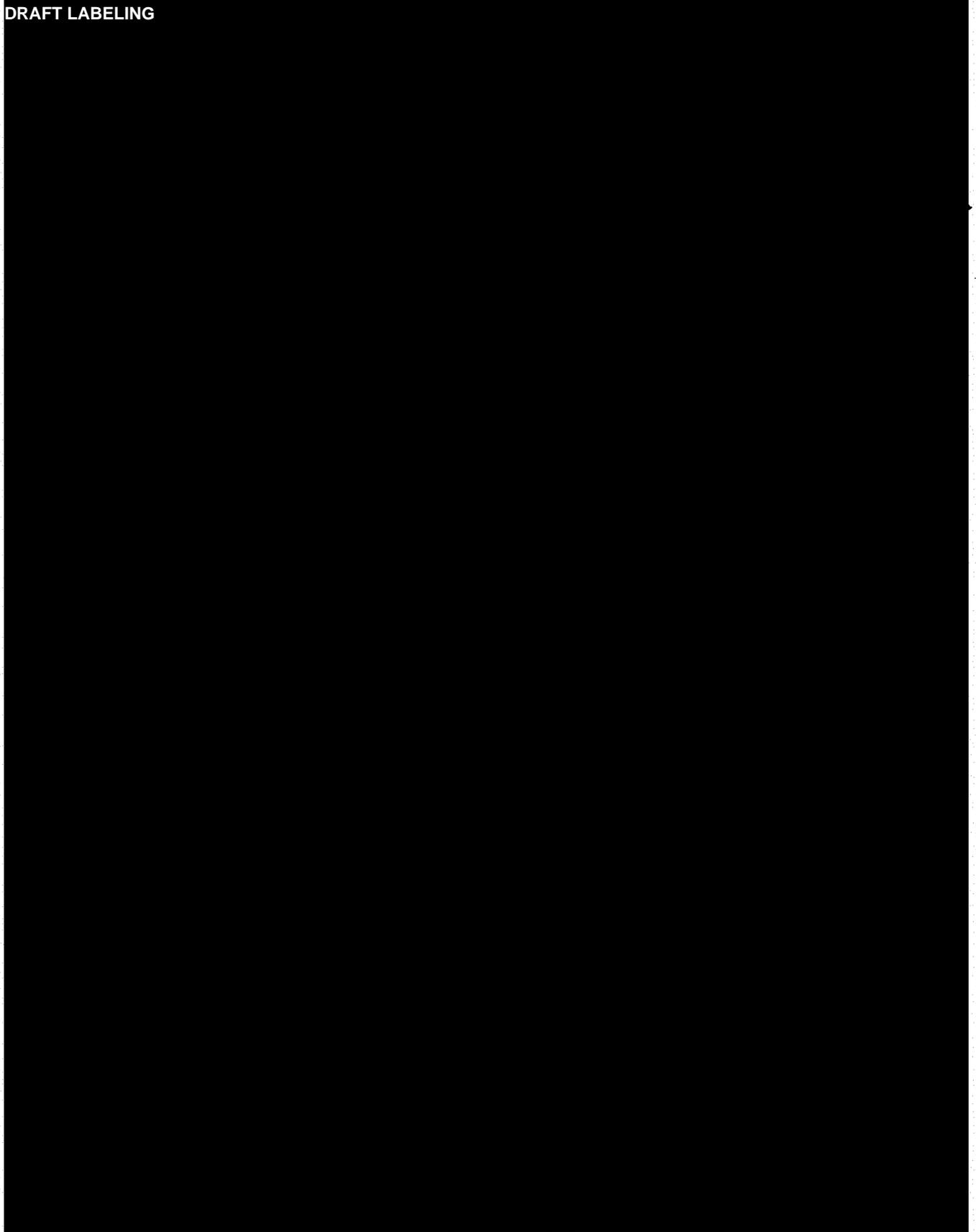
