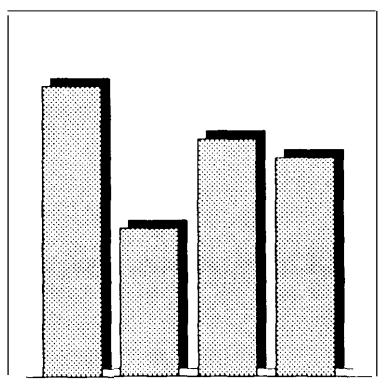
Results of the OTA Survey 3

The results presented here emerged from the process described in chapter 2. Quantitative results based on the product scores give a general picture of the quality of information found, but the detail behind the scores brings them into clearer focus. Detailed tables (addenda 3-1 to 3-6) at the end of this chapter catalogue every divergence from the medical importance standard that OTA scored for each of the products, but does so using only the type of drug as an identifier, and not the name. The rest of this chapter describes the types of problem encountered and gives quantitative results by section of the label, by overall scores, by company, and by country. Also included is an analysis provided by one of the survey companies, pitting OTA's evaluation against labeling in other industrialized countries; and an OTA analysis comparing our own evaluation against the information included in World Health Organization (WHO) monographs of drug prescribing information.

QUALITATIVE RESULTS: ADDENDA



The particular products evaluated in the survey are not listed by name in this report. These drugs constitute a representative *sample* and were not singled out as being potentially problematic; by themselves, they do not constitute a meaningful universe for action. It was realized, however, that with no detail on the types of divergences from OTA's standard that contributed to the scores and the results in general, it would be difficult to judge the fairness and consistency of the OTA process. To remedy this, the addenda to this chapter consist of tables listing each product, identified by therapeutic class and type of drug (where appropriate), and the divergences that contributed to its score. Illustrations are drawn from the addenda in the discussion that fol-

lows, but readers are encouraged to delve into the tables themselves to understand the nature of the OTA analysis, which cannot be judged adequately on the basis of numeric scores and averages.

QUANTITATIVE RESULTS

Overall Analysis

Of the 273 products in the survey, 241 were evaluated fully. The remaining 32 were excluded for a variety of reasons, most because they were no longer being marketed at the time OTA evaluated them. The rest were scored, as described in chapter 2, taking into account all the information the companies sent in response to OTA queries.

The scale for *overall scores* ranges from O to 3, with O signifying no important divergence from OTA's medical importance standard, and 3 signifying the **greatest** divergence. Labeling was assigned an overall score of 3 if two or more sections of labeling information were found to have the most medically serious divergence scores. (The scoring system is explained in detail in ch. 2.) The overall scores use the FDA-approved labeling as **a ceiling.** This means that labels were never held to a higher standard than what is required by FDA in U.S. labels.

Table 3-l-Summary of Overall Scores

Overall score	Number of products (%)
o	78 (32%)
1	40 (17%)
2	64 (27%)
3	59(24%)
All fully evaluated	241 (1 00%)
Not fully evaluated	32
Total in original sample	273

Degree of divergence from medical importance standard:
O: No divergence from medical importance standard
1: At least one category score = 1; no score >1
2: No more than one category score= 2; other categories may= O or 1
3: At least two category scores. 2

NOTE: See text for details of scoring.

SOURCE: Office of Technology Assessment, 1993.

In this analysis, about half the products had labels that were either completely in accord with OTA's medical importance standard, a score of O, or diverged to a small but medically important degree (score of 1). About 25 percent scored 2, and about 25 percent scored 3 (see table 3-l).

Analysis by Category of Labeling Information

INTRODUCTION

The sections listed below, which OTA used to categorize divergences from the medical importance standard, were adopted from the U.S. label format as a matter of convenience. Labels from other countries, developed and developing, are organized differently, and OTA did not require that specific items of information appear in the sample labels in sections of the same name. The labels were evaluated as whole entities, and the appearance of the appropriate information, as judged against the medical importance standard, was all that was required, regardless of the label's organization.

The scale for category scores ranges from O (no divergence) to 2 (the most serious category of divergence). The numbers and percentages reported in each section, below, and in table 3-2, are based on the 241 products that were evaluated fully.

DESCRIPTION AND CLINICAL PHARMACOLOGY

Problems were found in 51 (21 percent) of the *description and clinical pharmacology* sections of the labels, most of them (45) rated 1, and 6 rated 2. The most common concerns were failure to identify the drug class of the product and, more commonly, failure to include adequate pharmacokinetic information (especially half-life, metabolism, and route of elimination).

For example, a manufacturer of an antihistamine did not provide information about the half-life of the product, even though the half-life was particularly long (l-2 weeks).

INGREDIENTS

The *ingredients* section contributed to a divergence in the final scores in only four cases. This

contrasts markedly with OTA's interim scores, in which the lack of an inert (inactive) ingredient list was scored as an unsatisfied query. In the final analysis, lack of an inert ingredient list did *not* contribute to overall divergent scores, except in the few cases where a particular inert ingredient was known to be particularly sensitizing. A specific exception is failure to note alcohol as an ingredient of drugs that might be given to children, in whom even small amounts may cause serious adverse reactions, including central nervous system depression and seizures. For all the rest, lack of inert ingredient lists elicited a score of "R," which was tracked separate from the rest of the scores. In all, 17 of the products with a primary score of O lacked inert ingredient lists (scored "R"), as did 57 (24%) of those with scores of 1, 2, or 3. The "R" itself did not contribute to the score, however.

OTA and the Expert Review Group did consider it medically important to include a list of inert ingredients, and, in fact, all manufacturers in the OTA survey list them voluntarily on U.S. labels. By regulation, they are required to list inert ingredients only for injectable products, and to note the presence of only a small number of specific ingredients in oral products. In the past, countries of the European Community have not required a complete listing, but this is changing with the new harmonization efforts, and inert ingredient lists will be required. Japan first required inert ingredient disclosure for injectable drugs and those applied to mucous membranes in 1988. For drugs for internal use, however, listing is required only for particular ingredients. An independent drug bulletin in Japan has, however, assembled a database of all inert ingredients for about 6,000 products. Sales of the database are reported to be good (18).

These developments suggest that it is medically important for physicians to know what nonpharmacologic ingredients are in the preparations they prescribe. Nearly one-third of the labels evaluated by OTA lacked this information.

INDICATIONS

Indications was one of the most problematic sections. Sixty-three labels (26 percent) were divergent in this area, and 43 of those were rated 2, representing the most serious problems. These scores resulted from:

1. indications that did not appear in the U.S. label or in widely accepted drug compendia and for which inadequate evidence of efficacy was presented by the companies,
2. indications that were overly broad and vague, and
3. failure to inform when the product was not considered first-line treatment for an indication.

Table 3-2—Summary of Category Scores

Category score	DCP	ING	IND	CI	WP	AR	DA	OD
1	45 (19%)	1 (O%)	20 (8%)	12 (5%)	49 (20%)	25 (10%)	17 (7%)	8 (3%)
2	6 (2°/0)	3 (1%)	43 (18%)	15 (6°/0)	79 (33$40)	37 (15%)	11 (5%)	37 (15%)
R		74 (31 %)						

Categories:
DCP = Description/Clinical Pharmacology
ING = Ingredients
IND - Indications
- Contraindications
WP - Warnings and Precautions
AR = Adverse Reactions
DA = Dosage and Administration
OD . Overdosage

Category scores:
1: at least one unresolved query in category with score= 1
2: at least one unresolved query in category with score -2
R: lack of inactive (inert) ingredient list

NOTE: The percentage calculations use 241, the number of fully evaluated products, as the denominator. See text for details of scoring.

SOURCE: Office of Technology Assessment, 1993.

In the first situation, the Expert Review Group and OTA recognized that products are used and effective for some indications other than those approved by FDA, so the mere fact that an indication did not appear on the FDA-approved label did *not* automatically call it into question. For example, OTA accepted the indication of a beta-blocker for prophylaxis of migraine headache, even though it is not an indication on the FDA-approved label. OTA did not however, accept the indication of an androgenic steroid in frigidity therapy, in menopause, as therapy for benign mammary disturbances, or in suppression of lactation.

The second situation, vague or general indications, is illustrated by an injectable corticosteroid indicated for "arthritis in general" and "dermatitis in general" with no qualification.

The third type of divergence was failure to note that the product, although effective for a specific indication, was not the drug of choice. For example, an antidiarrheal combination with an aminoglycoside antibiotic did not note that oral dehydration therapy is considered first-line treatment for childhood diarrhea. This information is particularly important for drugs with relatively more common or more severe adverse effects compared with other choices, or which are less effective than alternatives, In general, labeling was considered deficient if it failed to note when a product was not first-line therapy. However, if the manufacturer provided some justification and supporting evidence for first-line use, it was accepted, even if it did not agree with U.S. labeling or other reference information.

CONTRAINDICATIONS

Contraindications diverged from the medical importance standard for 27 labels (11 percent), including 15 rated 2, the most serious category. Contraindications describe situations in which a drug should not be used because, for one reason or another, the risks of taking it are likely to outweigh the benefits. The reasons include:

1. the patient has another medical condition that could be made worse by the drug (e.g., failure to contraindicate an anthelminthic known to induce seizures in patients with epilepsy);
2. the patient is taking another drug known to interact with the product in an unacceptable way (e.g., failure to contraindicate the use of a monoamine oxidase inhibitor with the antidepressant fluoxetine);
3. the drug may harm a fetus in a pregnant woman (e.g., failure to contraindicate use of an androgenic steroid in pregnancy) or pass through a nursing mother's breast milk, potentially harming the child;
4. the drug should not be taken by children (because of lack of evidence of safety or because of a known unacceptable adverse effect) or by frail elderly people; and
5. the patient has known sensitivity to the drug itself or related products.

There is some disagreement about the last point, the need to contraindicate a drug specifically for hypersensitivity to the drug itself or to the class of drugs. Some people consider this self-evident. Silverman, Lydecker, and Lee, in their recent book, *Bad Medicine: The Prescription Drug Industry in the Third World (212),* comment:

> No attention is paid hereto statements that a particular agent is contraindicated in patients who may be allergic or hypersensitive to that product or related substances—advice that would be as useless and irritating as a warning that "this drug should not be used by a patient who should not use it. "

This view is not held universally, however. The WHO monographs of prescribing information, which are relatively brief, and were developed by a consensual process, do contain these statements, where appropriate.

In OTA's survey, five of the divergence scores in contraindications were for failure to mention

hypersensitivity to the product itself (in two cases, this was the only problem in contraindications, and in three, there was at least one other); and in two cases, the score was given for failure to contraindicate for hypersensitivity to the drug class (in one case, this was the only problem; in the other, it was one of several). Five labels had unresolved queries for having no contraindication section at all, and presumably, some of those might have specified hypersensitivity as a problem.

WARNINGS AND PRECAUTIONS

The greatest number of problems, and the greatest number rating a 2, was found in *warnings and precautions* sections. More than half the labels (128) evaluated deviated from the medical importance standard, and 79 of those were rated 2. warnings and precautions cover a broad range of information, so it may not be surprising that divergences were common there. The types of problem included:

1. failure to warn of relatively rare but potentially life-threatening effects;
2. failure to warn of less serious but more common effects;
3. providing too weak a warning in relation to the risk;
4. failure to warn about particular high-risk patients (e.g., with other chronic diseases);
5. failure to note interactions with other drugs;
6. failure to note effects on laboratory test results;
7. omission of instructions for monitoring patients on the drug;
8. lack of specificity about possible effects;
9. lack of information about use of drug in pregnancy, in nursing mothers, in pediatric patients, or in the elderly; and
10. lack of information on possible carcinogenicity.

Specific problems in warnings and precautions include:

- an antiepileptic that failed to warn about the increased risk of fatal hepatotoxicity in children under 2 years of age;
- a magnesium-containing antacid indicated for infant feedings "to prevent milk from souring and forming curds in the stomach" that did not warn about the risk of hypermagnesemia in infants from chronic administration;
- an antihypertensive that stated that hypotension is an "infrequent secondary reaction," whereas in the United States, hypotension is not considered infrequent, and potentially serious consequences of hypotension are noted in the labeling;
- an antihypertensive known to increase blood sugar levels that did not include information about appropriate use in diabetic patients; and
- an antihypertensive that failed to warn about interactions with other drugs, most notably other antihypertensive medications, which may lead to additive or synergistic effects in decreasing blood pressure.

ADVERSE REACTIONS

Widespread divergences were also noted in *adverse reactions* sections of the labels. Just over a quarter (62) had unresolved queries, of which 37 (59 percent) were rated 2, the most serious category. Adverse reactions noted as absent ranged from some that are possibly worrisome to patients though not medically serious (e.g., discoloration of urine or other body fluids) to life threatening (e.g., agranulocytosis, the complete absence of a type of blood cell; and Stevens-Johnson syndrome, an extremely severe skin manifestation), but all were considered important enough for physicians to be fully informed about them.

In some cases, an adverse reaction was listed on the sample label, but the seriousness of it was not conveyed. In one case, for example, granulo-

cytopenia-low numbers of blood cells known as granulocytes-was listed, but the product had, in rare cases, caused agranulocytosis, the complete absence of these cells, a potentially fatal condition. The company argued that the distinction was not essential, as physicians know the relationship between the two conditions. OTA, however, scored this and other similar instances as divergences, either a score or 1 or 2, depending on the seriousness of the reaction.

DOSAGE AND ADMINISTRATION (EXCLUDING OVERDOSAGE)

Most problems in *dosage and administration* had to do with regimens that included either higher or in a few cases, lower doses than recommended in the comparison labeling or in drug compendia, and for which inadequate support existed in the literature and other material supplied by the companies. The divergences occurred both in daily doses and in the length of the regimen, and often involved regimens specifically for infants or children. In a few cases, the label failed to state the maximum length of time the drug should be taken before either stopping or taking other measures. Twenty-eight (12 percent) of the labels scored 1 (17) or 2 (11) in this area.

OVERDOSAGE

Failure to include information on the signs and symptoms of *overdosage,* and for its management was common. Forty-five (19 percent) products diverged from the medical importance standard in this section, and most of those (37) instances were placed in the most serious category (score of 2). Lack of this information was considered particularly important (score of 2) if there were specific measures, as opposed to just general monitoring and supportive measures, recommended for treatment of the overdose. An example was a combination phenothiazine antipsy chotic and tricyclic antidepressant that did not include detailed information on the symptoms and management of overdose.

I Analysis by Company and Country

ANALYSIS BY COMPANY

The number of fully evaluated products (out of 241) per company ranged from 4 to 25, reflecting in part the number of products each company sells in the sample countries, and also the varying number of products not evaluated. OTA calculated average overall scores for each company (the scale for overall scores is O-3), and these ranged from O to 2.22, but most fell between 1 and 2. Two were less than 1, including one with a score of O, and two were more than 2. For the reasons discussed below, it was not considered appropriate to rank companies by their scores.

