

## **Executive Summary**

### **Nonprescription Drug Advisory Committee Meeting**

#### **September 25, 2006**

#### **Introduction**

The purpose of this memorandum is to summarize some of the issues to be discussed during the September 25, 2006 Nonprescription Drug Advisory Committee Meeting. The meeting will focus upon nonprescription labeling and three types of consumer behavior studies, Label Comprehension Studies (LCS), Self-Selection (SS) and Actual Use Studies (AUS). Data from these studies provide information about how well an over-the-counter (OTC) product label can inform the nonprescription drug consumer about the drug and whether the consumer can appropriately use the information on the label. Thus, these data play a major role in helping to determine whether a product should be marketed without a prescription.

LCS, SS, and AUS have unique characteristics and, as time has passed we have given considerable thought as to how to put them to maximum use. The Committee will consider the following issues:

- Assessment of what information must be on the Drug Facts Label and what information could go into a package insert so that we avoid overloading a label with information;
- Alternative study designs for LCS and actual use studies;
- Assessment of differences in correct understanding or behavior between low literate subjects and subjects of normal literacy
- Integration of data from multiple labels tested into a single label;
- The relevance of purchase decision data as being an adequate indicator of self-selection;
- Assessment and interpretation of self-selection data when multiple selection criteria are required (e.g. age + LDL cholesterol level + risk factors);
- Defining a threshold rate of success for self selection;
- Establishing the benefit of informational material provided to complement Drug Facts labeling;
- Balancing potential harm of a new OTC switch product in a small percentage of people compared to the potential benefit for a large percentage of the population;
- Necessity of validating study participants' discussions with their doctors if they interact with their doctor to discuss the OTC label;
- Defining acceptable success rates and failure rates for pivotal issues related to selection or use of a product OTC;
- Defining the types of consumer behavior information that may be acceptable for collection during a Phase 4 commitment rather than pre-approval;
- Testing of new warnings generated to address adverse events observed in postmarketing safety data;
- Presentation of data from LCS, SS, and AUS (e.g., point estimates, confidence intervals);
- Recommendations for study size for different types of studies.

The prescription to OTC switch process is guided by federal regulations. The Federal Food, Drug, and Cosmetic Act Sec. 201. [321] (g)(1) states that the term “drug” means articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease and intended to affect the structure or any function of the body of man. The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b) as follows:

“Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.”

When a drug that has been previously available only by prescription is switched to OTC status, the healthcare provider no longer serves as a gatekeeper to drug access. Thus, to comply with 21 CFR 310.200(b), it is important to take the indication, the target population, the safety concerns, and the behaviors that proper use of the drug demands of the consumer into account when considering whether a drug would be an appropriate candidate for nonprescription sale.

**The OTC Label:**

The Code of Federal Regulations 21 CFR 201 Subpart C establishes labeling requirements for OTC drugs. It consists of the following sections:

- 201.60 *Principal display panel*
- 201.61 *Statement of identity*
- 201.62 *Declaration of net quantity of contents*
- 201.63 *Pregnancy/breast-feeding warning*
- 201.64 *Sodium labeling*
- 201.66 *Format and content requirements for over-the-counter (OTC) drug product labeling*
- 201.70 *Calcium labeling*
- 201.71 *Magnesium labeling*
- 201.72 *Potassium labeling*

During the process of creating this “labeling rule,” consumer focus groups were conducted to help assure that the new regulations would result in labeling that consumers would find user friendly. The Federal Register publication of March 17, 1999 (Volume 64, Number 51) contains a description of the process that led to the development of the labeling rule. This publication is in your packet.

All OTC drug labels must comply with the codified regulations unless they can qualify for an exemption for specific reasons or they are given a deferral for implementation. The regulations limit what we can and cannot put on a product label and where we can put it.

The labeling regulations are included in this packet of briefing materials for the September 25, 2006 NDAC meeting. You may wish to refer to them while reading this section of the Executive Summary.

