

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202231Orig1s000**

**OTHER REVIEW(S)**

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**Application:** NDA 202231

**Name of Drug:** Proprietary name - none  
Established name - Levothyroxine Sodium for Injection

**Applicant:** APP Pharmaceuticals, LLC

## Labeling Reviewed

**Submission Date:** August 30, 2010

**Receipt Date:** August 30, 2010

## Summary Description

Indication: myxedema coma

Dosage form: Lyophilized Powder for Injection

Route of administration: Intravenous (IV)

Proposes new indication, dosage form, dosing regimen, and route of administration

Drug chemical classification: 7-Drug Already Marketed but Without an Approved NDA  
Review priority: Standard

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

## Recommendations

All labeling issues identified on the following pages with an "X" will be conveyed to the applicant. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues. The resubmitted labeling will be used for further labeling discussions.

Linda Galgay

Regulatory Project Manager

March 23, 2011

Date

LABELING CHECKLIST	FILING REVIEW
<b>SECTION I: Highlights Overview</b>	<b>08.30.10</b>
For more information, see Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements; also refer to <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> .	
Check that the following items appear (in the following order):	
<ul style="list-style-type: none"> <li>• <b>Highlights Limitation Statement</b> (required statement) (required bolding)</li> </ul>	X
<ul style="list-style-type: none"> <li>• <b>Drug names, dosage form, route of administration, and controlled substance symbol</b> (required information) (required bolding)</li> </ul>	X
<ul style="list-style-type: none"> <li>• <b>Initial U.S. Approval</b> (required information) (required bolding)</li> </ul>	<b>X – Date of moiety approval</b> 1969
<ul style="list-style-type: none"> <li>• <b>Boxed Warning</b> (required bolding)</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Recent Major Changes</b> (for a supplement)</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Indications and Usage</b></li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Dosage and Administration</b></li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Dosage Forms and Strengths</b></li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)</li> </ul>	X -Must keep heading with “None”
<ul style="list-style-type: none"> <li>• <b>Warnings and Precautions</b></li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Adverse Reactions</b> (required AR contact reporting statement) (required bolding for AR contact reporting statement)</li> </ul>	X
<ul style="list-style-type: none"> <li>• <b>Drug Interactions</b> (optional heading – can be omitted)</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Use in Specific Populations</b> (optional heading – can be omitted)</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Patient Counseling Information Statement</b> (required statement) (required bolding)</li> </ul>	<b>X – Not applicable</b>
<ul style="list-style-type: none"> <li>• <b>Revision Date</b> (required information) (required bolding)</li> </ul>	
[format] Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5” x 11 paper, single spaced, minimum 8 point type with ½ inch margins on all sides, in a two-column format)	
[format] All headings and subheadings must be in bold type.	
[format] All headings must be presented in the center of a horizontal line in upper-case letters and bold type. The horizontal line can be a solid or dashed line.	
[format] If there are multiple subheadings, each subheading must be preceded by a bullet point.	
[format] The information should be concisely summarized without repetition and presented in an easily accessible format (e.g., bulleted, tabular). <u>There should be no redundancy of information.</u>	
[format] Use command language (e.g., use “Discontinue” instead of “You should discontinue.”)	
[format] Each summarized statement should be located under the appropriate Highlights heading and must reference the section(s) or	

LABELING CHECKLIST	FILING REVIEW
subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.	
[format] The preferred presentation of referencing in Highlights is the numerical identifier in parentheses [e.g., (1.1)] following the summarized labeling information, corresponding to the location of information in the FPI.	
[format] There should be white space between each major heading in Highlights.	
[format] The type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed (i.e., trade labeling), which must be a minimum of 6 points. See Appendix E of Implementation Guidance for type size requirements.	<b>X</b>
[format] There is no requirement for a specific typeface for labeling as long as it is clear and legible. However, Arial Narrow font is not recommended because it may render the labeling illegible.	
[format] Do not use the asterisk (*) to footnote information in tables in Highlights since this symbol is used in the Table of Contents (i.e., *Sections or subsections omitted from the full prescribing information are not listed.)	
[format] We are no longer going to review the labeling for the “TM” or “R” symbols. Companies can add these symbols at will in Word and Adobe versions. These symbols will not appear in the rendering of labeling in SPL format due to style sheet restrictions.	

LABELING CHECKLIST	FILING REVIEW
<b>SECTION II: Highlights Details</b>	
<b>Highlights Limitation Statement</b>	
Must appear at beginning of Highlights in bold type and be placed on the line immediately beneath the heading - <b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b>	
The verbatim statement must read: “These highlights do not include all the information needed to use ( <u>insert name of drug product in upper case letters</u> ) safely and effectively. See full prescribing information for ( <u>insert name of drug product in upper case letters</u> ).”	X
<b>Drug names, dosage form, route of administration, and controlled substance symbol</b> (must appear in bold type)	
<ul style="list-style-type: none"> <li>With SPL R4, the product title in HL is no longer added automatically. Since this field is added as free text, check carefully.</li> </ul>	
<ul style="list-style-type: none"> <li>Include proprietary name and either established name of drug, OR proper name of biological product.</li> </ul>	
<ul style="list-style-type: none"> <li><b>For the established name of a drug</b>, the active moiety is generally used if the product is a salt. The salt is sometimes included in the name when it is important to know what salt is present for therapeutic reasons (e.g., a lot of Na or K; affect on therapeutic performance is known - absorption, distribution, metabolism, excretion). Include the entire drug substance name for esters, chelates, and complexes.</li> <li>Also, the established name and expression of strength should match. As a general rule, if the strength is in terms of the salt/ester, the name includes the salt/ester. If the strength is in terms of the active moiety, the name is in terms of the active moiety.</li> </ul>	X
<ul style="list-style-type: none"> <li>The drug names must be followed by drug’s dosage form and route of administration.</li> <li>Note that for biologic products, the dosage form and route of administration must be on the next line (i.e., underneath the proper name) since the proper name does not include the drug’s dosage form or route of administration. See 21 CFR 600.3 (k) and Section 351 of the PHS Act</li> <li>If the route of administration is typical for the dosage form and is commonly understood (e.g., tablets or capsules), omit the route of administration (for oral use). If the route of administration is not typical, it must be included.</li> </ul>	
<ul style="list-style-type: none"> <li>If applicable, must include the controlled substance symbol designating the schedule in which the controlled substance is listed.</li> <li>However, do not include a controlled substance symbol after drug names, dosage forms, and route of administration unless DEA scheduling action is final.</li> </ul>	N/A

LABELING CHECKLIST	FILING REVIEW
<p>[format] To conserve space in Highlights, the proprietary and established names should be presented on the same line, unless they are too long. (This does not apply for biological products – see above).</p>	
<p><b>Product Titles:</b> Because the drug names, dosage form, route of administration appears at the beginning of labeling, a <b>“Product Title” section is not needed for labeling in the new format</b> (See comment #39 to Preamble) and should be deleted from the prescribing information.</p>	
<p><b>Logos:</b> Current regulations (21 CFR 201.57) fully describe the format and content for labeling, including Highlights. There is no provision for a logo. <b>Therefore, do not include logos in Highlights or in the SPL file</b> since logos interfere with repurposing of the labeling in SPL. However, in WORD labeling documents, a small company logo can appear at the end of the labeling with the manufacturer information.</p>	
<p><b>Barcodes in Final Printed Labeling:</b> The barcode is not required to be on the labeling, only the label (see 21 CFR 201.25). If the barcode is compliant with 21 CFR 201.25, it is acceptable to include the barcode for the TRADE labeling. However, it should not be included in SPL.</p>	
<p><b>Initial U.S. Approval</b> (must appear in bold type)</p>	
<ul style="list-style-type: none"> <li>• [format] The verbatim statement “Initial U.S. Approval” followed by the four-digit year in which FDA initially approved a <b>new molecular entity</b>, new biological product, or new combination of active ingredients</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• Ensure that the 4-digit year is entered. If this is a NME, the year will correspond to the current approval action.</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• [format] The statement must be placed on the line immediately beneath established name or, for biological products, proper name of the product.</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>For DESI drugs:</b> Use the original date of approval of the NDA as the “Initial U.S. Approval” date and not the post-approval DESI update date. Therefore: <ul style="list-style-type: none"> <li>○ Do not list the DESI update date in the “Initial U.S. Approval” date field.</li> <li>○ Do not list multiple “Initial U.S. Approval” dates or use an asterisk after the date with a footnote regarding DESI approval.</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>• <b>For new formulations:</b> Use the original date of approval of the active ingredient, even if the labeling does not refer to the older formulations.</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• <b>For a combination product:</b> If a combination product is on the market first (Active Moiety A and Active Moiety B approved in 1950) and one of the active moieties (A or B) is approved at a later date (1982) as a single moiety, the initial U.S. approval date would be the date/first time there was general exposure to the molecular entity. In this case, it would be the date that the combination product was first approved (1950).</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>For racemates:</b> A racemate is not an NME. Use the originally approved racemic mixture approval date. The name of the</li> </ul>	

LABELING CHECKLIST	FILING REVIEW
<p>originally approved racemate or racemic mixture may be included in parentheses. For example, Nexium (esomeprazole magnesium) capsules would read: Initial U.S. Approval: 1989 (omeprazole).</p> <ul style="list-style-type: none"> <li>○ In the Description section, the following clarification may appear: Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. (Initial U.S. Approval of esomeprazole magnesium: 2001).</li> </ul>	
<p><b>For systemic antibacterial drug products</b>, the required statement about antibiotic resistance [see 21 CFR 201.24(a)] should be placed directly under the Initial U.S. Approval date.</p>	
<p><b>Boxed Warning</b></p>	
<p>(Also see <a href="#">Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</p>	
<ul style="list-style-type: none"> <li>• [format] Not to exceed a length of 20 lines. Summarize, rather than repeat verbatim, the warning from the FPI. Boxed Warning lines do not count against the ½ page Highlights’ requirement.</li> </ul>	
<ul style="list-style-type: none"> <li>• Summary must be preceded by a heading, in upper-case letters, containing the word “<b>WARNING</b>” and other words that are appropriate to identify subject of the warning.</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• [format] Heading and summary must be contained within a box and bolded. Use lower-case letters for the summary.</li> </ul>	
<ul style="list-style-type: none"> <li>• The verbatim statement “<i>See full prescribing information for complete boxed warning</i>” must be placed immediately following the heading of the boxed warning. If the boxed warning in HL is identical to the boxed warning in the FPI, this statement is not necessary.</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• [format] Summarize information in a bulleted format, with each bullet communicating a discrete warning or contraindication.</li> </ul>	
<ul style="list-style-type: none"> <li>• List each bulleted item in the boxed warning in decreasing order of importance (i.e., should reflect the relative public health significance).</li> </ul>	
<p><b>Recent Major Changes</b> (applies only to supplements)</p>	
<p>A list of the section(s) in the FPI, limited to 5 labeling sections that contain “substantive labeling changes” (i.e., to the content of the <b>Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warning and Precautions</b> sections) that have been approved by FDA</p>	
<ul style="list-style-type: none"> <li>• [format] 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 format) on which the change was incorporated in labeling. <b>The date will be the month/year that the supplement is approved.</b> Remember to update before approval.</li> </ul>	
<ul style="list-style-type: none"> <li>• [format] Highlights labeling sections must be listed in the order in which they appear in the full prescribing information.</li> </ul>	