In general, the samples sizes for individual companies are not large enough to sustain rigorous statistical manipulation, particularly because most of the scores fall into a relatively small range.

A major factor affecting company scores is the mix of products in the OTA sample. Many companies emphasize products for one or several clinical conditions, so their products tend to clump in particular therapeutic categories. Certain types of product, no matter how they are used, are unlikely to have effects that are life threatening or even serious. Such products would almost never berated as 3, diverging greatly from the medical importance standard, regardless of the labeling. Products fitting this description do, in fact, dominate in the sample from the company with the lowest overall score and form varying proportions of other company's products.

ANALYSIS BY COUNTRY

The average overall scores for the four sample countries ranged from 1.1 to 1.6 (out of 3), with the average of all scores at 1.4. Medically significant problems occurred in all countries, and no clear distinctions can be made in a country-by-country comparison. A sample of four countries is too small to conclude that labeling in *all* developing countries is in need of improvement, but it does suggest it is not an isolated problem.

Comparison With Other Industrialized Countries

Several survey companies criticized OTA's medical importance standard for adopting a U.S. perspective on labeling, to the exclusion of established standards in other industrialized countries. This is true in that FDA-approved labeling was used as a guide for evaluating sample labeling and that labels were not held to a standard higher than FDA requirements, OTA also required evidence of efficacy from formal clinical trials for questioned indications and documentation to justify the omission of warnings, adverse reactions, etc., that do appear in U.S. labels, so in this sense, the medical importance standard borrows from FDA standards of evidence.

Some companies believed the OTA standard to be particularly inappropriate when the sample label was based directly on labeling from the country of export. They stated their belief that it is important to consider European country labeling because former colonies have often patterned their drug regulatory systems after their colonizers. Some companies noted that, from a business perspective, it may be most practical to include the export country's label.

OTA recognizes that labels in other industrialized countries often contain different information from their U.S. equivalents. Some of the reasons for these differences are discussed in chapter 4, having to do with the history of drug regulation in different countries. In view of these concerns, OTA asked the companies to indicate the country of export for each sample product and to provide sample labeling from the exporting country so that a direct comparison could be made. No company responded systematically to this request.

One company did respond, however, by comparing OTA's interim evaluations against labeling for the same or similar products in each of the 21 countries named in the Drug Export Act of 1986 (see ch. 4 for a discussion of the Act) and documenting the labeling from those countries. During the final draft review, 16 other companies conducted similar analyses, which they provided to the Pharmaceutical Manufacturers Association (PMA) and which were included in PMA's comments to OTA. The PMA comments contained only the companies summaries of the comparison, and not the corroborating labeling from the other countries, so it was not possible for OTA to fully evaluate those analyses. These latter results are not discussed in this report, but the analysis of the first company is presented in detail in table 3-3 and summarized below.

The 21 countries included in the one company's "composite standard" are cited in the Drug Export Act as having regulatory systems adequate to allow the export to them of drugs not yet approved in the United States. The company takes this a step further, reasoning that Congress should then accept labeling from any of those countries as being adequate in developing countries (although his conclusion is not supported by the legislative history of the Act).

The company analysis took each *unsatisfied query* that OTA had scored 1 or 2 and checked the labeling of the 21 Drug Export Act countries (DEACs) to see whether they were similar to the original survey country label on the point OTA had questioned. If they found a correspondence in at least one of the 21 countries, they considered OTA's score invalid and rescored the query as O. They then retallied the overall scores.[1]

Nineteen of the company's products had been included in the survey and of those, 10 received *interim overall scores* of 1, 2, or 3; the rest scored O (no medically important divergences from the OTA standard). The company conducted their analysis on these 10 products. For two of them,

[1] The company was working with OTA'S *interim* evaluations. The material they submitted during their second opportunity to supply information resulted in changes reflected in OTA'S final scores. These instances are noted in table 3-3. The changes made by OTA occurred only in response to *medical evidence* supporting the original label, not the mere correspondence of the sample label to a label in a third country.

Table 3-3-Company Comparison of OTA Evaluation With Labeling in DEAC Countries

Product type	OTA Interim evaluation: divergence from standard	Company reevaluation	OTA final evacuation
Nonsteroidal anti-Inf lammatory drug	indication for pain and fever associated with acute respiratory tract inflammation. (IQS = 2)	indication accepted in Finland and Japan and for "competitor products" in several other countries. (CQS = O)	Company provided insufficient medical evidence to support efficacy for this indication. (FQS = 2)
	Labeling recommends a higher dosage than approved in U.S.(IQS = 2)	Higher dosage approved in 16 other countries. (CQS = O)	Company documented safety and efficacy of higher dose. (FQS = O)
Overall scorn	*OTA Interim score* = 3	*Company rescore = O*	*OTA final score*= 2
Nonsteroidal anti-inflammatory drug	Overly broad indication for conditions "requiring anti-inflammatory and/or analgesic activity, such as rheumatoid arthritis. . ."'(IQS= 2)	**Company stated that all labeling for this product contains specific indication state-'rents. Because specific conditions are mentioned, indication cannot be considered over-iy broad. (CQS = O)	Specific conditions are given in the nature of examples, not delimiting the appropriate use of the-product. (FQS =2)
	Labeling recommends a higher dosage than approved in U.S. (IQS =2)	Higher dosage is approved in 17 other countries. (CQS _O)	Company documented safety and efficacy of higher dose. (FQS = O)
Overall score	*OTA interim score = 3*	*Company rescore = O*	*OTA final score= 3t*
Asthma drug	No information on signs and treatment of overdosage. (IQS = 2*)	information not included in labeling in 2 comparison countries in which drug is marketed. (CQS = O)	This information is not required by FDA. (FQS = O)
Overall Score	*OTA interim score = 2*	*Company rescore = O*	*OTA final score= O*
Oral hypoglycemic agent	Labeling does not state that product is considered second-line treatment for one indication. (IQS = 1)	information not included in 10 of 17 countries in which drug is marketed. (CQS = O)	The company provided no medical evidence to modify this evaluation. (FQS = 1)
	No contraindication in patients with history of hypersensitivity. (IQS = 1)	Company agreed with this evaluation. (CQS = 1)	No change in OTA evaluation. (FQS . 1)
	No warning about increased cardiovascular mortality associated with this type of drug. (IQS = 2)	Labels in 15 other countries do not have this warning. (CQS = O)	OTA accepted company's additional argument that the study on which this warning is based is controversial and its results not widely accepted. (FQS. O)
	No information about use during pregnancy or by nursing mothers. (IQS = 1)	Company agreed with this evaluation, (CQS = 1)	No change in OTA evaluation. (FQS = 1)
	No warning about possible loss of blood glucose control when used with certain other drugs. (IQS = 2)	Company agreed with part of this evacuation, but not with mention of one specific drug. (CQS = 2)	No change in OTA evacuation. (FQS = 2)

	No advice about dosages for patients with impaired hepatic or renal function. (IQS = 2)	Company agreed with this evaluation. (CQS = 2)	No change in OTA evaluation. (FQS = 2)
	No information about safety and efficacy of another drug when used with this product. (IQS = 1)	Company agreed with this evaluation. (CQS = 1)	No change in OTA evaluation. (FQS = 1)
Overall *score*	***OTA interim score = 2***	***Company rescore = 2***	***OTA final score= 2***
Antibiotic	No susceptibility testing information. (IQS = 1)	Information not included in 9 of 12 countries in which drug is marketed. (CQS = O)	OTA accepted company's additional contention that sufficient information is included in label. (FQS = O)
Overall score	***OTA interim score = 1***	***Company rescore = O***	***OTA final score= O***
Antinausea antihistamine combination product	No rationale for the combination. (IQS = 1)	Product not marketed in U.S. or other DE-ACs. Company states that "comparable products" with similar labeling are available in 5 countries. (CQS = O)	Company provided no medical evidence that combination was more effective than any single ingredient. (FQS = 1)
	Indication for pyloric spasm and infant colic. (IQS = 2)	● *Company agreed with OTA evaluation but not with score of 2. (CQS = 1)	Company provided some evidence of efficacy in infant colic, but not for pyloric spasm. (FQS = 2)
	Indication for all types of vertigo, including vertigo of vestibular origin. (IQS = 1)	Indication appears in labeling for 1 component in 1 DEAC. (CQS = O)	Company provided evidence of efficacy in vertigo of vestibular origin. (FQS = O)
	No warning about use of product: a) with alcohol orb) by children under 12 years. (IQS = 2)	Labels in one DEAC and in other countries for "comparable products" do not include these warnings. (CQS = O)	Company provided no medical rationale for not including these warnings. (FQS = 2)
	No warning that antihistamines can cause excitability in children. (IQS = 1)	Labels in one DEAC and in other countries for''comparable products" do not include this warning. (CQS = O)	Company provided no medical rationale for not including this warning. (FQS = 1)
	Dosage recommendations for children (OTA requested evidence of safety and efficacy). (IQS = 2)	Dosage recommendations for children are similar to those in some DEACs. (CQS = O)	OTA found that dosages for children were significantly higher than in other countries, according to material supplied by company. However, this was rescored to O because it addresses the same concern as the warning about use in children under 12, above. (FQS = O)
	No information on signs and treatment of overdose. (IQS = 2*)	● *Company pointed out that FDA-approved labeling does not include this information. (CQS = O)	This information is not required by FDA. (FQS = O)
Overall score	***OTA interim score = 3***	***Company rescore = 1***	***OTA final score= 3***

(Cent/nued on next page)

Table 3-3-Company Comparison of OTA Evaluation With Labeling in DEAC Countries-(Continued)

Corticosterold	**No information about drug interactions. (IQS = 1)**	**Company agreed with this evaluation** (cm =1)	**No change in OTA evaluation. (FQS = 1)**
	No information on monitoring long-term therapy. (IQS = I*)	**This information does not appear in labeling for "comparable products" in DEACs.** (CQS = o)	**This information is not required by FDA. (FQS = O)**
	No information on risk of dermal and subdermal atrophy. (IQS = 1")	**This information does not appear in labeling for "comparable products" in DEACs.** (cm = o)	**This information is not required by FDA. (FQS = O)**
	No specification of maximum prescribing limits, pediatric doses, or doses for intra-articular administration. (IQS = 1)	**This information does not appear in labeling for "comparable products" in DEACs.** (CQS = o)	**No change in OTA evaluation. (FQS = 1)**
	No description of procedure for intra-articular administration. (IQS = 1•)	**This information does not appear in labeling for "comparable products" in DEACs. (CQS = O)**	**This information is not required by FDA. (FQS = O)**
Overall *score*	***OTA interim score = 1***	***Company rescore = 1***	***OTA final score= 1***
Antibiotic	**No description of allergic reaction to sodium formaldehyde sulfoxylate (an antioxidant). (IQS = 2*)**	● ***FDA-approved labeling at time of OTA review did not contain this warning. Product was discontinued in survey country 1 year before OTA review. (CQS = O)**	**Company documented discontinuation of product during second review. (FQS. NA)**
Overall score	***OTA interim scorn = 2***	**Company rescore = O**	**OTA final *score = NA***

"* Denotes company response based on rationale other than labeling in other countries.
1• and 2*:A single asterisk denotes a query that deals with information not required by FDA. All such queries were rescored to O in the final evaluation, so no label was held to a standard higher than that of FDA-approved labeling.
tThree additional queries concerning warnings and precautions with interim scores of O had final scores of 1 (one case) or 2 (two cases) because the company failed to document statements made in their first responses to the effect that they had initiated changes in the labeling before the OTA review. The final score remained a 3.

ABBREVIATIONS:
IQS=Interim Query Score (OTA)
CQS. Company Query Score (Company)
FQS - Final Query Score (OTA)
DEAC - Drug Export Act Country (i.e., the 21 countries named in the Drug Export Act of 1986)

NA = Not applicable (product was dropped from analysis because it has been withdrawn from market before OTA review).

SOURCE: Office of Technology Assessment, 1993.

the only outstanding query concerned a listing of inactive ingredients. OTA's final scoring excludes consideration of inert ingredients (see ch. 2), leaving eight of the company's products with queries of other types.

Using the company's "DEAC" standard, five products had overall scores of O, two had scores of 1, and one had a score of 2. After taking into account additional material submitted by the company during the second round of review, OTA final scores were two scores of O, two scores of 1, two scores of 2, and two scores of 3.

Comparison of OTA Evaluation With WHO Prescribing Information

OTA compared its final product evaluations with an independent standard, WHO model prescribing information monographs. These monographs are being prepared as part of WHO's revised drug strategy, adopted by the World Health Assembly in 1986 to complement their "Model List of Essential Drugs." The monographs represent a consensus of WHO's Expert Advisory Panel on Drug Evaluation and are reviewed by selected members of Advisory Panels representing relevant areas of medicine and nongovernmental professional and business organizations with official relations with WHO (including the International Federation of Pharmaceutical Manufacturers Associations, the International Pharmaceutical Federation, the International Union of Pharmacology, and the World Federation of Proprietary Medicine Manufacturers) (282).

Six monographs, organized by area of medicine, were available as of mid-1992. The entries for individual drugs are relatively short compared to FDA-approved labeling, and are intended to contain only essential medical information. For all drugs in the OTA sample that also were in the monograph, OTA compared the monograph entries with OTA's final evaluations of those products. This was done by checking each of the problems identified by OTA ("unresolved queries") with the monographs to see if the monograph agreed with OTA's evaluation. "Agreement" with OTA's evaluation in this case means that the monograph contained information OTA queried as missing from the sample label or did not include information OTA queried as not belonging in the label (mainly indications). Details of the comparisons are given in table 3-4 and summarized here.

Twenty-three products in OTA's sample are included in the six WHO monographs. Excluding queries about inactive ingredients,[2] there were 52 queries relevant to this analysis. Of these, the monographs "agreed" with OTA's evaluation in 40 cases. In 5 cases, the monographs were consistent with some, but not all, aspects of the query, and in 7 cases, the monographs agreed with the sample label and not with the OTA evaluation. This analysis suggests strongly that the majority of unresolved queries in OTA'S product evaluations represent significant problems in the content of the label, as measured against an independent standard.

Summary of Comparisons

The composite standard used by the participating company in its reanalysis resulted in great discrepancies with OTA scoring. The "DEAC standard," however, does not represent a particular set of guiding principles, so the meaning of the results is difficult to interpret. It could be seen as a "least common denominator"—labeling pieced together from the least rigorous points of each of 21 labels would be acceptable under this standard.

OTA's evaluations are generally consistent with the judgments of WHO for those products included in model prescribing information mono-

[2] Inactive ingredients vary among product formulations and, therefore, are not listed in these monographs dealing largely with generic products.