#### Principal Display Panel and Statement of Identity:

In section 21 CFR 201.60, the regulations describe the required elements of the *principal display panel* (often thought of as the front of the box). The principal display panel is “the part of a label most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.” It must “bear as one of its principal features a *statement of the identity* of the commodity.” The statement of identity (see 21 CFR 201.61) is the “established name of the drug” (loperamide HCl, loratadine, etc.) followed by “an accurate statement of the pharmacological category (ies) of the drug or the principal intended actions of the drug.” Such statements of pharmacological category could be, for example, “antidiarrheal,” or “antihistamine.”

The statement of identity must be provided in terms that are meaningful to the layman when there is no established name. The statement of identity needs to be located in “direct conjunction with the most prominent display of the proprietary name.” The labeling regulations also require a “declaration of the net quantity of contents” of the medication in the principal display panel and specify the placement of this information, size, type and other particulars. This can be expressed in terms of the weight, measure, numerical count or a combination of these things.

#### Drug Facts:

The principal display panel is a completely separate part of the label from the *Drug Facts*. The 21CFR 201.66 section “sets forth the content and format requirements for the Drug Facts labeling of all OTC drug products.” This regulation standardizes the OTC label construct. Hopefully consumers can become familiar with a standard label format so they can easily find the information they seek on any OTC label. The regulation mandates that the outside container or wrapper of the retail package, or the immediate container label (if there is no outside container or wrapper), shall contain the “*Drug Facts*” title and specified headings, subheadings, and information.

The regulations are very specific about the design of the label. For example:

- The regulations require a minimum font size (six) but encourage even larger fonts so consumers can easily read the label information;
- The regulations require that the type be easy to read with no more than 39 characters per inch;

- The continuation of the required content and format onto multiple panels must retain the required order and flow of headings, subheadings, and information and a visual graphic (e.g., an arrow) is to be used to signal the continuation of the Drug Facts labeling to the next adjacent panel;
- The regulations describe how to use hairlines to separate subheadings.

Regulations address a broad array of labeling content information. Some of these regulations are located in Subpart C and others are located elsewhere in Title 21 of the Code of Federal Regulations. A few examples of codified labeling content information follow:

- **Pregnancy/Breast-feeding Warning**  
The regulations state the specific language for a general pregnancy/breast-feeding warning that nonprescription drug products must have on the labeling. ‘If pregnant or breast-feeding ask a health professional before use.’ However, the regulations also state that where a particular drug product has an established specific pregnancy/breast-feeding warning, that warning may replace the general one. Certain products are exempt from having a pregnancy/breast-feeding warning (e.g., drugs intended to benefit the fetus or nursing infant, drugs that are labeled exclusively for pediatric use). (See 21 CFR 201.63.)
- **Electrolyte content**  
Regulations mandate that OTC products containing certain minimum quantities of sodium, calcium, magnesium, and/or potassium state the quantities and contain specific warnings.
- **Examples of specific warnings in the regulations for specific active ingredient categories or for specific product indications:**
  - “for external use only” for topical products;
  - Reye’s Syndrome warning for salicylate-containing products;
  - Kidney warning on aluminum-containing products;
  - Warning for products indicated to temporarily relieve minor sore throats.

To bring a new drug to the OTC market, the sponsor must comply with the CFR labeling rules.

Exemptions to the labeling regulations:

If a particular labeling requirement is inapplicable, impracticable, or contrary to public health or safety for a particular product the FDA can grant an exemption to the rule. Granting exemptions is precedent setting and can lead to inconsistency in labeling. There is also a significant regulatory hurdle that we must be able to explain that justifies the exemption. Therefore, it is important to consider the risk of the unforeseen consequences of granting an exemption at a given time to a given product and what an exemption for one product will mean for labeling on other products. Exemptions may possibly impact consumer literacy with regard to OTC labeling. Thus, granting exemptions is not done often. Examples of types of labeling modifications that would require an exemption are:

- Deviating from the mandated formatting or headings
- Pictograms

Two articles in your packet, one authored by Dr. Ruth Day and the other by Drs. Michael Wogatten and William Vigilante, describe research on the cognitive accessibility of information and on label design.

**Label Comprehension Studies:**

It is important to study whether consumers can understand the information on a product label, particularly when new OTC indications, directions for use, and new warnings are contained therein. LCS can help to develop labeling that communicates effectively.