LABELING CHECKLIST	FILING REVIEW
<ul style="list-style-type: none"> <li>• [format] The corresponding new or modified text in the FPI sections listed under Recent Major Changes must be marked with a vertical line (“margin mark”) on the left edge.</li> </ul>	
<ul style="list-style-type: none"> <li>• A section or subsection that is removed should be noted as such in Recent Major Changes. The text noting the change should include the title of the section/subsection removed, followed by the term “removal” and date of removal. For example, Dosage and Administration, Subsection Title (2.X) ~removal XX/2010.</li> </ul>	
<ul style="list-style-type: none"> <li>• A changed section must be listed under this heading in Highlights for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period.</li> </ul>	
<ul style="list-style-type: none"> <li>• Refer to draft guidance for Implementing the New Content and Format Requirements (pages 8-10) for additional information and examples of RMC.</li> </ul>	
<b>Indications and Usage</b>	
<i>(Also see <a href="#">Guidance for Industry and Review Staff: Labeling for Human Prescription Drugs and Biological Products – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information</a>)</i>	
[format] A concise statement of each of the drug’s indications (presented in bulleted format), with any appropriate subheadings	X
<ul style="list-style-type: none"> <li>• If the drug is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class as follows: “(Drug) is a (name of class) indicated for (indications(s)).” If the drug is not a member of an established pharmacologic class, the statement should be omitted.</li> <li>• For the pharmacological class web page see <a href="http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm">http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm</a>.</li> <li>• Major limitations of use must be briefly noted.</li> </ul>	X
<p><b>For accelerated approvals</b> [i.e., biological products approved under Subpart E (21 CFR 601.41) and drugs approved under Subpart H (21 CFR 314.510)], include a statement regarding the basis of approval. Suggest the following language: “[Drug] is indicated for the [treatment/prevention] of . . . . The effectiveness of [drug] is based on [describe the outcome, e.g., an improvement in drug activity/response rate/tumor shrinkage]. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.</p>	
<b>Dosage and Administration</b>	X
A concise summary including the following:	X
<ul style="list-style-type: none"> <li>• Recommended dosage regimen</li> </ul>	
<ul style="list-style-type: none"> <li>• Starting dose</li> </ul>	
<ul style="list-style-type: none"> <li>• Dose range</li> </ul>	
<ul style="list-style-type: none"> <li>• Critical differences among population subsets</li> </ul>	

LABELING CHECKLIST	FILING REVIEW
<ul style="list-style-type: none"> <li>Monitoring recommendations</li> </ul>	
<ul style="list-style-type: none"> <li>Other clinically significant clinical pharmacologic information that affects dosing recommendations.</li> </ul>	X
<ul style="list-style-type: none"> <li>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.)</li> </ul>	X
<ul style="list-style-type: none"> <li>[format] Should use tabular format to enhance accessibility of information (e.g., when there are different dosing regimens for different indications).</li> </ul>	
<ul style="list-style-type: none"> <li>[format] Avoid error-prone abbreviations, symbols and dose designations when describing dosage and administration information. Refer to the Institute for Safe Medication Practices' website at <a href="http://www.ismp.org/Tools/abbreviationslist.pdf">http://www.ismp.org/Tools/abbreviationslist.pdf</a>.</li> </ul>	
<ul style="list-style-type: none"> <li>[format] Avoid using "IV" as it is commonly mistaken for Roman numeral IV. Instead, use "intravenous."</li> </ul>	X
<ul style="list-style-type: none"> <li>[format] Do not use a "slash mark" (/) since it may be mistaken for the number 1. Use "per." For example, do not use 5 mg/10 mL. Use 5 mg per 10 mL.</li> </ul>	X
<b>Dosage Forms and Strengths</b>	
A concise summary of dosage forms and strengths including:	
<ul style="list-style-type: none"> <li>Any appropriate subheadings (e.g., tablets, capsules, injection, suspension)</li> </ul>	
<ul style="list-style-type: none"> <li>The strength or potency of the dosage form in metric system (e.g., 10 mg tablets) and whether the product is scored. If the product is not scored, do not say "not scored."</li> </ul>	
[format] If a drug product has numerous dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations are recommended.	
Do not include "How Supplied" information.	X
<b>Contraindications</b>	
All contraindications listed in the FPI must also be listed in HL.	
Must 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.	
List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.	
Use of pregnancy Category X drugs are contraindicated in pregnancy. Therefore, under Contraindications in HL, state "Pregnancy" and cross-reference to Contraindications section (4) and Pregnancy subsection (8.1).	
<b>Warnings and Precautions</b>	
A concise summary of the most clinically significant information, with any	

LABELING CHECKLIST	FILING REVIEW
appropriate subheadings, including information:	
<ul style="list-style-type: none"> <li>• That would affect decisions whether to prescribe the drug</li> </ul>	
<ul style="list-style-type: none"> <li>• Recommendations for patient monitoring that are critical to safe use of the drug</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• Measures that can be taken to prevent or mitigate harm</li> </ul>	<b>X</b>
All critical safety concerns should be addressed.	
List W&P in decreasing order of importance (i.e., reflecting the relative public health significance) regardless of drug class.	<b>X</b>
Pregnancy Category D drugs have positive human risk findings. These findings must be noted as a warning. Therefore, under W&P in HL state the following based on data: “Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus.” If a pregnancy registry exists, state: “Pregnancy registry available.” Conclude the entire statement with a cross-reference to Warnings and Precautions section (5.X ) and Pregnancy subsection (8.1).	
<b>Adverse Reactions</b>	
<p>A list of the most frequently occurring adverse reactions, along with the criteria used to determine inclusion (e.g., incidence rate greater than x%).</p> <ul style="list-style-type: none"> <li>• If some of the most frequently occurring adverse reactions are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications because they are serious) they should still be included in this list since it would be misleading to have a list of “most common” if it does not include <u>all</u> of the “most common” adverse reactions.</li> <li>• Adverse reactions important for reasons other than frequency (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be included under this heading in Highlights unless they meet the criteria as described above.</li> <li>• Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in Highlights. Other terms, such as “adverse events” or “treatment-emergent adverse events” should be avoided.</li> <li>• Do not include “adverse events” from postmarketing experience.</li> </ul>	<b>X</b>
<ul style="list-style-type: none"> <li>• *For drug products other than vaccines, the verbatim statement, “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a>.” This statement must be in bold type.</li> </ul>	
<ul style="list-style-type: none"> <li>• *For vaccines, the verbatim statement “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or VAERS at 1-800-822-7967 or <a href="http://www.vaers.hhs.gov">www.vaers.hhs.gov</a>.” This statement must be in bold type.</li> </ul>	
<ul style="list-style-type: none"> <li>• *With SPL Release 4, the Adverse Reactions Reporting Statement is no longer added automatically. The verbatim language required by regulation must be added as free text; therefore, check carefully.</li> </ul>	

LABELING CHECKLIST	FILING REVIEW
<ul style="list-style-type: none"> <li>For reporting suspected adverse reactions, the manufacturer must use a U.S. phone number (that should be a toll-free number) and not a foreign phone number. Using a foreign phone number would not meet the contact information requirement for U.S. labeling.</li> </ul>	
<ul style="list-style-type: none"> <li>For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site. <u>NOTE: An email address or general link to a company's website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights.</u> It would not provide a structured format for reporting. Delete this information if it appears in Highlights.</li> </ul>	
<b>Drug Interactions</b> (This heading can be omitted.)	
<p>A concise summary of the drug interactions includes:</p> <ul style="list-style-type: none"> <li>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</li> <li>A concise summary of the outcome of the interaction</li> <li>Practical instructions for preventing or decreasing the likelihood of the interaction</li> </ul>	<b>X</b>
<p>[format] A tabular format is recommended for presentation of drug interaction information for drugs with numerous clinically significant interactions.</p>	
<b>Use in Specific Populations</b> (This heading can be omitted.)	
<p>A concise summary of any clinically important differences in response or 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).</p>	
<p>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.</p>	
<p>The pregnancy category designation is not appropriate for inclusion in Highlights because the pregnancy category, in isolation, tends to oversimplify the risks of drugs in pregnancy, and, as a result, may be confusing. Therefore, <b>do not include the pregnancy category in Highlights.</b> (See comment #34 to Preamble)</p>	
<p>For pregnancy category C drugs, you may use the following statement: "Pregnancy: Based on animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." Conclude the entire statement with a cross-reference to Pregnancy subsection (8.1).</p>	
<p>In Highlights, if a <b>pregnancy registry</b> exists, state "Pregnancy registry available." Cross-reference to Pregnancy subsection (8.1). <b>DO NOT</b> include the telephone number or information on how to enroll patients in the study. This information should appear under the Pregnancy subsection (8.1) in the FPI.</p>	

LABELING CHECKLIST	FILING REVIEW
<b>Patient Counseling Information Statement</b> (must appear in bold type)	
<u>If the product does not have FDA-approved patient labeling</u> , use the verbatim statement: See 17 for <b>PATIENT COUNSELING INFORMATION</b>	
<u>If the product has (or will have) FDA-approved patient labeling</u> , use the verbatim statement: See 17 for <b>PATIENT COUNSELING INFORMATION and FDA-approved patient labeling</b>	
<u>If the product has (or will have) a Medication Guide</u> , use the verbatim statement: See 17 for <b>PATIENT COUNSELING INFORMATION and Medication Guide</b>	
In rare circumstances, there may be two pieces of patient labeling (i.e., Medication Guide and Instructions for Use). Both would not be cited in the patient counseling information statement. The Medication Guide takes precedence. Use the verbatim statement: See 17 for <b>PATIENT COUNSELING INFORMATION and Medication Guide</b> .	
<b>Revision Date</b> (must appear in bold type)	
The date of the most recent revision of the labeling must be presented at the end of Highlights.	
[format] The preferred format is “Revised: Month Year” or “Revised: Month/Year” (i.e., Revised: June 2003 or Revised: 6/2003).	
For a new NDA, BLA, or supplement, the revision date will be the month/year that the application or supplement is approved. Remember to update before approval.	
<u>The revision date at the end of highlights replaces the “revision” or “issued” date at the end of the full prescribing information and should not appear in both places.</u> A revision date may appear at the end of FDA-approved patient labeling. A Medication Guide will always have a revision date because it is required by regulation (see 21 CFR Part 208).	
<b><u>SECTION III: Contents - Table of Contents</u></b>	
[format] The heading - <b>FULL PRESCRIBING INFORMATION: CONTENTS</b> - must appear at the beginning of the table of contents in upper-case letters and bold type.	
[format] Agency recommends use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page.	
[format] If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.	
[format] A horizontal line must be located between Highlights and Table of Contents to separate Highlights information from the table of contents. A horizontal line must also be located between the Table of Contents and the FPI.	<b>X</b>
[format] There are no periods after the numbers for the section and	

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subsection headings.	
[format] The section and subsection headings in the Table of Contents must match the section and subsection headings in the FPI.	<b>X</b>
[format] The <u>same</u> title for the boxed warning that appears in the HL and FPI must also appear at the beginning of the Table of Contents in upper-case letters and bold type. For example, <b>WARNING: ANAPHYLAXIS</b> .	
[format] Table of Contents section headings must be in bold type and should be in upper-case letters.	
[format] Table of Contents subsection headings must be indented and not bolded and should be in lower-case letters.	
[format] Only include section and subsection headings in the Table of Contents. Do not include headings within a subsection.	
[format] 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.”	
Create subsection headings that identify the content. Avoid using the words “General” “Other” “Miscellaneous” for a subsection heading.	
Avoid using acronyms in subsection headings. Spell out. For example, do not use “CHF” as a subsection heading. Use “Congestive Heart Failure.”	
[format] Since SPL R4 validation does not permit the inclusion of the MG as a subsection under the Patient Counseling Information section, <u>do not</u> include the MG or PPI as a subsection heading in the Table of Contents.	
<b><u>SECTION IV: Full Prescribing Information – Overview</u></b>	
[format] The heading – FULL PRESCRIBING INFORMATION – must appear at the beginning of the FPI in upper-case letters and bold type.	
Check that the following headings and subheadings are named and numbered correctly as outlined under 21 CFR 201.56 (d)(1):	
<b>Boxed Warning</b>	
1 INDICATIONS AND USAGE	
2 DOSAGE AND ADMINISTRATION	
3 DOSAGE FORMS AND STRENGTHS	
4 CONTRAINDICATIONS	
5 WARNINGS AND PRECAUTIONS	
6 ADVERSE REACTIONS	
7 DRUG INTERACTIONS	
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	
9 DRUG ABUSE AND DEPENDENCE	