Table 3-4-Comparison of OTA Evaluations With WHO Model Prescribing Information

WHO monograph	WHO monograph agrees with OTA evaluation	WHO monograph does not agree with OTA evaluation
Drugs Used in Anesthesia (280)		
Product 1: Barbiturate anesthetic	No information on clinical pharmacology. (query score = 1) No contraindication for patients hypersensitive to barbiturates, in status asthmatics, or with porphyria. (query score =2) No recommendation for special care in patients with advanced cardiac disease, asthma, and endocrine insufficiency. (query score =2) No information about use in pregnancy and nursing mothers. (query score =1) No mention of following adverse reactions: respiratory depression, myocardial depression, prolonged somnolence, hypersensitivity reactions. (query score = 2) Too little information on use of product (advises physicians to consult the literature). (query score = 2) No information about management of overdose. (query score= 2)	No contraindication for patients without suitable veins for iv. administration. This was part of the overall query on contraindications, so had no individual query score. No recommendation for special care in patients with increased intracranial pressure. This was part of the overall query on patients requiring special care, so had no individual query score. No mention of the following adverse reaction: bronchospasm during recovery. This was part of the overall query on adverse reactions, so had no individual query score. No information about preparation of solutions and incompatibility of product with compounds that may acidify the solution. (query score = 1)
Product 2: Analgesic	No warning about allergic reactions to product. (query score= 1) No information about symptoms and management of overdose. (query score =2)	
Product 3: Anesthetic	inadequate data about safe use of product in pregnancy. (query score =1) No discussion of psychological manifestations during emergence and their avoidance. (query score = 1)	No information about several aspects of clinical pharmacology, including biotransformations, elimination, and half-life. (query score. 1)
Drugs Used In Epilepsy (288)		
Product 1: Antiepileptlc	No warning about use in children under *2* years. (query score. 2) No mention that acute pancreatitis associated with this antiepileptic may be fatal. (query score= *2)*	
Product 2: Antieplieptlc	No mention that acute pancreatitis associated with this antiepileptic may be fatal. (query score= 2)	

Product 3: Antiepllileptic	No warning that sudden withdrawal of this drug can precipitate absence (petit mat) status. (query score = 2) No information on Stevens-Johnson syndrome, a serious adverse reaction. (query score = 2)	
Product 4: Antieplieptic	No information on clinical pharmacology. (query score= 1) No information on indications and usage. (query score= 2) No information on contraindications. (query score = 2) No information on warnings and precautions. (query score =2) No information on drug interactions. (query score =2) No information on adverse reactions. (query score =2) Specific doses for initiation and maintenance not given. (query score =2)	
Product 5: Antieplieptic	No information on clinical pharmacology. (query score = 1) No precaution to discontinue drug if serious forms of dermatitis (bullous, exfoliative, or purpuric), lupus erythematosus, orStevens-Johnson syndrome are suspected. (query score =2) No information on drug interactions. (query score =2) No information on symptoms and management of overdose. (query score =1)	
Drugs Used in ParkInsonIsm (283)		
Product 1: Antiparkinsonism drug		No mention of interaction with tricyclic antidepressants. (query score =1)
Product 2: Antiparkinsonism drug	No information on symptoms and management of overdose. (query score = 2)	
Drugs Used In Mycobacterial Diseases (284)		
Product 1: Antituberculosis drug	No statement that this drug should not be used as monotherapy in light of rapid development of resistance. (query score = 2)	
Product 2: Antltuberculosis drug'	No warning about fatalities associated with hepatic dysfunction. (query score =2)	No warning about increased incidence of hepatomas in mice exposed to this drug. This was part of the warning about hepatic dysfunction, so had no separate query score. No mention that this drug may induce elevations of BUN and serum uric acid. (query score = 1)

(Continued on next page)

Table 3-4-Comparison of OTA Evaluations With WHO Model Prescribing Information-(Continued)

WHO monograph	WHO monograph agrees with OTA evaluation	WHO monograph does not agree with OTA evacuation
		No mention of a number of CNS effects (drowsiness, fatigue, ataxia, dizziness, mental confusion, inability to concentrate, pains in extremities, and generalized numbness). (query score = 1)
		No detailed description of hypersensitivity reaction. (query score =2)
Product 3: Antituberculosis drug		No discussion of the syndrome of CNS depression in infants who receive this drug. (query score = 2)
Drugs Used in Parasitic Diseases (282)[2]		
Product 1: Anthelmintic drug	No statement that other drugs are preferred for dracontiasis and no qualification of effectiveness in trichinosis. (query score= 1)	
	incomplete information on carcinogenesis and mutagenesis. (query score =1)	
	No information on pharmacokinetics. (query score = 1)	
Product 2: Anthelmintic drug	No specific warning about potential neurotoxicity of drug, especially in children. (query score = *2)*	No information on certain precautions (e.g., appropriate caution should be exercised for use in patients with severe malnutrition or anemia). This was part of the overall query on precautions, so had no individual query score.
	Nonformation on certain precautions (e.g., discontinue use if CNS, gastrointestinai, or hypersensitivit y reactions occur). (query score =2)	
	No information on adverse reactions. (query score = 2)	
	No statement that maximum cure rate is usually obtained with multiple-dose regimen. (query score =2)	
Product 3: Anthelmintic drug	No information on clinical pharmacology. (query score = 1)	
	No contraindication for patients with epilepsy. (query score =2)	
	No information on side effects, including transient neurological effects and urticarial reactions, (query score = 2)	
	No information on toxicity. (query score= 2)	

Drugs Used in Superficial Fungal Infections (289)[3]	
Product 1: Topical antifungal drug	No microbiology data. (query score= 1) No warning about possible irritation or allergic contact dermatitis. (query score =1) No precaution against contact with eyes. (query score = 1)
Product 2: Topical antifungal drug	No statement that this drug is not indicated for trivial infections. (query score =2) No warning regarding prophylactic use, tumorigenicity, use in pregnancy, teratogenicity, and suppression of spermatogenesis. (query score =2) (WHO monograph includes all except warning about suppression of spermatogenesis.)

[1] One of OTA's queries, related to use of this drug for indications other than mycobacterial diseases, was not addressed in the WHO monograph. That query is not included in this table.
[2] Four products in OTA's sample were included in this monograph: 1 had a final overall score of O. Only the remaining 3, with unresolved queries, are included in this table.
[3] Six products in OTA's sample were included in this monograph: 4 had final overall scores of 0. Only the remaining 2, with unresolved queries, are included in this table.

graphs. The monographs contain relatively short entries for products, containing only the most essential information. This analysis provides validation of OTA's method and evaluation standard.

EXPLANATION OF ADDENDUM TABLES 3-1 THROUGH 3-6

Addenda tables 3-1 through 3-6 detail the results of drug labeling analyses for each product in OTA's sample. The products are arranged in six tables based on their overall scores, and are arranged alphabetically by type of drug within each table. Products with labeling that was not fully evaluated are designated by the overall score "NA."

The column labeled Type of drug" gives a brief description of each drug, rather than the specific generic or brand name. (OTA agreed early on in the study that it would not include the specific generic or brand names of drugs in this report.)

The third column, labeled "Source," describes the source of labeling information that was evaluated. In most cases, the package insert was evaluated (indicated by the abbreviation pi). In other instances, the package insert pending approval by the local regulatory agency was evaluated (abbreviated pipa). Where package inserts were not available, other sources of information were used, including prescribing guide entries (pg) and package labels (pl), and in two instances, product documents (pals) were evaluated.[34]

The fourth column, labeled "Category," lists the category of labeling information in which each of the unresolved queries falls. Categories of information include: description and clinical pharmacology (abbreviated "dcp"), ingredients (ing), indications (ind), contraindications (ci), warnings and precautions (wp), adverse reactions (ar), dosage and administration (da), and overdose information (od).

A description of each unresolved query appears in the fifth column, labeled "Nature of problem." The queries are listed by the category of information to which they refer. Where several queries for a product fall in the same category of information, they are listed in succession.

The sixth column, "Query score;' lists the medical importance score assigned to each unresolved query.

---

[3] At the beginning of the study, OTA agreed to evaluate the company prod@ documents for two products that did not have package inserts. Later, however, OTA decided not to review company product documents because they are not universally available to the physicians who use the product (they are often only available by request to the company or sometimes are distributed by company detail men to physicians and pharmacists). However, because OTA had previously agreed to evaluate the documents for these two products, these evaluations appear in the sample.

[4] In several instances, the package insert for a product did not include some medically important information that was included in the product's prescribing guide entry. In these instances, indicated "pi, pg," credit was given both for medically important information included only in the prescribing guide entry and for information appearing in the package insert.

Addendum 3-I—Products With Adequate Labeling (Overall Score = O)

Type of drug	Source	Type of drug	Source
Absorbable hemostatic sponge	pi	Emollient dental paste	pi
Adrenergic decongestant for ocular administration	pi	Folic acid antagonist antineoplastic	pi
Aminocyclitol antibiotic	pi	Hair growth stimulant	pi
Aminoglycoside for ophthalmic administration	pi	Injectable corticosteroid with anesthetic	pipa
Antacid	pi	Injectable postmenopausal estrogen	pi
Antibiotic	pi	Insulin preparation	pi
Antiestrogenic drug	pg	Ion exchange resin	pi
Antifungal agent	pi	Monotropic cardiac drug	pi
Antifungal polyene antibiotic suspension	pg	Macrolide antibiotic	pipa
Antihistamine	pg	Nonsteroidal anti-inflammatory drug	pi
Antihistamine	pi	Nonsteroidal anti-inflammatory drug	pipa
Antihistamine, barbiturate, and methylxanthine combination	pi	Nonsteroidal anti-inflammatory drug	pi
Antineoplastic	pi	Nonsteroidal anti-inflammatory drug in suppository form	pg
Cephalosporin antibiotic	pi	Oral contraceptive	pi
Cephalosporin antibiotic	pi	Penicillin-derivative antibiotic	pi, pg
Cephalosporin antibiotic	pi	Penicillin-derivative antibiotic	pi
Cephalosporin antibiotic	pi	Progestin used for oncologic indications	pi
Cholinergic agonist for urologic indications	pi	Pyrimidine analogue antineoplastic	pi
Combination analgesic, antihistamine, and adrenergic decongestant	pi	Quinolone antibiotic	pi
Combination antifungal and antiprotozoal antibiotic	pg	Quinolone antibiotic	pi
Combination aspirin, antihistamine, caffeine, and adrenergic decongestant	pi	Selective alpha-ad renergic blocking agent	pg
Combination sulfa antibiotic and corticosteroid for ophthalmic administration	pi	Sulfonylurea oral hypoglycemic	pi
Combination sulfa antibiotic and corticosteroid for ophthalmic administration	pi	Sympathomimetic decongestant	pi
Combination topical anesthetic and antacid	pi	Systemic corticosteroid	pi
Combination topical decongestant and analgesic for otic administration	pi	Systemic corticosteroid	pi
Combination xanthine-derivative bronchodilator and expectorant	pg	Tetracycline antibiotic	pi
Dopamine antagonist antiemetic	pi	Tetracycline antibiotic	pi
Electrolyte dehydration solution	pi	Tetracycline antibiotic	pi
		Thioxanthene-derivative antipsychotic	pi
		Thyroid hormone synthesis inhibitor	pi
		Topical antifungal and steroid combination	pi
		Topical nonsteroidal anti-inflammatory drug	pi
		Tricydic antidepressant	pi

SOURCE KEY: pi - package insert; pg - prescribing guide entry; pipa - package insert pending approval.

330-065 0 - 93 - 3 QL 3

Addendum 3-2-Products With an Overall Score of 1

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Aminoglycoside antibiotic	pi	wp	Labeling does not have information about some drug-laboratory test interactions.	1
1	Aminoglycoside antibiotic	pi	wp	Insert has no information about carcinogenesis.	1
1	Antihistamine	pi	wp	Insert has no information about use of this product in patients with liver disease.	1
1	Antihistamine indicated for appetite stimulation	pi	dcp	Insert omits information on pharmacokinetics and metabolism.	1
			ing	Insert does not list inactive ingredients.	R
1	Antiparasitic drug	pi	dcp	Insert does not include information about pharmacokinetics.	1
			ind	Insert does not state that niridazole and metronidazole are preferred treatments for dracontiasis; insert does not adequately qualify effectiveness of this drug in trichinosis (the drug is not effective in altering the course of the infection once established, i.e., once the infection has reached the invasive stage).	1
1	Antiparkinsonian agent	pi	wp	Insert omits interaction with tricyclic antidepressants (resulting in hypertension, dyskinesia).	1
1	Beta blocker	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product broadly indicated for symptomatic treatment of hyperthyroidism (rather than for adjunctive therapy for thyrotoxicosis).	1
			ar	Insert does not list among adverse reactions depression, hailuanations, visual disturbances, and emotional lability.	1
1	Combination analgesic, antihistamine, opioid, and methylxanthine	pi	dcp	Manufacturer did not provide adequate rationale for this drug combination.	1
1	Combination antacid	pi	dcp	Insert contains promotional language (e.g., “the preferred dosage”).	1
			da	Insert does not include the maximum daily dosage.	1
1	Combination antihistamine and adrenergic decongestant	pg	a	Entry lacks a specific contraindication for children under 2 years of age. Product should be contraindicated in infants, who may have unpredictable reactions-e. g., central nervous excitation rather than sedation.	1
			od	Entry does not include information about overdose management.	1
1	Combination antihistamine, adrenergic decongestant, and antitussive	pg	dcp	Manufacturer did not provide data demonstrating the additive therapeutic actions and minimal potential for toxicity of this combination.	1
1	Combination centrally acting antiadrenergic agent and thiazide diuretic	pipa	ind	Insert has no warning that this fixed combination drug is not indicated for initial therapy for hypertension.	1