The label comprehension study is a trial in which no drug is administered. The study is a critical element to the label development process for an OTC drug. If a study succeeds, it can at least assure that respondents understand the label that will accompany the product to market or that will be used in the Actual Use Study. If the results suggest that certain elements are not understood, the study can still be contributory as long as information is collected to help establish the reasons for the errors. The LCS results may not accurately predict consumer behavior, such as self-selection, purchase decisions, or adherence. The main data collection tool for a LCS is the consumer Questionnaire, which should be administered by a trained study investigator. More information about the design of LCS Questionnaires can be found below.

LCS should have a series of key communication objectives, (the information that it is important to convey to the consumer). LCS can test how well consumers comprehend the information displayed on the outside of drug carton, contained inside the package (inserts), and any other crucial informational material. It is important to point out that a given study participant may technically answer a label comprehension question incorrectly, but the unique characteristic of that participant may mean that the response is acceptable. Thus, the investigators should ascertain why participants who answer incorrectly, answer the way they do.

Label comprehension studies can be useful under many different circumstances some of which are:

- The drug is the first in its class to enter the OTC market;
- The drug targets a new OTC population;
- There is a new OTC indication;
- There is a substantive labeling change to an existing OTC product (e.g., a new warning);
- There is a product with a new active ingredient that uses a proprietary name associated with another active ingredient;
- The sponsor generates multiple proprietary names for products containing identical active ingredients.

Normally, LCS are conducted prior to the approval of a drug product for OTC marketing or when the sponsor requests new labeling either for safety or efficacy reasons. It is important to

understand in what circumstances LCS can be conducted after a label change is already made. For example, one area that needs further clarification is whether there are circumstances when FDA should require comprehension testing of new warnings generated from postmarketing safety data as a phase IV commitment. It is important that information be provided to consumers in a timely manner. Delaying implementation of new labeling while waiting for a LCS may not be in the best interest of the public in some situations. It is not clear when we should request that postmarketing labeling changes should be tested.

Lately we have seen products (e.g., cholesterol lowering drugs) for which the proposed OTC labeling is becoming more and more complex. How to best assess what information must be on the Drug Facts Label and what information could go into a package insert to avoid overloading the carton label with information is a challenge. If too much information is on the label, consumers may not read it. We have already populated OTC pain reliever/fever reducer labels with liver warnings, stomach bleeding warnings, and cardioprotection warnings such that the labels may be very wordy. These warnings were added without testing in LCS.

#### Study Design:

We give considerable thought to what study designs should be considered for label comprehension studies. One approach has been to make the label development process an iterative one during which a single label may be tested. If the label does not communicate the important medical messages, the labeling can be revised and another LCS performed.

An alternative approach has been to simultaneously test multiple labels and compare results. The different labels could have variations in wording or could have label information positioned differently. This method of testing may allow us to understand the impact of positioning or variations of wording on effective communication. However, if multiple labels are tested, it is not always clear what should be done when sections test well in one label and not in the other. Where language that communicates well on one label is inserted into another that globally seemed to test better, it is not clear under what circumstances a new label comprehension study should be required. For example, we may not understand the effect of piecemeal shaping of a label.

#### Target Population:

We have often sought a LCS target population that is representative of the United States population of potential product users and nonusers. To attract this target population, tests have been administered in shopping malls and other purchase sites that are demographically diverse.

The general population is often enriched with subgroups of special interest, for example, those of a particular gender, age, race, sex, or those with a medical condition that would put them at high risk if they took the drug. The populations have included a low literacy cohort (which we have tended to define as those with less than a 9<sup>th</sup> grade reading level) whose literacy level is

determined by a validated literacy testing instrument that is administered by a trained investigator. Over the years, the FDA has tended to see studies that use the Rapid Estimate of Adult Literacy in Medicine (REALM) Test; however, we are open to considering use of other validated literacy testing instruments.

Although we gather data on the low literacy population, how to assess the potential differences between low literate subjects and those of normal literacy is unclear. For example, we deliberate over an acceptable comprehension difference, whether the two groups should be studied separately or en masse, or whether there should be different acceptable comprehension score “cut offs” for the two groups.