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9.1 Controlled Substance	
9.2 Abuse	
9.3 Dependence	
10 OVERDOSAGE	
11 DESCRIPTION	
12 CLINICAL PHARMACOLOGY	
12.1 Mechanism of Action	
12.2 Pharmacodynamics	
12.3 Pharmacokinetics	
13 NONCLINICAL TOXICOLOGY	<b>X</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	
13.2 Animal Toxicology and/or Pharmacology	
14 CLINICAL STUDIES	
15 REFERENCES	
16 HOW SUPPLIED/STORAGE AND HANDLING	
17 PATIENT COUNSELING INFORMATION	
[format] There are no periods after the numbers for the section or subsection headings (see above).	
[format] Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the FPI. However, <u>the numbering does not change</u> . This is important to remember for the required subsections in Sections 8 (Use in Specific Populations), 12 (Clinical Pharmacology) and 13 (Nonclinical Toxicology).	
[format] The use of subheadings to organize information in the FPI is encouraged. Each subheading that is used must be assigned a decimal number that corresponds to its placement and order in the FPI [e.g., (12.3 Pharmacokinetics)]. Do not number headings within a subsection [e.g., (12.3.1 Metabolism)]. Use headings within a subsection without numbering [e.g., Metabolism].	
[format] All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly. Use another method for emphasis such as italics or underline.	
[format] Identifying numbers must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).	
Create subsection headings that identify the content. Avoid using the words "General" "Other" "Miscellaneous" for the title of a subsection.	
[format] The preferred presentation of <b>cross-references</b> in the FPI is the <u>section</u> heading followed by the numerical identifier. For example, [ <i>see Indications and Usage (1.1)</i> ]. Do not include subsection headings or headings within a subsection in the cross reference. 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.	
[format] The proprietary and established names can be repeated at the beginning of the FPI, or at the beginning of each page of the FPI (e.g., as a header), if this enhances product identification on subsequent pages of	

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labeling (See Implementation Guidance - FAQ #4).	
<b><u>SECTION V: Full Prescribing Information – Details</u></b>	
<b>BOXED WARNING</b>	
<i>(Also see Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format)</i>	
Summary must be preceded by a heading, in upper-case letters, containing the word “WARNING” and other words that are appropriate to identify subject of the warning. Use lower-case letters for the summary.	
[format] Heading and summary must be contained within a box and bolded.	
Use Boxed Warning when:	
<ul style="list-style-type: none"> <li>• Adverse reaction is so serious in proportion to potential benefit that it must be considered in assessing risks/benefits <b>OR</b></li> <li>• A serious adverse reaction can be prevented or reduced in frequency or severity by appropriate use of the drug <b>OR</b></li> <li>• Drug has been approved with restrictions for use because drug can be safely used only if distribution or use is restricted.</li> </ul>	
Must include a <b>brief, concise summary</b> of critical information, with a cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).	
Ensure that contraindications and warnings listed are in decreasing order of importance (i.e., reflecting the relative public health significance) regardless of drug class.	
<b>For drugs with thyroid hormone activity</b> , include the required boxed warning about the treatment of obesity [see 21 CFR 201.316(b)].	
<b>For the oral dosage form of Digitalis and related cardiotonic drugs</b> , include the required boxed warning about the treatment of obesity [see 21 CFR 201.317(b)].	
<b>1 INDICATIONS AND USAGE</b>	
<i>(Also see <a href="#">Draft Guidance for Industry: Hypertension Indication – Drug Labeling for Cardiovascular Outcome Claims</a>)</i>	
Describe intended use as supported by study results.	
Include the following, if applicable:	
<ul style="list-style-type: none"> <li>• Important limitations for use of the drug (e.g., patient subgroups, only for short-term use)</li> <li>• Specific tests needed for selection or monitoring of patients using the drug (e.g., EGFR testing)</li> <li>• Statement if drug should be reserved for certain situations (e.g., not for use as a first-line agent)</li> <li>• Appropriate level of detail on population for whom drug is indicated (matching population studied)</li> <li>• Information if drug is an adjunct to another therapy</li> </ul>	

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<ul style="list-style-type: none"> <li>For pediatric indications, “minimum approved age” (e.g., Drug X is approved for patients with asthma age 6 and older)</li> </ul>	
Limit indication(s) to those that were studied.	
<p><b>[Format]</b> In cases where the FPI lists indications briefly with little or no accompanying text, bullet the indications in the FPI instead of assigning each indication a subsection number. There would be no reason to assign subsection numbers for cross referencing back to the Indications and Usage section in the FPI since there is no additional text.</p>	
<p><b>For accelerated approvals</b> [i.e., biological products approved under Subpart E (21 CFR 601.41) and drugs approved under Subpart H (21 CFR 314.510)], include a statement regarding the basis of approval. Suggest the following language: “[Drug] is indicated for the [treatment/prevention] of . . . . The effectiveness of [drug] is based on [describe the outcome, e.g., an improvement in drug activity/response rate/tumor shrinkage]. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.</p>	
<p><b>For systemic antibacterial drug products</b>, include the required statement about antibiotic resistance [see 21 CFR 201.24(b)] in the Indications and Usage section.</p>	
<p><b>For hexachlorophene containing drugs (bacteriostatic skin cleanser)</b>, include the required indications [see 21 CFR 201.250.250(c)(3)(i)] in the Indications and Usage section.</p>	
<b>2 DOSAGE AND ADMINISTRATION</b>	
<p>(Also see <a href="#">Draft Guidance for Industry. Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</p>	
<p><b>[format]</b> The Agency recommends that Latin abbreviations be avoided because of the greater potential for medication errors should an abbreviation be misread (e.g., <i>QD</i> being misread as <i>QID</i>).</p>	
<p><b>[format]</b> Avoid using “IV” as it is commonly mistaken for Roman numeral IV. Instead, use “intravenous.”</p>	X
<p><b>[format]</b> Do not use a “slash mark” (/) since it may be mistaken for the number 1. Use “per.” For example, do not use 5 mg/10 mL. Use 5 mg per 10 mL.</p>	X
<p><b>[format]</b> Refer to the Institute for Safe Medication Practices website (<a href="http://www.ismp.org/Tools/abbreviationslist.pdf">http://www.ismp.org/Tools/abbreviationslist.pdf</a>) for list of error-prone abbreviations, symbols, and dose designations. Avoid using when describing dosage and administration information.</p>	
<p>For complex administration schemes, flowcharts and diagrams are strongly recommended.</p>	
<p>Include recommended dose, and as appropriate:</p>	
<ul style="list-style-type: none"> <li>Dosage range</li> </ul>	
<ul style="list-style-type: none"> <li>Route of administration</li> </ul>	
<ul style="list-style-type: none"> <li>Upper limit for safety or effectiveness</li> </ul>	
<ul style="list-style-type: none"> <li>Dosages for each indication and subpopulation</li> </ul>	
<ul style="list-style-type: none"> <li>Intervals recommended between doses</li> </ul>	

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<ul style="list-style-type: none"> <li>Optimal method of titrating dosage</li> </ul>	
<ul style="list-style-type: none"> <li>Usual duration of treatment only when treatment duration is limited</li> </ul>	
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food or nutritional supplement effects)</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>Modifications of dosage needed because of drug interactions or special patient populations (e.g., pediatric, geriatric, renal or hepatic disease, groups defined by genetic characteristics)</li> </ul>	
<ul style="list-style-type: none"> <li>Important considerations concerning compliance with dosing regimen</li> </ul>	X
<ul style="list-style-type: none"> <li>Efficacious or toxic concentration ranges and therapeutic drug concentration monitoring if established and clinically significant</li> </ul>	X
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>If weight-based dosing, identify if ideal body weight or actual body weight.</li> </ul> </li> </ul>	
<p><b>Specific Content for <u>Reconstituted</u> Products:</b> The following must be included to the extent necessary for dosing and administering the drug [21 CFR 201.57(c)(3)].</p> <ul style="list-style-type: none"> <li>Directions for dilution, preparation, and, if needed, administration of the dosage form</li> <li>Strength (concentration) of the final dosage solution in milligrams of active ingredient per milliliter (unless another measure of strength is more appropriate)</li> <li>Storage conditions needed to maintain the stability of the drug or the reconstituted product</li> </ul>	X
<p><b>Specific Content for <u>Parenteral</u> Products:</b> The following must be included to the extent necessary for dosing and administering the drug [21 CFR 201.57(c)(3)].</p> <ul style="list-style-type: none"> <li>Rate of administration (usually in milligrams per minute) Essential information on drug incompatibilities, if the drug is mixed in vitro with other drug or diluents (should also identify compatible diluents)</li> <li>The verbatim statement “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”</li> </ul>	X  X
<p>For complex parenteral dilution and administration instructions:</p> <ul style="list-style-type: none"> <li>Include required calculations in the instructions</li> <li>Separate instructions for different types of administration devices if significant differences in preparation and administration techniques are required (e.g., syringe pumps versus infusion pumps)</li> </ul>	
<p>Premedication information, if applicable</p>	
<p>Radiation dosimetry for both patient and person administering, if applicable</p>	
<p><b>3 DOSAGE FORMS AND STRENGTHS</b></p>	
<p>Include information on the available dosage forms to which the labeling</p>	

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applies and for which the manufacturer or distributor is responsible, including:	
Strength or potency of dosage form in metric system (e.g., 10 mg tablets); [If apothecary system is used, place in parentheses after the metric designation (e.g., “Colchicine tablets, 0.6 mg (1/100 grain)” ]	
Description of identifying characteristics of the dosage forms: <ul style="list-style-type: none"> <li>• Imprinting</li> <li>• Scoring</li> <li>• Shape</li> <li>• Color</li> <li>• Coating</li> </ul> The description of identifying characteristics of the dosage forms must also appear under the How Supplied/Storage and Handling section.	
Only indicate if the product is scored. If the product is not scored, do not say “not scored.”	
<b>DO NOT INCLUDE NDC NUMBERS IN THIS SECTION</b>	
Do not include “How Supplied” information (i.e., packaging).	X
<b>4 CONTRAINDICATIONS</b>	
<i>(Also see <a href="#">Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</i>	
The order in which contraindications are presented should reflect the relative public health significance of the listed contraindications.	
[format] For <u>each</u> contraindication, use numbered subsection headings OR bullets.	
Describe any situations in which drug should not be used because risk of use clearly outweighs any possible therapeutic benefit.	
List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.	
For Pregnancy Category X drugs, list pregnancy as a contraindication. State the following: “(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Briefly describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.” Cross-reference to Pregnancy subsection (8.1).	
Contraindications based on drug interactions with serious outcomes should be described in the Contraindications section and cross-referenced to more detailed information in the Drug Interactions, Clinical Pharmacology, or Clinical Studies sections.	
For each contraindication, include:	
<ul style="list-style-type: none"> <li>• Brief description of the contraindicated situation and any demographic or identifiable predisposing characteristics</li> </ul>	

