

ORCA Meeting

Wednesday, November 19, 2008

**Location: Talaris Conference Center
Seattle, Washington**



Updates – Physician’s Labeling Rule and Promotional Considerations for Pharmaceutical Products.

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Meeting Handouts



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NOVEMBER 19, 2008

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AGENDA

- Physicians Labeling Rule
- Updates and the Future
 - PhRMA Code
 - Quality Assurance Unit
 - Good Storage Practices

<p>These highlights do not include all the information needed to use DermaCure safely and effectively. See full prescribing information for DermaCure.</p>	<p>--DOSAGE FORMS AND STRENGTHS-- DermaCure Disintegrating Tablets: 15 mg/packet (3)</p>
	<p>-----CONTRAINDICATIONS----- None (4)</p>
<p>DermaCure (atopicadermatica) Disintegrating Tablets</p>	<p>-----WARNINGS AND PRECAUTIONS-----</p> <ul style="list-style-type: none"> • Rare cases of severe inflammatory eruptions of the skin have been reported in patients using DermaCure continually on a long-term basis. Use should not exceed 14 continuous days. (5.1) • Use with caution in patients with severe hepatic impairment. (5.2)
<p>Initial U.S. Approval: 2008</p>	
<p>WARNING: LONG-TERM USE See full prescribing information for complete boxed warning.</p> <ul style="list-style-type: none"> • Rare cases of severe inflammatory eruptions of the skin have been reported in patients using DermaCure continually on a long-term basis (>30 days). (5.1) • DermaCure was not studied beyond 14 continuous days of therapy, and long-term use should be avoided. Extended exposure (>14 days) increases the risk of severe inflammatory adverse events. (5.1) 	

-----INDICATIONS AND USAGE-----

DermaCure is an anti-pruritic medication indicated for the short-term treatment of the pruritic manifestations associated with atopic dermatitis in adults. (1)

-----ADVERSE REACTIONS-----

Most common adverse reactions (>2%) are upper respiratory infection, tremor, and nervousness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MagicCure Pharmaceuticals at 1-800-555-1212 or www.mcp.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DOSAGE AND ADMINISTRATION-----

FOR DISSOLUTION. DO NOT TAKE WITHOUT DISSOLVING IN WATER. MUST BE TAKEN ON AN EMPTY STOMACH. (2)

DermaCure Disintegrating Tablets: 15 mg once daily on an empty stomach and four hours before a meal.

- Open packet containing DermaCure Disintegrating Tablets.
- Empty contents into 12 oz. glass.
- Fill glass with 8 oz. of water.
- Rapidly stir the contents until fully dissolved.
- Drink full glass of mixture.

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy Category B. (8.1)
- It is not known whether this drug is excreted in human milk. (8.2)
- Safety and effectiveness have not been established in pediatric and geriatric patients. (8.3, 8.4)

See 17 for PATIENT COUNSELING INFORMATION AND FDA-approved labeling

FULL PRESCRIBING INFORMATION CONTENTS*

WARNING – LONG-TERM USE	11	DESCRIPTION
1 INDICATIONS AND USAGE	12	CLINICAL PHARMACOLOGY
1.1 Atopic Dermatitis		12.1 Mechanism of Action
2 DOSAGE AND ADMINISTRATION		12.2 Pharmacodynamics
3 DOSAGE FORMS AND STRENGTHS	13	12.3 Pharmacokinetics
4 CONTRAINDICATIONS		NONCLINICAL TOXICOLOGY
5 WARNINGS AND PRECAUTIONS	14	13.1 Carcinogenesis, Mutagenesis, Impairment on Fertility
6 ADVERSE REACTIONS	16	CLINICAL STUDIES
6.1 Clinical Studies Experience	17	HOW SUPPLIED/STORAGE AND HANDLING
7 DRUG INTERACTIONS		PATIENT COUNSELING INFORMATION
8 USE IN SPECIFIC POPULATIONS		
8.1 Pregnancy Category B		
8.2 Nursing Mothers		
8.3 Pediatric		
8.4 Geriatric		

*Sections or subsections omitted from the full prescribing information are not listed.



PHYSICIANS LABELING RULE

- 21CFR Parts 201, 314, 601
- Final Rule January 24, 2006
- Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products



OVERVIEW

- **Highlights**
 - High level ½ page summary
 - Cited or concisely summarized information accompanied by identifying numbers indicating where to find in full prescribing information (FPI)
- **Contents**
 - Allows easy reference to FPI
 - Allows hyperlinks in electronic formats
- **Reorder and reorganizes sections**
 - Frequently referenced information moved forward
 - Safety information remains consolidated
- **Establishes format requirements**
 - Minimum 8-point font (trade labeling that accompanies drug product will have minimum 6-point font)
 - Standardized bolding and “white space”



Highlights

- Limitations Statement
- Product Names and Date of Initial US Approval
- Boxed Warning
- Major Recent Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warning and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Patient Counseling Information Statement



Contents and FPI

Boxed Warning

1 Indications and Usage

2 Dosage and Administration

3 Dosage Forms and Strengths

4 Contraindication

5 Warning and Precautions

6 Adverse Reactions

7 Drug Interactions

8 Use in Specific Populations

9 Drug Abuse and Dependence

10 Overdosage

11 Description

12 Clinical Pharmacology

13 Nonclinical Toxicology

14 Clinical Studies

15 References

16 How Supplied/Storage and Handling

17 Patient Counseling Information



Format Changes

- Warnings and Precautions consolidated
- Formerly in Precautions, now new sections
 - Drug Interactions
 - Use in Specific Populations
 - Patient Counseling Information
- Formerly optional, now required
 - Clinical Studies
 - Nonclinical Toxicology
- Created Dosage Forms and Strengths and moved How Supplied near the end



Appending Patient Labeling

FDA-approved patient labeling must be reprinted at end of labeling or accompany labeling by June 30, 2007

- Includes MedGuides, approved “PPIs,”
- Instructions for use, etc.
- Applies to all drugs, including “older” products that are not subject to the new requirements
- Can be submitted in the Annual Report



Improvements

- Emphasizes “Patient Counseling Information”
 - Referenced in Highlights
 - New section in FPI
 - Approved patient labeling, if available, is reprinted at the end
- Encourages Adverse Event Reporting
 - Includes toll-free number and internet address
- Adds initial U.S. approval date
- Identifies and Dates “Recent Major Changes”
 - Referenced in Highlights
 - Margin mark in FPI
- Adds the established pharmacologic class, if known, to Highlights



Revision of Safety Requirements

- Contraindications
 - Risk of use clearly outweighs any possible benefit
 - Includes only known hazards (e.g., eliminates “allergic to any component of the drug”)
- Warning and Precautions
 - Expanded to include clinically significant adverse reactions
- Adverse Reactions (ARs)
 - Retains and clarifies existing definition of what to include (reasonable association = some basis for causal relationship)
 - Separates ARs from clinical trials and postmarketing spontaneous reports
 - Revises requirements on how to classify and categorize ARs and how to describe AR rates
 - Requires a description of AR profile based on entire database



Adverse Reaction Definition

Previous § 201.57

An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

Revised § 201.57

For the purpose of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. **This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.**



Other Clarifications

- Dosage and Administration and Indication and Usage
 - Dosing requirements and indications or uses not included in these sections must not be implied or suggested in other sections
- For approval based on a surrogate, Indications and Usage must
 - Include a succinct description of the limitation of use
 - Describe any uncertainty about the anticipated benefit
 - Refer to a description of available evidence in Clinical Studies
- Clinical Studies
 - Include details pertinent to safe and effective use
 - Not an every trial ever performed
- References – include only when labeling must rely on either
 - Recommendations by authoritative body
 - Standardized methodology, scale or technique
- Expanded waiver provisions (§ 201.58)
- Explicit requirements to update labeling (§ 201.56) – annual report



Labeling Supplement Regulations (§ 314.70 and § 601.12)

- Changes to Highlights require submission of a prior-approval labeling supplement
- Exceptions – changes to Highlights that may be submitted in the Annual Report
 - Removal of a listed section from “Recent Major Changes” after 1 year
 - Changes to the revision date