#### Questionnaire:

The questionnaire should be designed to reflect the communication objectives of the study. The wording of the questionnaire, the order of questions, and the structure of the questions can affect the results of the study by not gathering the appropriate information, introducing respondent fatigue, or by introducing bias. As such, we have tended to think the questionnaire should:

- Be short and simple and use language that people of low literacy can understand;
- Address one objective per question;
- Address different levels of information processing;
- Contain questions of variable design;
- Allow the investigator to record verbatim responses from the respondent that can then be coded and analyzed.

There are many types of questions that have been used and each has advantages. Open-ended questions allow the respondent to give an unrestricted answer that can be recorded verbatim. Closed-ended questions offer the opportunity for the respondent to choose from among a restricted answer set as in a multiple choice question. Scenarios are questions that require the respondent to apply information from the label to respond correctly. The question consists of a brief description of a medical situation. The respondent responds to a question about whether, in this situation, the product would be appropriate to use. Scenario questions can provide very informative data and may offer a window into the ability of respondents to use the product properly. They are being used commonly in LCS because they require not just the comprehension of information, but the ability to process it.

Information from one question should not influence the responses to subsequent questions. It is important that multiple choice questions be mutually exclusive and that they not contain language that participants may interpret as a “safe” answer. They should not contain a default answer such as “ask a doctor” unless asking a doctor is the correct answer according to the label.

Trained investigators should administer the questionnaire using scripted interactions with the respondent. Generally respondents have been given unrestricted time to read the label and can

refer back to it during the testing. This methodology presents a dilemma since it may tend to favorably bias the study results; respondents are probably studying the label more intensely than they would in “real life” or in an actual use study (see below). On the other hand, it does not seem realistic to put respondents in a position where they need to essentially memorize the label to participate in the testing. However, we have noted that how well respondents perform in the LCS does not necessarily predict their behavior in the Actual Use Study. There are many factors that may influence behavior aside from comprehension alone. Actual Use studies are expensive to conduct and it would be helpful to be able to better correlate the results between the LCS and actual use.

#### Analysis:

It is important to note that “adequate” label communication is an issue of clinical judgment and varies depending upon the medical significance of a particular communication objective. Different healthcare professionals may have different thresholds for adequacy and thus this often has become a matter of discussion. It is debatable what a realistic expectation of consumer comprehension should be.

Results for each communication objective have been analyzed by the general population and by specific subgroups to determine the percentage of correct responses. We often make a decision based on a point estimate of correct responses for comprehension. Consideration needs to be given as to whether the LCS data should be provided differently, such as with 95% confidence intervals. More thought also needs to go into how the studies should be powered and the sample size calculated. In some situations, we are looking for information from specific populations (e.g. a population identified on the label to not use the drug) and it is not clear what size of study is acceptable. It is also important to consider the meaning of correct, acceptable, and incorrect responses and how that data should be interpreted.

An article on label development and the label comprehension study for OTC drugs by Drs. Eric Brass and Michael Weintraub is in your packet.

#### **Self-Selection Studies:**

Self-selection data is collected to determine if a consumer can, after reading the product label, make a correct decision about whether or not the product is appropriate for him/her to use based upon the indications and warnings. SS should assess the ability of a consumer to correctly self-diagnose the condition for which a product is indicated and determine whether the product is appropriate for them to use. Sometimes the self-selection question has been included in the LCS or the AUS and sometimes it has been the focus of a stand alone study. This has occurred in the situation where we have concerns about the consumers’ ability to self-diagnose a condition or about the impact of a new warning on the ability to properly choose whether to use the product but are not concerned about the ability to follow the directions for product use. The language used to pose a self-selection question can influence how people may respond to it.

The target population of the SS should be potential users of the product some of whom could use the product and some of whom should not use the product. Validating the self-selection response can be difficult and it is sometimes unclear how aggressive we should be in attempting to validate the information. For a cholesterol lowering drug, do we need to see the lab data? Do we need to document that the study participant actually asked her doctor about a particular warning before choosing to use the product? We often debate when and whether the self-reported information from the study participant is sufficient. If self-selection is part of the AUS, we debate whether and when validation should occur at the self-selection phase of the study. Other areas that need attention with regard to the self-selection study design are:

- The best wording for posing the self-selection question
- The appropriate way to assess self-selection in populations at risk for using the drug

Discussion has focused on how to interpret data when multiple selection criteria are required for correct self-selection. For example, consider a cholesterol lowering drug with an indication comprised of multiple components (high density lipoprotein, low density lipoprotein, total cholesterol, age, etc.) and many label warnings. Do participants need to weigh every piece of label information correctly for us to say that they have made a correct self-selection decision?