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<ul style="list-style-type: none"> <li>Description of anticipated consequences of the contraindicated use</li> </ul>	
If no Contraindications are known, this section must state "None"	
<p><b>For hexachlorophene containing drugs (bacteriostatic skin cleanser),</b> include the required contraindications [see 21 CFR 201.250.250(c)(3)(i)] in the Contraindications section.</p>	
<b>5 WARNINGS AND PRECAUTIONS</b>	
<p>(Also see <a href="#">Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</p>	
A subheading should be used for each adverse reaction, syndrome, or constellation of reactions prioritized based on relative public health significance. (The subheading should convey the risk.)	
List W&P in decreasing order of importance (i.e., reflecting the relative public health significance) regardless of drug class.	X
Describe clinically significant adverse reactions, including any that are potentially fatal or serious even if infrequent, and steps to take if they occur.	
Describe other potential safety hazards including those that are expected for the pharmacologic class or those resulting from drug-drug interactions.	
Describe limitations of use imposed by them including avoiding certain concomitant therapy.	
Describe steps to take if they occur (e.g., dosage modification).	
Describe those that can be prevented or mitigated through appropriate use of the drug (e.g., include information regarding any special care to be exercised by the practitioner for safe and effective use of the drug or known risk factors).	
Describe absolute risk/rate of the adverse reaction if known.	
Include expected adverse reactions or toxic effects if serious or clinically significant and the drug's class is associated with the adverse reaction or animal data raise concerns.	
Clinically significant adverse reactions that appear to be linked primarily to an unapproved use of drug should be identified.	
Identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions.	
Note information on any known interference by the product with laboratory tests.	
<p><b>For Pregnancy Category D drugs,</b> list pregnancy as a Warning and Precaution and state the following:  “(Name of drug) can cause fetal harm when administered to a pregnant woman. (Briefly describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.”  Cross reference to Pregnancy subsection (8.1).</p>	
<p><b>For products containing plasma-derived albumin,</b> add the recommended warning: "This product contains albumin, a derivative of human blood.</p>	

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Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin." (See Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products.)	
<b><u>For products containing FD&amp;C Yellow No. 5 (tartrazine)</u></b> , include the required warning statement [see 21 CFR 201.20(b)] in the Warnings and Precautions section.	
<b><u>For products containing aspartame as an inactive ingredient</u></b> , include the required precaution statement to alert those with Phenylketonuria to the amount of Phenylalanine in the drug product [see 21 CFR 201.21(c)] in the Warnings and Precautions section.	
<b><u>For products containing sulfites as an inactive ingredient</u></b> , include the required warning statement about allergic-type reactions [see 21 CFR 201.22 (b) and (c)] in the Warnings and Precautions section.	
<b><u>For systemic antibacterial drug products</u></b> , include the required statement about antibiotic resistance [see 21 CFR 201.24(c)] in the Warnings and Precautions section.	
<b><u>Products for internal use which contain mineral oil</u></b> , include the required warning statement against consumption other than at bedtime and against administration to infants [see 21 CFR 201.302(d)] in the Warnings and Precautions section.	
<b><u>For Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders)</u></b> , include the required warning statement about severe paradoxical airway resistance [see 21 CFR 201.305(b)] in the Warnings and Precautions section.	
<b><u>For potassium salt preparations for oral use</u></b> , include the required warning statement about small-bowel lesions [see 21 CFR 201.306(a)(1)(ii)] in the Warnings and Precautions section.	
<b><u>For Acetophenetidin (phenacetin)-containing preparations</u></b> , include the required warning statement about kidney damage [see 21 CFR 201.309(b)] in the Warnings and Precautions section.	
<b><u>For Phenindione containing preparations</u></b> , include the required warning statement about agranulocytosis and hepatitis [see 21 CFR 201.310(a)] in the Warnings and Precautions section.	
<b><u>For drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances</u></b> , include the required warning statement [see 21 CFR 201.320(a)(1)] in the Warnings and Precautions section.	
<b><u>For the aluminum content of large and small volume parenterals used in total parenteral nutrition</u></b> , include the required warning statement [see 21 CFR 201.323(b) and (e)] in the Warnings and Precautions section.	
<b><u>For hexachlorophene containing drugs (bacteriostatic skin cleanser)</u></b> , include the required warning statement [see 21 CFR 201.250.250(c)(3)(i)] in the Warnings and Precautions section.	
<b><u>For oral hypoglycemic drugs of the sulfonylurea class</u></b> , include the	

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required warning statement concerning the possible increased risk of cardiovascular mortality [see 21 CFR 310.517(b)] at the beginning of the Warnings and Precautions section.	
<p><b>For products containing benzyl alcohol</b>, include the following warning statement in the Warnings and Precautions section, if the product is approved for use in the pediatric population: Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gaspings syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages &gt;99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.</p> <p>If a product containing benzyl alcohol is NOT approved for use in the pediatric population, then this information would go in subsection 8.4 Pediatric Use.</p>	
<b>6 ADVERSE REACTIONS</b>	
<i>(Also see <a href="#">Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</i>	
Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events" should be avoided.	
Must describe overall adverse reaction profile of the drug based on entire safety database (i.e., pool AR profile using data from all trials).	
Must list adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.	
Within a listing, adverse reactions must be categorized by body system, severity of reaction, or in order of decreasing frequency, or by a combination of these.	
Within a category, adverse reactions must be listed in decreasing order of frequency (If frequency information cannot be reliably determined, list in decreasing order of severity).	
Potentially fatal adverse reactions described in the "Warnings and Precautions" or "Contraindications" section(s) must be listed in this section.	
Comparisons of adverse reactions between drugs must be based on adequate and well-controlled studies. (For biological products, any such claims must be based on substantial evidence.)	
<b>Clinical Trials Experience</b> subsection:	
<ul style="list-style-type: none"> <li>• [format] Include following statement (or appropriate</li> </ul>	

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<p>modification) preceding presentation of adverse reactions from clinical trials: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”</p>	
<ul style="list-style-type: none"> <li>• Provide description of overall clinical trial database including overall exposure (number of patients, dose, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database</li> </ul>	
<ul style="list-style-type: none"> <li>• [format] List adverse reactions (in table format) identified in clinical trials that occurred at or above a specified rate appropriate to the safety database (Include event, number of patients, incidence, and comparators, if appropriate).</li> </ul>	
<ul style="list-style-type: none"> <li>• Present rate of occurrence for the drug and comparators (or placebo), unless data cannot be determined or would be misleading.</li> </ul>	
<ul style="list-style-type: none"> <li>• If adverse reactions that occurred below the specified rate are included, use a separate listing.</li> </ul>	
<p><b>AVOID:</b></p>	
<ul style="list-style-type: none"> <li>• Exhaustive lists of less common ARs</li> </ul>	
<ul style="list-style-type: none"> <li>• Inclusion of AR rates equal to or less than placebo rates</li> </ul>	
<ul style="list-style-type: none"> <li>• Statistics unless studied with a prespecified hypothesis</li> </ul>	
<ul style="list-style-type: none"> <li>• Impractical ARs (e.g., accidental injuries)</li> </ul>	
<p><b>For therapeutic proteins</b>, immunogenicity information should be included as its own subsection following the Clinical Trials Experience subsection, including the following standard statement: "As with all therapeutic proteins, there is potential for immunogenicity. [INSERT DESCRIPTION OF DATA] The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to DRUG with the incidence of antibodies to other products may be misleading."</p> <p>If the immunogenicity has clinical impact, it should also be mentioned in the Warnings and Precautions section.</p>	
<p><b>Postmarketing Experience</b> subsection:</p>	
<ul style="list-style-type: none"> <li>• [format] Include following statement (or appropriate modification) preceding the presentation of adverse reactions from spontaneous reports: “The following adverse reactions have been identified during post approval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”</li> </ul>	
<ul style="list-style-type: none"> <li>• List adverse reactions identified from domestic and foreign</li> </ul>	

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spontaneous reports. Decision to include AR is based on seriousness of event, frequency of reporting, or strength of causal connection to the drug.	
<ul style="list-style-type: none"> <li>This listing must be separate from the listing of ARs identified in clinical trials.</li> </ul>	
<ul style="list-style-type: none"> <li>Adverse reactions from clinical trials conducted post-approval should be described under Clinical Trials Experience, rather than Postmarketing Experience (which presents adverse reactions from spontaneous reports).</li> </ul>	
<ul style="list-style-type: none"> <li>The Postmarketing Experience subsection should NOT include events observed in the premarketing clinical trials. The focus should be on new events or concerns observed after approval. Do not repeat the same adverse events reported under the Clinical Trials Experience subsection.</li> </ul>	
<b>7 DRUG INTERACTIONS</b>	
(Also see <a href="#">Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling</a> )	
Describe all clinically significant interactions, either observed or predicted (with cross-referencing to other sections as needed):	
<ul style="list-style-type: none"> <li>Other prescription drugs or over-the-counter drugs</li> </ul>	
<ul style="list-style-type: none"> <li>Classes of drugs</li> </ul>	
<ul style="list-style-type: none"> <li>Foods (e.g., dietary supplements, grapefruit juice)</li> </ul>	
Describe specific practical instructions for preventing or managing interactions.	
Describe DI mechanism of action, if known.	
Interactions described in “Contraindications” or “Warnings and Precautions” sections must be mentioned and discussed in more detail under this section.	
Do not repeat details of drug pharmacokinetic studies included in the “Clinical Pharmacology” section.	
If known, include guidance on interference of drug with laboratory tests.	
<b>8 USE IN SPECIFIC POPULATIONS</b>	
<b>8.1 Pregnancy</b>	
(Also see <a href="#">Draft Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling</a> ;	
<a href="#">Guidance for Industry: Establishing Pregnancy Exposure Registries, and; Guidance for Reviewers. Evaluating the Risks of Drug Exposure in Human Pregnancies.</a> )	
The regulation allows omission of this subsection if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to a fetus. However, it is recommended that the labeling includes the subsection and state that the drug is not systemically absorbed	

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or that it does not result in fetal exposure.	
For all other drugs, this subsection should include a description of any available human or animal reproductive and developmental toxicity data or studies with human data preceding the animal data and must contain the following information:	
<p><b>Teratogenic effects</b></p> <ul style="list-style-type: none"> <li>• Labeling must identify one of the Pregnancy Categories (A,B,C,D, or X) that applies to the drug, and include the regulatory statement required for the category. See 21 CFR 201.57(c)(9)(i).</li> <li>• If increased human teratogenic risk is suspected or known based on animal and/or human studies, the labeling should describe, to the extent possible: <ul style="list-style-type: none"> <li>○ the specific abnormality</li> <li>○ the incidence, seriousness, reversibility, and correctability of the abnormality</li> <li>○ the effect of dose, duration of exposure or gestational timing of exposure on the likelihood of risk</li> </ul> </li> <li>• Include a description of all adequate studies that show minimal or no risk from gestational exposure.</li> <li>• All studies should include confidence limits and power calculations to establish the power of the study to identify or rule out a specified level of risk.</li> <li>• Do not include isolated case reports unless there has been a conscious, scientific judgment made that the quality of the reports and other factors (e.g., consistency with animal findings; information on dose, duration, and timing of gestational exposure; or biologic plausibility) support inclusion.</li> </ul>	
<p><b>Nonteratogenic effects</b></p> <ul style="list-style-type: none"> <li>• If relevant, describe 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.</li> </ul>	
Based on Guidance for Industry: ICH E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, any significant new information should be mentioned for positive or negative experiences during pregnancy. Applicants should submit published studies on drug use during human pregnancy that can inform this portion of the labeling.	
Under the Nonclinical Toxicology section, create subsection 13.3 “Reproductive and Developmental Toxicology” for detailed information from animal reproductive and developmental toxicity studies that are not included in the Pregnancy subsection (8.1). The Pregnancy subsection should cross-reference the Reproductive and Developmental Toxicology subsection.	
If pharmacokinetics (PK) in pregnancy data are available, the Pregnancy subsection should briefly describe the PK changes found in pregnancy (with a cross reference to the Clinical Pharmacology section), and any	