Affected Products

- New NDAs, BLAs, and efficacy supplements (e.g., new indication, new dosage regimen, new route of administration)
- Applications and efficacy supplements approved up to 5 years prior to final rule
- Encourage voluntary compliance by older products
- All products must append FDA-approved patient labeling within 1 year



Implementation Schedule

**NDA, BLA or efficacy
supplement**

Labeling must conform at or by

Submitted on or after 6/30/06	At time of submission
Pending on 6/30/06	
Approved 6/30/05-6/30/06	6/30/09 (3 years)
Approved 6/30/04-6/29/05	6/30/10 (4 years)
Approved 6/30/03-6/29/04	6/30/11 (5 years)
Approved 6/30/02-6/29/03	6/30/12 (6 years)
Approved 6/30/01-6/29/02	6/30/13 (7 years)
Approved Pre-6/30/01	Voluntary at any time (encouraged to confirm)



Resources

- Federal Register (Final Rule: 1/24/06)
- www.fda.gov/cder
 - Physicians' Labeling Rule
- Guidance for Industry
 - Implementing the New Content and Format Requirements
 - Adverse Reactions
 - Clinical Studies
 - Warnings and Precautions, Contraindications, and Boxed Warning Sections



Other Hot Issues

- Revised PhRMA Code (effective 1/1/09)
 - **NO** gifts to Physicians, including investigators
 - **No** reminder items (pens and pads)
 - Must be directly related to education of the Healthcare Professional or patient
 - Informational presentations (Field Sales)
 - Hospital or office setting
 - Modest meals (hospital or office setting only)



PhRMA Code Revisions (cont'd)

- CME
 - Grants must be separate from Sales and Marketing
 - Company **cannot** provide a meal or earmark grant money for meals
 - Company should not provide advice or guidance on the content or faculty, **even if asked**
 - Companies **CAN** publicize that it will consider funding meeting on a general topic



PhRMA Code Revisions (cont'd)

- Speaker Programs and Training
 - Cap the total amount of annual compensation
 - Train speakers on FDA regulations
 - Develop policies for hiring the appropriate number of speakers and number of presentations
 - Ensure speakers disclose they are presenting on behalf of the company and presentations are consistent with the regulations



PhRMA Code Revisions (cont'd)

- Use of Prescriber Data
 - New section of the code focusing on protection of patient confidentiality
 - Implement disciplinary actions for misuse of these data
- Sales Training
 - Requires training that includes applicable laws, regulations, and industry codes and practices, including the revised PhRMA Code
- Adherence to the Code
 - Recommends external verification, every three years, that the company has policies and procedures in place to foster compliance with the code
- www.phrma.org



More Hot Issues (coming next year)

- Good Storage Practices (coming next year)
 - Increasing concern with who will lay hands on the product
 - FIFO (first in/first out) will be replaced by FEFO (first expired/first out)



More Hot Issues (coming next year)

- Quality Assurance Unit (01/01/09)
 - Equivalent to a QP in the EU
 - Must report to the CEO
 - Responsibilities include but are not limited to
 - Study Plan (or Protocol) Review
 - Standard Operating Procedure (SOP) Review
 - Planning (Master Schedule, Inspection Plan)



FINAL HOT ISSUE

**DRUG IS A
FOUR LETTER WORD!**

**ANY QUESTIONS?
AND
THANK YOU!**

JLC.PI GUIDE

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION¹

The purpose of Highlights is to provide immediate access to the information that practitioners most commonly refer to and view as most important. Highlights is intended to serve as an information tool, drawing attention to this information and guiding the practitioner to the section in the Full Prescribing Information (FPI) where detailed information can be obtained. Highlights is not a verbatim repetition of selected information from the FPI, or simply a repetition of the Contents, but a concise, informative summary of crucial prescribing information. Rarely, it may be appropriate to repeat information verbatim from the FPI (e.g., a succinct boxed warning statement or short indication statement), but in most cases, the information should be summarized and presented in an easily accessible format (e.g., bulleted, tabular).

It is critical that the summarized content of Highlights be consistent with the more detailed information in the FPI, but not all of that information will be included in Highlights. Selecting the information to include in Highlights requires judgment about the data in relation to the clinical setting in which the drug is used. The information considered of greatest importance will vary, depending on factors such as differences in safety profiles or dosing considerations for different indications or populations.

Information about a topic, or similar topics, extracted from the FPI should be grouped together and summarized with a brief, clear statement. For example, several warnings from the FPI about a similar issue could be condensed into one bulleted item under the Warnings and Precautions heading in Highlights.

Summarized information should be presented in direct language that is succinct and imparts a complete piece of information (e.g., for a warning: a description of the risk, its consequences,

¹ Guidance for the Highlights section and subsections: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements. Pages 7 and following.

and the actions to take to prevent or mitigate it). In some cases, the information can be summarized in a few words, while in others, a few short phrases or sentences are more appropriate. Each summarized statement should be located under the appropriate Highlights heading and must cross-reference the section(s) or subsection(s) of the FPI that contains more detailed information (§ 201.56(d)(3)).

NOTE: The new regulations require that Highlights, excluding the boxed warning, be limited in length to one-half page (§ 201.57(d)(8)). FDA recognizes that under certain circumstances, particularly when a product has many indications or many serious warnings that merit inclusion in Highlights, it may not be possible to accommodate all the required information within one-half page. In this case, the applicant can submit a waiver request with the submission. (See 21 CFR 201.58.) The applicant should prominently identify the submission as one that includes a waiver request. In the waiver request, the applicant should explain why the one-half page during labeling negotiations and will formally document its decision in an action letter.²

The following information must appear in the Highlights section of all prescription drug labeling.

Limitation Statement

Required Verbatim Statement:

These highlights do not include all the information needed to use {insert name of drug product} safely and effectively. See full prescribing information for {insert name of drug product}.

Product Name(s), Dosage Form, Route of Administration

Include the proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act or, for biological products, the proper name (as defined in § 600.3) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04.

² From: Guidance, January 2006, "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (lines 621 to 631).

Date of Initial U.S. Approval

In the required verbatim statement, enter the year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients.

Required Verbatim Statement:

Initial U.S. Approval: 200X

RECENT MAJOR CHANGES

When substantive labeling changes are made to any of the following sections of the FPI, the heading (s) of the changed section(s) must be listed in Highlights under the heading Recent Major Changes:

- *Boxed Warning*
- *Indications and Usage*
- *Dosage and Administration*
- *Contraindications*
- *Warnings and Precautions*

Minor corrections, such as typographical errors or grammatical changes, are not considered substantive labeling changes.

The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1-year period.

Insert list of the affected section(s) here.

INDICATIONS AND USAGE

Provide a concise statement of each of the drug's indications, briefly noting any major limitations. FDA recommends that the information be presented in a bulleted format. In unusual circumstances, it may be appropriate to present the indications verbatim from the FPI (e.g., when a product has one indication and the statement in the FPI is sufficiently concise). For a product with limitations of use that are applicable to all of the product's indications or with a major safety concern associated with all its uses, it is appropriate to list those limitations or concerns together, under an appropriately titled subheading (e.g., Important Limitations).

Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted.

*If the drug is a member of an established pharmacologic class, identify the class with the following concise **Required Verbatim Statement**:*

{Insert name of drug} is a {insert name of class} indicated for {insert indication(s)}.

DOSAGE AND ADMINISTRATION

Provide a concise summary of the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, if any, and other clinically significant clinical pharmacology information that affects dosing recommendations (e.g., dosing adjustments recommended for concomitant therapy, specific populations with coexisting conditions, clinically relevant food effects). FDA recommends a tabular format to enhance accessibility of information (e.g., when there are different dosing regimens for different indications). When applicable and important, special storage or handling information can be mentioned under this heading (e.g., special handling of chemotherapeutic agents, need for refrigeration, reconstitution prior to administration of the drug).

Insert concise summary here (in tabular form, if applicable).

DOSAGE FORMS AND STRENGTHS

Provide a concise summary of the dosage form and strength and whether the drug product is scored. If a drug product has numerous dosage forms, bulleted subheadings (e.g., capsules, tablets, injectable, suspension) or tabular presentations are recommended.

Include the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets).

