



Regulatory Education  
for Industry (REdI):

## **PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES**

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# **Challenges and Issues With the CLINICAL STUDIES Section of Labeling**

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# Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are fictitious and are provided only to demonstrate current labeling development challenges.

# CLINICAL STUDIES Section: Resources

Code of Federal Regulations:

- 21 CFR 201.57(c)(15)

Labeling Guidance:

- Clinical Studies Section of Labeling Guidance



# CLINICAL STUDIES Section (1 of 3)

- Must discuss those clinical studies that facilitate an understanding of how to use drug safely and effectively\*
- Any clinical study discussed in CLINICAL STUDIES section must be adequate and well-controlled as per 21 CFR 314.126(b) [drugs] or contribute to substantial evidence [biological products]\*
- Do not include active control studies that imply comparative effectiveness or safety claims not supported by substantial evidence\*\*

\* 21 CFR 201.57(c)(15); \*\* 21 CFR 201.57(c)(2)(iii)

# CLINICAL STUDIES Section (2 of 3)

To improve readability recommend:

- Only using one statistical population
- Only using mean or median (not both)
- Rounding up when displaying treatment effects in percentages (if appropriate)
- Including results in a table or text (not both)
- Defining acronyms
- Using consistent terminology throughout
  - DRUGOXIDE-treated patients vs. patients treated with DRUGOXIDE vs. patients who received DRUGOXIDE
  - Using subsections to organize information (e.g., three different study populations)

# CLINICAL STUDIES Section (3 of 3)

- Recommend not discussing future or ongoing studies
- When developing labeling, think about treatment arms in studies in CLINICAL STUDIES section vs. recommended dosage in D&A section

# No Implied Indications, Uses, Claims, or Dosage Regimens

21 CFR 201.56(a)(3)	“No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.”
21 CFR 201.57(c)(2)(iv) and (v)	“Indications or uses must not be implied or suggested in other sections of the labeling if not included in” the INDICATIONS AND USAGE section.
21 CFR 201.57(c)(3)(ii)	“Dosing regimens must not be implied or suggested in other sections of the labeling if not included in” the DOSAGE AND ADMINISTRATION section.
21 CFR 201.57(c)(15)(i)	“Any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug ... must not imply or suggest indications or uses or dosing regimens not stated in the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION section.”
<a href="#"><u>Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling</u></a> guidance	WARNINGS AND PRECAUTIONS that discuss an adverse reaction associated with an unapproved use “should include a statement that safety and effectiveness have not been established in that setting and that the use is not approved by the FDA.”

# ENTYVIO: CLINICAL STUDIES Section (1 of 5)

Include study design\*



## 14 CLINICAL STUDIES

### 14.1 Clinical Studies in Ulcerative Colitis

The safety and efficacy of ENTYVIO were evaluated in two randomized, double-blind, placebo-controlled trials (UC Trials I and II) in adult patients with moderately to severely active ulcerative colitis (UC) defined as Mayo score of six to 12 with endoscopy subscore of two or three. The Mayo score ranges from zero to 12 and has four subscales that are each scored from zero (normal) to three (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. An endoscopy subscore of two is defined by marked erythema, lack of vascular pattern, friability, and erosions; an endoscopy subscore of three is defined by spontaneous bleeding and ulceration.



Define terms that may not be well-understood\*

\* Sections III(B and C) - Clinical Studies Section of Labeling Guidance



# ENTYVIO: CLINICAL STUDIES Section (2 of 5)

Enrolled patients in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine or 6-mercaptopurine) and/or an inadequate response, loss of response, or intolerance to a TNF blocker. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response or intolerance to corticosteroids.

Patients that had received natalizumab ever in the past, and patients that had received a TNF blocker in the past 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF blocker was not allowed.

Include inclusion and exclusion criteria important for understanding treatment effect\*

\* Section III(B)(4) - Clinical Studies Section of Labeling Guidance

# ENTYVIO: CLINICAL STUDIES Section (3 of 5)

## UC Trial I

In UC Trial I, 374 patients were randomized in a double-blind fashion (3:2) to receive ENTYVIO 300 mg or placebo by intravenous infusion at Week 0 and Week 2. Efficacy assessments were at Week 6. Concomitant stable dosages of aminosalicylates, corticosteroids (prednisone dosage  $\leq 30$  mg/day or equivalent), and immunomodulators (azathioprine or 6-mercaptopurine) were permitted through Week 6.

At baseline, patients received corticosteroids (54%), immunomodulators (azathioprine or 6-mercaptopurine) (30%), and/or aminosalicylates (74%). Thirty-nine percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. Eighteen percent of patients had an inadequate response, inability to taper or intolerance to prior corticosteroid treatment only (i.e., had not received prior immunomodulators or TNF blockers). The median baseline Mayo score was nine in the ENTYVIO group and eight in the placebo group.

### Include:\*

- Treatment arms (e.g., dosage regimens)
- Inclusion and exclusion criteria important for understanding treatment effect
- Concomitant medications
- Important baseline disease characteristics

\* Section III(B) - Clinical Studies Section of Labeling Guidance

# ENTYVIO: CLINICAL STUDIES Section (4 of 5)

## Study Results\*

In UC Trial I, a greater percentage of patients treated with ENTYVIO compared to patients treated with placebo achieved clinical response at Week 6 (defined in *Table 3*). A greater percentage of patients treated with ENTYVIO compared to patients treated with placebo also achieved clinical remission at Week 6 (defined in *Table 3*). In addition, a greater percentage of patients treated with ENTYVIO had improvement of endoscopic appearance of the mucosa at Week 6 (defined in *Table 3*).

\* Section III(C) - Clinical Studies Section of Labeling Guidance

# ENTYVIO: CLINICAL STUDIES Section (5 of 5)

## Study Results

Table 3. Proportion of Patients Meeting Efficacy Endpoints at Week 6 (UC Trial I)

Endpoint	Placebo N=149	ENTYVIO N=225	p-value	Treatment Difference and 95% CI
Clinical response* at Week 6	26%	47%	<0.001	22% (12%, 32%)
Clinical remission† at Week 6	5%	17%	0.001	12% (5%, 18%)
Improvement of endoscopic appearance of the mucosa‡ at Week 6	25%	41%	0.001	16% (6%, 26%)

\*Clinical response: reduction in complete Mayo score of  $\geq 3$  points and  $\geq 30\%$  from baseline with an accompanying decrease in rectal bleeding subscore of  $\geq 1$  point or absolute rectal bleeding subscore of  $\leq 1$  point.

†Clinical remission: complete Mayo score of  $\leq 2$  points and no individual subscore  $> 1$  point.

‡Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

- Define endpoints that are not commonly understood\*
- Include confidence intervals\*
- Include study population and number, type of data, time point in table title\*\*

\* Sections III(C, B) - Clinical Studies Section of Labeling Guidance

\*\* Appendix C - Clinical Studies Section of Labeling Guidance



# References

- PLR Requirements for Prescribing Information website:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Thank you!