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<p>dosing adjustments required for pregnant patients (with a cross reference to the Dosage and Administration section). State if no PK studies have been conducted in pregnant patients.</p>	
<p>If the product has a pregnancy exposure registry, the Pregnancy subsection should include information on how to enroll pregnant patients in the study.</p>	
<p><b>8.2 Labor and Delivery</b></p>	
<p>If the drug has a recognized use during labor or delivery, whether or not the use is stated in the Indications and Usage section, this subsection must describe the available information about the effect of the drug on the mother and fetus:</p>	
<ul style="list-style-type: none"> <li>• duration of labor or delivery</li> <li>• increased risk for intrapartum interventions to effect delivery</li> <li>• increased risk for resuscitation of the newborn</li> <li>• later growth, development, and functional maturation of the child</li> </ul>	
<p>If any information required under this subsection is unknown, it must state that the information is unknown.</p>	
<p><b>8.3 Nursing Mothers</b></p>	
<p>(Also see <a href="#">Draft Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling</a>)</p>	
<p>If a drug is absorbed systemically, this subsection must contain, if known, information about the excretion of the drug in human milk and effects on nursing infant.</p>	
<p>If clinical lactation studies have been done, this subsection should include the following information:</p> <ul style="list-style-type: none"> <li>• Effect of drug on milk production (e.g., quality and quantity of milk including milk production and composition)</li> <li>• Presence of drug in milk, including the limitation of the assay used if drug not detected in milk</li> <li>• Amount of drug in breast milk over a 24-hour period</li> <li>• Amount of drug consumed daily by the breast-fed infant</li> <li>• Percent of maternal dose delivered via breast milk</li> <li>• Possible ways to minimize exposure in the breast-fed child</li> <li>• Any adverse effects observed in the breast-fed infant</li> <li>• Serum levels of drug in the breast-fed infant when available.</li> </ul> <p>Based on Guidance for Industry: ICH E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, any significant new information should be mentioned for positive or negative experiences during lactation. Applicants should submit published lactation studies that can inform this portion of the labeling.</p>	
<p>If a drug is absorbed systemically and is known to be excreted in human milk or excretion in human milk is unknown, this subsection must</p>	

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describe if drug is associated with serious adverse reactions or has known tumorigenic potential and include required statements, as appropriate [See 21 CFR 201.57(c)(9)(iii)].	
Describe pertinent adverse effects in animal offspring.	
<b>8.4 Pediatric Use</b> (required subsection)	
(Also see <a href="#">Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs in Infants and Children</a> )	
Describe the following:	
<ul style="list-style-type: none"> <li>Any limitations on the pediatric indication and why (e.g., not studied versus studied with negative results)</li> </ul>	
<ul style="list-style-type: none"> <li>Need for specific monitoring</li> </ul>	
<ul style="list-style-type: none"> <li>Specific hazards associated with use of drug in any subsets of pediatric population (e.g. neonates)</li> </ul>	
<ul style="list-style-type: none"> <li>Differences between pediatric and adult responses to drug</li> </ul>	
<ul style="list-style-type: none"> <li>Other information related to safe and effective pediatric use of drug</li> </ul>	
<ul style="list-style-type: none"> <li>Need for dosing adjustments (appropriate pediatric dosing must be included in the D&amp;A section)</li> </ul>	
As appropriate, also cite in the “Contraindications,” “Warnings and Precautions,” and “Dosage and Administration” sections.	
If requirements do not support a pediatric indication include following statement: “Safety and effectiveness have not been established in pediatric patients.”	
Use appropriate statement if drug is approved for pediatric use based adequate and well controlled studies in adults. See 21 CFR 201.57(c)(9)(iv).	
<p><b><u>Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)</u></b>: Data submitted in response to a Written Request under BPCA and Assessments submitted in response to PREA study requirement are now required to be described in the labeling whether findings are positive, negative or inconclusive. If required studies under PREA are waived because of <u>evidence</u> that a product would be ineffective or unsafe, the information shall be included in the labeling.</p> <ul style="list-style-type: none"> <li>If new data are sufficient to warrant a pediatric indication, the information should be incorporated into the applicable sections of the labeling (I&amp;U; D&amp;A; AR; Use in Specific Populations; Clinical Pharmacology).</li> <li>If new data are not sufficient to warrant a pediatric indication, all information should appear <u>only</u> in the Pediatric subsection of the labeling. This will avoid implication of “approval.” It is not necessary to include all details of an inconclusive study (e.g., dosing or outcomes).</li> </ul>	
<b>8.5 Geriatric Use</b> (required subsection)	
(Also see <a href="#">Guidance for Industry: Content and Format of Geriatric Labeling</a> and <a href="#">Guidance for Industry: Study of Drugs Likely to be Used in the Elderly</a> )	

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Describe the following:	
<ul style="list-style-type: none"> <li>Any limitations on the geriatric indication</li> </ul>	
<ul style="list-style-type: none"> <li>Need for specific monitoring</li> </ul>	
<ul style="list-style-type: none"> <li>Specific hazards associated with use of drug in the elderly</li> </ul>	
<ul style="list-style-type: none"> <li>Differences between geriatric and adult responses to drug</li> </ul>	
<ul style="list-style-type: none"> <li>Other information related to the safe and effective use of drug in elderly (e.g. sedating drug)</li> </ul>	
<ul style="list-style-type: none"> <li>Need for dosing adjustments (appropriate geriatric dosing must be included in the D&amp;A section)</li> </ul>	
<ul style="list-style-type: none"> <li>Whether drug is known to be substantially excreted by the kidney</li> </ul>	
As appropriate, cite in the “Contraindications,” “Warnings and Precautions,” and “Dosage and Administration” sections.	
Describe if specific PK or PD studies have been carried out in the elderly.	
Based on clinical studies, use appropriate statements for geriatric use (e.g., insufficient numbers of subjects aged 65 and over, percent of patients in studies over 65 and 75 years of age). See 21 CFR 201.57(c)(9)(v).	
<b>8.6 Additional Subsections</b>	
Include if sufficient data available concerning use of drug in other specified subpopulations (e.g., those with renal or hepatic impairment).	
For more information, also see:	
<ul style="list-style-type: none"> <li>Renal disease (<a href="#">Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling</a>)</li> </ul>	
<ul style="list-style-type: none"> <li>Hepatic disease (<a href="#">Guidance for Industry: Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling</a>)</li> </ul>	
<ul style="list-style-type: none"> <li>Gender (<a href="#">Guidance for Industry: Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs</a>)</li> </ul>	
<ul style="list-style-type: none"> <li>Race or Ethnicity (<a href="#">Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials</a>)</li> </ul>	
<b>9 DRUG ABUSE AND DEPENDENCE</b>	
Do not include any scheduling information in approved labeling unless the DEA scheduling action is final.	
<b>9.1 Controlled Substance</b>	
If DEA-controlled substance, identify schedule.	
<b>9.2 Abuse</b>	
Identify types of abuse and pertinent adverse reactions pertinent to them, and identify particularly susceptible patient populations.	

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<p><b>9.3 Dependence</b></p> <ul style="list-style-type: none"> <li>• Describe characteristic effects resulting from psychological and physical dependence.</li> <li>• Describe adverse effects of chronic abuse and the effects of abrupt withdrawal.</li> <li>• Describe procedures necessary to diagnose the dependent state and principles of treating the effects of abrupt withdrawal.</li> </ul>	
<p><b>10 OVERDOSAGE</b></p>	
Describe:	
<ul style="list-style-type: none"> <li>• Signs, symptoms, and laboratory findings of overdose</li> </ul>	
<ul style="list-style-type: none"> <li>• Complications that can occur with the drug (e.g., organ toxicity, delayed acidosis)</li> </ul>	
<ul style="list-style-type: none"> <li>• Concentrations of drug in biologic fluids associated with toxicity or death</li> </ul>	
<ul style="list-style-type: none"> <li>• Physiologic variables influencing excretion of drug</li> </ul>	
<ul style="list-style-type: none"> <li>• Factors that influence dose response relationship of drug</li> </ul>	
<ul style="list-style-type: none"> <li>• Amount of drug in single dose associated with symptoms of overdose and that is likely to be life threatening</li> </ul>	
<ul style="list-style-type: none"> <li>• Whether drug is dialyzable</li> </ul>	
<ul style="list-style-type: none"> <li>• General treatment procedures and specific measure for support of vital functions (e.g., antidotes, gastric lavage, forced diuresis)</li> </ul>	
<p><b>11 DESCRIPTION</b></p>	
<p>[Also see <a href="#">Draft Guidance for Industry. NOT FOR PUBLIC RELEASE: Good Naming, Labeling and Packaging (GNLP) Practices</a>]</p>	
Include the following:	
<ul style="list-style-type: none"> <li>• Proprietary and established name</li> </ul>	
<ul style="list-style-type: none"> <li>• For biological products, the proper name</li> </ul>	
<ul style="list-style-type: none"> <li>• Type of dosage form(s) and routes of administration</li> </ul>	
<ul style="list-style-type: none"> <li>• Qualitative and/or quantitative ingredient information (Section 201.100 (b) for drug labels or Sections 610.60 and 610.61 for biological product labels)</li> </ul>	
<ul style="list-style-type: none"> <li>• Statement if product is sterile</li> </ul>	
<ul style="list-style-type: none"> <li>• Pharmacologic or therapeutic class of the drug</li> </ul>	
<ul style="list-style-type: none"> <li>• Chemical name and structural formula of drug</li> </ul>	
<ul style="list-style-type: none"> <li>• If radioactive, statement of important nuclear characteristics</li> </ul>	
<ul style="list-style-type: none"> <li>• Other important chemical and physical information</li> </ul>	
<p><b>12 CLINICAL PHARMACOLOGY</b></p>	
<p>(Also see <a href="#">Draft Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</a>)</p>	
Include information relating to human clinical pharmacology and actions of the drug in humans.	

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Information based on in vitro data using human biomaterials or animal models, or relevant details about in vivo study results from human data may be included if essential to understanding dosing or drug interaction information.	
Note absence of important PK or PD information if unavailable.	
<b>12.1 Mechanism of Action</b>	
Summarize <b>established</b> mechanism(s) of action in humans at various levels (e.g., receptor membrane, tissue, organ, whole body). Do not include theorized mechanism(s) of action.	
If mechanism of action is not known, include statement about lack of information.	
<b>For antimicrobial drugs</b> , only the following statement should appear in this subsection: “X is an anti- (bacterial, viral, as appropriate) drug [see <b>Clinical Pharmacology (12.4)</b> ]”. For “X” insert the established/proper name.	
<b>12.2 Pharmacodynamics</b> <i>(Also see <a href="#">Guidance for Industry: Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications</a>)</i>	
Include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug’s clinical effect or those related to adverse effects or toxicity.	
Include data on exposure-response relationship (e.g., concentration-response, dose-response) and time course of PD response (including short term clinical response if known).	
If <b>clinically significant</b> , include information regarding:	
<ul style="list-style-type: none"> <li>• Selectivity for receptor(s), reversibility of receptor binding, and considerations related to up- or down-regulation of receptors (e.g., tolerance, rebound, abuse/dependence, and withdrawal effects)</li> </ul>	
<ul style="list-style-type: none"> <li>• Mechanisms for known sources of variability in response (e.g., disease severity, hormonal status, concomitant drugs, age, genetic or racial/ethnic factors, diurnal variation, environmental factors)</li> </ul>	
<b>12.3 Pharmacokinetics</b>	
<i>(Also see <a href="#">Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling</a> and <a href="#">Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro</a>)</i>	
[format] Include all PK information under subsection 12.3 (e.g., PK information about geriatric, pediatric, gender, race, hepatic or renal subpopulations). Do not include PK information under a separate subsection heading (i.e., 12.6 Special Populations).	
Describe clinically significant PK of a drug or active metabolites (i.e., pertinent absorption, distribution, metabolism, and excretion parameters).	
If <b>clinically significant</b> , include information regarding:	
<ul style="list-style-type: none"> <li>• Bioavailability</li> </ul>	