1	Combination methylxanthine bronchodilator, barbiturate, and adrenergic agonist	pi	ing	Insert does not list inert ingredients.	R
			ci	Insert has no contraindication for patients with prostatic hypertrophy.	1
1	Folic acid analogue	pi	dcp	Insert does not have section describing clinical pharmacology,	1
			wp	Insert does not have information about drug interactions (with neuroleptics).	1
			da	Insert does not specifically advise monitoring methotrexate levels to ensure that the dose of this folic acid analogue is adequate for rescue.	1
1	H-2 receptor antagonist	pipa	wp	Labeling omits mention of the pharmacologic interaction of this H-2 receptor antagonist and some other drugs, such as propranoloi, tricydic antidepressants, and lidocahe.	1
1	Long-acting nitrate vasodilator	pi, pg	ci	insert does not include contraindication for hypersensitivity or idiosyncrasy to other nitrates or nitrites.	1
			wp	Insert has no warning about the following: risks inherent in concurrent with calcium channel blockers; risk of paroxysmal bradycardia; risk of aggravation of angina.	1
				Insert has no information about use in pregnancy, use in nursing mothers, or pediatric use.	1
1	Macrolide antibiotic	pl, pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry indicates this macrolideantibiotic for treatment of *Giardia lamblia, Clostridium tetanii*, and *Ureaplasma urealyticum*.	1
			ar	Entry does not note that rare reports of pseudomembranous enterocolitis have been reported with therapy with this antibiotic; entry does not list adverse reactions for which a cause and effect relationship has not been established, including isolated reports of central nervous system side effects, cardiovascular symptoms, and, in persons with renal insufficiency and/or who are receiving high doses of this antibiotic, reversible hearing loss,	1
1	Multivitamin and multimineral	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product indicated for "undernourishment."	1
1	Multivitamin with iron	pi	ing	Insert does not list inactive ingredients.	R
			da	Insert does not have appropriate dosage information for infants less than one year of age.	1
1	Non-barbiturate anesthetic	pi	dcp	Insert does not provide information about several aspects of clinical pharmacology, including biotransformation, elimination, and half-life.	1
			ing	Insert does not list inactive ingredients.	R
			wp	Manufacturer provided inadequate data about safe use of this product in pregnancy (this product may induce uterine contractions during the first trimester of pregnancy),	1
				Insert does not have a detailed discussion about psychological manifestations during emergence and its avoidance.	1

Continued on next page

Addendum 3-2—Products With an Overall Score of I-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Nonsteroidal anti-inflammatory drug	pi	dcp	Insert does not have clinical pharmacology information, including half-life, onset and duration of action, and route of elimination.	1
			ing	Insert does not list inactive ingredients.	R
1	Nonsteroidal anti-inflammatory drug	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not contain a precaution regarding NSAID-induced aseptic meningitis.	1
1	Ophthalmic aminoglycoside antibiotic	pg	ind	Manufacturer did not provide data supporting efficacy against certain strains of mycoplasma	1
1	Ophthalmic tetracycline analogue antibiotic	pi	ind	Insert does not limit indications to ophthalmic infections that are superficial.	1
1	Opioid-derivative antidiarrheal	pi	ind	Labeling does not note that pediatric use for treating chronic diarrhea has not been established.	1
1	Oral contraceptive	pi	ind	Insert indicates product for menstrual irregularities in general without specifying causes.	1
1	Oral contraceptive	pi, pg	ind	Insert indicates product for correction of certain menstrual irregularities, without specifying causes.	1
1	Penicillin-derivative antibiotic	pi, pg	wp	Insert does not warn about possible development of pseudomembranous colitis (merely warns about the possibility of superinfection).	1
1	Potassium-sparing diuretic	pg	dcp	Entry does not describe chemical properties or pharmacokinetics.	1
			ing	Entry does not list inactive ingredients.	R
			ind	Entry does not state that the product is not first-line therapy for congestive heart failure.	1
				Entry includes indications for “idiopathic edema,” myasthenia gratis, and malignant hypertension.	1
				Indication for malignant hypertension contradicts the contraindication in acute renal dysfunction.	1
			wp	Entry has no warnings about drug interactions with indomethacin and captopril.	1
			da	Entry does not recommend adding another diuretic if adequate response is not obtained with the product alone.	1
1	Substituted benzamide antipsychotic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not caution about use in patients with cardiovascular disease, CNS depression, blood dyscrasias, hepatic impairment, and in comatose patients.	1
			ar	Insert does not warn about the following adverse reactions: blurred vision, pigmentary retinopathy, difficulty with urination, photosensitivity, rash.	1

1	Substituted benzamide antipsychotic	pi	wp	Insert does not include a precaution about the potentiating effect of alcohol.	1
				Insert omits precautions about use in patients with respiratory disease or cardiovascular disease; no warning about use in patients with liver dysfunction or a history of jaundice.	1
				Insert does not have information about drug-lab test interactions.	1
1	Systemic corticosteroid	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert has no information about drug interactions.	1
			da	insert does not give pediatric dosages.	1
1	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			od	Insert does not have information on overdose.	1
1	Systemic corticosteroid	pds	wp	Insert does not warn that this drug may prolong coma in cerebral malaria.	1
1	Systemic corticosteroid	pi	wp	Insert does not warn about enhanced effect of steroids in patients with hypothyroidism or cirrhosis.	1
1	Topical analgesic	pg	ind	Indications not appropriately limited to minor wounds.	1
1	Topical antifungal	pi	dcp	Insert does not provide microbiology data.	1
			wp	Insert does not warn about possibility of irritation or allergic contact dermatitis.	1
				Insert does not have precaution against contact with eyes.	1
1	Topical bacteriostatic agent	pi	ind	Product is indicated for cleansing of infants in certain circumstances.	1
			wp	Insert does not note that detectable blood levels of this topical bacteriostatic agent have been found after repeated cleansings.	1
				Insert provides no information on use in nursing mothers or about carcinogenesis and impairment of fertility,	1
1	Topical combination corticosteroid and 8-hydroxyquinolone antibiotic	pg	ing	Entry does not list inactive ingredients.	R
			wp	There are no precautions about interference with thyroid function tests and interference with laboratory assays for phenylketonuria.	1
				Entry does not note potential for adrenal suppression with substantial systemic absorption and other adverse effects of systemically absorbed steroids.	1
1	Topical corticosteroid	pi	dcp	Insert has no information about pharmacokinetics of topically absorbed corticosteroids.	1
			wp	Insert does not note that patients receiving large doses of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests.	1

Continued *on next page*

Addendum 3-2—Products With an Overall Score of l-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
1	Tricydic antidepressant	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert does not warn about cross sensitivity with other tricyclic antidepressants.	1
				Insert does not warn about the following: concurrent use with antithyoid agents may increase the risk of agranulocytosis; delirium has been reported with concurrent administration of the tricyclic antidepressant and disulfiram.	1
				Insert does not warn that paralytic ileus may occur in patients taking tricyclic antidepressants with anticholinergics; schizophrenic patients may have increased symptoms of psychosis; patients with paranoid symptoms may have an exaggeration of such symptoms.	1
				Insert does not note that withdrawal symptoms of nausea headache, and malaise may occur with abrupt cessation of therapy.	1
			ar	The following adverse reactions are not listed: drowsiness, dizziness, and neuroleptic malignant syndrome.	1
1	Urinary tract antiseptic	pi	wp	Insert does not state that urine pH should be monitored to maintain urine acidity.	1

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pipa. package insert pending approval; pl= package label; pds - product document.

CATEGORY KEY: dcp= description/clinical pharmacology; ing. ingredients; ind - indications; ci - contraindications; wp= warnings and precaution; ar= adverse reactions; da. dosage and administration; od = overdose information.

Addendum 3-3-Products With an Overall Score of 2

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Aminocyclitol antibiotic	pi	dcp	Insert does not mention need for susceptibility y testing of isolates associated with treatment failure.	1
			wp	Insert does not have warning about the benzyl alcohol content of the product's diluent.	1
				Insert does not include precautions regarding development of resistance to ***Neisseria*** *gonorrhoeae.*	1
				Insert has no warning about risk of anaphylaxis or anaphylactoid reactions.	2
2	Aminoglycoside antibiotic	pi, pg	ind	Insert indicates product for methicillin-resistant S. *aureus* and gonococcal infections without noting that this aminoglycoside antibiotic is not drug of choice for these infections.	2
			Wp	Although labeling states that safety of this aminoglycoside antibiotic during pregnancy has not been established, the insert fails to warn specifically about the risk of total irreversible bilateral congenital deafness to children whose mothers receive aminoglycosides during pregnancy.	1
2	Aminoglycoside antibiotic	pi	dcp	Insert states that this aminoglycoside antibiotic is effective *in vitro* against *Neisseria meningitidis, Neisseria gonorrhoeae,* and *Streptococcus pyogenes.*	1
			wp	Insert does not include a discussion of the syndrome of CNS depression in infants who receive this aminoglycoside antibiotic.	2
2	Analgesic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about allergic reactions to this product.	1
			od	Insert does not have information about the symptoms and management of overdose.	2
2	Anesthetic for ophthalmic administration	pi	dcp	Insert does not describe clinical pharmacology.	1
			ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about risk of corneal opacification with prolonged use.	2
				Insert does not warn about risk of systemic toxicity.	1
				Insert does not caution that the patient should protect eyes from irritants during the period of anesthesia.	2
			ar	Insert does not list among adverse reactions systemic hypersensitivity, pupillary dilatation, or cycloplegic effects.	1
2	Antacid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert fails to warn about risk of hypermagnesemia in patients with renal disease.	2
				Insert omits information about the interaction of aluminum in this antacid with tetracycline.	2
2	Antacid combination	pi	wp	Label omits warning concerning use in patients with renal dysfunction.	2
				Label omits warning about known drug interaction with tetracycline.	1

Continued on next page

Addendum 3-3-Products With an Overall Score of 2-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Antidiarrheal combination with aminoglycoside antibiotic	pi	ind	Product is broadly indicated for "bacterial diarrhea" (rather than specifically for preoperative suppression of intestinal bacteria and treatment of diarrhea due to enteropathogenic *Escherichia coli).*	2
				Insert does not note that oral dehydration therapy is considered first-line treatment for childhood diarrhea.	1
			ci	Insert does not contraindicate use in children.	1
2	Antidopanergic antiemetic and gastrokinetic	pi	ind	Product is indicated broadly for gastrointestinal motility disturbances (rather than for symptomatic gastroesophageal reflux, diabetic gastroparesis, prevention of nausea and vomiting associated with cancer chemotherapy, and small bowel incubation).	2
			wp	Insert has weak warning about tardive dyskinesia.	1
			da	Insert does not include information about admixture compatibilities of intravenous solution.	1
2	Antiepileptic drug	pg	ar	Entry does not note that acute pancreatitis associated with use of this antiepileptic drug may be fatal.	2
2	Antiepileptic drug	pg	dcp	Entry does not include information about clinical pharmacology.	1
			wp	Entry does not include precaution to discontinue this antiepileptic if more serious forms of dermatitis (bullous, exfoliative, or purpuric dermatitis), or if lupus erythematosus or Stevens-Johnson syndrome are suspected.	2
				Entry does not have information about drug interactions, including drugs which may increase levels of this antiepileptic (e.g., chloramphenicol, acute alcohol intake, estrogens, sulfonamides, cimetidine); drugs which may decrease levels of this antiepileptic (e.g., chronic alcohol abuse, reserpine, antacids containing calcium); drugs which may either increase or decrease serum levels of this antiepileptic (phenobarbital, valproic acid, sodium valproate); and drugs whose efficacy is impaired by this antiepileptic (corticosteroids, quinidine, digitoxin, rifampin, doxycydine, estrogens).	2
2	Antihistamine	pi	ing	Insert does not list inactive ingredients.	R
			ar	Insert does not mention among adverse reactions the following: nervousness, weakness, appetite increase, cough, angioedema, hypotension, photosensitivity, seizures, prolonged QT interval on EKG, and ventricular arrhythmias.	2
			od	Entry does not have information on symptoms and management of overdose.	1
2	Antiparkinsonian agent	pipa	od	Insert does not include information on signs and management of overdose.	2
2	Antituberculosis drug	pi	ind	Insert does not state that this antituberculosis drug should not be used as monotherapy in light of rapid development of resistance.	2

2	Benzodiazepine	pg	dcp	Company provided no adequate rationale for description of this product as a "tranquilizer."	1
			ci	Entry does not include a contraindication against use by patients with hypersensitivity to this product.	1
			wp	Entry does not include warnings against use in psychotic states and psychiatric disorders in which anxiety is not a prominent feature; no warning about use in addiction-prone patients, such as drug addicts and alcoholics; no information about withdrawal symptoms.	2
				Entry does not include information on drug interactions.	1
				Entry does not note the need for frequent patient reassessment; insert does not warn about use in depressed patients in case of suicidal tendencies; does not warn that this benzodiazepine may increase depression; no evidence of safety and efficacy of this benzodiazepine in patients below age 18; no information on long-term use.	2
			od	Entry does not have information on treatment of overdose.	1
2	Benzodiazepine hypnotic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert claims that this benzodiazepine hypnotic has no withdrawal effects (omits mention of daytime anxiety and rebound insomnia).	2
				Insert does not state that fetal damage may occur if drug is used in the first trimester (insert merely states that the safety of drug during pregnancy has not been established).	1
				Insert does not warn that hypnotics can increase depression in patients who are already depressed, and may therefore increase risk of attempted suicide.	1
			ar	Insert does not mention common (greater than 4 percent incidence) adverse reactions, including nervousness, nausea and vomiting.	1
2	Cephalosporin antibiotic	pg	ind	No adequate support for indication for use in treatment of endocarditis.	2
			wp	Entry does not have information about potential for superinfection with prolonged use of this antibiotic.	1
2	Cephalosporin antibiotic	pi	ind	No adequate support for indication for use in treatment of endocarditis.	2
2	Combination "hepatic protector"	pg	dcp	Entry does not have description and information about clinical pharmacology.	1
				Company did not provide adequate justification for this drug combination and the ratio of its components.	2
			ind	Product is indicated for treatment of "hepatobiliary dysfunction" but also includes a warning about use in persons with jaundice.	1
			wp	Entry omits precautions for an amino acid component of this combination (nausea and vomiting; may precipitate hepatic encephalopathy in patients with established liver disease; concurrent use with MAO inhibitors could superimpose symptoms of intoxication, such as delirium, visual hallucinations, ataxia, speech disturbances, increased salivation, and hyperhidrosis).	1
			ar	Entry omits adverse effects associated with one component of this combination (nausea, vomiting, gastrointestinal discomfort and diarrhea, incontinence, depression, and an unpleasant fishy odor).	1

Continued on next page

Addendum 3-3-Products With an Overall Score of 2-Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Combination analgesic and centrally acting muscle relaxant	pi	ing	insert does not list inactive ingredients.	R
			dcp	Insert does not describe chemical properties of this combination.	1
				Insert does not describe the clinical pharmacology of this combination.	1
			ind	Company failed to provide evidence of efficacy and safety of this centrally acting muscle relaxant in humans.	2
			wp	Insert has no warning about cross-sensitivity with aspirin.	1
				Insert has no information about carcinogenesis, mutagenesis, or impairment of fertility.	1
2	Combination antiflatulent and antacid	pg	wp	Entry omits mention of a drug interaction with tetracycline.	2
			da	Entry omits maximum dosage.	1
2	Combination antihistamine and adrenergic decongestant	pl	ing	Label does not list inactive ingredients.	R
			wp	Label provides no warning about use in patients with cardiac disease, diabetes, or asthma.	2
				Label has no information about use in pregnancy.	1
				Label has no warning about use with MAO inhibitors or with antihypertensive drugs.	1
			ar	Labeling does not warn about sleeplessness, dizziness, and nervousness.	1
2	Combination antihistamine, analgesic, and adrenergic decongestant	pi	ing	Insert does not include alcohol content of product.	2
2	Combination antihistamine, antitussive, and adrenergic decongestant	pi, pg	ing	Insert does not list inactive ingredients.	R
			ind	No evidence that components of this product are effective as expectorants.	1
			wp	Insert does not caution about using antihistamines inpatients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction, and ventricular tachycardia.	1
			ar	Insert does not note adverse effects associated with antihistamines (such as dry mouth, dizziness, disturbed coordination, confusion, epigastic distress, thickening of bronchial secretions), adrenergic decongestants (such as tachycardia palpitations, headache, nervousness, tremor), and the antitussive in this preparation (such as confusion, nervousness, or irritability).	2
			od	No information is provided about overdose.	1
2	Combination aspirin with antacid	pi	ing	Label does not list inactive ingredients.	R
			od	No information about management of overdose.	2

