CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-104

APPROVABLE LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-104

Osmotica Pharmaceutical Corporation
Attention: Timothy W. Davis
Manager, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Mr. Davis:

Please refer to your new drug application (NDA) dated December 11, 2006, received December 12, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended Release 37.5mg, 75mg, 150mg and 225mg tablets.

We acknowledge receipt of your submission dated December 28, 2007.

The December 28, 2007 submission constituted a complete response to our October 4, 2007 action letter.

This new drug application provides for the use of Venlafaxine Hydrochloride Extended Release tablets for major depressive disorder and social anxiety disorder,

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following deficiencies.

OFFICE OF CLINICAL PHARMACOLOGY

Please adopt the following "interim" dissolution specifications for Venlafaxine Extended Release tablets. As a condition of this "interim" specification, please collect dissolution data for 24 tablets (up to L3 stage of testing) on the first 12 batches at release or on all batches at release post approval for a period of 12 months, which ever comes first, for each strength. Please submit this information to the Agency by 14 months from the date of approval so that a 'final' specification can be set for the product.

Dissolution Method for All Strengths of Venlafaxine ER

Method

Apparatus:	USP Apparatus II (Paddle)
Speed:	50 rpm
Media:	Water at 37°C
Volume:	900 mL

if possible, to use the IVIVC developed to propose a single dissolution specification. Therefore, we request that you consult the Agency's Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of IVIVC and submit the required data (e.g., details of model development including equations, data sets, and control files) for review in your resubmission. The guidance can be found at http://www.fda.gov/cder/guidance/index.htm.

Existing Patent and Exclusivity Protection
We note that [redacted] b(4)

Your application also contains certifications to some of the listed patents stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications"). An action may be brought for infringement of one or more of the patents that were the subject of the Paragraph IV certification. This action must be taken prior to the expiration of forty-five days from the date the notice provided is received by the patent owner/approved application holder. You have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit. Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt (March 8, 2007) of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or

   b. the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,

   c. the listed patent(s) has/have expired, and

2. we are assured there is no new information that would affect whether final approval should be granted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call LCDR Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

"Interim" Dissolution Specifications

37.5 mg		75 mg, 150 mg and 225 mg		
4 hour	—	4 hour	—	b(4)
12 hour	—	12 hour	—	
20 hour	NLT —	20 hour	NLT —	

In the submission to the Agency by 14 months post approval, please provide justification, based on the data available after the requested testing period, why a single dissolution specification, such as the one proposed by the Agency below, could not be adopted for all strengths of Venlafaxine ER.

Agency's Proposed Specification for all Strengths of Venlafaxine ER

4 hours	—	b(4)
12 hours	—	
20 hours	NLT —	

CONTENT OF LABELING

Please review the attached labeling provided in track changes. All the deficiencies in labeling have been included in the enclosed labeling. Please submit revised draft labeling in correct PLR content and format labeling according to our guidance documents that can be found at (http://www.fda.gov/cder/regulatory/physLabel/default.htm) and (http://www.fda.gov/cder/guidance/5534fnl.htm).

POST MARKETING COMMITMENT

1. **Investigate Dose Dumping And Perform Ethanol Dissolution Studies**

   In your December 28, 2007 response to our action letter you agreed to conduct studies to investigate dose-dumping in the presence of alcohol as well as agreeing to perform dissolution studies for all Venlafaxine Extended Release strengths using the accepted dissolution conditions with the addition of — of ethanol to the dissolution media. The accepted dissolution method is: b(4)

   Apparatus: USP Apparatus II (Paddle)
   Speed: 50 rpm
   Media: Water at 37°C
   Volume: 900 mL

   We request that you submit this information no later than 6 months from the date of approval

IVIVC

The agency also acknowledges your commitment to submit the data requested for the IVIVC. This could also facilitate the setting of a 'final' dissolution specification for this product. It is recommended,

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

Enclosure: Package Insert & Medguide

35 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Approvable Letter # 1 / 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
2/26/2008 03:16:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-104

Osmotica Pharmaceutical Corporation
Attention: Timothy W. Davis
Manager, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Mr. Davis:

Please refer to your new drug application (NDA) dated December 11, 2006, received December 12, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended-Release 37.5mg, 75mg, 150mg and 225mg tablets.