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<ul style="list-style-type: none"> <li>• Effect of food</li> </ul>	
<ul style="list-style-type: none"> <li>• Minimum concentration (C<sub>min</sub>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Maximum concentration (C<sub>max</sub>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Time to maximum concentration (T<sub>max</sub>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Area under the curve (AUC)</li> </ul>	
<ul style="list-style-type: none"> <li>• Pertinent half-lives (t<sub>1/2</sub>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Time to reach steady state</li> </ul>	
<ul style="list-style-type: none"> <li>• Extent of accumulation</li> </ul>	
<ul style="list-style-type: none"> <li>• Route(s) of elimination, clearance (renal, hepatic total)</li> </ul>	
<ul style="list-style-type: none"> <li>• Mechanism of clearance (e.g., specific enzyme systems)</li> </ul>	
<ul style="list-style-type: none"> <li>• Drug/Drug and Drug/Food (e.g., dietary supplements, grapefruit juice) PK interactions (including inhibition, induction, and genetic characteristics)</li> </ul>	
<ul style="list-style-type: none"> <li>• Volume of distribution (V<sub>d</sub>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Non-linearity in PK parameters</li> </ul>	
<ul style="list-style-type: none"> <li>• Changes in PK over time</li> </ul>	
<ul style="list-style-type: none"> <li>• Binding (plasma protein, erythrocyte) parameters</li> </ul>	
<ul style="list-style-type: none"> <li>• Include information about bioequivalence among marketed formulations</li> </ul>	
<p>Include results of PK studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data.</p>	
<p><b>For anti-infective drugs only</b>, in vitro data 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.”</p>	
<p>For other classes of drugs that are not anti-infective drugs, in vitro and animal data may be included in this section only if a waiver is granted [see 21 CFR 201.58 or 21 CFR 314.126(c)].</p>	
<p><b>For antimicrobial data</b>, a subsection can be created (e.g., <b>12.4 Microbiology</b>) and all of the microbiology information for antimicrobial products consolidated into that subsection. (Also see <a href="#">Draft Guidance for Industry: Microbiological Data for Systemic Antibacterial Drug Products – Development, Analysis, and Presentation</a>)</p>	
<p><b>For pharmacogenomic (PG) information</b>, the location of the PG data will largely depend upon the proposed clinical usage of the information and should be presented in the section of labeling with the greatest clinical relevance, and cross-referenced in the related sections. If applicable, a subsection can be created (e.g., <b>12.5 Pharmacogenomics</b>) to include the PG information under this section, or as appropriate, under other sections of the labeling (e.g., Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions; Adverse Reactions, Clinical Studies). (Also see <a href="#">Guidance for Industry: Pharmacogenomic Data Submissions</a>)</p>	
<p>[format] Since subsection 12.4 is created for Microbiology and 12.5 for Pharmacogenomics, do not use these subsection numbers for other subsection headings. If warranted, subsection 12.6 can be created for another PK topic that does not fit under the subsection headings 12.1 thru 12.5.</p>	

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<b>13 NONCLINICAL TOXICOLOGY</b>	
(Also see <a href="#">Draft Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route</a> )	
This section must contain the following subsections as appropriate:	
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>	
State if long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results.	
Describe if results from reproduction studies or other animal data in animals raise concern about mutagenesis or impairment of fertility in males or females.	
Do not include human data suggesting carcinogenic, mutagenic, or impairment of fertility. This must be described in Warnings and Precautions section or Pregnancy subsection.	
<b>13.2 Animal Toxicology and/or Pharmacology</b>	
Clinically significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of the labeling may be included in this section.	
<b>For reproductive and developmental toxicology information</b> , a subsection can be created (e.g., 13.3 Reproductive and Developmental Toxicology) to include a detailed description of animal reproduction and developmental studies with a focus on details not included in the Pregnancy subsection. (Also see <a href="#">Draft Reviewer Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities</a> )	
<b>14 CLINICAL STUDIES</b>	
This section must contain a discussion of clinical studies that are important to a prescriber’s understanding of the safe and effective use of the drug. (Also see <a href="#">Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</a> )	
Include studies that:	
<ul style="list-style-type: none"> <li>• Provide primary support for effectiveness</li> </ul>	
<ul style="list-style-type: none"> <li>• Provide important supporting evidence of effectiveness (Also see <a href="#">Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Biological and Drug Product</a>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Provide other clinically important information (e.g., differential effects in subpopulations, absence of expected effectiveness)</li> </ul>	
<ul style="list-style-type: none"> <li>• Prospectively evaluate a safety benefit (with cross-reference in AR section)</li> </ul>	
Exclude studies that:	

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<ul style="list-style-type: none"> <li>• Imply effectiveness for an unapproved use</li> </ul>	
<ul style="list-style-type: none"> <li>• Are not adequate and well-controlled</li> </ul>	
Include active comparator data only if a comparative claim can be supported	
OR	
If comparison to an active control is essential to understand drug's effects; explain limitations of conclusions.	
Avoid meta-analyses.	
For study design description include:	
<ul style="list-style-type: none"> <li>• Major design characteristics</li> </ul>	
<ul style="list-style-type: none"> <li>• Treatment arms</li> </ul>	
<ul style="list-style-type: none"> <li>• Important concomitant therapy</li> </ul>	
<ul style="list-style-type: none"> <li>• Study-population important characteristics (e.g., inclusion criteria, exclusion criteria, demographic characteristics, age distribution, baseline values of clinically relevant variables)</li> </ul>	
<ul style="list-style-type: none"> <li>• Endpoints critical to establishing effectiveness. Critical endpoints that are not commonly understood should be defined.</li> </ul>	
When summarizing study findings:	
<ul style="list-style-type: none"> <li>• Include description of patients.</li> </ul>	
<ul style="list-style-type: none"> <li>• Include number enrolled, completers, discontinuations.</li> </ul>	
<ul style="list-style-type: none"> <li>• Give absolute and relative differences in study results.</li> </ul>	
<ul style="list-style-type: none"> <li>• Present all components of composite endpoints and then results.</li> </ul>	
<ul style="list-style-type: none"> <li>• Include confidence intervals. This is true even if, in addition, p-values are presented.</li> </ul>	
<ul style="list-style-type: none"> <li>• Show change from baseline between groups, not just within.</li> </ul>	
<ul style="list-style-type: none"> <li>• Describe patient variability within a treatment group with standard deviations.</li> </ul>	
<ul style="list-style-type: none"> <li>• Include summary statement about effects in age, gender, racial subgroups.</li> </ul>	
<ul style="list-style-type: none"> <li>• Include all randomized patients and results of categorical outcomes and give denominators.</li> </ul>	
<ul style="list-style-type: none"> <li>• For continuous variables, include measures of distribution.</li> </ul>	
<ul style="list-style-type: none"> <li>• For time-to-event endpoints, include number of patients evaluated at each interval.</li> </ul>	
Regarding titles for tables and figures, do not make conclusions about results (e.g., “HIV RNA results at 8 weeks” preferred over “Improvement at 8 weeks.”)	
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. Limit discussions for risk to safety benefits.	
Do not include <b>National Clinical Trial (NCT) numbers</b> in labeling. The NCT numbers are posted at <a href="http://www.clinicaltrials.gov/">http://www.clinicaltrials.gov/</a> .	
<b>15 REFERENCES</b>	
May include when labeling must summarize or otherwise rely on recommendation by authoritative scientific body, or a standardized methodology, scale, or technique, because information is necessary for safe	

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and effective use.	
If a reference is listed, ensure that it is cited in the text of the label.	
Check for outdated references.	
Do not use a website link as a reference.	
Update safe handling REFERENCES to:	
<ul style="list-style-type: none"> <li>Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004:165.</li> </ul>	
<ul style="list-style-type: none"> <li>OSHA Technical Manual. TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. <a href="http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html">http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html</a></li> </ul>	
<ul style="list-style-type: none"> <li>American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006; 63:1172-1193.</li> </ul>	
<ul style="list-style-type: none"> <li>Polovich, M., White, J.M., &amp; Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd ed.) Pittsburgh, PA: Oncology Nursing Society</li> </ul>	
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>	
<i>(Also see Guidance for Industry: Bar Code Label Requirements – Questions and Answers)</i>	
<i>(Also see Draft Guidance for Industry, Investigators and Reviewers. NOT FOR PUBLIC RELEASE: Guidance for Establishing Safe Handling Designations for Human Pharmaceuticals)</i>	
Include information on available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:	
<ul style="list-style-type: none"> <li>Strength or potency of dosage form in metric system (e.g., 10 mg tablets); [If apothecary system is used place in parentheses after the metric designation (e.g., “Colchicine tablets, 0.6 mg (1/100 grain)” ]</li> </ul>	
<ul style="list-style-type: none"> <li>Units in which dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100)</li> </ul>	
<ul style="list-style-type: none"> <li>Appropriate information to facilitate identification of dosage forms (i.e., shape, color, coating, scoring, imprinting, and NDC number). The description of identifying characteristics of the dosage forms (except for NDC number) must also appear under the Dosage Forms and Strengths section.</li> </ul>	
<ul style="list-style-type: none"> <li>Special storage and handling conditions (e.g., protect from light, do not shake, do not freeze, store in refrigerator)</li> </ul>	
<b>Do not list physician sample sizes.</b> Only describe and list products for sale.	
Indicate if biohazard. If distribution is restricted under 21 CFR 314.520 or 601.42, state restrictions under this section, and elsewhere if applicable.	
See REFERENCES for safe handling	

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Any controlled substance or drug that would present a risk if not taken as prescribed should include language for safe disposal practices.	
<b>For drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances</b> , include the required warning statement [see 21 CFR 201.320(b)(3)] in the How Supplied/Storage and Handling section.	
<b>17 PATIENT COUNSELING INFORMATION</b>	
<p>[format] This section must reference any FDA-approved patient labeling. Include the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling)” should appear at the beginning of Section 17 to give it prominence. For example:</p> <ul style="list-style-type: none"> <li>• “See FDA-approved patient labeling (Medication Guide)”</li> <li>• “See FDA-approved patient labeling (Instructions for Use)”</li> <li>• “See FDA-approved patient labeling (Medication Guide Instructions for Use)”</li> <li>• “See FDA-approved patient labeling (Patient Information)”</li> <li>• “See FDA-approved patient labeling (Patient Information and Instructions for Use)”</li> </ul> <p>The purpose of this requirement is to draw the prescriber’s attention to the presence and content of a PPI, MG or Instructions for Use at the end of the labeling.</p>	
[format] Since SPL R4 validation does not permit the inclusion of the MG as a subsection, the MG or PPI should not be a subsection under the Patient Counseling Information section. Include at the end without numbering as a subsection.	
Except in rare circumstances, a Patient Counseling Information section always appears. When updating a label to the new format, this section should be drafted if it does not exist in the old format.	
[format] Do not insert a PPI or MG under the Patient Counseling Information section in lieu of developing this section.	
Include information for prescribers to convey to patients to use the drug safely and effectively (e.g., precautions concerning driving, concomitant use of other substances that may have harmful additive effects, adverse reactions reasonably associated with use of the drug, potential risks and benefits of use of the drug in pregnancy).	
All broad clinical recommendations should be in the Patient Counseling Information section.	
<b>For systemic antibacterial drug products</b> , include the required statement about antibiotic resistance [see 21 CFR 201.24(d)] in the Patient	