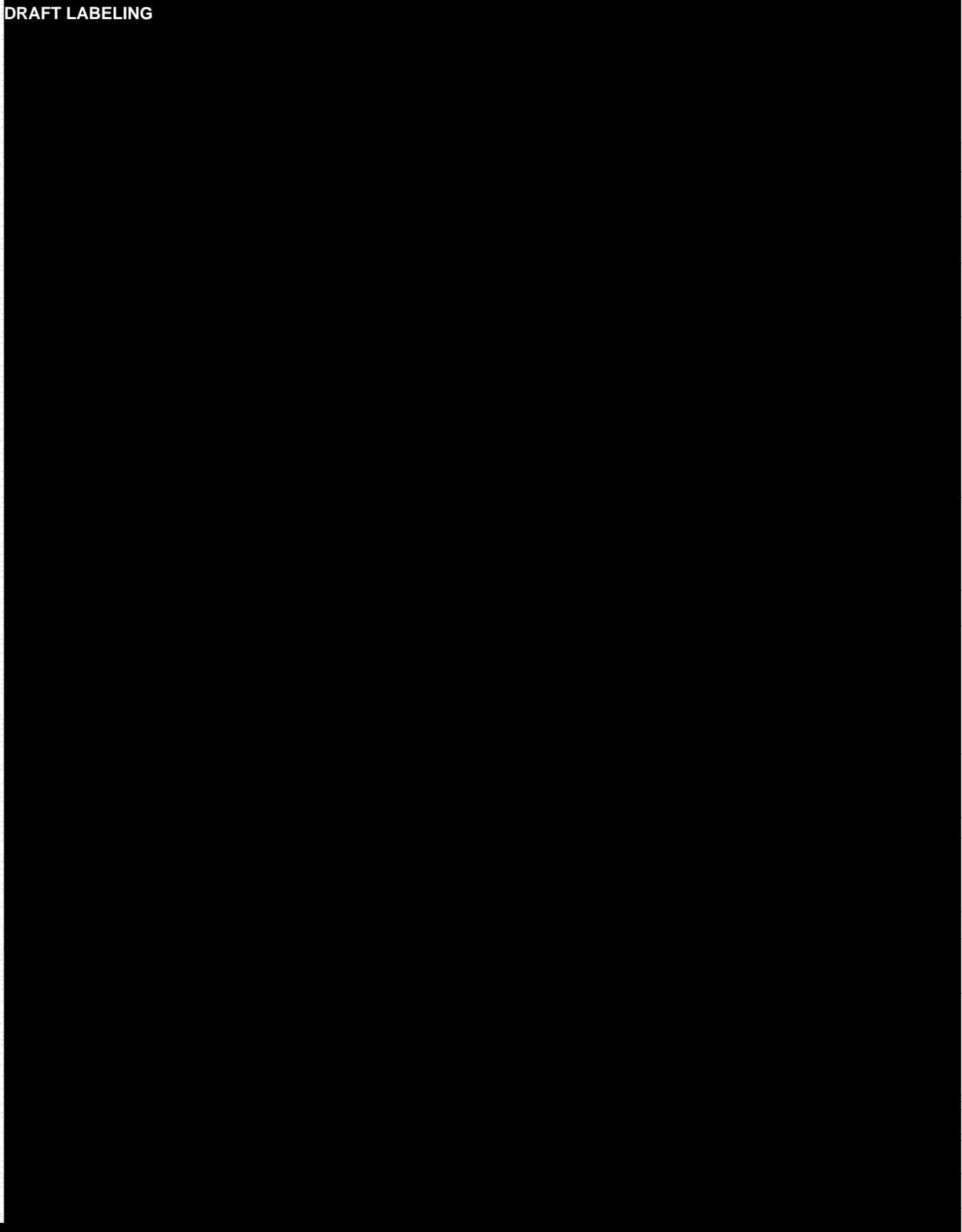


