role of consensus, or expert opinion, in the evaluation of evidence. Consensus is assigned to the lowest tier of evidence[3] and is superseded by data derived from rigorous, randomized controlled clinical trials.

Thomson Micromedex uses three distinct evidence based rating parameters that are applied to both FDA-labeled and off-label indications: Efficacy, Strength of Recommendation, and Strength of Evidence. All indications are assigned one rating for each of the three rating types. The assigned ratings appear in DrugDex®.

Efficacy ratings are used relative to the general standard of care for the appropriate drug indication or treatment recommendation and are defined as follows:

Efficacy Rating Type	Rating Definition
Class I – Effective	Evidence – and/or expert opinion – suggests that a given drug treatment for a specific indication is effective.
Class IIa –	Evidence – and/or expert opinion – is conflicting as to whether a given drug

[2] U.S. Preventive Services Task Force Ratings: Strength of Recommendations and Quality of Evidence. Guide to Clinical Preventive Services, Third Edition: Periodic Updates, 2000-2003. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/3rduspstf/ratings.htm (accessed on 04/04/2007).

[3] Methodology Manual for ACC/AHA, Guideline Writing Committees. Methodologies and Policies from the ACC/AHA Task Force on Practice Guidelines, April 2006. http://www.americanheart.org/downloadable/heart/1148391822076Methodology_Manual_for_ACC_AHA.pdf (accessed on 04/04/2007).

Evidence Favors Efficacy	treatment for a specific indication is effective, but the weight of evidence – and/or expert opinion – favors efficacy.
Class IIb – Evidence Is Inconclusive	Evidence – and/or expert opinion – is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence – and/or expert opinion – argues against efficacy.
Class III – Ineffective	Evidence – and/or expert opinion – suggests that the given drug treatment for a specific indication is not effective.

Strength of Recommendation ratings for tests and treatment interventions are defined as follows:

Strength of Recommendation Rating Type	Rating Definition
Class I – Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa – Recommended, In Most Cases	The given test or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb – Recommended, In Some Cases	The given test or treatment may be useful, and is indicated in some, but not most, cases.
Class III – Not Recommended	The given test or treatment is not useful and should be avoided.

Strength of Evidence ratings represents the evidence upon which recommendations or evaluations of efficacy are based on and are defined as follows:

Strength of Evidence Rating Type	Rating Definition
Category A	Category A evidence is based on data derived from: • Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies • Multiple, well done randomized clinical trials involving large numbers of patients
Category B	Category B evidence is based on data derived from: • Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies • Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). • Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: • Expert opinion or consensus • Case reports or case series

Thomson Micromedex' evidence-based rating system provides an appropriately granular view of off-label indications and is designed to assist clinicians in making informed, evidence-based decisions about the proper care and treatment of their patients. In providing physicians and other health care professionals with more information to inform their clinical decision-making, and in providing CMS and its contractors with more information to make coverage determinations, DrugDex is consistent with CMS's efforts to improve quality of care for Medicare beneficiaries by driving the program toward more evidence-based care.

D. Other Information

Thomson Micromedex has been meeting the healthcare industry's clinical information needs since 1974 by providing comprehensive databases for pharmacology and a variety of other specialized areas. Today, over 9000 facilities (3,200 in the United States) in 92 countries rely on the Thomson Micromedex knowledge bases. Industry wide, Micromedex is recognized as the premier medical reference content provider.

We appreciate your consideration of this request and encourage you to contact us directly should you require any additional information in order to make a fully informed decision.

Sincerely,

Alan Ying
Chief Medical Officer
Thomson Healthcare

Attachments:

Copies of Thomson Micromedex Policies:
- Editorial Workflow
- Off-Label Indications
- Conflict of Interest Policy
- Requesting Inclusion of Information in Thomson Micromedex Databases