Insert concise summary here (in bulleted or tabular form, if applicable).

CONTRAINDICATIONS

Include either a concise summary of the situations in which the drug should not be used because the risk clearly outweighs any possible therapeutic benefit or the statement “none” if no contraindicated situations have been identified. “Relative contraindications”

(i.e., circumstances under which the drug may be used with caution) are not true contraindications and are not appropriate for inclusion under this heading.

Insert concise statement here.

WARNINGS AND PRECAUTIONS

Include a concise summary of the most clinically significant safety concerns that affect decisions about whether to prescribe the drug, recommendations for patient monitoring to ensure safe use of the drug, and measures that can be taken to prevent or mitigate harm. Thus, although it is unlikely that all of the safety information listed in the FPI will be included in Highlights, the most clinically significant safety concerns should be addressed.

Insert concise summary here.

ADVERSE REACTIONS

Most frequently occurring adverse reactions: *Include a listing of the most frequently occurring adverse reactions, even if they are included elsewhere in Highlights, and the criteria used to determine inclusion (e.g., incidence rate). The listing should be concise, not lengthy or comprehensive. This listing may include adverse reactions that are important for reasons other than frequency (e.g., leading to discontinuation or dosage adjustments) unless they are included elsewhere in Highlights (e.g., under Warnings and Precautions or Contraindications).*

Insert concise listing here.

Adverse reaction reporting contact information: *Highlights must also contain adverse reaction reporting contact information that includes:*

- 1. The verbatim statement “To report SUSPECTED ADVERSE REACTIONS, contact” followed by the manufacturer’s name and phone number for adverse reaction reporting.*
- 2. The manufacturer’s Web address of the direct link to its Web site for voluntary reporting of adverse reactions (if available),*
- 3. FDA’s phone number and Web address for voluntary reporting of adverse reactions.*

Required Verbatim Statement *for drug products other than vaccines:*

To report SUSPECTED ADVERSE REACTIONS, contact {insert name of manufacturer} at {insert manufacturer's phone number (and web address if applicable)} or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Provide a concise summary of:

- *A list of other drugs (or classes of drugs) or foods that interact or are predicted to interact in clinically significant ways with the drug*
- *Practical instructions for preventing or decreasing the likelihood of the interaction*

Descriptive subheadings of summary concepts (e.g., CYP3A inhibitor) may precede specific information. In general, drugs that were found not to interact or to interact in a nonclinically relevant way should not be included under this heading, nor should details of drug interaction studies. However, it may be appropriate to include pertinent negative findings of drug interaction studies under this heading if the interaction would otherwise be anticipated or is of special concern (e.g., other drugs in the class need a dosage adjustment or if the drugs are commonly coadministered). A tabular format is recommended for presentation of drug interaction information for drugs with numerous clinically significant interactions.

Interactions with particularly serious clinical consequences that are summarized under the Contraindications or Warnings and Precautions heading in Highlights would be described in greater detail in the DRUG INTERACTIONS section in the FPI.

Because some drugs are associated with a large number of clinically significant drug interactions, it may not be possible to concisely summarize all the critical information in Highlights. In these instances, include a statement under the Drug Interactions heading in Highlights that alerts the prescriber to the presence and significance of the drug interaction information in the FPI.

Insert concise summary here (in tabular format, if applicable).

USE IN SPECIFIC POPULATIONS

Provide a concise summary of any clinically important differences in response or recommendations for use of the drug in specific populations (e.g., differences between adult and

pediatric responses, need for specific monitoring in patients with hepatic impairment, need for dosing adjustments in patients with renal impairment). Typically, information under this heading includes limitations or precautions for specific populations or established differences in response.

Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, children) should not be included under this heading. It may be appropriate to include some information about use in specific populations under other headings in Highlights (e.g., Contraindications, Warnings and Precautions, Dosage and Administration) based on the type and clinical relevance of the information.

Insert concise summary here.

PATIENT COUNSELING INFORMATION STATEMENT

Select the correct Required Verbatim Statement from the two listed below.

*If the product does not yet have FDA-approved patient labeling, use the following **Required Verbatim Statement**:*

See 17 for Patient Counseling Information.

or

*If the product has FDA-approved patient labeling, use the following **Required Verbatim Statement**:*

See 17 for Patient Counseling Information and *{insert either FDA-approved patient labeling or Medication Guide}*.

REVISION DATE

Provide the date (month and year) of the most recent revision of the labeling.

Revised: *{Insert Month}* 200X

FULL PRESCRIBING INFORMATION: CONTENTS*

The table of contents is a navigation tool that lists all headings and subheadings contained in the Full Prescribing Information section. Its purpose is to allow the healthcare professional to quickly be aware of all available information and where to find it.

When a section or subsection is omitted from the FPI, the section must also be omitted from the Contents (§ 201.56(d)(4)). The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “ Sections or subsections omitted from the Full Prescribing Information are not listed” (§ 201.56(d)(4)).³*

1 INDICATIONS AND USAGE

- 1.1 Insert subheading, if applicable
- 1.2 Insert subheading, if applicable

2 DOSAGE AND ADMINISTRATION

- 2.1 Insert subheading, if applicable
- 2.2 Insert subheading, if applicable

3 DOSAGE FORMS AND STRENGTHS

- 3.1 Insert subheading, if applicable
- 3.2 Insert subheading, if applicable

4 CONTRAINDICATIONS

- 4.1 Insert subheading, if applicable
- 4.2 Insert subheading, if applicable

³ Guidance: Drug and Biological Products — Implementing the New Content and Format Requirements. Page 19.

5 WARNINGS AND PRECAUTIONS

5.1 Insert subheading, if applicable

5.2 Insert subheading, if applicable

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

6.3 Insert subheading, if applicable

7 DRUG INTERACTIONS

7.1 Insert subheading, if applicable

7.2 Insert subheading, if applicable

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Other Specified Subpopulation(s)

9 DRUG ABUSE AND DEPENDENCE

9.1 Insert subheading, if applicable

9.2 Insert subheading, if applicable

10 OVERDOSAGE

10.1 Insert subheading, if applicable

10.2 Insert subheading, if applicable

11 DESCRIPTION

11.1 Insert subheading, if applicable

11.2 Insert subheading, if applicable

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL PHARMACOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Insert subheading, if applicable
- 14.2 Insert subheading, if applicable

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 Insert subheading, if applicable
- 16.2 Insert subheading, if applicable

17 PATIENT COUNSELING INFORMATION

- 17.1 Insert subheading, if applicable
- 17.2 Insert subheading, if applicable

Delete the following footnote if no sections or subsections were omitted. (See instructions at beginning of this section.)

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Requirements for the Full Prescribing Information section are detailed in the New Regulations from 21 CFR 201.57.⁴

1 INDICATIONS AND USAGE

Provide a statement that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

Include the following information when the conditions listed are applicable:

- *If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.*
- *If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the “Clinical Studies” section for a discussion of the available evidence.*
- *If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.*
- *If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the “Dosage and Administration” section.*
- *If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.*
- *If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.*

⁴ From this point on, most of the material is taken from Sharlin’s Appendix 1—from the table column entitled Reprint of New Regulations from 21 CFR 201.57. It has been formatted differently and sometimes slightly revised. Some sections also include statements from Sharlin’s Table 4: Required Verbatim Statements. (Sharlin, Joshua. Teleconference Course Materials: Understanding FDA’s New Package Insert Requirements for Drugs & Biologics. 23 February 2006.)

If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in §314.126(b) unless this requirement is waived under §201.58 or §314.126(c). For biological products, such statements must be supported by substantial evidence.

For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in §314.126(b) unless the requirement is waived under §201.58 or §314.126(c). Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

Insert text here.

2 DOSAGE AND ADMINISTRATION

FDA recommends that Latin abbreviations be avoided in this section, because of the greater potential for medication errors should an abbreviation be misread.

State the recommended dose and, as appropriate:

- *The dosage range*
- *An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness*
- *Dosages for each indication and subpopulation*

- *The intervals recommended between doses*
- *The optimal method of titrating dosage*
- *The usual duration of treatment when treatment duration should be limited*
- *Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects)*
- *Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease)*
- *Important considerations concerning compliance with the dosage regimen*
- *Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.*

Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

Provide specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals.