2	Combination bismuth, anesthetic and corticosteroid for topical administration	pi	ing	Insert does not list inert ingredients.	R
			wp	Insert does not have a precaution concerning systemic absorption and development of HPA axis suppression and the need for monitoring; use over large areas; caution against ophthalmic contact; and warning to discontinue use if irritation develops.	1
				Insert does not warn against using tight-fitting diapers or plastic pants on children being treated in the diaper area (these garments may constitute occlusive dressings).	2
				Insert has no information on use in nursing mothers.	1
			ar	Insert does not list the following adverse reactions: skin atrophy, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of skin, secondary infections, and striae.	1
			da	Insert does not provide information on duration of therapy.	1
2	Combination cortcosteroid, antifungal polyene antibiotic, and aminoglycoside antibiotic for topical administration	pg	wp	Entry contains no warning against ophthalmic use.	1
				Entry Contains no warning about the following: nephrotoxicity and ototoxicity of aminoglycoside antibiotic, risk of HPA axis suppression and Cushing's syndrome with systemic absorption of topical corticosteroids, and risk of overgrowth of nonsusceptible organisms.	2
				Entry contains no recommendation to perform appropriate microbiological studies if there is a lack of therapeutic response.	2
				Entry has no information about carcinogenesis, mutagenesis, and impairment of fertility.	1
				Entry does not mention precautions about the following: use in pediatric patients, use in pregnancy, use in nursing mothers, risk of systemic absorption of topical carticosteroids, and types of conditions that augment systemic absorption.	2
			ar	Entry does not mention the following adverse effects: ototoxicity, nephrotoxicity, burning, itching, dryness, folliculitis, hypertrichosis, acneform eruptions, hyperpigmentation, perioral dermatitis, allergic contact dermatitis, maceration of skin, secondary infection, skin atrophy, and striae.	1
			da	Entry does not advise against use of this product under occlusive dressings.	1
2	Combination urinary tract antiseptic and analgesic	pi	wp	Insert omits precaution against use in prepubertal children and pregnant women just prior to labor.	1
			od	Insert omits overdose treatment information for this combination.	2
2	Combination xanthine bronchodilator, barbiturate, and adrenergic agonist	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not state that acute or severe asthma attacks may necessitate supplemental therapy with other inhaled or parenterally administered drugs.	2
			da	Dosages are not adjusted for the weight of the patient.	1
				Insert recommends dosing three times a day rather than every eight hours.	1

Continued on next page

Addendum 3-3-Products With an Overall Score of 2

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Corticosteroid for ophthalmic and otic administration	pi	ing	Insert does not list inactive ingredients.	R
			ind	Insert indicates this topical corticosteroid for treatment of herpes zoster ophthalmia, without noting that other topical steroid preparations are preferred.	2
				Insert indicates this topical corticosteroid for neovascularization, keratoconjunctivitis (without qualification), phiyctenularkeratitis (other references recommend a combination topical corticosteroid-antibiotic combination).	2
			wp	Insert lacks information about use in pregnancy, in pediatric patients, and in geriatric patients.	1
			ar	Insert does not list the following adverse reactions: globe perforation, exacerbation of glaucoma or ocular hypertension, Posterior subcapsular cataracts, and burning or stinging of ears.	1
2	Direct-acting arterial vasodilator	pg	wp	Weak warning about hypotension (listed as an "infrequent" serious secondary reaction).	2
				Entry omits precaution that product is for use in closely monitored settings, such as in the hospital.	2
2	Hypolipidemic drug	pi	ind	Insert does not note that diet is the initial therapy of choice for hyperlipidemias, and that drug therapy should not be used for routine treatment.	1
			ci	Labeling does not include a contraindication for patients with preexisting gallbladder disease and for patients with hypersensitivity to this drug.	1
			wp	No warning that this drug maybe associated with cholelithiasis.	1
				insert does not state that adequate studies on caranogenicity have not been done in humans, and that hepatic carcinomas have been found in rats that have been exposed to this drug.	2
				Insert does not include the following precautions: insert does not state that treatment should be discontinued if response is inadequate after 3 months; labeling omits rare hematologic changes; no information on impairment of fertility (based on animal studies); labeling has no statement about pediatric use.	1
2	Injectable progestin	pi	a	Insert does not contraindicate use in carcinoma of the breast and missed abortions.	1
			wp	Insert states that "[n]o teratogenic effects were observed in mice and rats" although progestins have been shown to have teratogenic effects in animals and humans.	2
				Insert does not address evidence of development of mammary nodules in monkeys.	1
2	Lincosamide antibiotic	pi	ind	Insert indicates antibiotic for use in upper respiratory infections, although most upper respiratory infections are non-bacterial.	1
			wp	Insert has weak warning about association between antibiotic use and the development of pseudomembranous colitis.	1
				Insert does not warn that this antibiotic should not be used for treatment of meningitis (due to poor penetration of the blood-brain barrier).	2

			ar	Insert does not note that eosinophilia, agranulocytosis, and thrombocytopenia have occurred with use of this antibiotic.	1
2	Macrolide antibiotic	pi	ind	Insert includes indication for respiratory tract infections due to staphylococci, streptococci, and haemophilus.	2
				Insert does not limit the treatment of Staphylococcus *aureus* with this antibiotic to skin and soft tissue infections.	2
2	Multivitamin with calcium and iron	pg	wp	Entry does not note that iron absorption is inhibited by the concurrent ingestion of eggs and milk.	1
				Entry does not mention interactions with other drugs, including antacids, tetracycline, and levodopa	1
			od	Entry does not include information about the signs, symptoms, and management of overdose.	2
2	Multivitamin with iron	pg	ing	Entry does not list inactive ingredients.	R
			ind	Product is indicated as an appetite stimulant.	2
			wp	Entry does not have recommendation for pregnant women and nursing mothers to seek medical advice before using this product.	1
2	Multivitamin with minerals	pi	ing	Insert does not list inactive ingredients.	R
			ci	Insert does not have contraindication for patients with hemochromatosis.	1
			wp	Insert does not warn that the presence of pernicious anemia should be excluded before initiating therapy because folic acid may mask symptoms of pernicious anemia, allowing untreated necrologic deficits arising from vitamin B-1 2 deficiency to progress.	2
				Insert does not have the following precautions: calcium content should be considered before prescribing for patients with kidney stones, do not exceed recommended dosage, need for periodic hematologic tests to monitor therapy.	1
			ar	Insert does not list adverse reactions such as allergic reactions, skin rashes, gastrointestinal disturbances, nausea vomiting, diarrhea, constipation, generalized flushing and feeling of warmth with niacinamide, allergic sensitization following administration of folic acid.	1
			da	Dosage of iron inadequate for pregnant women.	1
			od	Insert does not have information on management of iron overdose.	1
2	Multivitamin with protein and minerals	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not state that product is merely supplemental and not a replacement for oral food intake or for treatment of protein-calorie deficiency states.	2
2	Nitrosourea antineoplastic	pi	wp	Insert does not note that past history of lung disease is a risk for pulmonary toxicity.	2
				Insert has no information about the relation of pulmonary toxicity to total cumulative dose.	2
				Insert fails to recommend monitoring of complete blood count for hematologic adverse reactions for at least six weeks after receiving a dose of this antineoplastic agent.	1
			da	Insert has no warning about use of this product with glass containers.	1

Continued on next page

Addendum 3-&Products With an Overall Score of 2-Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Nonsteroidal anti-inflammatory drug	pi	wp	insert does not have a warning about the pharmacologic idiosyncratic type of anaphylactic reaction to anti-inflammatory drugs.	1
				Insert does not mention that the usefulness of fever and inflammation as diagnostic signs of infection in patients on nonsteroidal anti-inflammatory drugs is reduced.	1
			ar	insert does not mention that this nonsteroidal anti-inflammatory drug has been associated with skin reactions, including erythema multiform; insert also does not note that agranulocytosis (which may be fatal) may occur (insert only mentions granulocytosis which suggests a less serious effect).	2
2	Nonsteroidal anti-inflammatory drug	pi	dcp	Insert does not have full information on clinical pharmacology.	1
			ar	insert does not warn specifically about the following adverse reactions: risk of erythema multiforme and StevensJohnson syndrome, ulcers, renal effects, fluid retention, and use in cardiac patients.	2
2	Nonsteroidal anti-inflammatory drug	pds	dcp	Document does not include medically important pharmacokinetic information, including half-life and route of elimination.	1
			ing	Document does not list inactive ingredients.	R
			wp	Document does not warn that there are known effects of this class of drug on the human fetus, including closure of the fetus, arteriosus, platelet dysfunction with resultant bleeding, renai dysfunction or failure with oiigohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes.	1
				Document states that concomitant administration of this drug and sulindac results in a substantial, "but not statistically significant," lowering of plasma levels of sulindac, despite the fact that plasma levels in the 13 male volunteers included in the study dted had plasma levels of sulindac lowered by one-third.	1
				Document has no recommendation against use in children.	1
			ar	Document does not include proteinuria among adverse reactions.	1
			od	Document has no information on the management of overdose.	2
2	Nonsteroidal anti-inflammatory drug	*pg*	od	Entry does not have information about signs and treatment of overdose.	2
2	Nonsteroidal anti-inflammatory drug	pi	wp	Insert has no information about proteinuria or the nephrotic syndrome.	1
				Insert does not state that this drug is a known teratogen in animals.	2
2	Nonsteroidal anti-inflammatory drug	pi	ing	insert does not list inactive ingredients.	R
			ind	Manufacturer did not provide adequate evidence of efficacy for relief of pain and fever associated with acute upper respiratory tract inflammation.	2
2	Opioid analgesic used in anesthesia	pi	wp	insert does not include information about use in nursing mothers.	1
				Insert does not warn about the euphoria and miosis that may occur with narcotic analgesics.	1

			ar	Insert does not contain information on secondary rebound respiratory depression or about a number of other adverse reactions that may occur when this narcotic analgesic is used in combination with droperidol.	2
2	Penicillin-derivative antibiotic	pi	ind	Insert lists indications by types of susceptible pathogen and site of infection separately rather than listing indications by site of infection, qualifying each by type of susceptible pathogen.	1
				Insert includes the following indications: ear, nose, throat, and oral cavity infections; endocarditis.	2
2	Penicillin derivative antibiotic	pi	wp	Insert fails to warn about risk of anaphylactic reactions.	2
				Insert has no information about several drug-lab test interactions (e.g., fake positive glucose reactions with Clinitest, Benedict's solution, or Fehling's solution).	1
			ar	Insert does not include information about the following adverse reactions: gastrointestinal system (e.g., pseudomembranous colitis), liver function (enzyme elevations), hemato-poietic system (anemia, eosinophilia, agranulocytosis).	1
2	Postmenopausal estrogen	pi, pg	ing	Insert does not list inactive ingredients.	R
			wp	Insert has no information on carcinogenesis, mutagenesis, use in nursing mothers, and pediatric use.	1
			ar	Insert does not list gallbladder disease among adverse effects.	1
			da	No justification for recommendation on insert to increase dosage to 2.5 mg/day in 3-4 days if no improvement occurs at a dosage of 1.25 mg/day.	2
2	Progesterone-derivative oral contraceptive	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product is indicated for treatment of pelvic pain and mastodynia; company provided no adequate evidence of efficacy for these indications.	2
			wp	Insert does not caution about the use of oral contraceptives in patients with impaired liver function.	1
				Insert does not warn about the increased risk of pyridoxine and folate deficiency in oral contraceptive users.	1
2	Sulfonylurea oral hypoglycemic	pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry indicates oral hypoglycemic for diabetes insipidus, but does not note that desmopressin is the preferred treatment.	1
			ci	Entry does not contraindicate use by patients with known hypersensitivity to the drug.	1
			wp	Entry does not have information about use in pregnancy and nursing mothers.	1
				Entry does not describe the following: loss of control of blood glucose when drugs which produce hyperglycemia are used; interaction of oral miconazole and oral hypoglycemic.	2
				Entry does not advise conservative doses in patients with impaired hepatic or renal function.	2
				Entry does not provide data on the safety and efficacy of use of phenformin with sulfonylurea oral hypoglycemic in patients who are unresponsive to sulfonylurea oral hypoglycemic alone.	1

Continued on next page

Addendum 3-&Products With an Overall Score of 2-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
2	Synthetic androgen	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert lacks warning regarding decreased HDL and increased LDL in patients receiving this synthetic androgen.	1
			ar	Insert does not list the following adverse effects: pancreatitis, carpal tunnel syndrome, prolonged post-therapy amenorrhea thrombocytopenia, Stevens-Johnson syndrome, cataracts, bleeding gums, fever, nipple discharge, and Guillain-Barre syndrome.	2
2	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not warn about prolongation of coma in cerebral malaria risk of activation of latent amebiasis, and steroid inducement of glaucoma, cataracts, or secondary ocular infections.	2
				Warnings about enhanced effects of corticosteroids in patients with hypothyroidism and cirrhosis, and warnings about fat embolism are not included.	1
				Insert has no specific warnings about use of this systemic corticosteroid in cases where there is a probability of abscess, pyogenic infection, and in patients with intestinal anastomoses; insert does not have warning about use in patients with myasthenia gravis.	2
			ar	Cutaneous reactions, convulsions, pseudotumor cerebri, vertigo, headache, ophthalmic disorders, nausea and malaise were not mentioned in the insert.	1
2	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not have warning about increased calcium excretion associated with systemic corticosteroids.	1
				No warning about enhanced effect of steroids in hypothyroidism and cirrhosis.	1
				No warning about need to monitor growth and development of infants and children on systemic corticosteroids.	2
				No warning about need for gradual reduction of dosage following prolonged therapy.	2
				No outline of routine tests to monitor therapy.	1
2	Thyroid hormone supplement	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not include the following: recommendations about monitoring thyroid status when receiving this product; information about drug interactions (only interactions with anticoagulants and hypoglycemics are mentioned in entry); information about drug-laboratory test interactions; information about use in nursing mothers, infants, and children.	2
2	Topical antifungal agent	pi	ind	Company did not provide adequate justification for indicating this topical antifungal for treatment of staphylococcal and streptococcal skin infections.	2
			wp	Insert has no warnings and precautions.	1
				Insert has no information about use in pregnancy and in nursing mothers.	1
			da	insert lacks information on duration of therapy.	1