LABELING CHECKLIST	FILING REVIEW
Counseling Information section.	
<b>For Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders)</b> , include the required warning statement about difficulty breathing [see 21 CFR 201.305(c)(1)] in the Patient Counseling Information section.	
<b>Manufacturer information</b> is required in labeling (see 21 CFR 201.1 and 201.100(e) for drugs and 21 CFR 610 - Subpart G for biologics) and should be located after the Patient Counseling Information section, at the end of labeling. If the product has FDA-approved patient labeling that is not a separate document, the manufacturer information should be located at the end of the labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.	
The <b>revision date</b> at the end of highlights replaces the “revision” or “issued” date at the end of the full prescribing information and should not appear in both places. A revision date may appear at the end of FDA-approved patient labeling. A Medication Guide will always have a revision date because it is required by regulation (see 21 CFR Part 208).	
A <b>website address</b> is permitted in any type of labeling when inclusion of the website address is part of the applicant’s business address, unless the website name is promotional in nature. Therefore, a website address can appear at the end of the labeling with the manufacturer information.	
<b>Patent Numbers:</b> If a patent number is listed for an off label use, delete it. If patent numbers do appear in labeling, the patent numbers should appear at the end of the labeling, after the manufacturer information.	
If the “Rx only” statement appears anywhere in the prescribing information, delete it. This statement is only required for container and carton labels. (See <a href="#">Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements</a> ).	
<b>FDA-APPROVED PATIENT LABELING</b>	
<b>[format]</b> All approved patient labeling must be appended in SPL whether it is one document in the paper format or not. See 21 CFR 201.56(e)(6) and 201.80(f)(2).	
<b>[format]</b> Since SPL R4 validation does not permit the inclusion of the Medication Guide (MG) as a subsection, the MG or PPI should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.	
<b>[format]</b> Medication Guide that is for distribution to patients requires minimum 10-point type size.	
<b>[format]</b> Any FDA-approved patient labeling (except a Medication Guide)	

LABELING CHECKLIST	FILING REVIEW
that is for distribution to patients requires minimum 6-point type size for trade labeling and 8-point for all other labeling. However, FDA encourages a minimum type size of 10-point.	
<u>All FDA-approved patient labeling (Medication Guides, PPI and Instructions for Use) must be in the English language.</u> See 21 CFR 201.15(c)(1) and 208.20(a)(1) and CDER's MAPP 6020.7 regarding NDAs: Foreign Language Labeling.	
A Medication Guide will be required if the FDA determines that one or more of the following circumstances exist (21 CFR Part 208):	
<ul style="list-style-type: none"> <li>• The drug product is one for which patient labeling could help prevent serious adverse effects.</li> </ul>	
<ul style="list-style-type: none"> <li>• The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.</li> </ul>	
<ul style="list-style-type: none"> <li>• The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.</li> </ul>	
<b>Side Effects Statement:</b> For drug products approved under section 505 of the Act, the two-sentence verbatim statement [" <b>Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.</b> "] must be used and NOT modified to include the manufacturer's/applicant's phone number. This should also be included in the Medication Guide for any products approved under section 351 of the Public Health Service Act.	
<b>NOTE:</b> The label of each container (or package if the container is too small) of drug product for which a Medication Guide is required must contain a prominent and conspicuous statement instructing the dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided (21 CFR 208.24). Suggested text is " <b>ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide,</b> " and should be in bold type.	
Patient Package inserts are required for: <ul style="list-style-type: none"> <li>• Oral Contraceptives (21 CFR 310.501)</li> <li>• Estrogens (21 CFR 310.515)</li> <li>• Drugs approved based solely on animal studies [21 CFR 314.610(b)(3) and 601.91(b)(3)].</li> </ul>	
<u>For drug products containing or manufactured with chlorofluorocarbons or other ozone-depleting substances,</u> include the required warning statement [see 21 CFR 201.320(b)(1)] in the FDA-approved patient labeling.	

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LINDA V GALGAY  
06/24/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

Date: June 1, 2011

Application Type/Number: NDA 202231

Through: Todd Bridges, RPh, Acting Deputy Director  
Kellie Taylor, PharmD, MPH, Associate Director  
Carol Holquist, RPh., Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name and Strength (s): Levothyroxine Sodium for Injection  
100 mcg per vial, 200 mcg per vial, 500 mcg per vial

Applicant: APP Pharmaceuticals, LLC

OSE RCM #: 2010-2604

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## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA)'s evaluation of the proposed labels and labeling for Levothyroxine Sodium for Injection, for areas of vulnerability that could lead to medication errors. The Applicant proposes to market a new strength, 100 mcg. The 200 mcg and 500 mcg strengths have previously existed in the marketplace as unapproved products. Since color is a well-known feature associated with specific strengths of the oral levothyroxine products, we evaluated the use of color and its potential for confusion between the injection and oral products. We also analyzed the use of color between the proposed and marketed injection dosage form. This is a 505(b)(2) application; no listed drug is cited.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, principals of human factors, and lessons learned from post marketing experience in our evaluation of the labels and labeling of drug products. We also searched the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors due to labels and labeling have occurred with the existing marketed product, Levothyroxine Sodium for Injection.

### 2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Levothyroxine Sodium for Injection is a marketed product and, therefore, the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) database to identify medication error reports related to the use of these products and thus relevant to this review. We considered these cases in our review of the labels and labeling.

A search of the AERS database was conducted on May 11, 2011, using the following criteria: High Level Terms (HLT) "*maladministrations*", "*overdoses*", and "*medication errors NEC*", active ingredient "*levothyroxine*", trade name "*Synthroid*", and verbatim substance search terms, "*Synthr%*" and "*Levothyro%*". To limit the search to parenteral levothyroxine products, the advanced product criteria chosen were [REDACTED] "*intravenous*", "*intravenous bolus*", "*intravenous drip*", "*parenteral*", "*other*", and "*unknown*".

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Those that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events not related to a medication error, accidental exposure, intentional overdose, no medication errors, errors due to knowledge or performance deficit) were excluded from further analysis. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of Levothyroxine Sodium for Injection and thus pertinent to this review.

### 2.2 CONTAINER LABELS AND CARTON LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container label, carton and insert labeling submitted August 31, 2010. (See Appendix A for images of the carton and container labels; no image for insert labeling). Additionally, we compared the proposed and currently marketed color schemes of the container label and carton

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

labeling for the injection with regard to the 200 mcg and 500 mcg strengths (See Appendix B for images of the currently marketed 200 mcg and 500 mcg labels and labeling). Furthermore, we compared the color schemes proposed for all three strengths (100 mcg, 200 mcg, and 500 mcg) of the injection dosage form against those used for the (Synthroid and levothyroxine) oral tablet for their potential for confusion since color is a well-known feature associated with specific strengths of the oral products. (See Appendix C for the carton labeling for Synthroid 100 mcg and 200 mcg oral tablets submitted with the Annual Report dated September 17, 2010).

### **3 RESULTS**

The following section describes the results of our AERS search.

#### **3.1 AERS SELECTION OF CASES**

A total of 37 cases were retrieved in the AERS search, however, after excluding cases as described in Section 2.1, three cases involved wrong dose medication errors with Levothyroxine Sodium for Injection. They are described as follows:

##### **3.1.1 Wrong Dose ( $n = 3$ )**

Two of the 3 wrong dose cases describe confusion between the units of measurement “micrograms” and “milligrams”. In the first case (ISR# 3852308-6), a reporter states that a nursing supervisor gave 5 vials of 200 mcg vials of levothyroxine sodium to the patient’s nurse. The nurse administered 500 mg of levothyroxine intravenously although the prescription was for 0.025 mg. The reporter further states that the nurses misread the order as 0.05 mg and they failed to convert the milligrams to micrograms. The reporter then conveys that this error could have been avoided had the bottle been labeled with the milligram content of levothyroxine. No outcome was stated. See Section 4 (Discussion) for the analysis of this case.

In the second case (ISR# 3636127-1), the Institute of Safe Medication Practices (ISMP) cited a report in the literature of a patient who received a fatal intravenous dose of Synthroid 25 mg prior to surgery. The patient had been taking Synthroid 25 mcg orally each day prior to that time and the reason for the confusion was not explicitly stated. We tried to retrieve the actual article to confirm the details of this case and to elicit the contributing factors to this error. However, we were unable to find this information.

The third wrong dose case (ISR# 4453755-4) concerns the misinterpretation of the final concentration after reconstitution. The nurse believed that after reconstituting the product with 5 mL of diluent, the total volume was 10 mL because this was the volume stated on the vial. The reporter states that this “unclear labeling” resulted in an overdose (dose not specified); however, the final outcome was not given.

#### **3.2 LABEL AND LABELING**

Our review of the proposed container labels and carton labeling noted areas of vulnerability that could lead to error. Additionally, we were informed at the labeling meetings that the (b) (4) would not be included on the label and labeling and that the sole diluent for this drug product would be 0.9% Sodium Chloride for Injection, USP. Our recommendations are detailed in Section 5. Following are our concerns regarding the proposed color schemes and the potential for confusion with currently marketed products:

### **3.2.1 Comparison of the Color Schemes for the Proposed and Marketed Levothyroxine Injections**

The proposed color scheme for the 200 mcg and 500 mcg strengths appear to match the currently marketed injection product strengths (see Appendix B). The 200 mcg strength is presented in white font within a grey color block and the 500 mcg strength is presented in a black font within a yellow color block.

### **3.2.2 Comparison of the Color Schemes between Levothyroxine Injection and Levothyroxine Tablets**

We note that the color schemes used for the strengths, 100 mcg and 200 mcg, differ when comparing the injection to the oral tablets. The statements of strengths for the injection are presented as white font within a purple color block (100 mcg) and white font within a grey color block (200 mcg). In contrast, the colors used for the same strengths in the oral dosage form are yellow and pink. Additionally, although there is no 500 mcg oral tablet available, the color used for this strength (yellow) in the injection dosage form overlaps with the 100 mcg oral product (yellow).

## **4 DISCUSSION**

Our evaluation of the proposed product identified three main areas of concern: (a) potential for confusion between the units of measurement (micrograms versus milligrams) and regarding the final concentration after reconstitution; (b) potential for confusion between the color schemes for the proposed and currently marketed 200 mcg and 500 mcg levothyroxine injection products; (c) the potential for confusion between the proposed color schemes for levothyroxine injection and the color schemes used for marketed oral levothyroxine products. These issues are discussed in sections 4.1 through 4.4. We further note that the proposed strength, 100 mcg, is supported in the dosage and administration section of the insert labeling.

### **4.1 CONFUSION BETWEEN MICROGRAMS AND MILLIGRAMS**

DMEPA retrieved two cases of wrong strength that were related to confusion between the units of measurement, 'mcg' and 'mg' for levothyroxine injection. Based upon the facts presented in the cases, we found it difficult to envision the amount of levothyroxine vials required to achieve the reported dose. It would have taken *fifty* 500 mcg vials to achieve the 25 mg dose in the first case (which had a fatal outcome) and *one thousand* 500 mcg vials to achieve the 500 mg dose in the second case. Additionally, none of the potential (e.g., illegible handwriting, miscalculations, or oversight) or stated (e.g., misinterpretation) sources of confusion could be addressed with labeling changes.

DMEPA acknowledges the confusion between micrograms and milligrams and its contribution to the wrong strength of levothyroxine being prescribed, dispensed and/or administered. Additionally, the two cases that we evaluated in this review may demonstrate that this confusion translates to reporting the problem as well since the reporters' statements imply that very large amounts of drug were given to achieve 25 mg and 500 mg of levothyroxine respectively. We cannot tell if this was confusion on the reporters' part or a typographical error.

In a previous review of oral Synthroid (OSE# 2009-2352 dated January 25, 2010) DMEPA supported the continued presentation of both units of measurement on the principle display panel because we were concerned that the elimination of this information (which had been included

when levothyroxine was marketed as an unapproved drug product) would introduce new problems. For intravenous levothyroxine, the unapproved products did not contain dual expressions of strength. Therefore, a similar presentation for this drug product may introduce more issues than it resolves by allowing for another opportunity for confusion, thereby exacerbating the problem. Additionally, contributing factors such as miscalculation errors, illegible handwriting or overlooking the letter 'c' when the abbreviation is used (e.g., mcg, vs. mg) cannot be resolved with labeling changes. Finally, the presentation of both units of measurement is not consistent with the insert labeling for this product. As such, we agree with the Applicant's proposed presentation of one unit of measurement (mcg) on the label since this does not provide an added venue for confusion.