Required Verbatim Statement for Parenteral Drug Products:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Insert text here.

3 DOSAGE FORMS AND STRENGTHS

This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

- *The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and*
- *A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.*

Insert text here.

4 CONTRAINDICATIONS⁵

Describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state “None.”

Insert text here.

5 WARNINGS AND PRECAUTIONS⁶

General. Describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse

⁵ Guidance: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format.

⁶ Guidance: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format.

reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7). In accordance with §§314.70 and 601.12, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the “Indications and Usage” section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

Insert text here.

Other special care precautions. Provide information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

Insert text here.

6 ADVERSE REACTIONS⁷

Describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Insert text here.

Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in

⁷ Guidance: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.

decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

- *Clinical trials experience. List the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.*

Insert text here.

Comparisons of adverse reactions between drugs. For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in §314.126(b) unless this requirement is waived under §201.58 or §314.126(c). For biological products, any such claim must be based on substantial evidence.

Insert text here.

7 DRUG INTERACTIONS

Provide a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the “Contraindications” or “Warnings and Precautions” sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the “Clinical Pharmacology” section that are pertinent to clinical use of the drug must not be repeated in this section.

Insert text here.

8 USE IN SPECIFIC POPULATIONS

This section must contain the following subsections:

8.1 Pregnancy

This subsection may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection must contain the following information:

Teratogenic Effects

Under this subheading, the labeling must identify one of the following categories that applies to the drug, and the labeling must bear the statement required under the category:

Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling must state:

Pregnancy Category B. Reproduction studies have been performed in {kind(s) of animal(s)} at doses up to {x} times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to {insert name of drug}. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:

Pregnancy Category B. Reproduction studies in {kind(s) of animal(s)} have shown {describe findings} at {x} times the human dose. Studies in pregnant women, however, have not shown that {name of drug} increases the risk of abnormalities when administered during the first {second, third, or all} trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless,

because the studies in humans cannot rule out the possibility of harm, {name of drug} should be used during pregnancy only if clearly needed.

The labeling must also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

Insert description here.

Nonteratogenic Effects

Under this subheading the labeling must contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading must include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

Insert text here.

8.2 Labor and Delivery

<Product Name> is indicated for a patient population of 3-18 years of age.

8.3 Nursing Mothers

<Product Name> is indicated for a patient population of 3-18 years of age.

8.4 Pediatric Use

Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H), the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section, and appropriate pediatric dosage

information must be given under the “Dosage and Administration” section. The “Pediatric use” subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the “Clinical Pharmacology” or “Clinical Studies” section. As appropriate, this information must also be contained in the “Contraindications” and/or “Warnings and Precautions” section(s).

If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the “Pediatric use” subsection and discussed in more detail, if appropriate, under the “Clinical Pharmacology” and “Clinical Studies” sections. Appropriate pediatric dosage must be given under the “Dosage and Administration” section. The “Pediatric use” subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the “Contraindications” and/or “Warnings and Precautions” section(s).

When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the “Pediatric use” subsection of the labeling must contain either the following statement or a reasonable alternative:

The safety and effectiveness of {insert name of drug} have been established in the age groups ___ to ___ {note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults}. Use of (insert name of drug) in these age groups is supported by evidence from adequate and well-controlled studies of (insert name of drug) in adults with additional data {insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population}.

Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the “Clinical Pharmacology” or the “Clinical Studies”

section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the “Clinical Pharmacology” section. Pediatric dosing instructions must be included in the “Dosage and Administration” section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the “Pediatric use” subsection and, as appropriate, in the “Contraindications,” “Warnings and Precautions,” and “Dosage and Administration” sections.

If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the “Pediatric use” subsection must contain an appropriate statement such as:

Safety and effectiveness in pediatric patients below the age of (__) have not been established.

If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the “Contraindications” or “Warnings and Precautions” section and this subsection must refer to it.

Safety and effectiveness in pediatric patients below the age of (__) have not been established.

8.5 Geriatric Use

If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug’s labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

9 DRUG ABUSE AND DEPENDENCE

<Product Name> has no known drug abuse or dependence potential.

10 OVERDOSAGE

This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

- *Signs, symptoms, and laboratory findings associated with an overdose of the drug;*
- *Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);*
- *Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the “Clinical Pharmacology” section also may be referenced here, if applicable to overdoses;*
- *The amount of the drug in a single dose that is ordinarily associated with symptoms of overdose and the amount of the drug in a single dose that is likely to be life threatening;*
- *Whether the drug is dialyzable; and*
- *Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.*

Insert text here.

11 DESCRIPTION

This section must contain:

- *The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in §600.3) and any appropriate descriptors;*
- *The type of dosage form(s) and the route(s) of administration to which the labeling applies;*
- *The same qualitative and/or quantitative ingredient information as required under §201.100(b) for drug labels or §§610.60 and 610.61 for biological product labels;*
- *If the product is sterile, a statement of that fact;*
- *The pharmacological or therapeutic class of the drug;*
- *For drug products other than biological products, the chemical name and structural formula of the drug; and*
- *If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.*

If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

Insert text here.

12 CLINICAL PHARMACOLOGY

Provide information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

12.1 Mechanism of Action

Summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

Insert text here.

12.2 Pharmacodynamics

Describe any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the location of such recommendations must be referenced.

Insert text here.

12.3 Pharmacokinetics

Describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that

establish the absence of an effect, including pertinent human studies and in significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

- *In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."*
- *For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in §314.126(b), to be necessary for the safe and effective use may be included in this section only if a waiver is granted under §201.58 or §314.126(c).*

Insert text here.

13 NONCLINICAL TOXICOLOGY (ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY)

This section must contain the following subsections as appropriate:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

State whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

Insert study information, as appropriate.

13.2 Animal Toxicology and/or Pharmacology

Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

Insert animal toxicology and/or pharmacology information, as appropriate.

14 CLINICAL STUDIES⁸

Discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in §314.126(b) and must not imply or suggest indications or uses or dosing regimens not stated in the “Indications and Usage” or “Dosage and Administration” section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the “Indications and Usage” or “Dosage and Administration” section.

Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

The clinical studies section is a required section under the new format. It was an optional section in the old format.

⁸ Guidance: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.

Selecting Studies to Include/Exclude⁹

1. **Include** studies with the following characteristics
 - a. Adequate and well-controlled (as defined by §201.314.126)
 - b. Investigated safety and/or effectiveness
 - c. Collected information that indirectly impacts either safety or efficacy.
For example:
 - i. Patient populations
 - ii. Unexpected lack of effectiveness in a clinical situation
 - iii. Dose selection or adjustment
 - iv. Characteristics of the treatment effect
2. **Exclude** studies with the following characteristics
 - a. Not adequate or well-controlled (as defined by §201.314.126)
 - b. Investigated unapproved indication
 - c. Active control studies not supported by substantial evidence

Describing Studies

1. Emphasize effectiveness data
2. Provide additional details regarding:
 - a. Study results of critical health importance
 - b. Data that shows the drug has
 - i. a clear advantage over existing therapy
 - ii. superior benefit relative to other drugs in the same therapeutic class
 - c. Study results were from a narrow population and not necessarily applicable to broader populations
 - d. Study results were unexpected for that drug class
 - e. Uncommon endpoints were used (e.g., unusual surrogate endpoints)
3. Provide Animal toxicology and/or pharmacology reduced details about the following:
 - a. The effects of the new drug were typical of its class
 - b. Study endpoints are not readily translatable to clinical practice
4. Consider the following when developing the presentation of information about endpoints
 - a. Emphasize endpoints directly related to effectiveness
 - b. For components of composite endpoint that can be evaluated separately, discuss each individual component

⁹ This outline is adapted from Sharlin, pages 24–29.

