

Current Trends and Best Practices in ANDA Labeling

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Best practices for ANDA labeling submissions – Questions to consider

Are you routinely checking for the following changes?



Reference Listed Drug (RLD) update in Drugs@FDA

www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Do not rely on other publicly available labeling such as DailyMed.



Patent and exclusivity update in Orange Book

www.accessdata.fda.gov/scripts/cder/ob/index.cfm



USP update – Prepare for pending changes. On the day that new monograph is effective your ANDA needs to meet the monograph.

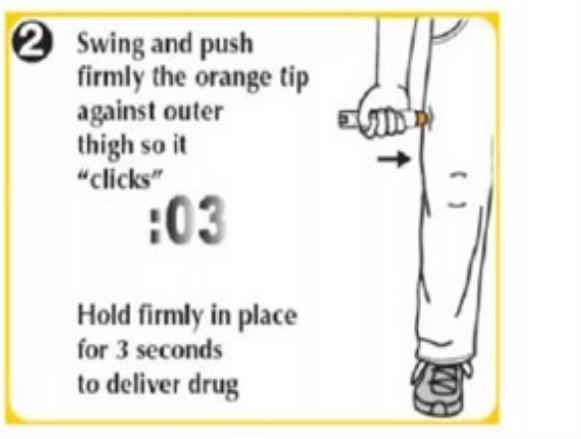
www.uspnf.com

Are you being too creative with ANDA labeling?

Labeling needs to be the same as RLD... not “better” or ...“worse”.

Some examples of very preventable errors we observed:

- Instructions for Use (IFU):

RLD	Proposed ANDA
<p>RLD has a picture of an entire leg with details.</p>  <p>② Swing and push firmly the orange tip against outer thigh so it “clicks” :03 Hold firmly in place for 3 seconds to deliver drug</p>	<p>ANDA proposed a picture of waist and part of leg with no details; not the full leg. Layout of text instructions was also different. The ANDA was asked to be more in line with respect to the RLD.</p>

Are you being too creative with ANDA labeling? (Examples Cont'd)

IFU: RLD has a picture of a child, whereas, ANDA has a diagram of an adult.

RLD	Proposed ANDA
 <p>Figure H</p>	<p>ANDA proposed a picture of an adult man with extra instructions.</p>

Are you being too creative with ANDA labeling? (Examples Cont'd)

RLD emphasizes text to bring attention to it (e.g., **bolding**/underlining/*italics*/etc.); ANDA does not.

DOSAGE AND ADMINISTRATION: Apply a thin layer of TEMOVATE Cream or Ointment to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).

TEMOVATE Cream and Ointment are super-high potency topical corticosteroids; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/week should not be used.**

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

TEMOVATE Cream and Ointment should not be used with occlusive dressings.

Are you being too creative with ANDA labeling? (Examples Cont'd)

- ANDA proposes the same device as the RLD but creates an IFU that RLD does not have
or conversely
ANDA proposes a device that appears different from RLD and the proposed picture of the device is copied from the RLD
- Renumbering Tables and Figures in the Prescribing Information when information is carved out
- Proposing additional phrases in ANDA that do not appear in RLD
- Substituting certain words (e.g., “risk” with “chance”)

Has the alcohol content of your drug product been declared?

- Declare the alcohol (ethanol) content in your drug product in conjunction with the active ingredient and inactive ingredients.
- Include the calculations used to determine the alcohol % v/v content in your drug product per **section 502(e)** of the **FD&C** Act and 21 CFR 201.10(d)(2).



Has the alcohol content of your drug product been declared?

- Calculation should be submitted in 3.2.P.1 Description and Composition of drug product

See Guidance: ANDA Submissions- Content and Format (p. 20)

<https://www.fda.gov/media/128127/download>

- The guidance states the following: For products that contain alcohol, a calculation of the absolute alcohol in terms of percent volume (volume/volume)

Declaring Alcohol Content: Example

Description Section example...

Inactive ingredients include sorbitol, alcohol 7% , and water.

Promethazine DM Oral Solution

(Promethazine Hydrochloride and
Dextromethorphan Hydrobromide
Oral Solution)

EACH 5 mL (ONE TEASPOONFUL) CONTAINS:

Promethazine Hydrochloride	6.25 mg
Dextromethorphan Hydrobromide	15 mg
Alcohol	7%

USUAL DOSAGE: See accompanying package insert.
Dispense in a tight, light-resistant container with a
child-resistant closure as defined in the USP.



Is the Prescribing Information (PI) Consistent with all other Labeling pieces?

Check the following for consistency in
PI/MG/IFU/Container/Carton/SPL:

- NDC numbers
(may use place-holder XXXX-XXX-XX if not available)
- Excipient list
- Storage conditions
- Manufacturer/distributor statement

Is your drug product in compliance with the STIC (Susceptibility Test Interpretive Criteria) regulations?