We acknowledge receipt of your submissions dated January 19, 2007, January 31, 2007, June 28, 2007, and September 7, 2007.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following issues:

Office of Clinical Pharmacology

1. We request that you adopt the following dissolution method and specification for all strengths (37.5mg, 75mg, 150mg and 225mg tablets) of Venlafaxine Hydrochloride Extended-Release tablets:

   Apparatus: USP Apparatus II (Paddle)
   Speed: 50 rpm
   Media: Water at 37°C
   Volume: 900 mL
   Specification: Q at
   4 hours: . —
   12 hours —
   20 hours NLT —

   b(4)

Chemistry, Manufacturing, and Controls

1. Your revised label includes the term "equivalent to" the label strength in terms of Venlafaxine. This is not acceptable. Please revise your label to include the product strength as follows:

   Venlafaxine
   Extended Release Tablets
   37.5 mg*

*present as venlafaxine hydrochloride

2. Please submit updated stability data and re-evaluate your dissolution data according to the dissolution specifications proposed above.

Labeling

Your label needs to be converted to PLR format. We recommend that you carefully review and implement your PLR labeling according to our guidance documents that can be found at (http://www.fda.gov/cder/regulatory/physLabel/default.htm) and (http://www.fda.gov/cder/guidance/5534fnl.htm). Our Study Endpoints and Label Development (SEALD) Team have created a list (attached) of the most frequently encountered PLR format/content deficiencies. You should carefully review both our guidance documents and attachment to ensure that you are compliant with the PLR content and format.

We additionally have the following comments related to your proposed PLR labeling which was submitted to us in WORD format on 7-13-07.

Under HIGHLIGHTS

1. Highlights should be formatted to fit on one-half page. If this is not possible, you should formally request a waiver of this requirement.
2. Year of initial approval for venlafaxine was 1993, not 2007.
3. Recent Major Changes consist of labeling to describe mortality after overdose under OVERDOSAGE (9/2006) and interstitial lung disease and eosinophilic pneumonia under PRECAUTIONS (1/2007).
4. [redacted] b(4)
5. The DOSAGE AND ADMINISTRATION section must provide dosing instructions per 21 CFR 201.57, such as the initial starting dose.
6. Under the WARNINGS AND PRECAUTIONS section, the first two bullets are described by the third bullet and should be deleted. The following events appear to merit bullets in this section: MAOI interaction, serotonin syndrome, sustained hypertension, mydriasis, hyponatremia, interstitial pneumonia, use a lower dose in patients with hepatic or renal impairment, and use cautiously with drugs that inhibit both CYP2D6 and CYP3A4. These events should be prioritized by clinical importance.
7. ADVERSE REACTIONS should include only those events that were present in at least 5% of venlafaxine-treated patients at a rate at least twice the placebo incidence.
8. DRUG INTERACTIONS should include triptans and other serotonergic drugs.
9. USE IN SPECIFIC POPULATIONS should indicate that venlafaxine should be used during pregnancy "only if clearly needed." The statement regarding use in nursing mothers should indicate the potential for serious adverse events in the nursing infant.

Under FULL PRESCRIBING INFORMATION

10. Section 3, DOSAGE FORMS AND STRENGTHS, must include a description of physical identifying characteristics, such as shape and color of the tablets.
11. Section 4, CONTRAINDICATIONS, should not include hypersensitivity to the drug or any excipients since this is a universal contraindication for all drugs.