- c. *Don't distinguish between primary and secondary endpoints. The test is whether the endpoint data is properly collected and analyzed and is statistically and clinically meaningful d. If two endpoint are closely related, report on only one*
5. *How to write about comparative data*
 - a. *If a drug is superior to a placebo, don't include information about comparison to an active control unless there is an explicit comparative claim (either superior or similar effectiveness)*
 - b. *If making a comparison to an active control, identify the active control if it assists a healthcare provider understand the drug's effects*
 - c. *A claim of superior or similar effectiveness must be supported by substantial evidence (i.e., from an adequate and well-controlled study) (21 CFR 201.56(a)(3))*
 6. *How to describe a study design*
 - a. *Major characteristics*
 - i. *Level of blinding*
 - ii. *Type of controls*
 - iii. *Duration*
 - iv. *Method of randomization*
 - v. *Run-in period*
 - b. *Dose for each treatment group*
 - c. *Concomitant therapy should be described if it's relevant to understanding the effects of the study drug*
 - d. *Characteristics of the study population including important inclusion and exclusion criteria e. Endpoint description*

Describing Study Results

1. *Disposition of subjects. Reports the number of subjects:*
 - a. *Enrolled*
 - b. *Completed the study*
 - c. *Discontinued*
 - d. *Entering each phase (for a multi-phase study)*
2. *Methods of describing study results*
 - a. *Report both absolute and relative differences for study group and comparator*
 - i. *For example; For example, if mortality is 6 percent in one study arm and 8 percent in the other, the absolute difference (2 percent) should be presented along with the 25 percent relative risk reduction.*

- b. *Consider reporting both group results and individual subject data*
 - i. *For group results use mean or median*
 - ii. *For individual results, use a distribution or cumulative distribution of individual responses*
 - c. *Report treatment effect employing more than one method*
 - i. *Use both*
 - 1. *Confidence interval*
 - 2. *p-value*
3. *Describing within treatment results*
- a. *Change from baseline*
 - i. *Insufficient: Reporting change from baseline in a treatment group*
 - ii. *Better method: Comparison of change from baseline between treatment groups*
 - b. *Continuous data*
 - i. *Report individual variability, include standard deviations or standard errors*
4. *Reporting about subgroups*
- a. *Examples: age, gender, race*
 - b. *Describe subgroup results if meaningful*
 - c. *Describe a lack of subgroup results and the reasons for the lack of information*
5. *Handling different types of data*
- a. *Categorical (yes or no)*
 - i. *Include all responses (e.g., success, failure, unknown)*
 - ii. *When reporting percentages, include the denominator*
 - b. *Continuous*
 - i. *Use mean or median plus a standard deviation or standard error*
 - ii. *Consider a graphical display of individual responses (e.g., vertical bar chart where height of the bar is the number of subjects with the same response)*
 - c. *Time-to-Event Endpoints*
 - i. *Measure the amount of time to an event, e.g., death, cure, etc.*
 - ii. *Use a survival curve or histograms*

Insert text here.

15 REFERENCES

When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the

information is important to prescribing decisions, the labeling may include a reference to the source of the information.

Insert references here.

16 HOW SUPPLIED/STORAGE AND HANDLING

This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

- *The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;*
- *The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);*
- *Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and*
- *Special handling and storage conditions.*

Insert text here.

17 PATIENT COUNSELING INFORMATION

Provide information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with §208.24. Medication Guides for distribution to patients are subject to the type size requirements set forth in § 208.20.

Insert text here.

Question and Answer Supplement for Response to Preproposal Statement of Inquiry (WSR 02-05-054) by Interagency Regulatory Analysis Committee Pharmaceutical Workgroup

Who is the IRAC Pharmaceutical Workgroup?

The Interagency Regulatory Analysis Committee (IRAC) is composed of more than 350 members from 160 regulatory agencies in Washington State and is staffed by the Local Hazardous Waste Management Program in King County. IRAC encourages and addresses regulatory coordination and interagency cooperation and provides a forum for agencies to work together to address regulatory issues, conflicts and inconsistencies. Issue-specific workgroups are formed to study the circumstances around a conflict or inconsistency and the needs of all involved parties and to recommend improvements or changes in local ordinances or state or national regulations.

Questions relating to the proper disposal and recycling of pharmaceutical wastes in Washington were brought to IRAC by the Medical Industry Roundtable (MIRT). In March 2001 IRAC formed a Pharmaceutical Workgroup to address these issues and make recommendations.

The IRAC Pharmaceutical Workgroup is comprised of representatives from the pharmaceutical industry, reverse distribution businesses, non-profit organizations, educational institutions and regulators. For a complete list of participants, see the signature page of the attached letter.

What has precipitated the proposed rule change?

In response to a citizen's inquiry in May 2001, the Washington State Department of Ecology (Ecology) determined that some expired and unusable pharmaceuticals designated as Washington state-only dangerous wastes. With that determination, the entire management process then in place for handling expired and unusable pharmaceuticals was brought to a halt. Wastes should be handled properly. Unfortunately, the process to identify and designate pharmaceuticals as state-only dangerous waste is a burdensome, overwhelming and virtually impossible task. Therefore, the proposed rule change creates conditions under which these wastes could be conditionally excluded from regulation as state-only dangerous waste and still be properly managed.

After a review of the entire pharmaceutical distribution process—from drug development to final destruction—the Pharmaceutical Workgroup determined that the dangerous waste management system, created primarily for industrial process waste, is not well suited for managing expired and unusable drugs generated in health care settings. A reliable method of designating drugs as dangerous waste based on available information has not been developed. In addition, it was stated by Department of Ecology spokeswoman Caitlin Cormier, in the Thursday, January 24, 2002 **Spokesman-Review** article *Drugs pile up; incinerator can't take them* written by Dan Hansen, that, "the agency never intended to classify drugs as a hazardous waste." (See <http://www.spokesmanreview.com/news-story.asp?date=012402&ID=s1090288>.)

In order to facilitate the proper reuse, recycling and disposal of pharmaceuticals, and to provide information and education to generators of this waste, change is needed. In January 2002, Ecology passed an emergency rule (WSR: 02-05-030) that excludes law enforcement agencies in possession of DEA-regulated controlled substances from the provisions of the Dangerous Waste regulations when certain disposal conditions are met. The Pharmaceutical Workgroup would like to expand and clarify the provisions of this emergency rule and make it permanent.

The ultimate goal of the Workgroup is to provide regulators in the state of Washington with a regulatory framework that provides for the proper management of this wastestream and that addresses the needs of generators.

What is Ecology being asked to do?

The Pharmaceutical Workgroup has requested that Ecology phrase the permanent rule (WSR:02-05-054) currently under consideration to conditionally exclude pharmaceuticals from the dangerous waste regulations to read as follows:

Drugs regulated by the Drug Enforcement Administration (DEA) Schedules I through V that are held by any licensee or registrant of the state authorized to possess these drugs or that are held in the custody of law enforcement agencies within the state of Washington; and drugs as defined by Section 201 (g) of the Federal Food, Drug and Cosmetic Act (excluding compressed gases and radioactive drug products); and managed for destruction: Provided, that they are disposed of by incineration in a controlled combustion unit permitted to handle solid waste or disposed by other methods approved by Ecology.

The Dangerous Waste regulations at WAC 173-303-071(2) state that “No waste class will be excluded if any of the wastes in the class are regulated as hazardous waste under 40 CFR Part 261.” Therefore, the proposed language is limited to excluding state-only dangerous wastes.

What does the proposed language do?

The emergency rule (WSR: 02-04-030) passed by Ecology on January 25, 2002 to address this issue allows an exclusion only for law enforcement agencies in possession of DEA-regulated controlled substances. To ensure that the wastestream of controlled substances is handled consistently, regardless of the generator, this proposal includes DEA registrants such as doctors, hospitals, pharmacies, etc. The language change proposed above clarifies the scope of the waste and includes other generators of this waste in addition to law enforcement agencies.

- ◆ **Scope of the Waste:** The conditional exclusion proposed above acknowledges the similarities in toxicity, volume and generation of DEA-regulated controlled substances, pharmaceuticals and over-the-counter drugs; while the original emergency rule addressed DEA-regulated controlled substances alone.
- ◆ **Scope of the generators:** The original emergency rule addressed only law enforcement agencies. The conditional exclusion proposed above addresses all generators.

What types of businesses are faced with managing expired and unusable pharmaceuticals?

The emergency rule addresses only law enforcement agencies. The conditional exclusion proposed above expands the scope to include other businesses faced with managing controlled substances and other pharmaceuticals.