2	Tricyclic antidepressant	pipa	wp	Insert has no information about drug interactions.	1
			od	Insert does not describe signs and symptoms of toxicity.	2
2	Uninary anticholinergic and antispasmodic	pi	dcp	Insert does not have pharmacokinetic information, including mode of excretion, time of onset of action, or peak effect.	1
			wp	Insert has no information about use in pregnancy and nursing mothers.	1
			ar	Insert does not list among adverse reactions the following: vertigo, mental confusion, nervousness, leukopenia, tachycardia, palpitations, urticaria, eosinophilia, hyperpyrexia, disturbances of eye accommodation, and dysuria.	2
2	Urinary tract analgesic	pi	ing	Insert does not list inactive ingredients.	R
			ci	Insert does not include contraindication for use by patients with hypersensitivity to this product.	1
			wp	Insert does not note that the use of this urinary analgesic should not delay the definitive diagnosis and treatment of causative conditions.	1
				Insert does not note that this urinary analgesic may interfere with urinalysis based on spectrometry or color reactions.	1
				Insert does not have section on carcinogenesis, mutagenesis, or impairment of fertility. (U.S. labeling notes that long-term use of this product has induced neoplasia in rats.)	1
			od	Insert does not have information on management of overdose, including treatment of methemoglobinemia.	2
2	Urinary tract analgesic	pi, pg	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not note that this urinary tract analgesic may stain all body fluids, not just urine; insert does not note that the use of this agent for symptomatic relief should not delay definitive diagnosis and treatment of causative organisms.	1
				Insert does not caution that this urinary tract analgesic may interfere with urinalysis based on spectrometry or color reactions.	1
				Insert has no information about use in pregnancy and by nursing mothers.	1
				Insert has no information on caranogenesis, mutagenesis, or impairment of fertility.	1
			ar	Insert does not list the following adverse reactions: headache, rash, gastrointestinal disturbances, renal toxicity, hepatic toxicity.	1
			od	Insert does not provide information on management of overdose.	2
2	Urinary tract antiseptic	pg	ind	Entry does not note that the same degree of effectiveness against susceptible organisms is achieved by a related agent with a lower incidence of CNS side effects.	1
			wp	Insert does not state that this urinary tract antiseptic may enhance the effects of oral anticoagulants, warfarin, or bishydroxycoumarin.	2
2	Urinary tract antiseptic	pi	ing	Insert does not list inactive ingredients.	R
			ind	Product is indicated for pyelonephritis and intestinal bacterial diarrhea.	2
			da	Children's dosages are adjusted by age rather than weight of the patient.	1

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pipa - package insert pending approval; pl - package label; pds = product document.

CATEGORY KEY: dcp = description/clinical pharmacology; ing = ingredients; ind = indications; ci = contraindications; wp = warnings and precautions; ar = adverse reactions; da = dosage and administration; od - overdose information.

Addendum 3-4-Products With a Primary Overall Score of 3

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Adrenergic drug	pi	ing	Label does not list inactive ingredients other than alcohol.	R
			ind	Label does not include information on indications and usage.	2
			ci	Label does not include information about contraindications.	2
			wp	Label does not list warnings and precautions.	2
			ar	Label does not list adverse reactions.	2
			od	Label does not have overdose information.	2
3	Analgesic and proteolytic enzyme combination	pi	dcp	Company did not provide adequate evidence of efficacy for this drug combination in human beings.	1
			wp	insert omits precautions regarding use inpatients with severe hepatic insuffidency, renal damage, or pulmonary hemorrhage.	2
			od	insert does not have information about signs and treatment of overdose.	2
3	Analgesic, decongestant, and antihistamine combination	pi	ing	insert does not list inactive ingredients.	R
			ci	insert does not list contraindications.	2
			wp	insert does not list warnings and precautions.	2
				insert does not have information about use in pregnancy and by nursing mothers.	2
			ar	insert does not list adverse reactions other than drowsiness.	2
			od	insert has no information about management of overdose.	2
3	Androgenic steroid	pi	ind	No adequate support for use of this androgenic steroid in the following: in menopause, in benign mammary disturbances, in suppression of lactation, and in frigidity therapy.	2
			a	important contraindications (such as use in pregnancy) are omitted.	2
			wp	Warnings are omitted regarding use in children and development of hepatic adenomas.	2
				insert does not describe laboratory test interactions (decreased levels of thyroxine-binding globulin) and drug interactions (may decrease blood glucose in diabetic patients).	1
3	Antacid	pi	ind	Product is indicated for infant feedings to "prevent milk from souring and forming curds in the stomach," to aid in digestion, and to prevent constipation; company provided no adequate evidence of efficacy for these indications.	2
			Wp	Label does not warn about use of magnesium containing compounds in renal disease.	2
				Label does not warn about risk of hypermagnesemia in infants subject to chronic administration.	2
3	Antacid combined with bismuth and digestive enzyme	pi	dcp	Company did not provide rationale for this combination.	1
			d	insert does not note that magnesium containlng compounds are contraindicated in severe renal impairment or that calcium-containing compounds are contraindicated in hypercalcemia	2

			wp	Insert does not warn about the following: risk of hypermagnesemia in very young children, bismuth may cause impaction in elderly patients, do not take this antacid if symptoms of appendicitis are present, do not take within 1-2 hours of other oral medication, do not take with large amounts of milk or milk products.	2
				Insert has no information about drug interactions, including: cellulose sodium phosphate, ketoconazole, mecamylamine, methenamine, oral tetracydines, and sodium polystyrene sulfonate resin.	2
				Insert has no information on drug-test interactions, such as with gastric acid secretion test, and assessments of serum calcium, phosphate, potassium, and gastrin.	1
				Insert does not note that bismuth may cause black discoloration of feces.	1
			ar	Insert does not list the following adverse effects: constipation or diarrhea metabolic alkalosis (in renal insuffidency), hypercalcemia, renal calculi, hypermagnesemia, nausea, vomiting, and stomach cramps.	2
3	Anthelmintic	pl	wp	Label omits specific warning about potential neurotoxicity of the drug, especially in children.	2
				Label omits precautions for use (e.g., discontinue use if CNS, gastrointestinal, or hypersensitivity reactions occur; appropriate caution should be exercised for use in patients with severe malnutrition or anemia).	2
			ar	Label omits reported adverse reactions (e.g., gastrointestinal system and central nervous system adverse reactions).	2
			da	Label does not state that the maximum cure rate is usually obtained with a multiple-dose regimen.	2
3	Anthelmintic	pl	dcp	Label does not have information on clinical pharmacology.	1
			ci	Label has no contraindication in patients with epilepsy.	2
			ar	Label has no information on side effects, Including transient neurological effects and urticarial reactions.	2
			od	Label has no information on toxicity.	2
3	Antibiotic	pi	ind	Insert does not note that this antibiotic is not indicated for treatment of the carrier state of *Salmonella typhi.*	2
			da	Company did not provide adequate support for intramuscular injection as an effective method of administration.	2
				No adequate support for pleural lavage as an effective method of administration.	2
				Company did not provide support for dosage intervals of 8 hours for adults and 12 hours for children (U.S. labeling recommends dosages at 6-hour intervals).	1

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Anticholinergic antispasmodic	pg	dcp	Entry does not include information on pharmacology.	1
			ing	Entry does not list inactive ingredients.	R
			ind	Entry includes indications for symptomatic treatment of irritable bowel syndrome and renal colic, and as adjunctive therapy in ulcerative colitis, diverticulitis, cholecystitis, and pancreatitis.	2
			wp	Entry does not note that this anticholinergic drug may potentate the sedative effect of phenothiazines.	1
			ar	Entry does not note that mental confusion, bloating, suppression of lactation, and anaphylaxis may occur.	1
			od	Entry does not note that, with overdose, a curare-like action may occur.	2
3	Antidiarrheal combination containing an aminoglycoside antibiotic	pi, pg	w p	Manufacturer claims that the components of this product have synergistic action, but did not provide evidence that this was the case.	1
				Insert is promotional in tone (e.g., through use of adjectives “powerful,” “extraordinary,” and “extremely effective”).	1
				Insert states that one component of the product can eliminate toxins, bacteria and add from the gastrointestinal tract; manufacturer did not provide evidence that this was the case.	1
			ind	Insert states that oral aminoglycoside antibiotic is effective in bacterial diarrhea; manufacturer did not provide evidence of efficacy.	2
				Insert broadly indicates product for symptomatic treatment of diarrhea implying that it is indicated for nonbacterial diarrheas.	2
			wp	Insert states that the aminoglycoside antibiotic orally “has never provoked reactions that are generally presented with its parenteral administration.”	2
				Insert does not caution about the following: administration of other nephrotoxic drugs should be avoided; respiratory parafysis from neuromuscular blockade may occur; monitoring for development of ototoxicity (insert recommends discontinuation of therapy if tinnitus develops); CNS depression syndrome has occurred in infants; encephalopathy has developed from high doses of one component of the product in patients with renal failure.	2
			ar	The following adverse reactions were not listed: nausea, vomiting, paraesthesias, rash, fever, urticaria, angioneurotic edema, eosinophilia, deafness, exfoliative dermatitis, Stevens-Johnson syndrome, dermatitis, anaphylaxis, urticaria, azotemia, leukopenia, thrombocytopenia, pancytopenia, hemolytic anemia, muscular weakness, amblyopia, vestibular dysfunction, visual disturbances including blindness.	2
			od	Insert provides no information about the management of overdose.	2
3	Antiepileptic drug	pi	wp	Insert omits specific warning about use in children under 2 years of age.	2
			ar	Insert does not note that acute pancreatitis associated with use of this antiepileptic may be fatal.	2

3	Antiepileptic drug	pl	dcp	Information on clinical pharmacology is not included in the label.	1
			ind	Label does not have indications and usage information.	2
			ci	Label does not provide information about contraindications.	2
			wp	Label does not provide information on warnings and precautions.	2
				Label provides no information on drug interactions.	2
			ar	Label does not provide information on adverse reactions.	2
			da	Label gives no specific doses for initiation and maintenance.	2
3	Antiepileptic drug	pi	wp	Insert does not warn that sudden withdrawal of this antiepileptic drug could precipitate absence (petit real) status.	2
			ar	Insert does not include information on Stevens-Johnson syndrome, a serious adverse effect of treatment with this antiepileptic.	2
3	Antiestrogenic drug	pg	dcp	Entry does not include a section on clinical pharmacology.	1
			ind	Entry broadly indicates drug for anovulatory women, without emphasizing need to diagnose the cause of anovulation first.	2
			wp	Entry does not include warning about use of this drug in pregnancy.	2
				Entry does not recommend endometrial biopsy in all patients with ovulatory disorders to rule out endometrial carcinoma as a cause.	2
			ar	Entry does not mention among adverse reactions abnormal uterine bleeding, breast tenderness, increased urination, weight gain, and rare incidence of massive ovarian enlargement.	1
3	Antihistamine	pi	dcp	Insert does not include distribution and elimination half-life of drug and its metabolizes (the half-life is particularly long).	2
			ing	Insert does not list inactive ingredients.	R
			ind	Insert broadly indicates this antihistamine for allergic conjunctivitis and “other allergic conditions.”	2
			a	Insert does not contraindicate this drug in patients with hypersensitivity to the drug or any of its inactive ingredients.	1
			wp	Insert does not have precaution about use in patients with hepatic impairment.	1
				Insert has no information about use in nursing mothers.	1
3	Antihistamine	pg	ing	Entry does not list inactive ingredients.	R
			ind	Entry includes indications for use in pregnancy, electroconvulsive therapy, anesthesia, surgery, disease due to radiation, post-fenestration syndrome, and migraine headaches.	2
			wp	Entry does not caution against use in patients with conditions that maybe aggravated by anticholinergic therapy.	1
			ar	Entry does not warn about dizziness, dry mouth, dry nose, dry throat, blurred vision, difficult or painful urination, headache, anorexia, nervousness, restlessness, insomnia, skin rash, thickening of bronchial secretions, tachycardia, epigastric distress, lassitude, excitation, and nausea.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Antihistamine	pi	dcp	Insert does not list mechanism of action.	1
			ing	Insert does not list inactive ingredients.	R
			ind	Insert adds indications for nausea and vomiting associated with electroshock therapy, anesthesia and surgery, labyrinthine disturbances, radiation sickness, and post-fenestration syndrome; company did not provide adequate evidence of eff icacy for these indications.	2
			wp	Insert does not have precautions regarding use in conditions that maybe aggravated by this product's anticholinergic actions, such as gallbladder obstruction, asthma, narrow angle glaucoma, emphysema, and prostatic hypertrophy.	2
				Drug interactions, such as with alcohol and other sedatives, are not listed.	1
			ar	Insert does not note that this product may cause anticholinergic effects.	2
			od	Insert does not have information about symptoms and management of overdose.	1
3	Antihistamine and vitamin B-6 combination	pg	dcp	No evidence was provided to justify this combination.	1
			ind	Manufacturer submitted no adequate well-controlled studies demonstrating the efficacy for use in pyloric spasm.	2
			wp	Entry does not include warnings about use of this antihistamine with alcohol or for children under 12 years of age.	2
				Entry does not include warning that use of antihistamines in children can cause excitability.	1
3	Antinausea and antivertigo drug	pg	ing	Entry omits mention of tartrazine, a particularly sensitizing agent.	2
			ind	Entry includes indication for motion sickness (i.e., any disorder caused by unaccustomed motions), despite potent side effects; entry indicates product for nausea caused by renal disease, but does not qualify use by noting that renal function impairment may increase the risk of side effects due to decreased excretion.	2
			wp	Entry fails to warn physicians to use this product in closely monitored settings.	2
			da	Company did not provide evidence of safety and efficacy of this drug in children weighing less than 22.8 kg.	2
3	Antitubercuiosis drug	pi	ing	Insert does not list inactive ingredients.	R
			ind	No adequate support for indication for enterococci and Proteus sp.; no statement that rapid development of resistance to Neisseria *gonorrhoeae* can occur.	2
			wp	Insert does not warn about fatalities associated with antibiotic-induced hepatic dysfunction and about increased incidence of hepatomas in mice exposed to this antibiotic.	2
				Insert does not mention that this antibiotic may induce elevations of BUN and serum uric acid.	1