12. Section 5, WARNINGS AND PRECAUTIONS, must combine WARNINGS (proposed as section 5.1) and PRECAUTIONS (proposed as section 5.2) under one major section (section 5). All references to this section should be corrected accordingly.
13. All references to data derived from studies with Effexor XR must indicate "venlafaxine hydrochloride extended-release capsules" to distinguish these data from data with venlafaxine extended-release tablets. This applies to several section of labeling.
14. Under section 5, a subsection for Interstitial Lung Disease and Eosinophilic Pneumonia should be added (see current Effexor XR labeling).
15. Section 6, ADVERSE REACTIONS, must be reformatted as follows: 1) the initial section should include, in three separate paragraphs, brief descriptions of serious adverse events, the most common adverse events, and adverse events that led to discontinuation; 2) subsection 6.1 should describe the clinical studies experience (database, caveat regarding prediction of incidence in medical practice, and a 2% table), and subsection 6.2 for postmarketing reports.
16. Throughout section 6, data from studies in SAD should be described only to the extent that it differs in a meaningful way from the data in the MDD studies.
17. [redacted] b(4)
18. Also in section 6, adverse events for which the placebo reporting rate was equal to or greater than the venlafaxine rate should be deleted.
19. The subsection listing other adverse events observed during premarketing trials should be abbreviated considerably to include only those events for which there is some basis to believe that venlafaxine had a causal relationship in the emergence of the event. For non-serious, infrequent or rare events, these should be deleted unless there is strong evidence for causality. For guidelines on assessing causality, please refer to the "Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" dated January, 2006.
20. Comment 18 above also applies to the Postmarketing Events subsection. In addition, this subsection should be preceded by the standard introductory statement indicated in the above guidance.
21. The last paragraph under subsection 9.3 (Dependence) should be moved to subsection 9.2 (Abuse).
22. Regarding Section 12, CLINICAL PHARMACOLOGY, the PHARMOKINETICS section, you should delete Tables 1 and 2 and include the following information specific to your product in addition to any other necessary data:

    "The mean ± SD apparent elimination half-life for venlafaxine and ODV after administration of 75 mg Venlafaxine extended release tablets under fed conditions were 10.7 ± 3.2 hours and 12.5 ± 3.0 hours, respectively."

    Under the Absorption and Distribution section, the following information specific to your product in addition to any other necessary data should be added:

    " Administration of 75 mg Venlafaxine Hydrochloride Extended-release tablet under fed conditions resulted in mean ± SD venlafaxine Cmax of 26.9 ± 13.4 ng/mL and AUC of 1536.3 ± 496.8 nghr/mL. Tmax was 6.3 ± 2.3 hours. ODV mean ± SD Cmax, AUC, Tmax after administration of 75 mg Venlafaxine Hydrochloride Extended-release tablet under fed conditions were 97.9 ± 29.4 ng/mL, 2926.0 ± 746.1 ng-hr/mL and 11.6 ± 2.9 hours, respectively.

When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release form of venlafaxine, the exposure to both venlafaxine and ODV would be similar for the two treatments. Venlafaxine Hydrochloride Extended-release Tablets would therefore provide a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the pharmacokinetic parameters of AUC, Cmax, and Tmax of venlafaxine or its active metabolite, ODV after administration of Venlafaxine Hydrochloride Extended release tablet. Time of administration (AM vs PM) would not affect the pharmacokinetics of venlafaxine and ODV."

23. Section 12, CLINICAL PHARMACOLOGY, should include a subsection 12.1 (Mechanism of Action). This appears to have been inadvertently omitted.
24. Subsection 14.2 (Social Anxiety Disorder) contains a typographical error in describing the dose range for these studies (75 to /day should read 75 to 225 mg/day).
25. The table of adverse events from MDD studies contains a numerical error: the placebo reporting rate for hypertension should be 1%, not 4%.
26. The table of adverse events from SAD studies has omitted the footnote notation immediately after Abnormal Vision.

Your resubmission should also incorporate all of the innovator's recent labeling changes approved in Agency letters dated August 1, 2007 and September 20, 2007. These approvals can be found at the following web site:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

Additionally, please provide a reference document justifying your approach to comply and convert the innovator's labeling to PLR format.