Issues with managing expired and unusable pharmaceuticals are encountered by thousands of businesses ranging from large hospital generators to very small businesses. They include nursing home facilities, veterinarians, missionary organizations, medical centers, fire stations, hospices, doctor's offices, adult daycare centers, dentists, ambulance services, and correctional facilities, to name a few.

How are most unusable or expired pharmaceuticals currently managed?

Most unusable or expired pharmaceuticals are sent to *reverse distributors* who facilitate their return to the manufacturer. This system allows unusable or expired pharmaceuticals to flow back through the reverse distribution system as *products* until a decision is made to discard them by the reverse distributor. At the reverse distributor, about 70 percent of a typical shipment received will be returned to the manufacturer for credit and the remaining 30 percent will designate as either hazardous or nonhazardous waste based on federal Resource Conservation and Recovery (RCRA) regulations. Of the items being discarded (30 percent of the original shipment), only about 10 percent (or three percent of the original shipment) typically designates as hazardous waste under RCRA, which must be managed as regulated hazardous waste and is not eligible for the conditional exclusion proposed above.

The reverse distributor is responsible for properly storing, manifesting, and arranging for transport and disposal of the hazardous waste by a federally permitted RCRA incineration facility. The nonhazardous waste must be disposed of by a facility permitted to destroy nonhazardous pharmaceutical waste.

How are pharmaceuticals that are not processed by a reverse distributor managed?

Lack of generator knowledge about proper disposal requirements is reflected in the many disposal methods used for pharmaceuticals that are not returned to a reverse distributor. Prior to May 2001, some pharmaceutical wastes were managed as solid waste and incinerated by high-temperature combustion at the Spokane Waste-to-Energy facility. The Spokane Waste-to-Energy facility is not permitted to handle dangerous wastes, and stopped this practice pending review. As of January 25, 2002 the facility began to accept shipments of controlled substances excluded from the Dangerous Waste regulations by the emergency rule (WSR 02-04-030).

Some chemotherapy wastes are disposed through permitted hazardous waste treatment, storage, and disposal companies. Finally, a small percentage of non-returned pharmaceuticals is being improperly disposed as biohazardous waste, solid waste or put down the drain to the sewer.

Workgroup participants representing solid waste and sanitary sewer interests reported that they do not approve disposal of pharmaceuticals into their systems. Examples include:

- partially filled chemotherapy bags specially blended for patients who are too ill to receive them or have died
- partial doses of injections
- individual tablets or capsules that have spilled and then been swept into the garbage.

How will conditional exclusion improve the disposal practices of hospitals, pharmacies, doctor's offices, etc.?

With the conditional exclusion of expired and unusable pharmaceuticals from the state-only portion of the Washington State Dangerous Waste regulations, regulators will have feasible and practical guidelines to give to pharmaceutical waste generators. Currently, regulators must tell generators to examine each pharmaceutical for dangerous waste characteristics and criteria. Due to a lack of toxicity data and the general complexity of drugs, regulators as well as generators are overwhelmed with the task of book designating more than 10,000 pharmaceuticals currently on the market.

In order for a waste disposal program to be effective, health care industry staff need clear procedures for how to deal with any wastestream. For example, a nurse caring for six cancer patients on a night shift may, within the course of an hour, generate a half-full IV bag of chemotherapy medication, spilled pills, and an unused dose of injectable pharmaceutical. It is unreasonable to expect him or her to designate and segregate each waste before placing it into a waste receptacle. Since reverse distributors cannot accept wastes like those described in this example—e.g., out of the container or modified for specific patients—the most practical and safe solution is to place state-only pharmaceutical waste into a single receptacle designated for incineration by high-temperature combustion (or another Ecology-approved disposal method.) This is clear guidance a regulator could give to professional healthcare or other personnel in health care settings.

How will Washington State businesses be impacted if pharmaceutical wastes are not conditionally excluded from state-only dangerous waste?

The Washington State Dangerous Waste Regulations create an unfair competitive advantage for out-of-state businesses that manage pharmaceutical wastes. Any United States hospital, retail pharmacy or drug distributor can send their unopened, unneeded or expired pharmaceuticals to a reverse distributor. There is no reverse distribution system available to medical doctors, dentists, veterinarians and other types of non-pharmacy dispensers. Only pharmacies and their drug distributors have the manufacturer credit policies available to them. Expired drugs generated at these other sites would become waste.

Upon receipt of the unused pharmaceutical, the reverse distributor decides if it can be returned to the manufacturer for credit or if it is waste. Because the reverse distributor designates the waste, the hazardous waste laws of the state where the reverse distributor is located apply. The majority of large hospitals and pharmacies use these reverse distributors to handle much of their expired

or unusable pharmaceuticals. However, most of the reverse distributors are located in states in which only federal RCRA regulations apply to pharmaceutical waste. Because pharmaceutical waste in our state is also subject to state-only dangerous waste regulations, Washington State reverse distributors are at a great competitive disadvantage. The costs to dispose of unusable pharmaceuticals are currently significantly higher in Washington State than, for example, in New Jersey. It is less expensive because Washington criteria are not applied in New Jersey and therefore the wastes are not managed as dangerous. Excluding unusable pharmaceuticals from designation as Washington state-only dangerous waste would put Washington State reverse distributors on par with those operating in other states.

Why should waste pharmaceuticals be conditionally excluded from state-only dangerous waste criteria when other wastes are not?

Unusable and expired pharmaceuticals do not fit within the system used to determine if a waste is a state-only dangerous waste. The Dangerous Waste regulations do not allow for the differences between FDA-regulated chemicals intended for human or animal consumption and chemicals intended for use in industrial processes. Further, according to the previously cited statement by Caitlin Cormier of Ecology in the **Spokesman-Review**, the Dangerous Waste Regulations never intended to regulate pharmaceuticals.

To determine if a product is hazardous waste under the state-only criteria of Washington State Dangerous Waste regulations, one must have specific toxicity data as defined by the Washington State Dangerous Waste regulations for the product or chemical. This information does not exist for many pharmaceuticals because the manufacturers of pharmaceuticals are regulated under the Food and Drug Administration (FDA). Until May 2001 most generators were not aware that pharmaceuticals fell under the purview of the Washington State Dangerous Waste Regulations. Although the FDA requires extensive testing prior to the release new pharmaceuticals, this does not typically include acute toxicity testing by the methods needed for state toxicity designation (e.g., lethal concentrations in water for fish, oral rat lethal doses, inhalation rat lethal concentrations in air, or dermal rabbit lethal doses).

Another way to determine if a waste is a Washington state-only dangerous waste is to conduct bioassays. These tests are extremely expensive. Because drug formulations are continually modified, new bioassays would have to be conducted continually, with each reformulation. This is a prohibitive and arduous undertaking.

Do pharmaceuticals included within the proposed changes meet the criteria required for an excluded category of waste?

WAC 173-303-071 excludes certain categories of waste from the provisions of the dangerous waste regulations “because they generally are not dangerous waste, are regulated under other state and federal programs, or are recycled in ways which do not threaten the public health or the environment.”

“...because they ... are regulated under other state and federal programs...”

- ◆ The Environmental Protection Agency (EPA) regulates wastes designated as hazardous under the Resource Conservation and Recovery Act (RCRA).
- ◆ The Drug Enforcement Administration (DEA) regulates the manufacture, transport and destruction of pharmaceuticals that are Controlled Substances, Schedules I, II, III, IV and V as outlined in the 21 CFR 1300.01 Definitions relating to Controlled Substances, and 1308.03 – 1308.15 Administration Controlled Substance Code Number.
- ◆ The Food and Drug Administration (FDA) promotes and protects the public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety once in use.
- ◆ The Washington Board of Pharmacy regulates pharmaceuticals as outlined in the Washington State Department of Health, Board of Pharmacy, Pharmacy Lawbook, Chapter 69.50 RCW Uniform Controlled Substances Act, Chapter 69.41 RCW Legend Drugs-Prescription Drugs, and Chapter 69.60 RCW Over-The-Counter Medications.
- ◆ The federal Prescription Drug Marketing Act (PDMA) regulates management of the return of expired or unusable pharmaceuticals to the manufacturers.
- ◆ The Washington State Department of Health has delegated authority from the Nuclear Regulatory Commission to enforce regulations pertaining to nuclear energy and radiation under Chapter 70.98 RCW with implementing regulations found in Chapters 246-221, 246-231, 246-232, 246-235, 246-239, and 246-249 WAC. The Washington State Department of Ecology regulates radioactive wastes under Chapters 173-44, 173-325, 173-326, and 173-328 WAC.