#### **4.2 CONFUSION REGARDING FINAL CONCENTRATION AFTER RECONSTITUTION**

In the AERS case of confusion regarding the final concentration of levothyroxine after reconstitution, the user was confused because the volume used to reconstitute the product (5 mL) was different from the volume stated on the vial (10 mL). Although this appears to be an isolated case, we reviewed the proposed label and labeling for a similar vulnerability to confusion and found none. Despite this finding, we added language which addresses the resultant concentration after reconstitution in the preparation instructions of the insert labeling. See Section 5.1.1(2) under 'Comments to the Division'.

#### **4.3 COMPARISON OF COLOR SCHEMES BETWEEN PROPOSED AND CURRENTLY MARKETED LEVOTHYROXINE INJECTION PRODUCTS**

The colors used on the proposed containers and cartons to identify levothyroxine 200 mcg (grey) and 500 mcg (yellow) injection are similar to the colors currently used for the marketed, unapproved products. Since we did not retrieve any AERS reports which identified the color as a source of confusion, we do not envision that this will be a problem in the future.

#### **4.4 COMPARISON OF COLOR SCHEMES BETWEEN LEVOTHYROXINE INJECTION AND ORAL PRODUCTS**

In our comparison of the color schemes for the injection versus the oral tablet for the 100 mcg and 200 mcg strengths, we found that they do not follow the same color scheme. The 500 mcg strength is only marketed as an injection formulation. Since there is no oral tablet in this strength, there is no overlap in the color schemes between these strengths.

We do not anticipate that this absence of color coordination between the dosage forms will lead to medication errors nor do we envision confusion in the future with the introduction of the proposed 100 mcg strength (of the injection). Furthermore, the dose for the oral and injection dosage forms do not possess 1:1 equivalency (e.g., 250 mcg levothyroxine intravenous does not equal 250 mcg oral) and therefore, it would seem appropriate that there is no overlap in color between them.

However, in our comparison of the color schemes for the injection versus the oral tablet, we noted two areas of overlap between the product lines. First, the color for the proposed 100 mcg injection formulation (purple) was found to be similar to the 75 mcg oral tablet (lavender). Secondly, we noted the 500 mcg strength for the injection color (yellow) overlaps with the yellow color used for the 100 mcg oral tablet. Although the colors are the same for the 500 mcg injection and 100 mcg oral tablet products, we do not believe this will lead to errors since the color schemes have been used concurrently in the marketplace previously without leading to errors. This experience also provides some reassurance that the similarity between the 100 mcg

injection formulation and 75 mcg oral tablet will not be problematic, although we have no direct experience since the 100 mcg injection formulation has never been marketed.

## 5 CONCLUSIONS AND RECOMMENDATIONS

Our analysis identified two main concerns with the proposed product: confusion between the units of measurement, ‘mcg’ and ‘mg’ and confusion involving final concentration after reconstitution. To mitigate such areas of confusion we have made recommendations which increase the prominence of the statement of strength as well as the units of measurement and added language in the insert labeling to address the final concentration after reconstitution of this drug product.

Additionally, we identified other areas in the product labels and labeling that can be revised to minimize errors. See Section 5.1 (*Comments to the Division*) contains our recommendations for the insert labeling and Section 5.2 (*Comments to the Applicant*) contains our recommendations regarding the container labels and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Margarita Tossa at 301-796-4053.

### 5.1 COMMENTS TO THE DIVISION

#### 5.1.1 *Insert Labeling (Full Prescribing Information)*

1. Section 2.3 (titled Reconstitution (b) (4) – revise the statement, “Parenteral drug products should be inspected visually . . . prior to administration” to read “Parenteral drug products should be inspected visually . . . prior to administration, *whenever solution and container permit*”.
2. Section 2.3 (Reconstitution Directions) – add the statement, “the resultant solution will have a final concentration of approximately 20 mcg/mL, 40 mcg/mL, and 100 mcg/mL for the 100 mcg, 200 mcg, and 500 mcg vials respectively”. This statement may follow the sentence, “Shake vial to ensure complete mixing”.
3. Section 3 (Dosage Forms and Strengths) – only needs the three strengths (100 mcg, 200 mcg, and 500 mcg); not necessary to add the words (b) (4)
4. Section 16.1 (How Supplied) – To decrease redundancy, the only information needed prior to the table is “Levothyroxine Sodium for Injection is available in three different dosage strengths.

All of these recommendations were accepted by the CMC reviewer and incorporated into the insert labeling as requested.

### 5.2 COMMENTS TO THE APPLICANT

- A. Carton Labeling and Container Label (100 mcg/vial, 200 mcg/vial, 500 mcg/vial)
1. Increase the prominence of the dosage form, ‘Injection, USP’ as this is important information used by the healthcare practitioner to identify this drug product.

2. [REDACTED] (b) (4)
  3. Revise the statement [REDACTED] (b) (4) to read “Single Use Vial” and follow this revised statement with “Discard any unused portion”.
  4. [REDACTED] (b) (4)
  5. Replace the phrase cited in #3 above with “The resultant solution will have a final concentration of XX/mL” (e.g., 20 mcg/mL, 40 mcg/mL, and 100 mcg/mL for the 100 mcg, 200 mcg, and 500 mcg vials respectively).
  6. Revise the statement [REDACTED] (b) (4) to read “Not made with Natural Rubber Latex”.
  7. Increase the prominence of the statement of strength and revise this statement to reflect the total drug content per vial (e.g, 100 mcg/vial, 200 mcg/vial, and 500 mcg/vial).
  8. Revise the statement “For ... IV Use” to read “For Intravenous Use”. Generally, the Agency does not approve labeling with the use of abbreviations because they may be misinterpreted. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations, or symbols. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling. We discourage the abbreviation “IV” because it may be misinterpreted to mean “IU” (international units) or the roman numeral ‘four’ when used in the medical community.
  9. Delete the statement [REDACTED] (b) (4)  
[REDACTED] Otherwise, revise this statement to inform the practitioner of the impact of adding this product to other fluids and provide the details in the insert labeling.
  10. Add the statement “Discard unused portion” immediately following the statement “Use immediately after reconstitution”.
- B. Carton Labeling (100 mcg/vial, 200 mcg/vial, 500 mcg/vial)  
Add the statement, “Lot” and Exp” to allow for addition of these details.

## 6 REFERENCES

### Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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06/02/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 31, 2011

**To:** Linda Galgay, Regulatory Project Manager,  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Samuel Skariah, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** NDA 202231 Levothyroxine sodium for injection  
  
DDMAC's review of the proposed Prescribing Information (PI) and  
carton/container labeling

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This review is in response to DMEP's January 10, 2011, request for DDMAC's review on labeling materials for Levothyroxine sodium for injection (Levothyroxine). DDMAC has reviewed the substantially complete proposed PI and carton/container labeling for Levothyroxine accessed from the DMEP eRoom on March 31, 2011. Comments regarding the proposed PI are provided directly in the document attached below.

### **Carton/Container Labeling**

DDMAC has reviewed the 100, 200, and 500 mcg proposed carton/container and vial labeling. DDMAC does not have any comments regarding these labels.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Sam Skariah at 301. 796. 2774 or [Sam.Skariah@fda.hhs.gov](mailto:Sam.Skariah@fda.hhs.gov).

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SAMUEL M SKARIAH  
05/31/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 202231	NDA Supplement N/A      Efficacy Supplement Type N/A
Proprietary Name: None requested Established/Proper Name: Levothyroxine Sodium for Injection Dosage Form: Lyophilized Powder for Injection Strengths: 100 mcg, 200 mcg, 500 mcg/vial Route of Administration: Intravenous (IV)	
Applicant: APP Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A	
Date of Application: 8/30/10 Date of Receipt: 8/30/10 Date clock started after UN: N/A	
PDUFA Goal Date: Thursday, 6/30/11	Action Goal Date (if different): N/A
Filing Date: 10/29/10	Date of Filing Meeting: 10/14/10
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 7 – Drug Already Marketed but Without an Approved NDA	
Proposed indications: (1) Myxedema Coma <span style="float: right;">(b) (4)</span> <div style="background-color: #cccccc; height: 20px; width: 100%;"></div>	
Proposed changes: New dosage form, indications, dosing regimen, route of administration	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) N/A <input type="checkbox"/> 505(b)(2) N/A
<b><i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a> and refer to Appendix A for further information.</i></b>	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> N/A	Resubmission after refuse to file? <input type="checkbox"/> N/A
Part 3 Combination Product? <input type="checkbox"/> N/A  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package N/A <input type="checkbox"/> Pre-filled drug delivery device/system N/A <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling

	<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	N/A		
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): PIND 101385				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			No proprietary name requested
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system?  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X		
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X		
<b>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</b>  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>		X		

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		X		

Format and Content				
<p>↓ <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> eCTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
	<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup> If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				N/A
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?			X	No clinical studies.
<i>Forms must be signed by the <b>APPLICANT</b>, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act</i>				

<i>section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic submissions

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			New dosage form, indications, dosing regimen, route of administration
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			
<p><b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b></p> <p><i>If no, request in 74-day letter</i></p>			X	

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)  <i>If no, request in 74-day letter</i>	X			
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			X	
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>			X	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?			X	

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA <b>Date(s):</b> 3/18/08	X			
<i>If yes, distribute minutes before filing meeting</i>				

Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			X	
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ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/14/10

NDA (b) (4)

PROPRIETARY NAME: None requested

ESTABLISHED/PROPER NAME: Levothyroxine Sodium for Injection

DOSAGE FORM/STRENGTH: Lyophilized Powder for Injection/ 100 mcg, 200 mcg, 500 mcg/vial

APPLICANT: APP Pharmaceuticals, LLC

PROPOSED INDICATIONS: (1) Myxedema Coma (b) (4)

PROPOSED CHANGES: New dosage form, indications, dosing regimen, route of administration

BACKGROUND: Levothyroxine for injection is a marketed, unapproved product, and the Agency has stated that unapproved products must obtain approved applications to continue marketing. In this 505(b)(2) application, APP seeks approval for an injectable levothyroxine product that it has marketed for years. This NDA proposes the indications of treatment of myxedema coma (b) (4). The applicant includes three presentations (strengths) of lyophilized powder for reconstitution: 100, 200, and 500 mcg/ vial.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda Galgay	Y
	CPMS/TL:	Enid Galliers	Y
Cross-Discipline Team Leader (CDTL)	Dragos Roman		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Dragos Roman	Y

Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Bob Mello	Y
	TL:	John Metcalfe	N

Clinical Pharmacology	Reviewer:	Johnny Lau	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis-Bruno	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Joseph Leginus	Y
	TL:	Ali Al Hakim	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Robert Mello	Y
	TL:	John Metcalfe	N
CMC Labeling Review	Reviewer:	Joseph Leginus	Y
	TL:	Ali Al Hakim	N
Facility Review/Inspection	Reviewer:	Lori Gorski. EES requested.	N
	TL:	N/A	N/A
OSE/DMEPA (proprietary name)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE/DRISK (REMS)	Reviewer:	N	N
	TL:	N	N
OC/DCRMS (REMS)	Reviewer:	N	N
	TL:	N	N

Bioresearch Monitoring (DSI)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers: Biopharmaceutics ONDQA	Angelica Dorantes Su Tran		Y Y
Other attendees:			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b> N/A</p>	
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> No clinical studies were submitted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> Labeling Review will be presented at first labeling meeting 4/14/11.</p>	<p>Joseph Leginus</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Division Director</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b> Mid-Cycle Review – 2/7/10  Labeling Meetings – 4/14, 4/28, 5/5, 5/23, 5/26, 5/31/11  Proposed date for labeling to sponsor – 5/12/11  Wrap-Up Meeting – 5/9/11  Primary Reviews due in DARRTS – 5/12/11  CDTL Review due in DARRTS – 5/26/11  Post-Decisional Meeting – 7/7/11</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a>]</p>
<input type="checkbox"/>	Other

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LINDA V GALGAY  
04/19/2011