For some drug products, a consumer has to consider multiple selection criteria in the form of warnings or criteria identifying a specific population to use the product. It is not clear how we should evaluate drug products with multiple criteria or warnings. Should the scoring of self-selection criteria be cumulative or should a hierarchical system of success be created? If a consumer is self-selecting to use a weight loss drug, must he comply perfectly with all of the indications and warnings on the product label to have successfully self-selected? Is there a way to create and pre-define a hierarchy of warnings based upon risk/benefit that could define a correct self-selection decision?

Clearly, it is important to understand why consumers self-select incorrectly. Perhaps what appears to be an error is really medically acceptable for the individual. For example, one could argue that a woman in her 40s who has had a hysterectomy and has a high risk of developing heart disease may self-select to use a cholesterol lowering drug even though she is younger than the labeled target population. It is also important to consider the meaning of correct, acceptable, and incorrect responses and how that data should be interpreted.

The acceptability of the success rate for pivotal issues related to self-selection for an OTC product and the acceptability of the failure rate is the topic of much debate and will be discussed at the NDAC meeting. When should the majority who could benefit from access to an OTC drug be denied that access because of self-selection errors made by a small subpopulation that could be at risk for using the drug?

Sponsors often provide data on purchase decisions as well as data on self-selection. It should be clear that the ability to appropriately self-select or de-select is not the same thing as a decision to purchase the medication. A purchase decision can depend upon other factors such as price. Young teenagers may self-select to use a product which is not targeted for those less than 18 years of age but the price may discourage them from purchasing the product. How should we weigh data on purchase decisions when considering a drug for approval? FDA does not control the pricing of drugs.

#### Analysis

We often have made a decision from a point estimate of correct response for self-selection but are considering whether we should look at the data differently. Also, it is not always clear how to power these studies, particularly with regard to subpopulations.

#### **Actual Use Studies:**

Unlike a LCS, in an actual use study participants actually take the study drug home and ingest it. The purpose of an actual use study is to simulate the OTC use of a product. Hopefully, the AUS can provide meaningful consumer data so we can attempt to predict if a drug will be used properly, safely, and effectively in the OTC setting. Examples of things an actual use study can assess are:

- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label);
- Safety (adverse events that occur during the study);
- Efficacy (whether the clinical benefit in the prescription setting is reproduced in the OTC setting). This seldom has been done.

AUS can evaluate the relationship between a self-selection decision and the decision to actually purchase the drug. They can assess the ability of the consumer to use the product for the indicated purpose (self-treat) and can also assess whether consumers are abusing or misusing, the study drug. Generally we have not been concerned with under-using of OTC drugs because, to date, most OTC medications have been indicated for short term symptomatic treatment.

Some issues that might trigger the need for an actual use study include:

- New OTC indication;
- New method of use for an OTC drug;
- New OTC warnings;
- New OTC medical follow-up requirements or recommendations;
- Specific concerns about self-selection or de-selection.

The types of consumer behavior information that should be considered for collection as a Phase 4 commitment should be discussed.

### Study Design:

The design of an AUS can vary. It makes sense that the label used in the AUS should be one that tests well in a LCS. Nevertheless, it is important to note that we have seen very well comprehended labels that do not lead to successful outcomes in SS or AUS.