For your convenience, these recent revisions to Effexor XR labeling require changes to the following sections of the PLR labeling for your product:

- Information pertaining to the emergence of suicidality with antidepressant drugs must be updated in the following sections: 1) BOX WARNING, 2) WARNINGS AND PRECAUTIONS, 3) PATIENT COUNSELING INFORMATION, and 4) MEDICATION GUIDE.
- The following sections pertaining to the use of venlafaxine in patients with liver disease should be updated: 1) DOSAGE AND ADMINISTRATION, Special Populations and 2) CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.
- The section DRUG INTERACTIONS should be updated as follows to reflect data from an interaction study with metoprolol.
- Information pertaining to hyponatremia associated with venlafaxine, particularly in elderly patients, should be updated in the following sections: 1) WARNINGS AND PRECAUTIONS and 2) DOSAGE AND ADMINISTRATION, Special Populations, Elderly Patients.
- Information pertaining to impaired coordination and balance must be added to the following sections: 1) WARNINGS AND PRECAUTIONS, Discontinuation of Treatment with Venlafaxine Hydrochloride Extended-Release Tablets and 2) ADVERSE REACTIONS, Postmarketing Reports.

Post Marketing Commitment

1. We request that you agree to conduct studies to investigate dose-dumping in the presence of alcohol. You should also perform dissolution studies for all Venlafaxine Extended Release strengths using the accepted dissolution conditions with the addition of [redacted] of ethanol to the dissolution media. The accepted dissolution method is: b(4)
   Apparatus: USP Apparatus II (Paddle)
   Speed: 50 rpm
   Media: Water at 37°C
   Volume: 900 mL

Existing Patent and Exclusivity Protection

In addition to addressing the above deficiencies, [redacted] b(4)

Your application also contains certifications to some of the listed patents stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications"). An action may be brought for infringement of one or more of the patents that were the subject of the Paragraph IV certification. This action must be taken prior to the expiration of forty-five days from the date the notice provided is received by the patent owner/approved application holder. You have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit.[1] Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides[2] that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patent(s) has/have expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

Other Comments

Although not a condition for approval, your *in vitro/in vivo* (IVIVC) model developed is not acceptable at this time. It is recommended that you consult the Agency's Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of IVIVC and submit the required data (e.g., details of model development including equations, data sets, and control files) for review in your resubmission. The guidance can be found at http://www.fda.gov/cder/guidance/index.htm.

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1 We note that you failed to timely advise the FDA that you were sued in response to your notice of Paragraph IV certification. We remind you that the Agency's regulations require that a "505(b)(2) applicant *shall* notify FDA *immediately* of the filing of any legal action filed within 45 days of receipt of the notice of [paragraph IV] certification" (21 CFR 314.107(f)(2))(emphasis added).

2 This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. Additionally, we recommend that you carefully review and implement PLR labeling according to guidance that we provided you. If there are significant deficiencies with your PLR labeling, another cycle may be necessary to correct labeling. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact CDR Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Common Proposed Labeling Deficiencies

Attachment

Common Proposed Labeling Deficiencies
Identify and Correct before Labeling Content Review Begins

Highlights:
• Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.
[See 21 CFR 201.57(d)(6) and Implementation Guidance]
• The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
• The highlights limitation statement must read as follows: 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].
[See 21 CFR 201.57(a)(1)]
• The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
• The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
• For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
• The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

• Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
• A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.
[See 21 CFR 201.57 (a)(11)].
• Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
[See comment #34 Preamble]
• The Patient Counseling Information statement must appear in Highlights and must read

See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
• A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
• A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Contents:
• The wording of the headings and sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]
• The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
• Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
• Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
• When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. 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."

Full Prescribing Information (FPI):
• Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
• Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.
• The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
[See Implementation Guidance]
• Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

• Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
• The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
• There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
• The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
• Regarding information at the end of the labeling, company website addresses are not encouraged. Delete from package insert labeling. The same applies to PPI and MG.
• If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
• Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Created: J. Delasko, SEALD Team, 1/29/07
Revised: R. Anderson, SEALD Team, 3/1/07

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/s/

Thomas Laughren
10/4/2007 11:42:53 AM