			ar	Insert does not list a number of CNS effects, including drowsiness, fatigue, ataxia, dizziness, mental confusion, inability to concentrate, pains in extremities,and generalized numbness.	1
				Insert does not describe in detail the types of hypersensitivity reactions, including urticaria, pemphigoid reactions, eosinophilia, sore mouth, sore tongue, exudative conjunctivitis, and fever.	2
3	Barbiturate anesthetic	pg, pi	dcp	Entry does not include information on clinical pharmacology.	1
			a	Entry does not contraindicate this barbiturate anesthetic in patients without veins suitable for intravenous administration, patients hypersensitive to barbiturates, patients in status asthmatics, and patients with porphyria.	2
			wp	Entry has no recommendation for special care in administering this barbiturate anesthetic to patients with advanced cardiac disease, increased intracranial pressure, asthma, myasthenia gravis, and endocrine insufficiency.	2
				Entry does not have information about use in pregnancy and in nursing mothers.	1
			ar	Entry does not include among adverse reactions respiratory depression, myocardial depression, prolonged somnolence and recovering bronchospasm, and hypersensitivity reactions.	2
			da	Entry does not provide detailed information about the use of this barbiturate anesthetic; the entry only advises physicians to consult the literature.	2
				Entry does not provide information on preparation of solutions and the incompatibility of this barbiturate anesthetic with other compounds that may acidify the solution.	1
			od	Entry has no information about management of overdose.	2
3	Beta blocker	pl	dcp	Description, actions, and indications are not included in the label.	2
			wp	Label does not have information about warnings and precautions.	2
			ar	Label does not have information about adverse reactions.	2
			da	Label does not have information on dosage and administration.	2
			od	Label does not have information on overdose management.	2
3	Beta blocker	pg	ing	Entry does not list inactive ingredients.	R
			ind	No adequate support for broad indication for thyrotoxicosis (rather than as adjunctive therapy for thyrotoxicosis).	1
			wp	Entry has no section on drug interactions.	2
				Entry does not include the following warnings about the use of beta blockers: the signs and symptoms of acute hypoglycemia and thyrotoxicosis may be masked, the risks of general anesthesia and surgical procedures may be increased.	2
				Entry does not have information about use in nursing mothers or pediatric use.	1
			ar	Entry does not warn about some adverse effects, including impotence and depression.	1
			da	Specific dosing recommendations for patients in renal failure are not provided.	1
			od	Entry has no information about management of overdose.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3—Continued

Overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Butyrophenonederivative antipsychotic	pi	ing	Insert does not list inactive ingredients, including tartrazine.	2
			wp	Insert has no precautions about the following: risk of extrapyramidal symptoms with concomitant discontinuation of antiparkinsonian medications; and risk of increased intraocular pressure.	1
			od	For management of overdose, insert recommends supportive care rather than gastric lavage, induction of emesis, charcoal slurry, and other specific measures.	2
3	Calcium channel blocking agent	pg, pi	dcp	Insert does not have information on pharmacokinetics.	1
			ci	Insert incorrectly relates contraindication regarding hypersensitivity to the products teratogenicity (i.e., insert states that the product "should not be administered to patients with known sensitivity to the treatment since teratogenic effects in animals have been reported").	1
			wp	Insert has no warning about the potential of this calcium channel blocker to induce hypotension.	2
				Insert does not note that this calcium channel blocker interacts with digoxin by prolonging AV conduction.	1
			da	Company did not provide adequate support for the long-term dosage regimen suggested in the insert.	1
			od	Insert does not have information on management of overdose.	2
3	Cephalosporin antibiotic	pi	ind	Product indicated for use in treatment of typhoid fever; company did not provide adequate evidence of efficacy for this indication.	2
				Insert does not state that penicillin is the drug of choice in the treatment and prevention of streptococcal infections.	1
			wp	Insert does not make specific reference to risk of pseudomembranous colitis.	2
3	Combination aminoglycoside antibiotic, opiate, antispasmodic, and bulk-forming agents	pg	dcp	Company did not provide rationale for this drug combination and the ratios of its ingredients.	1
			ind	Company did not support the safety of this combination in children and infants.	2
				Company provided no adequate rationale for indicating use as a general treatment for "diarrhea"	2
			wp	Entry does not state that oral dehydration therapy is the primary treatment for acute diarrheal disease.	2
				Entry does not warn against the risk of nephrotoxicity and ototoxicity associated with the use of an aminoglycoside antibiotic.	2
			od	Entry recommends an outdated treatment of overdose (in the U.S., activated charcoal rather than the "universal antidote" is recommended treatment of overdose).	2

3	Combination analgesic	pi	dcp	Company did not provlde justificatlon for this combination.	1
			wp	Insert does not include a warning about the association between aspirin and Reye's syndrome in children.	2
				Insert does not have the following precautions for opiate analgesics: use in pregnant women; use in patients with ulcerative colitis; increase in biliary tract pressure may result in biliary spasm or relic; combination may cause urinary retention and oliguria; combination drug may cause impotence or decline in libido; combination has a prolonged duration and cumulative effect in patients with hepatic or renal dysfunction; use with extreme caution in patients with seizures, acute alcoholism, delirium tremens, shock, untreated myxedema, cor pulmonale, bronchial asthma and chronic pulmonary disease; tolerance, psychological dependence, and physical dependence may occur in patients receiving opiate agonists.	2
			ar	Insert omits certain adverse effects associated with opiate analgesics including respiratory depression and circulatory depression; respiratory arrest, shock, and cardiac arrest; dizziness; visual disturbances; mental clouding or depression; sedation; coma; euphoria; dysphoria; weakness; faintness; agitation; restlessness; nervousness; seizures; delirium; insomnia; dizziness; nausea; vomiting; hypotension; pruritis; urticaria.	2
			da	Insert omits dosage recommendations for children.	2
			od	Insert omits information about overdose signs and management.	2
3	Combination antihistamine, adrenergic decongestant, and anticholinergic	pi	ing	Insert does not list inactive ingredients.	R
			wp	Insert does not note the anticholinergic effects that are associated with antihistamines.	1
				Insert lacks information about numerous drug interactions.	2
				Insert has no information on use in nursing mothers, caranogenesis, mutagenesis, or impairment of fertility.	1
				Insert does not state that in children antihistamines can produce paradoxical reactions, such as irritability and excitation.	1
			ar	Insert does not warn that antihistamines may cause confusion, excitement agitation, severe memory impairment, and that geriatric patients in particular are susceptible to the anticholinergic side effects of antihistamines, especially when they are receiving other drugs that also have anticholinergic effects.	2
				Insert omits mention of numerous adverse reactions associated with antihistamines and/or sympathomimetic amines.	2
			od	Insert does not warn that, in children, overdose of antihistamines can cause hallucinations or death.	2
				Insert does not mention that deaths have been associated with overdose.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Combination antihistamine, corticosteroid, and phenothiazine antipsychotic	pi	dcp	The manufacturer has not provided justification for this fixed combination product over each of the components individually.	2
			wp	Insert does not include the following warnings regarding the corticosteroid in this product: since mineralocorticoid secretion may be impaired, salt and mineralocorticoid may need to be administered; corticosteroids may cause psychic derangements, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations; corticosteroids can cause elevation of blood pressure, salt and water retention, and increased calcium excretion.	1
				Insert does not have specific warnings about phenothiazine use: development of tardive dyskinesia associated with phenothiazine antipsychotics,	2
				Insert does not have warning about neuroleptic malignant syndrome; no precaution about cross-sensitivities to other phenothiazines; no warning about the possibility of liver damage; no warning about pigmentary retinopathy, lenticular deposits, and corneal deposits.	2
				Insert does not have the following warnings for antihistamines: overdoses of antihistamines may cause hallucinations, convulsions, or death, especially in infants and children; products containing antihistamines have additive effects with alcohol and other CNS depressants.	1
			ar	Adverse reactions associated with each of the components of this product are not listed with specificity.	2
			od	Insert does not have information about overdose and treatment.	2
3	Combination expectorant and analgesic	pl	wp	Label provides inadequate information about the enclosed free sample.	2
			od	Label does not contain information on the management of overdose.	2
3	Combination opioid analgesic, aspirin, and acetaminophen	pi	dcp	Insert does not have section describing clinical pharmacology.	1
			ing	Insert does not list inactive ingredients.	R
			ind	Company did not provide evidence of additive analgesic effects of this compound and decreased toxicity compared with the individual components.	1
			ci	Insert does not have contraindication for persons with hypersensitivity to the components of this combination analgesic,	1
			wp	Insert does not warn about the following: potential for drug dependence for this opiate analgesic-containing compound; possibility of Reye's syndrome and the need to avoid giving this product to children with flu-like symptoms; warning about giving this combination to children with asthma; warning about the potential of this drug to cause drowsiness, and a warning about driving or operating machinery after taking this drug; warning about the potential for gastric ulceration and gastrointestinal blood loss in this aspirin-containing combination; precautions about use in patients with head injury, acute abdominal conditions, or in elderly or debilitated patients; precaution advising to avoid using this combination in patients with bleeding disorders or in those patients receiving anticoagulants.	2

				Insert does not have information about use in pregnancy, use in nursing mothers, and pediatric use.	1
				Insert does not have information about drug interactions with CNS-active drugs.	1
			od	Insert does not have information about management of overdose.	2
3	Combination phenothiazine antipsychotic and tricyclic antidepressant	pi	wp	Insert does not have warnings about risk of tardive dyskinesia, cardiovascular concerns, and interaction with guanethidine-like drugs.	2
				Insert does not warn that patients with high suicide potential should not be given large supplies of this drug.	2
			ar	Insert does not list specific adverse reactions associated with this combination phenothiazine antipsychotic and tricyclic antidepressant.	2
			od	Insert does not mention some signs of toxicity (e.g., plasma levels associated with overdose, widening of the QRS complex on ECG, oculomotor paresis).	1
3	Combination phenothiazine antipsychotic and tricyclic antidepressant	pi	ind	Product is indicated for "anxiety" generally, rather than only for those patients for whom anxiety and depression cannot be clearly differentiated.	2
			wp	Insert does not warn about risk of neuroleptic malignant syndrome; insert does not warn specifically about risk of cardiac arrhythmias, myocardial infarction, and stroke.	2
				Insert does not warn that this combination can lower the convulsive threshold in susceptible individuals.	1
				Insert does not warn that prolactin levels maybe elevated, and that galactorrhea, amenorrhea, gynecomastia, and impotence may occur; also, an increase in mammary neoplasms has occurred in rodents.	1
				Insert does not warn about photosensitivity; insert does not warn about risk of paralytic ileus when product is taken with other anticholinergics.	1
			ar	Insert does not mention the following adverse reactions: persistent tardive dyskinesia, cerebral edema, abnormal CSF proteins, neuroleptic malignant syndrome, increased psychotic symptoms, lethargy, paradoxical excitement, restlessness, hyperactivity, nocturnal confusion, bizarre dreams, and insomnia.	2
			od	Insert does not describe symptoms and management of overdose in detail.	2
3	Combination phenothiazine, anticholinergic, and antispasmodic	pi	dcp	No adequate clinical data were provided supporting rationale for this combination.	2
			ind	No adequate clinical data were provided to support indication for "digestive disorders produced or intensified by psychic tension."	2
			wp	Insert has relatively weak warning on tardive dyskinesia.	2

Continued on next page

Addendum 3-&Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Corticosteroid for intramuscular administration	pi	ing	Insert does not list inactive ingredients or preservatives.	R
			ci	Insert does not have contraindication for use in systemic fungal infections, idiopathic thrombocytopenic purpura, and septic arthritis.	2
			wp	Insert does not warn about masking signs and symptoms of infection, elevation of blood pressure, avoidance of vaccinations, and potential for local atrophy at injection site.	2
				There are no precautions about enhanced effects of this corticosteroid in hypothyroidism and cirrhosis, caution for use in ocular herpes simplex, risk of psychic derangements, impairment of growth and development in children, muscle wasting, and menstrual irregularities.	2
			ar	Insert does not have comprehensive list of adverse reactions by organ system.	2
3	Methylxanthine bronchodilator	pg	dcp	Entry does not include bioavailability data, including information about differences in half-life for different types of patients (e.g., patients with renal deficiency, alcoholics, smokers, newborns).	1
			wp	Entry does not have the following precautions: use with caution in patients with severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, or liver disease; use with caution in the elderly and in neonates; use cautiously in patients with history of peptic ulcer.	2
				Insert does not mention drug interactions with lithium carbonate, propranoiol, furosemide, hexamethonium, reserpine, chlordiazepoxide, troleandomycin, erythromycin.	2
				No support for statement in entry that when the drug is taken with foods, its absorption will be slowed, but complete.	1
			od	Labeling omits information about symptoms and management of overdose.	2
3	Monoamine oxidase inhibitor	pi	ci	Insert does not contraindicate use of this monoamine oxidase inhibitor with fluoxetine, buspirone, or dextromethorphan.	2
			wp	Insert does not note that this monoamine oxidase inhibitor should be administered with caution to patients receiving disulfiram (Antabuse) because severe toxicity, including convulsions and death, have been noted in animals who had received this combination of drugs.	1
				Insert does not note incidence of hematologic disorders with use of this drug.	1
				Insert has no information on risk of developing dependency (particularly in patients with a history of drug abuse) or information about withdrawal symptoms.	2
			da	Insert notes that if no response occurs with 30 mg per day “continued administration will probably not be beneficial” (compare U.S. labeling, which notes that dosage maybe increased to 60 mg per day).	1
3	Neuroleptic tranquilizer	pi	dcp	Language in the properties section of the foreign labeling appears to be promotional in tone (e.g., “notably favorable therapeutic index” and “an excellent neuroleptic”).	1
			ind	Company provided inadequate data to support use in shock patients.	2