Under the conditional exclusion proposed above, the Dangerous Waste Regulations (Chapter 173-303) continues to regulate unusable and expired pharmaceuticals so that they are reused or disposed in accordance with federal, state and local regulations. The conditional exclusion ensures that pharmaceuticals regulated as Washington State-only dangerous wastes are disposed in a way that prevents their release to the environment. Any pharmaceutical regulated as waste under 40 CFR Part 261 may not be excluded.

“... because they ... are recycled in ways which do not threaten the public health or the environment...”

As a result of the Prescription Drug Marketing Act (PDMA), the reverse distribution system now addresses the recycling and reuse of unused and expired pharmaceuticals.

Additionally, the proposed language provides that drugs not accepted in the reverse distribution system undergo high-temperature combustion in Spokane’s Waste-to-Energy facility (recycling for energy recovery).

How are pharmaceuticals regulated under other state and federal programs?

Environmental Protection Agency (EPA)

Pharmaceuticals regulated under the federal Environmental Protection Agency (EPA) hazardous waste regulations, the Resource Conservation and Recovery Act (RCRA), must be disposed of at a permitted hazardous waste facility. RCRA regulates drugs that are ignitable, reactive, or hazardous compressed gases. Wastes containing hazardous levels of certain toxic chemicals (e.g., barium, mercury, silver and cresol) are also regulated by RCRA. Some drugs contain active ingredients listed as hazardous discarded chemical products on the RCRA U and P lists. The State of Florida has compiled a fact sheet on regulation of pharmaceuticals that provides examples of federally regulated pharmaceutical wastes (attached). See http://www.floridacenter.org/brochures_bulletins/rcra_pharmacies.pdf for the complete fact sheet. *The proposed exclusion makes no change in how these materials are handled.*

The Drug Enforcement Administration (DEA)

The DEA tracks controlled substances through their life cycles—from raw material through the manufacturing process to the pharmacy and ultimately to the patient or to the substance's destruction. DEA can track a single tablet from its manufacture to its ultimate fate. DEA strictly regulates destruction of controlled substances, licensing some people to witness the destruction of controlled substances on its behalf. About ten percent of pharmaceuticals fall into one of five "schedules" under the category of controlled substances. Each schedule requires a different level of reporting. The DEA enforces a closed system of distribution.

The Food and Drug Administration (FDA)

Since 1938 FDA has approved new drugs used for humans or animals for safety. Drug efficacy was added to the approval process in 1962. Drugs already on the market prior to these dates are not typically reviewed for approval (aspirin is an example of a "grandfathered" drug). Drugs included in the FDA review process are legend drugs that require a prescription from a doctor, veterinarian or other qualified professional, over-the-counter drugs, and DEA controlled substances.

The FDA new drug approval process encompasses drug selection, preclinical study (chemical characterization, animal testing and screening), clinical study (human testing), long-term toxicity studies of animals, effects on fertility and reproduction, special studies on young animals and other requested studies.

FDA is conducting a review of grandfathered over-the-counter (OTC) drugs to examine their safety and efficacy. More than 300,000 products were classified according to treatment category and active ingredients. Each class is reviewed and monographs produced. Based on these reviews, FDA banned several hundred OTCs in 1990 and 1993. The OTC review is still continuing.

The Washington State Board of Pharmacy

Washington state pharmacies must keep records of the receipt, dispensing and disposition of prescription drugs and controlled substances. Most pharmacies either return the drugs to the wholesaler or manufacturer or use a reverse distributor to manage expired and some unusable drugs.

Pharmaceutical reverse distributors maintain databases of manufacturers' return policies and complete all inventory and paperwork required for the return. In some cases reverse distributors inventory and pack up drugs being returned, in other cases the pharmacist handles this. Pharmacies must keep records of all transactions. The State Board of Pharmacy advises pharmacies to ensure their disposal methods are in compliance with the Washington State Department of Ecology and federal law. Additionally, the State Board of Pharmacy assumes that reverse distributors are in compliance with state environmental laws and with the laws of those states to which drugs are shipped.

The Federal Prescription Drug Marketing Act

To insure that pharmacies continued to stock new product, pharmaceutical manufacturers traditionally offered credit for unusable or expired pharmaceuticals not dispensed by the pharmacy. Prior to passage of the federal Prescription Drug Marketing Act (PDMA) in 1987, manufacturers' representatives either offered credit for expired products or exchanged them for fresh stock at the pharmacy. In some cases outdated or unusable items were returned to a drug wholesaler, which in turn shipped them back to the manufacturer for credit.

The PDMA put restrictions on the return of drugs to manufacturers and, in the case of hospitals, to drug wholesalers. The complexity of returning pharmaceuticals to hundreds of different manufacturers was cost prohibitive for any single pharmacy, and this situation provided an opportunity for entrepreneurs to develop the business model for reverse distribution. Based on two letters of interpretation (attached)—one to Merck & Co. in 1981, the other to BFI Pharmaceutical Services in 1991—the EPA has allowed unusable or expired pharmaceuticals to flow back through the reverse distribution system as products. While pharmacies ship back unusable or expired pharmaceuticals as 'products' via reverse distributors, the reverse distributor decides whether the items in the shipment are returnable. About 70 percent of a typical shipment is returnable for credit, while the remaining 30 percent will designate as either hazardous or nonhazardous waste (based on RCRA). Of the items being discarded, about 10 percent will typically designate as hazardous waste under RCRA; this is about three percent of the original shipment. The reverse distributor is responsible for properly storing, manifesting, and arranging for transport and disposal of the hazardous waste by a federally permitted RCRA incineration facility. The nonhazardous waste must be disposed of by a facility permitted to destroy nonhazardous pharmaceutical waste.

Reverse distribution is a well-accepted practice and has the approval of the EPA and Ecology. The majority of hospitals, pharmacies and drug wholesalers use this process for expired and unusable pharmaceuticals.

Washington State Departments of Health and Ecology (Radioactive Drugs)

The Nuclear Regulatory Commission delegates authority to the Washington State Department of Health. The Department of Health licenses those involved with radioactive materials including nuclear pharmacies, nuclear medicine, nuclear cardiology, radiopharmaceutical therapies, etc. Additionally, the Department of Health regulates radioactive waste management facilities, low-level radioactive waste disposal, and low-level radioactive waste disposal site users. EPA delegates authority to the Department of Ecology. The Department of Ecology issues site-use permits to users of the commercial low-level radioactive waste disposal site, and regulates mixed waste management. No nuclear or radioactive drugs are included in the proposed exclusion.

When reverse distribution is not an option, how do generators of pharmaceutical waste deal with the dangerous waste regulations?

Most pharmaceutical waste generators are aware of FDA, DEA and Board of Pharmacy regulations and are careful to follow them. In contrast, most small generators of pharmaceutical waste are not aware that they are also regulated by Washington State's Dangerous Waste Regulations (including the requirement to designate wastes to find out if the Dangerous Waste regulations apply.) In fact, for these wastes, designation can be the most burdensome requirement of the Dangerous Waste regulations.

Even though larger generators with dedicated waste management staff are more familiar with the Dangerous Waste regulations, lack of toxicity data and poor oversight and direction from Washington's own waste regulatory agencies have hindered the proper management of their dangerous waste pharmaceuticals. For example, University of Washington waste management staff initially attempted to manage pharmaceutical waste by individually designating each drug wastestream. However, lack of toxicity data and other problems made this task so overwhelming that they abandoned the effort and decided to manage all pharmaceutical waste as dangerous waste. This approach works for the University of Washington because adding a few more wastestreams to the large quantities of dangerous waste generated by the facility does not add much to their disposal costs. However, a smaller operation such as a neighborhood pharmacy would find it cost prohibitive to automatically designate all pharmaceutical waste as dangerous waste and absorb the associated disposal costs.