- The text from the replaced sections should reference the Interpretive Criteria Website with the following language at the end of the “microbiology” section and directly before the “Human Pharmacology” section:

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: www.fda.gov/STIC

- ANDAs can include the change even if the NDA RLD has not updated its labeling to include reference to the website. This is a permissible difference.



Are you using RS Labeling rather than the RLD labeling?

If RLD is discontinued, still use the last approved RLD labeling UNLESS RLD is withdrawn under section 505(e)(1) through (5) or section (j)(6) of the [FD&C Act] per Federal Register AND not withdrawn from sale for reasons of safety or effectiveness.

We refer you to the Draft Guidance, “Referencing Approved Drug Products in ANDA Submissions”.

www.fda.gov/media/102360/download

Are you using RS Labeling rather than the RLD labeling? (cont'd)

Excerpts from the Draft Guidance (continued):

Footnote 28:

An applicant is responsible for checking appropriate sources in order to obtain the RLD labeling. In instances where the RLD labeling cannot be located, an applicant for convenience initially may compare its proposed generic drug's labeling with the labeling of another ANDA that referenced the same RLD and currently is marketed. Prior to approval, the applicant may need to revise labeling to reflect certain updated information that would have been necessary had the RLD not been withdrawn. See FDA's draft guidance for industry on *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016). 29 21 CFR 314.94(a)(3)(i).

Does your Prescribing Information include a revision date?



- PLR format: Per 21 CFR 201.57(a)(15)
The revision date should appear at the end of the **HIGHLIGHTS** section. [Not at the end of the Full Prescribing Information.]
(Preferred format “Revised: M/YYYY” or “Revised: MM/YYYY”)
- Non-PLR format: 21 CFR 201.56(e)(5)
“The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of labeling”.

Does your product title in the Prescribing Information include route of administration?

- PLR format: Per 21 CFR 201.57(a)(2), in the HIGHLIGHTS of Prescribing Information, route of administration needs to be included as part of the title.
- Examples of acceptable presentations:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use **HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS** safely and effectively. See full prescribing information for **HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS**.
HYDROMORPHONE HYDROCHLORIDE extended-release tablets, **for oral use**, CII
Initial U.S. Approval: 1984

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use **VALGANCICLOVIR HYDROCHLORIDE FOR ORAL SOLUTION** safely and effectively. See full prescribing information for **VALGANCICLOVIR HYDROCHLORIDE FOR ORAL SOLUTION**.
VALGANCICLOVIR HYDROCHLORIDE, **for oral solution**
Initial U.S. Approval: 2001

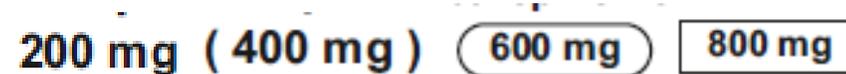


Does each Unit-dose Blister Label contain the following elements?

- Established name and proprietary name (if applicable)
- Strength
- Identifying lot or control number and expiration date
- Linear Bar code
- Manufacturer, packer or distributor
- Use of capsule or tablet (singular)
- Refer to 21 CFR 201.10(i) and the draft Guidance “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors”
www.fda.gov/media/85879/download

Blister Label (cont'd)

- Has the strength statement on each blister been differentiated (e.g., color, shapes around strength)?



- If you choose to use differentiating colors, ensure that the coloring scheme matches with other labeling components.

Other Tips and Clarifications



Considerations for OTC products

Note the 21 CFR Part 201, Subpart C, Labeling Requirements for Over the Counter Drugs

[§ 201.60](#) - Principal display panel.

[§ 201.61](#) - Statement of identity.

[§ 201.62](#) - Declaration of net quantity of contents.

[§ 201.63](#) - Pregnancy/breast-feeding warning.

[§ 201.64](#) - Sodium labeling.

[§ 201.66](#) - Format and content requirements for over-the-counter (OTC) drug product labeling.

[§ 201.70](#) - Calcium labeling.

[§ 201.71](#) - Magnesium labeling.

[§ 201.72](#) - Potassium labeling.

[§ 201.80](#) - Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in 201.56(b)(1).

Remember to declare Na, K, Ca, and Mg contents & Include font size legend for Drug Facts!