DRAFT LABELING



DRAFT LABELING

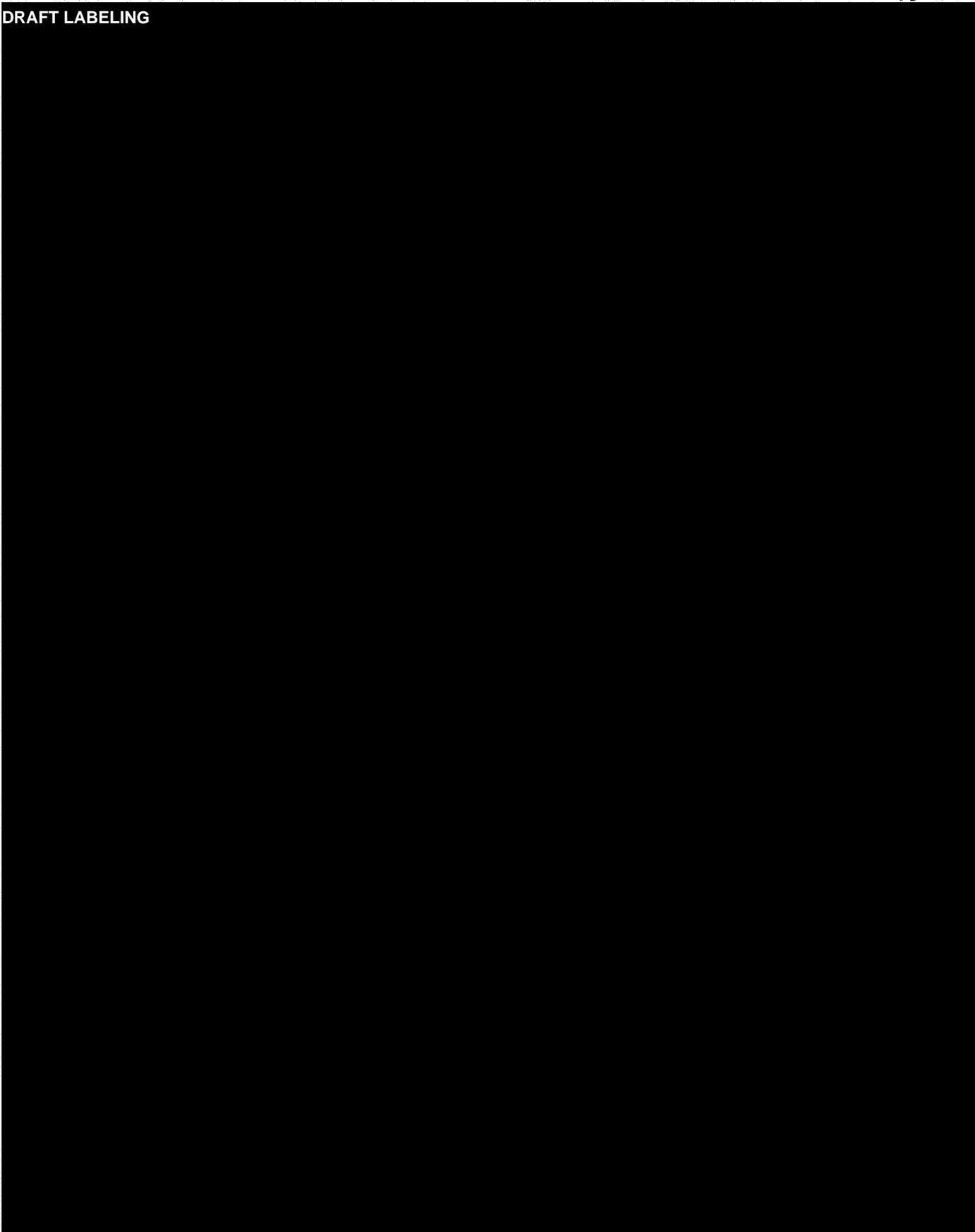


DRAFT LABELING

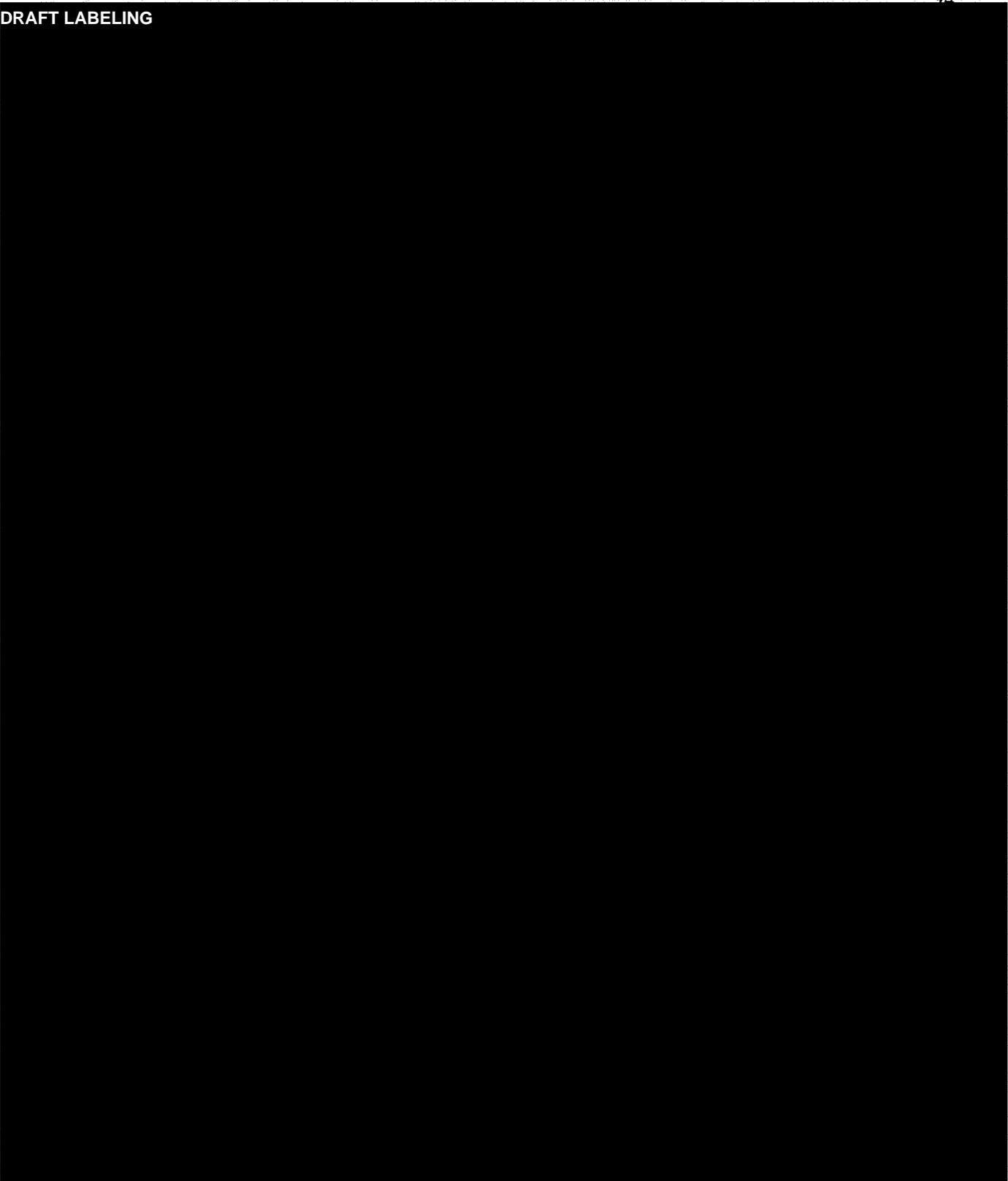
02

DRAFT LABELING

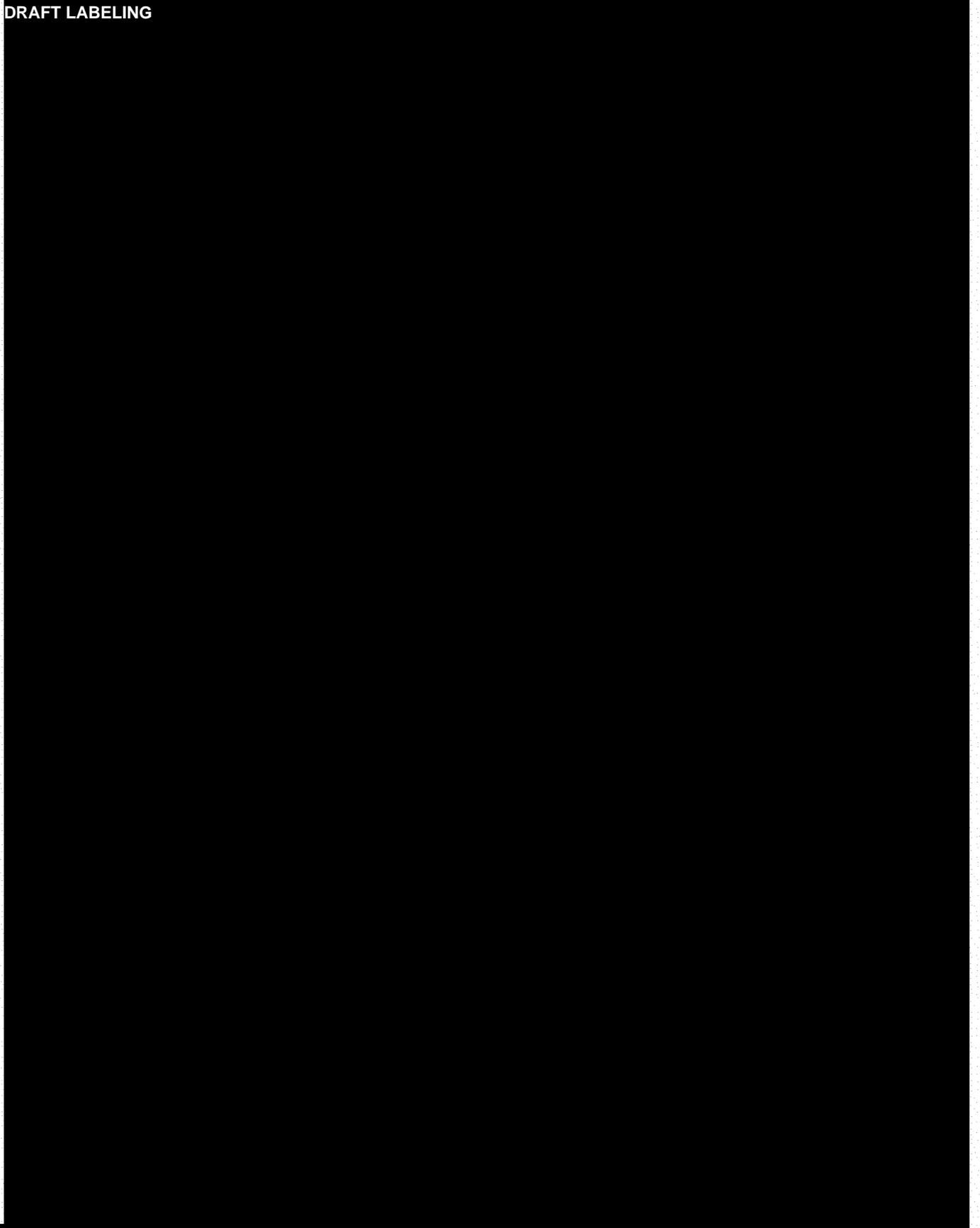
DRAFT LABELING

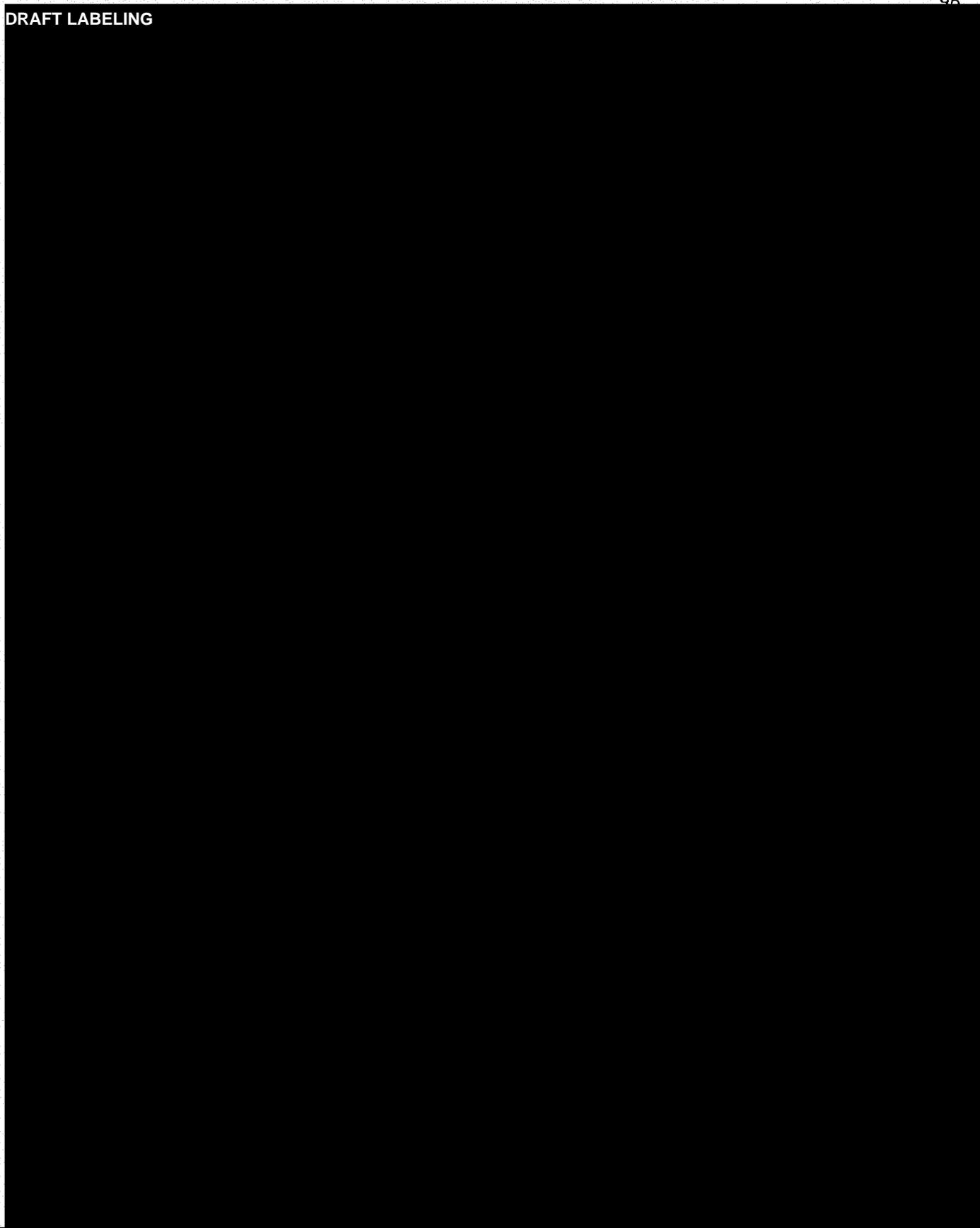


DRAFT LABELING



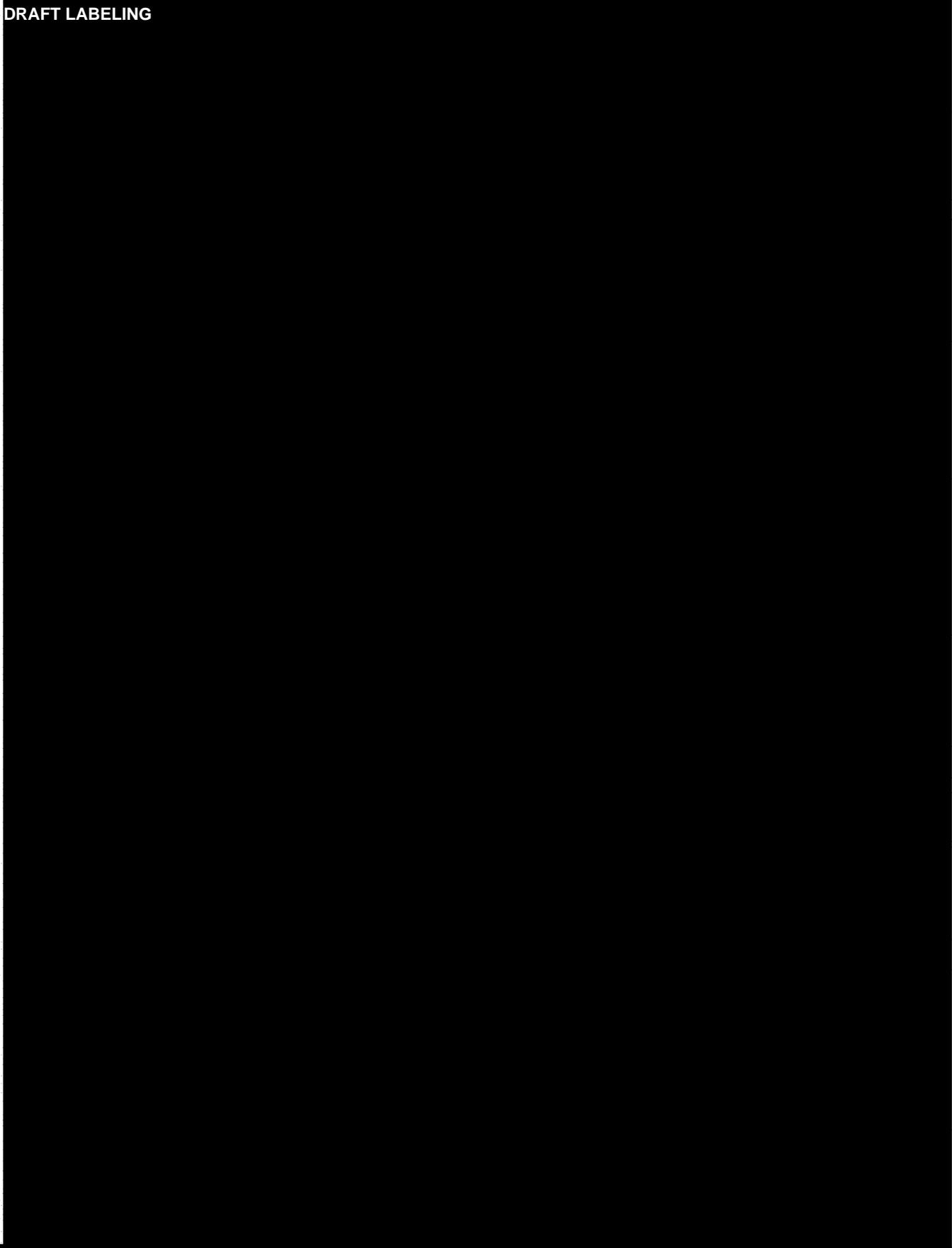
DRAFT LABELING





DRAFT LABELING

DRAFT LABELING



DRAFT LABELING



APPEARS THIS WAY ON ORIGINAL



12 DISCUSSION/CONCLUSIONS

The mean percent reduction in body weight following one year of treatment with 120mg tid of orlistat ranged from approximately 8.0 - 10.0%, with placebo-subtracted values of 3.0 - 4.0%. This difference between drug and placebo falls short of the 5% difference recommended in the Division's Obesity Guidance Document. However, the efficacy of orlistat was evident in the categorical analyses. Pooled data from five phase III studies indicate that nearly 60% of orlistat-treated patients and 31% of placebo-treated patients lost at least 5% of baseline body weight following one year of treatment ($p < 0.01$). Moreover, 27% of drug-treated subjects lost at least 10% of baseline body weight after one year of treatment compared with only 11% of patients randomized to placebo ($p < 0.01$).