Often AUS have been single-arm, multi-center, uncontrolled, open-label studies. However, it is possible that we should be considering other designs such as those where multiple arms compare different methods of communication and consumer education (e.g. additional educational material versus none) or the inclusion of a control group. The goal of the study is to provide a venue that simulates, as closely as possible, the true OTC environment. It is clear that a truly “naturalistic” environment cannot be perfectly achieved; data needs to be collected. However, if no clinical sites are used, if the study participant can purchase study drug without restriction, and if there is no unsolicited healthcare provider involvement, hopefully a study can come close to simulating a real nonprescription purchase setting. Study elements that limit the naturalistic setting are the informed consent form, data collection tools like diaries which can serve as memory prompts to the study participant, and any other educational tools that may not be carried over into the true OTC setting. When study elements that limit the naturalistic setting are used in the AUS we cannot be certain that the same level of safety and efficacy will be achieved if the consumer uses the product without these additional elements. This issue is always considered when we provide comments to a sponsor about their AUS study design.

Ideally, all consumers who have an interest in the product should be the target of recruitment efforts. It is reasonable to attract people with a certain symptom or condition. Although we do not have the data to support this supposition, it appears that people generally enter a pharmacy because they have a specific medical need and are looking for a product to take care of that need. They are not just “window shopping” for an OTC medication.

It is also reasonable to recruit targeted subgroups of interest (e.g., low literacy, specific demographics, and medical conditions). These subgroups can provide more information about the potential safety (or efficacy) concerns. As with the LCS and SS, sometimes it has been difficult to determine how to factor the low literacy data and data from other subpopulations into the decision about drug approval. What is, or how do we determine the minimum threshold for performance for the low literacy population in actual use studies? How low do their scores need to be in comparison to the normal literacy group before we decide not to approve a drug? This is an issue of consideration for the NDAC meeting.

Lately, sponsors have proposed providing supplementary educational materials to achieve good self-selection and adherence. These materials have been in the form of videos, internet, booklets, etc. A question that has come up repeatedly is whether there is value in sponsors evaluating components of a proposed marketing program other than the enforceable components (those that qualify as labeling) as part of their behavioral studies? If informational materials are to be

provided, how should the benefit of those materials be established? Should the actual use study be designed with multiple arms to test those materials?

How should we determine what are acceptable rates of success and failure in an actual use study? We grapple with what an acceptable success rate is for pivotal issues related to actual use for an OTC product. Acceptable error depends upon the specific drug, specific indication, and safety concerns. Consideration needs to be given to how we should make decisions on approval of a drug when a small percentage of users could potentially be harmed by inappropriate use (for example, a pregnant woman who uses a weight loss drug) but, on the other hand, a large percentage of users may benefit.

Analysis:

There is no magic number that has defined the size of AUS and how to power these studies is always a question. The number of study participants enrolled has varied with each drug and situation. Among the factors that could influence the number would be the incidence of the condition, the drug risks, and the cohorts. A study that is addressing primarily self-selection might be smaller than one that is designed to assess primarily safety.

As with the LCS and SS, data has been presented for AUS as a point estimate of correct response. NDAC will deliberate the best ways to request AUS data from the sponsors (e.g., point estimates, confidence intervals) and how to power these studies.

An article by Dr. Eric Brass that discusses OTC drug availability and actual use considerations is among those in your packet.

### **Closing Comments:**

At the NDAC meeting we will hear talks from:

- Ralph D'Agostino, Ph.D.
- Terry Davis, Ph.D.
- Ruth Day, Ph.D.
- Ruth Parker, M.D.
- Saul Shiffman, Ph.D.
- Alastair Wood, M.D.

Their talks will cover a range of topics including statistics, product labels, information processing, health literacy, self-management challenges, and subpopulation risk versus general population benefit in decision making about nonprescription drugs. The NDAC will discuss and vet issues related to the methodology and analysis of LCS, SS, and AUS such as:

- How to prioritize what information must be on the Drug Facts label and what can go into a package insert;
- How to assess the value of a package insert or other educational materials;

- The types of latitude (exemptions) we should consider when designing the Drug Facts labeling;
- Principles related to the individualization of consumer behavior study results with the consideration that a correct answer to self-selection might be different for different study participants based upon their personal medical situations;
- Whether, it is reasonable to develop a hierarchy of correct answers for self-selection or whether correct decision making should be based upon a composite score;
- Powering of studies and data presentation.

When contemplating these studies, it is important to recognize that none of them are validated surrogates for consumer behavior in the marketplace. However, hopefully, the discussion at the meeting will generate ideas that help us all forge a path to better consumer behavior research for OTC drugs.

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August 18, 2006