Considerations for OTC products (cont'd)

Actual example of a legend from a submission:

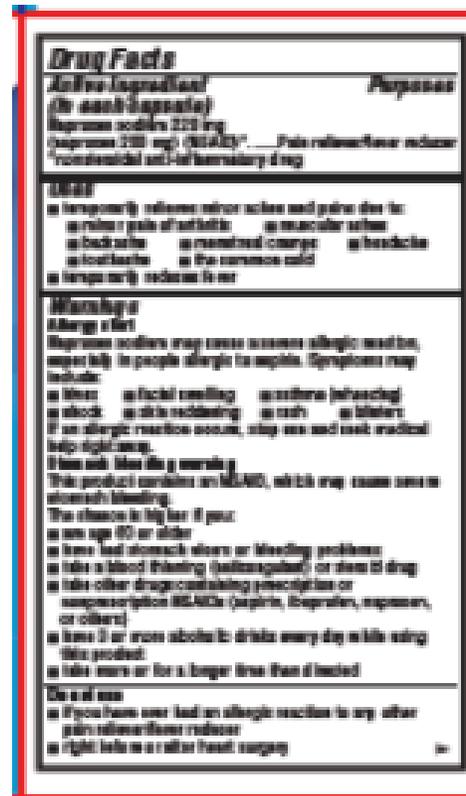
(Label represents actual size)

Labeling Format Information

Fonts:	Helvetica Neue LT Standard
Drug Facts:	10 pt
Header:	8 pt
Subheader:	6 pt
Body Text:	6 pt
Drug Facts (cont.):	9 pt
Bullets:	6 pt
Barlines:	2.5 pt
Hairlines:	.5 pt

Other Tips

- Ensure labeling components have adequate resolution



Other Tips (cont'd)

- For Prescribing Information and other information that follows (e.g., Medication Guide, Patient Information, Instructions for use) ensure you are submitting draft labeling in text-based PDF and MS Word files, not just final printed labeling.

See p 11 of the Guidance, “ANDA Submissions- Content and Format”:
www.fda.gov/media/128127/download

Reminder: Ensure that all forms of labeling are **consistent** (If FPL is submitted ensure that it matches the PDF and MS Word documents).

- When proposing a proprietary name, we recommend that you submit two sets of labeling: one with the proprietary name and one without it (i.e., established name only).
- Note for Antiretroviral products: please provide statement of intent to join APR for non-PEPFAR ANDAs.
- When there is a transfer of ownership, be sure to provide updated labeling, as applicable.

USP Statement Clarification

Examples of USP statements in Labeling:

- * Meets USP organic impurities test 2
- * Meets USP dissolution test 3
- * FDA approved dissolution test specifications differ from USP

Tips:

Resolve USP statement issues as soon as possible. Last minute resolution may result in last minute changes in Labeling AND re-review by DLR.

Placement of USP statements

Rx Products:

Place Dissolution statement at the end of the DESCRIPTION section of the Prescribing Information, only

Place Assay or Organic impurities statement at the end of the DESCRIPTION section of the Prescribing Information AND the side panel of the CONTAINER and CARTON labeling, as applicable

OTC Product:

Place USP statements In the Other Information section of DRUG FACTS

Clarification on Removal of Pregnancy Category

- On 12/4/14, FDA published the “Pregnancy and Lactation Labeling Rule” (PLLR), effective 6/30/15.

www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- How does PLLR affect ANDA Labeling:

For non-PLR labeling, ANDAs can remove the Pregnancy Category prior to RLD update. Also, the removal of Pregnancy Category is annual reportable.

For PLR labeling, ANDAs follow RLD labeling update.

Lifecycle Considerations (PAS, CBE, and AR)

- Check for updates in RLD labeling at Drugs@FDA, Orange Book, and the USP.
- Choose the appropriate category to request or report labeling changes: Prior Approval Supplement (PAS), Changes Being Effected Supplement (CBE-30 and CBE-0), or Annual Report (AR).
- Use appropriate reporting/submission category
Please refer to the following Guidances.
 - Guidance for industry, Changes to an Approved NDA or ANDA:
www.fda.gov/media/71846/download
 - Guidance for industry, CMC Post-approval Manufacturing Changes to be Documented in Annual Reports
www.fda.gov/media/79182/download
 - Guidance for industry, Prior Approval Supplements Under GDUFA
www.fda.gov/media/89263/download

Lifecycle considerations (PAS, CBE, and AR) cont'd.

Example situations where ANDA submitted CBEs when the changes were annual reportable:

- Minor change to trade dress
- Change in distributor's information
- Change in NDC number
- Annual reportable packaging changes
- Annual reportable imprint changes
- Updating labeling to reflect a new product manufacturing facility (in this case, only Quality section would be reviewed as CBE-30; labeling is AR after facility is approved)



Question? Ask the right people

The following website provides point-of-contact list.

www.fda.gov/drugs/generic-drugs/points-contact-questions-related-generic-drugs

If you have a question about updated labeling on Drugs@FDA, please contact DrugInfo@fda.hhs.gov .

Thank You!

The text "Thank You!" is written in a black, elegant cursive font. Below the text are several horizontal, overlapping brushstrokes in various colors including blue, purple, pink, red, orange, and yellow. The background of the text and brushstrokes is a light, textured yellow.

Questions??