On balance, treatment with orlistat was associated with small, relative improvements in the levels of total and LDL cholesterol and systolic and diastolic blood pressure. In addition, there were modest improvements in the concentrations of fasting and post-load glucose and insulin following one year of drug treatment. When considered in isolation, the magnitude of these improvements was of questionable clinical significance; yet, taken together, the data argue in favor of a clinically meaningful improvement in the overall risk factor profile. Moreover, the data are compatible with the notion that the comorbidities continue to improve as orlistat-associated weight loss increases.

Since negligible amounts of orlistat and its metabolites reach the systemic circulation, the central safety issues relate to the drug's effect in the GI tract. Based on the pharmacodynamic action of orlistat, one might expect the drug to inhibit the absorption of fat-soluble vitamins and β -carotene. And indeed, the totality of the phase III data indicate that the use of orlistat is associated with a lowering of plasma levels of vitamins E, D, and β -carotene. While it's true that the magnitude of the reduction in the plasma levels of these nutrients was small, the magnitude of the vitamin depleting effect of long-term orlistat use was undoubtedly underestimated because significantly more drug vs placebo-treated patients required (per protocol) vitamin supplementation for low plasma levels. Moreover, up to 22% of drug-treated patients had a plasma vitamin levels below the 'normal limit' on two or more consecutive occasions — reductions consistent with a deficiency state.

There is evidence that fat malabsorption is associated with vitamin K deficiency¹. It is interesting, therefore, that the Sponsor states that orlistat does not reduce the absorption of vitamin K. The Sponsor's use of prothrombin time — an insensitive indicator of vitamin K status — to assess the effect of orlistat on vitamin K precludes one from making definitive statements about the effect of this drug on vitamin K homeostasis^{2,3}. Serum levels of undercarboxylated osteocalcin, plasma levels of phylloquinone, and urinary levels of γ -carboxyglutamic acid are sensitive measures of vitamin K status^{4,2} and the Sponsor should be encouraged to use one of these surrogates to further investigate the interaction between orlistat and vitamin K.

Regarding vitamin A, the mean levels of plasma retinol did not significantly differ between orlistat and placebo patients following one or two years of treatment. Still, plasma levels of this vitamin are tightly regulated and one cannot discount the possibility that a marginal deficiency of vitamin A — one reflected by reduced hepatic but not plasma levels — may develop after extended use of orlistat⁵.

Thus, taken together, the data in this NDA suggest that orlistat reduces the absorption of vitamins D, E and β -carotene and leave open the question of its effect on vitamins A and K. Undoubtedly, the benefit-to-risk profile of orlistat would be maximized if the vitamin depleting effect of the drug were minimized. To this end, thought should be given to universal vitamin supplementation. Although the qualitative and quantitative composition of the most appropriate supplement is open to debate, this alternative may prove salutary and should be discussed with the Sponsor.

Because orlistat has a "steatorrhea-like" effect, there is some concern for drug-induced deficiencies of calcium and magnesium, and possibly other minerals⁶. The Sponsor attempted to address this concern with a mineral balance study. Unfortunately, methodological problems prevented the successful completion of that study. The Sponsor has committed to conducting another balance study and therefore, conclusive comments regarding the effect of orlistat on mineral balance must await the completion of this study.

To summarize, from the perspective of efficacy, the long-term use of 120mg tid of orlistat is more effective than placebo (diet counseling) in producing a 5% reduction in body weight. Furthermore, orlistat-associated weight loss is accompanied by an improvement — albeit modest — in comorbidities. From the perspective of safety, a central issue is orlistat's inhibition of the absorption of fat-soluble nutrients including some vitamins and β -carotene. The provision of a vitamin supplement may well mitigate the drug's nutrient-depleting action and this could easily be tested post-approval.

APPEARS THIS WAY ON ORIGINAL

13 RECOMMENDATIONS

This Reviewer believes that the data in this NDA support the approval of orlistat for the treatment of obesity. A post-marketing study evaluating the efficacy and safety of vitamin supplementation might be useful and this option should be discussed with the Sponsor. In addition, Dr. Hugo Gallo Torres, a consultant from the Division of Gastrointestinal and Coagulation Drug Products, recommends conducting a post-marketing study in a high-risk population (i.e., hx of adenomatous polyps) to address the question of colonic cell proliferation.

/S/

Eric G. Colman, M.D.