			wp	Insert omitted several warnings (e.g., reduce concomitantly-administered opioids, monitor patient closely, and have available treatments for hypotension induced by this drug).	2
				Insert omits precautions about use in patients with impaired liver function, use in pregnancy, and use in labor and delivery.	1
			ar	Insert does not list hallucinations among adverse effects.	1
			da	Insert omits information about dosage and administration.	2
			od	Insert omits information about signs of overdose and treatment.	2
3	Nonsteroidal anti-flammatory drug	pi	ind	Product is indicated broadly for conditions "requiring] analgesic or anti-inflammatory activity," as opposed to just osteoarthritis and rheumatoid arthritis.	2
			wp	insert does not warn about the following: severe hepatic reactions, serum-sickness-like syndrome, anaphylaxis, and bronchospasm.	2
				Insert does not have a section on drug interactions.	1
				Insert does not warn about the markedly increased ulcer risk with doses above 20 mg per day.	2
3	Nonsteroidal anti-inflammatory drug	w	ci	Contraindications are omitted for use in pregnant women, based on animal studies of fetotoxicity, minor skeletal malformations, and delayed ossification.	2
			wp	Entry omits mention of drug interactions with aspirin and other nonsteroidal anti-inflammatory drugs.	1
			ar	Several important adverse reactions are not included in the entry (e.g., edema, urticaria, pruritis, tinnitus).	1
			od	Insert does not have information on symptoms and management of overdose.	2
3	Nonsteroidal anti-inflammatory drug	pi	ind	Product is indicated for minor ailments (such as headaches) despite potent side effects; insert does not note that safer alternatives are available.	2
			wp	Insert does not caution about use in patients with acute porphyria.	2
				Insert has no information about use in pregnancy or in nursing mothers.	1
				Insert does not note that agranulocytosis and death have occurred with use of product (notes only that granulocytopenia rarely occurs).	1
			ar	Insert does not mention the following adverse effects: skin reactions, allergic reactions, fever, anaphylactic shock, brochospasm, gastrointestinal symptoms, and drug-induced toxic epidermal necrolysis.	2
			od	Insert has no information about management of overdose.	2
3	Ocular sympathomimetic decongestant combination	pi	dcp	Company did not provide evidence of efficacy of combination over individual components alone.	1
			wp	Insert does not list warnings and precautions.	2
			ar	Insert does not list adverse reactions.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Oral contraceptive	pl	dcp	Label does not include section on clinical pharmacology.	1
			ing	Label does not list inactive ingredients.	R
			ind	Label has no information on indications and usage.	2
			a	Label does not list contraindications.	2
			wp	Label has no warnings about cardiovascular disorders, myocardial infarction, other thromboembolic and thrombotic diseases, and other risks associated with oral contraceptives.	2
				Label does not include precautions.	2
			ar	Label does not list adverse reactions.	2
3	Phenothiazine antipsychotic	pi	ind	Insert does not note that this phenothiazine antipsychotic is not drug of choice for generalized nonpsychotic anxiety because of the risk of tardive dyskinesia.	2
				Insert does not note that use in "anxiety states" is limited to generalized anxiety disorder and does not note lack of evidence of efficacy in other anxiety states (e.g., due to physical disease, agitated depression mimicking anxiety, character pathologies).	2
			a	Insert contradicts U.S. labeling in recommending use in behavioral disorders associated with mental retardation.	2
			wp	Insert does not note that this phenothiazine antipsychotic may have additive effects with anticholinergics (such as atropine) and interaction with organophosphate insecticides.	1
				Insert does not warn about risk of exfoliative dermatitis, lupus-like syndrome, and cardiac arrest.	2
			ar	Insert does not mention among adverse reactions risk of sudden death secondary to asphyxia due to inhibition of cough reflex.	1
3	Piperazine-derivative antihistamine/vasodilator	pi	ind	Manufacturer provided inadequate evidence, or poorly designed studies to support indications for cerebral trauma sequelae, postapoplectic sequelae, and symptoms of cerebral arteriosclerosis,	2
			wp	Insert does not note that extrapyramidal symptoms have been associated with this drug.	2
				Insert asserts that product "hardly affects blood pressure."	2
				Insert does not provide recommendations about pediatric use.	1
			da	The pediatric dose on the current labeling is too high; adult dosages may also be too high.	2
			od	Insert provides no information about overdose.	2
3	Piperazine-derivative antihistaminehasodilator	pi	dcp	Insert omits information about clinical pharmacology.	1
			ind	Company provided inadequate evidence of efficacy of drug in treatment of cerebral arteriosclerosis, cerebral or cranial trauma, and postapopiectic disorders.	2
			wp	Insert omits general antihistamine precautions.	2
			ar	Insert omits general antihistamine adverse effects.	2
			od	Insert omits information about signs and treatment of overdose.	2

3	Synthetic androgen	pi	ind	Product is indicated for the treatment of virginal breast hyperplasia; company did not provide adequate evidence of efficacy for this indication.	1
				Product is indicated for the treatment of precocious puberty.	1
			ci	Insert omits contraindications regarding use in patients with undiagnosed genital bleeding.	2
			wp	Insert omits warning that patients should be monitored during treatment for signs of hepatic dysfunction.	2
3	Systemic antifungal agent	pg	ind	Entry does not state that this product is not indicated for trivial infections.	2
			wp	Entry omits warnings regarding prophylactic use, tumorigeniaty, use in pregnancy, teratogenicity, and suppression of spermatogenesis.	2
3	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients.	R
			ind	A number of overly broad and unsupported indications are listed: indication for "arthritis in general," "dermatitis in general," allergic rhinitis (without qualification that systemic corticosteroids should only be used in severe cases), osteoarthritis, corneal marginal ulcers, "purpura vascular alergica," "pseudohemophilia" cirrhosis of the liver, hepatic coma, hepatitis A virus, acute pancreatitis, orchitis, toxoplasmosis (without qualification regarding the limited situations where its use as adjunctive therapy maybe indicated), "certain types of tuberculosis" (without qualification about the limited situations where it may be indicated).	2
			wp	Insert does not warn about the following: increased potassium and calcium excretion, development of cataracts, increased risk of ocular infections, risk of reactivation of tuberculosis in those with a positive tuberculosis test (the insert lists tuberculosis as a relative contraindication to glucocorticoid therapy).	2
				Insert does not caution about the following: increased effect of steroids in hypothyroidism and cirrhosis; risk of hemorrhage with concurrent administration of steroids and aspirin in hypoprothrombinemia; risk of using systemic steroids in diseases where intestinal perforation may occur, including recent intestinal anastomosis and diverticulitis; caution about use in renal insufficiency; and caution about use in patients with myasthenia gratis.	2
3	Systemic corticosteroid	pi	ing	Insert does not list inactive ingredients or preservatives.	R
			ind	Product is indicated for torticollis and is indicated for hay fever without qualification that the use of systemic corticosteroids is only justified in severe cases of hay fever that are intractable to adequate trials of conventional treatment.	2
			wp	Insert does not provide the following precautions: warning against vacdnating patients who are receiving this corticosteroid; precautions regarding the enhanced effects of systemic steroids in hypothyroidism and cirrhosis; caution about use in patients with ocular herpes simplex, psychic derangements, and ulcerative colitis.	2
				Insert has no information about use in pregnancy.	1
			ar	Insert omits significant adverse reactions, including fluid retention and electrolyte disturbances, muscle weakness, peptic ulcers, and impaired wound healing.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Systemic corticosteroid	pi	dcp	Insert does not have information about actions or pharmacokinetics.	1
			ind	Insert includes indications for hemodynamic shock and endotoxic shock.	2
			wp	Insert does not warn about increased calcium excretion with corticosteroid administration.	1
				Insert does not have a warning about the possible need for salt or mineralocorticoid replacement if mineralocorticoid secretion is impaired; insert does not note that the rate of absorption with intramuscular administration is slower than with intravenous administration.	2
			ar	Insert does not list the following adverse reactions: congestive heart failure in susceptible patients, hypokaiemic alkalosis, musculoskeletal side effects (e.g., muscle weakness, steroid myopathy, decreased muscle mass, osteoporosis, vertebral compression fractures), pancreatitis, ulcerative esophagitis, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, suppression of reactions to skin tests, convulsions, pseudotumor cerebri, headache, menstrual irregularities, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, ophthalmic disorders (cataracts, exacerbation of glaucoma etc.), blindness with intralesional therapy around the face and head, negative nitrogen balance, hyperpigmentation, hypopigmentation, subcutaneous atrophy, sterile abscess, Charcot-like arthropathy.	2
3	Systemic corticosteroid	pg	ing	Entry does not list inactive ingredients.	R
			wp	Entry does not warn about patients' decreased resistance to infections while on steroids.	2
			ar	Entry does not describe with specificity the adverse reactions associated with corticosteroids.	2
				Entry has no warning about blood pressure elevation.	1
3	Thiuram-derivative drug used in alcoholism treatment	pi, pg	dcp	Insert does not have section on clinical pharmacology.	1
			ing	Insert does not list chemical or structural formula or inactive ingredients.	R
			wp	Insert does not warn against possible severe reactions to this product.	2
				Insert does not warn about carcinogenicity.	1
				Insert does not contain a suggestion that patient carry an ID card indicating that he or she is taking this drug.	1
				Insert does not have warning about possible reaction with alcohol that may occur in hepatic insufficiency and in patients with cerebral damage.	2
				Insert states that "precautions should be taken" when using this product in concomitant conditions (such as diabetes and hypothyroidism) but does not state specifically that these conditions may elicit an accidental reaction.	2
				insert does not alert physicians to the possibility y that patients who are dependent on alcohol may also be dependent on narcotics and sedatives.	1
				insert does not list all of the characteristics of the reaction of this drug with alcohol.	1
			ar	insert states that this drug "does not produce any side effect unless an alcoholic drink is ingested."	2

3	Topical corticosteroid oral paste	pi	dcp	Inadequate evidence to justify statement in insert that [w]hen, used topically in 0.1 % concentration [this product] produces results clinically superior to 1% concentrations of other corticosteroids."	1
			ci	Insert does not contraindicate product in patients with hypersensitivity to its ingredients, and in patients with viral, fungal, or bacterial infections of the mouth or throat.	2
			wp	Insert does not warn about use in pregnancy.	1
				Insert does not warn about masking signs and symptoms of infection.	2
				Insert does not recommend further evaluation if substantial repair of oral tissues has not occurred in 7 days.	2
			ar	Insert does not warn about adverse reactions that may occur from systemic absorption of steroid preparations.	1
3	Topical nitrofuran antibiotic	pi	dcp	Insert does not describe the antimicrobial spectrum of this antibiotic.	2
			ing	Insert does not list inactive ingredients.	R
			wp	Insert does not caution about overgrowth of nonsusceptible organisms.	2
				Insert does not warn that various skin reactions may occur.	1
				Insert has no information about use in pregnancy.	1
3	Tricyclic antidepressant	pg	dcp	Entry has no clinical pharmacology section.	1
			ing	Entry does not list inactive ingredients.	R
			wp	Entry has no warning about risk of developing extrapyramidal symptoms, tardive dyskinesia or neuroleptic malignant syndrome.	2
				There is no warning about the following: that this tricyclic antidepressant may cause an exacerbation of paranoid symptoms in paranoiacs, the drug may cause manic depressive patients to shift into mania the drug may cause schizophrenic patients to develop increased symptoms of psychosis.	2
				Entry does not include list of drug interactions other than with monoamine oxidase inhibitors (e.g., alcohol, barbiturates, other CNS depressants, anticholinergics, and interactions with electroconvulsive therapy).	2
				Entry does not include admonition to prescribe this antidepressant in the smallest suitable amount in view of the risks of suicidal overdose.	2
			ar	Entry lacks warnings about the following adverse reactions: skin rash, drug fever, drowsiness.	1
			da	There is no mention that dosage should not exceed 300 mg per day until this dosage is tried for two weeks.	2
			od	Entry does not have information about overdose.	2

Continued on next page

Addendum 3-4-Products With a Primary Overall Score of 3-Continued

overall score	Type of drug	Source	Category	Nature of problem	Query score
3	Xanthine-derivative bronchodilator	pg	dcp	Entry does not include information on bioavailability (including differences in half-life for newborns, renal deficient patients, alcoholics, and smokers).	1
			wp	Entry does not warn about manifestations of toxidty from conventional doses and excessive doses, including convulsions, tachycardia ventricular arrhythmias; or that children may have a marked sensitivity to the CNS stimulant action of this drug.	2
				Entry does not include caution about use in patients with liver impairment or severe hypoxia.	1
				Entry does not list drug interactions, such as with erythromycin, troleandomycin, and lincomycin.	1
			ar	Entry omits adverse reactions associated with this xanthinederivative bronchodilator, including tachycardia extrasystoles, flushing, hypotension, circulatory failure, life-threatening ventricular arrhythmias, tachypnea albuminuria increased excretion of renal tubular cells and red blood cells, diuresis, hyperglycemia, syndrome of inappropriate antidiuretic hormone.	2
			od	Entry does not include information on treatment of overdose.	2

SOURCE KEY: pi - package insert; pg. prescribing guide entry; pipa. package insert pending approval; pl -. package label; pds - product document.

CATEGORY KEY: dcp= description/clinical pharmacology; ing - ingredients; ind = indications; ci - contraindications; wp - warnings and precautions; ar - adverse reactions; da - dosage and administration; od - ovedose information.

Addendum 3-5-Products With Labeling That Was Adequate Except for Failure To List Inactive Ingredients

Type of drug	Source
Aminoglycoside antibiotic for ophthalmic and otic administration	pi
Antacid	pl
Anthelmintic drug	pg
Antihistamine	pi
B complex vitamin	pi
Combination aminoglycoside and polymyxin antibiotic for ophthalmic use	pi
Combination synthetic opioid and aspirin	pi
Corticosteroid for ophthalmic administration	pi
Dietary fiber supplement	pg
Long-acting nitrate vasodilator	pi
Multivitamin and multimineral preparation	pi
Multivitamin and multimineral preparation	pi
Quinoline-derivative antiprotozoal agent	pi
Selective alpha-blocking agent	pi
Synthetic androgen	pi
Topical analgesic combination	pi

SOURCE KEY: pi - package insert; pg - prescribing guide entry; pl - package label.

Addendum 3-6-Products With Labeling That Was Not Evaluated Fully (Score = NA)

Type of drug	Source
Aminoglycoside antibiotic	pi
Aminoglycoside antibiotic for ophthalmic and otic administration	pi
Anabolic steroid	pi
Anesthetic for ophthalmic administration	pi
Anticholinergic antispasmodic	pi
Arterial vasodilator antihypertensive	pi
Artificial sweetener	pi
Combination corticosteroid and antibiotic for ophthalmic administration	pi
Combination topical antifungal	pl
Corticosteroid and anesthetic combination for topical administration	pg
Direct-acting arterial vasodilator	pi
Methylxanthine bronchodilator	pl
Multivitamin and multimineral preparation	pg
Multivitamin and multimineral preparation	pi
Multivitamin with iron and calcium	pi
Nitrate vasodilator	pi
Nitrate vasodilator	pi
Opioid analgesic	pi
Oral contraceptive	pg
Penicillin-derivative antibiotic	pi
Phosphoric acid-derivative antibiotic with anesthetic	pi
Polyene antifungal agent	pi
Polyene antifungal and antiprotozoal agent	pi
Quinolone antibiotic	pg
Quinoline antiprotozoal drug	pi
Systemic corticosteroid	pi
Tetracycline analogue antibiotic	pi
Thiazide diuretic	pi
Topical anthelmintic	pi
Vinca alkaloid antineoplastic agent	pi
Vitamin and vasodilator combination	pi

SOURCE KEY: pi= package insert; pg - prescribing guide entry; pl - package label.