What pharmaceuticals may designate as RCRA hazardous waste?

See the attached examples compiled by the State of Florida in a fact sheet available on the Internet at http://www.floridacenter.org/brochures_bulletins/rcra_pharmacies.pdf .

What is the nature of pharmaceutical waste?

Expired pharmaceuticals are not waste when returned to a reverse distributor. However, when not returned to a reverse distributor they may become waste.

Expired or unusable pharmaceuticals include those that were originally purchased in a drug store or prescribed by a doctor or veterinarian. Expired pharmaceuticals are those that have exceeded

the FDA expiration date printed on the product or prescription label. They are within the original packaging (boxes, bottles, blister packs, etc.) and still have the manufacturer-provided package inserts.

Unusable pharmaceuticals are those that have been contaminated, adulterated, improperly stored, incorrectly compounded, unlabeled and/or dispensed to a patient and returned. They may be residues or partial doses prepared for administration to a patient in syringes, bags, tubing, cups, etc. or may be drugs that were dropped or spilled and swept off the floor.

Pharmaceutical waste may be liquid or solid (e.g., tablets, capsules, powders, patches or liquid). Although chemotherapy drugs are often managed as dangerous waste because they are perceived to be more toxic, this might not be the case. In one examination of 47 chemotherapy drugs, 18 had insufficient data to designate according to state toxicity criteria, 21 designated WT02 (dangerous waste), and the remaining eight designated WT01 (extremely hazardous waste).

DEA-scheduled drugs are also perceived as having higher toxicity. In a list of 143 scheduled drug (active ingredients only), 80 had insufficient data to designate according to State toxicity criteria, 2 were toxic category B, 35 were toxic category C, and 26 were toxic category D.

For comparison, active ingredients of several well-known prescription and over-the-counter drugs, including Prozac, Viagra, Aleve, Pepto-Bismol, Ritalin and Aspirin, were evaluated for State toxicity criteria. Aluminum hydroxide, fluoxetine hydrochloride (in Prozac), sildenafil citrate (in Viagra), naproxen sodium (in Aleve), bismuth subsalicylate (in Pepto-Bismol) have insufficient data to designate. Aspirin and methyl phenidate (in Ritalin) were toxic category C. Tetracycline, ephedrine, pseudoephedrine, ibuprofen, dimenhydrinate (in Dramamine) were toxic category D. Mangesium hydroxide was not toxic.

As in the examples above, other pharmaceuticals are comparable in toxicity to those already conditionally excluded in the emergency rule, which allows the Spokane Waste-to-Energy facility to accept and incinerate controlled substances as solid waste. The conditional exclusion proposed above incorporates these pharmaceuticals into the final rule along with controlled substances.

Do pharmaceuticals contain mercury?

Regulation of drugs that classify as federally regulated hazardous waste for mercury will not be affected by this rule proposal. Mercury is primarily used as a preservative in drug and biological products. Approximately 200 products (primarily nasal solutions/sprays, ophthalmic solutions/ointments, otic solutions, vaccines, and injectable products) contain mercury. The most common mercury compounds used as a preservative are thimerosal and phenylmercuric acetate.

According to Charlotte Smith of PharmEcology and founder of Capital Returns, a reverse distributor, mercury-containing formulations all designate for the characteristic of toxicity under RCRA and therefore are not a part of the conditional exclusion proposed above.

Does incinerating pharmaceutical waste in a high-temperature combustion unit harm the environment?

No. “Incineration is an appropriate method of disposal for these low volume, low toxicity wastes,” as stated in Ecology’s Purpose Statement for Emergency Rule WSR-02-04-030, and supported by the workgroup’s information on the controls in place at the Spokane Waste-to-Energy facility. Pharmaceuticals that potentially fall under state-only dangerous waste are primarily regulated due to their low toxicity. A few compounds are also halogenated organic compounds and may designate for persistence. The volume of waste pharmaceuticals going to the Spokane Waste-to-Energy facility prior to May 2001 was very low.

Under the proposed language change, how much waste would go to the Spokane Waste-to-Energy facility?

There is no clear data to answer this question. However, it is estimated to be a relatively small amount. According to Damon Taam at the Spokane Regional Solid Waste System, the facility might receive one truckload per year of pharmaceutical waste out of the total 200,000 truckloads of waste going to the incinerator each year. In addition, Spokane Waste-to-Energy facility data indicate that combustion of waste pharmaceuticals has not impacted its air releases. Testing reveals that emission thresholds for all contaminants of concern, including mercury, are far below permitting requirements.

What controls are in place at the Spokane Waste-to-Energy facility to keep contaminants from entering the environment?

The goal of the Waste-to-Energy facility in Spokane is to properly dispose of solid wastes by high temperature combustion. High temperature combustion destroys hazardous products within the solid wastes and as a byproduct generates electricity and an inert ash. The following is a description of how controls at the permitted municipal Waste-to-Energy facility in Spokane keep contaminants from entering the environment, provided by Damon Taam at the Spokane Regional Solid Waste System:

Solid wastes brought to the Waste-to-Energy facility are combusted in the boilers at 2500 degrees F and are kept at this temperature for about 45 minutes. The combustion chamber has very sophisticated combustion control systems that distribute the solid waste evenly to ensure that combustion is complete. The volume of solid waste combusted is reduced by 90 percent, leaving only ferrous metal scrap, glass and ash. The majority of problematic constituents in expired or unusable pharmaceuticals are organic in nature, which are destroyed almost completely through combustion. The combustion in this facility also destroys other hazardous products in the solid wastes, such as PCBs, dioxins and furans.

The Thermal deNO_x system injects anhydrous ammonia into the boiler where nitrous oxide (NO) and dioxides (NO₂), thought to be precursors to acid rain and components of smog, are broken down into the elements nitrogen and oxygen.

The exhaust gases are rapidly cooled down (critical so that gases cannot recreate dioxins and furans) through heat transfer. At this point powdered activated carbon is injected. The activated carbon enhances the ability of the air pollution control equipment to capture heavy metals and volatile organic chemicals. After the injection of the powdered activated carbon, the exhaust gases are directed to the air pollution control building. Within the air pollution control building the exhaust gases pass through the spray dryer absorber and bag house.

The acid gas scrubber, actually called a spray dryer absorber, is where a lime slurry is injected into a reaction chamber, causing the temperature of the flue gases to drop from 450 to less than 300 degrees F and scrubbing out hydrochloric, sulfuric and hydrofluoric acids. The gas now enters the bag house.

The bag house at the Spokane facility uses 3,420 state-of-the-art fiberglass bags lined with Goretex™ to scrub out fine particulates – small bits of lime, ash or dust that cause air pollution. The stack is monitored for air pollutants continuously and tested thoroughly (to parts per trillion) on a regular basis.

What goes into the Waste-to-Energy facility in Spokane is solid waste – three million tons of garbage since its inception in September 1991 from cities and towns in and around Spokane and beyond. What leaves the Waste-to-Energy facility in Spokane are air emissions equivalent to that of ten EPA-certified wood stoves, ash, scrap metal, and enough electricity to serve about 13,000 homes (about 26 megawatts sold to Puget Sound Power and Light).

What is biohazardous waste and how is it disposed?

Biohazardous waste includes anything contaminated with bodily fluids. A typical “red bag” of biohazardous waste may contain bloody gloves, bandages, sponges, gowns and possibly body parts. A sharps container, also part of biohazardous waste, contains syringes and needles.

Biohazardous waste generated in Washington is generally heat-treated (autoclaved or ‘microwaved’) and disposed as solid waste. The only firm currently permitted to haul biohazardous waste in Washington is Stericycle. Waste handled by Stericycle is sterilized by radiowave, with temperatures reaching 204 degrees F, and then disposed in the solid waste.

The IRAC Pharmaceutical workgroup concludes that the incineration of expired and unusable pharmaceuticals by high-temperature combustion is better than treatment and disposal of pharmaceuticals as biohazardous waste. Neither the radiowave nor autoclave process destroy the shape or activity of the pharmaceutical, whereas incineration destroys both.