4/30/97

cc: NDA Arch
HFD-510

/S/

5-1-97

APPEARS THIS WAY ON ORIGINAL

REFERENCES

1. Krasinski SD, Russel RM, Furie BC, et al. The prevalence of vitamin K deficiency in chronic gastrointestinal disorders. *Am J Clin Nutr* 41: 639, 1985
2. Ferland G, Sadowski JA, O'Brien ME. Dietary induced subclinical vitamin K deficiency in normal human subjects. *J Clin Invest* 91: 1761, 1993
3. Suttie JW, Schendel LL, Shah DV, et al. Vitamin K deficiency from dietary vitamin K restriction in humans. *Am J Clin Nutr* 47: 475, 1988
4. Sokoll LJ, Booth SL, O'Brien ME, et al. Changes in serum osteocalcin, plasma phylloquinone, and urinary γ -carboxyglutamic acid in response to altered intakes of dietary phylloquinone in human subjects. *Am J Clin Nutr* 65: 779, 1997
5. Modern nutrition in health and disease. Shils ME, Olson JA, Shike M, eds. Eight edition, 1995.
6. Cerda JJ and Artnak EJ. Nutritional aspects of malabsorption syndromes. *Comp Ther* 9:35, 1983
7. Jeppesen PB, Christensen MS, Hoy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. *Am J Clin Nutr* 65: 837, 1997
8. Siguel EN, Lerman RH. Prevalence of essential fatty acid deficiency in patients with chronic gastrointestinal disorders. *Metabolism* 45: 12, 1996
9. Kathpalia SC, Favus MJ, Coe FL. Evidence for size and change permselectivity of rat ascending colon: Effects of ricinoleate and bile salts on oxalic acid and neutral sugar transport. *J Clin Invest* 74: 805, 1984
10. Primer on metabolic bone disease and disorders of mineral metabolism. Murray J. Favus, editor. First edition, 1990.

APPEARS THIS WAY ON ORIGINAL

HESS

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S CONSULT REVIEW

NDA: 20-766 MAR - 6 1997

Sponsor: Hoffmann-LaRoche, Inc.

Drug: XENICAL™ (orlistat; Ro 18-0647)
(derivative of lipstatin)
(tetrahydrolipstatin)

Pharmacological Category: Lipase inhibitor (Anti-obesity)
(Anti-hypercholesterolemic)

Formulation: Capsules

Indication: Treatment of obesity

Material Reviewed: Research Report W-144999 (Protocol NP15138)
"Effect of oral administration of orlistat
(XENICAL™) on fecal fat, fecal biliary acids and
colonic mucosa cell turnover in obese subjects."

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.



EXECUTIVE SUMMARY

Orlistat is an inhibitor of gastrointestinal lipases that reduces the absorption of dietary triglycerides and cholesterol. Orlistat is poorly absorbed (97% of orally administered ¹⁴C-labeled orlistat was recovered in the feces; 83% of the recovered radioactivity represented unmetabolized compound). Since the compound is not made available to the body, its potential for systemic toxicity due to the drug per se is probably insignificant. But the long-term effects of orlistat (alone or covalently bound to serine or a small peptide taken from the active site of the enzyme) on gastrointestinal-colonic function and/or morphology are unknown. The sponsor carried out a placebo-controlled pharmacodynamic study in obese subjects given a hypocaloric diet and orlistat at the recommended dose (120 mg with each main meal) and regimen (t.i.d.) for six weeks. Fecal matter was analyzed for total weight, total fat, FFAs, total and individual BA content and Ca⁺⁺ and phosphorus. Fecal water was analyzed for FFAs, total and individual BA concentration and pH. Rectal biopsies before and after treatment were processed for crypt compartment analysis of three biomarkers [Bromodeoxyuridine (BrdU) labeling index; proliferating cell nuclear antigen (PCNA) labeling under and whole crypt mitotic count (WCMC) value]. The consultant concluded that both the biopsy site (rectum) and the assessment of cell proliferation by quantification of proliferation with the labeling index (a numerical parameter) and crypt compartmentalization were all appropriate.

Analysis of the data from both the solid and liquid phase of the stool did not reveal findings of concern following orlistat treatment. Under the experimental conditions used in this PD evaluation, orlistat did not induce colonic epithelial cell proliferation. These data, together with a decrease in UDCA in both the solid and the liquid phase of the stool, are reassuring.

Nonetheless, obesity is a lifetime disease. Treatment with orlistat is expected to last several years and in reality, the long-term effects of the drug on colonic function/morphology are unknown. Marketing surveillance is recommended in general and specially in those patients for whom the drug may be most dangerous when administered long-term. These include those with risk factors (i.e. low fiber diet), those with predisposing conditions (i.e. ulcerative colitis > 10 years) and those with premalignant lesions, such as dysplasia, adenomatous polyps, villous adenomas, familial polyposis, previous colon cancer and schistosomiasis. Also recommended are further explorations of the PD effect of orlistat on DCA, including pre-clinical (and eventually clinical) studies set to evaluate the role of orlistat as a chemopreventive agent in colorectal cancer in man.

APPEARS THIS WAY ON ORIGINAL