BASIS FOR THE RECOMMENDATION TO (b)(5) (b)(5) CONTROLLED SUBSTANCES ACT

I. Introduction

Background

On October 6, 2022, President Joseph R. Biden released a statement asking the Secretary of the Department of Health and Human Services (HHS) and the Attorney General "to initiate the administrative process to review expeditiously how marijuana is scheduled under federal law."[1] This Presidential request led HHS to initiate a scientific and medical evaluation for botanical cannabis (*Cannabis sativa* L.) that is within the definition "marihuana" or "marijuana" in the federal Controlled Substances Act (CSA),[2] currently controlled under Schedule I of the CSA. As with prior evaluations conducted to reconsider the control status of marijuana under the CSA, the Food and Drug Administration (FDA) is conducting this evaluation and providing input and a scheduling recommendation to the Drug Enforcement Administration (DEA) in the form of an Eight Factor Analysis (8FA), pursuant to paragraphs (a) through (c) of section 201 and paragraph (b) of section 202 of the CSA (21 U.S.C. 811 (a-c) and 21 U.S.C. 812(b)).[3]

Since 2000, HHS (through the FDA and the National Institute on Drug Abuse (NIDA)) has conducted four scientific and medical evaluations of marijuana for drug scheduling purposes, in the form of 8FAs. (The process for developing an 8FA is elaborated below under *Considerations for Scheduling of Marijuana.*) The two most recent HHS 8FAs for marijuana were conducted in 2015 at the request of the DEA to enable them to respond to two petitions requesting removal of marijuana from Schedule I and placement in another schedule of the CSA. After reviewing the 8FAs conducted by HHS, DEA denied both petitions and maintained marijuana in Schedule I of the CSA.[4]

At the conclusion of an 8FA, three findings need to be made to determine the scheduling recommendation for a substance: its relative abuse potential compared to other drugs, whether it has a currently accepted medical use (CAMU) in treatment in the United States (or a currently

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[1] Statement from President Biden on Marijuana Reform; https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/.

[2] Under 21 U.S.C. 802(16): "(16)(A) Subject to subparagraph (B), the terms "marihuana" and "marijuana" mean all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.
(B) The terms "marihuana" and "marijuana" do not include—
(i) hemp, as defined in section 1639o of title 7; or
(ii) the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom)

[3] We acknowledge that the DEA, acting on behalf of the Attorney General, may ultimately implement any changes in the federal control status of marijuana pursuant to section 201(d)(1) of the CSA (21 U.S.C. 811(d)(1)), due to the control of cannabis and cannabis preparations internationally in Schedule I of the Single Convention on Narcotic Drugs of 1961 (hereafter, the Single Convention), and the requirement for the United States to be compliant with control measures stipulated for drugs controlled under the Single Convention.

[4] Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 81 FR 53688 (Aug. 12, 2016); Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 81 FR 53767 (Aug. 12, 2016).

accepted medical use with severe restrictions (21 U.S.C. 812(b)(2)(B)), and its relative safety or ability to produce physical dependence compared to other drugs, as provided under 21 U.S.C. 812(b). (b)(5)

(b)(5)

An important difference in the present scientific and medical evaluation relative to the HHS 8FAs for marijuana from 2015 is that Congress amended the definition of "marijuana" in the CSA in 2018. This action narrowed the scope of what is considered marijuana under the CSA by removing "hemp" and chemical derivatives of "hemp", as discussed below. When the CSA was enacted in 1970, the term "marijuana" covered all varieties of *Cannabis sativa* L., including chemovars and preparations with high concentrations of cannabinoid compounds with intoxicating effects, such as delta-9-tetrahydrocannabinol (Δ9-THC), as well as chemovars and preparations with lower concentrations of Δ9-THC and other cannabinoid compounds, which could include "industrial hemp." Specifically, the 1970 definition of "marihuana" under section 102(16) of the CSA (21 U.S.C. 802(16)) stated that:

> The term 'marihuana' means all parts of the plant *Cannabis sativa L.*, whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

In December 2018, the Agriculture Improvement Act (also known as the 2018 Farm Bill), was signed into law, which defined "hemp" as "a plant species *Cannabis sativa L.* and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a total Δ9-THC concentration of not more than 0.3 percent on a dry weight basis" (revising Section 297A of the Agricultural Marketing Act of 1946 (specifically, 7 U.S.C. 1639o). The 2018 Farm Bill explicitly removed "hemp" categorically from the definition of marijuana in the CSA, which removed it from control under any drug schedule of the CSA. Based on the provisions of the 2018 Farm Bill, the current definition of marijuana under 21 U.S.C. 802(16) is as follows:

> (16)(A) Subject to subparagraph (B), the terms "marihuana" and "marijuana" mean all parts of the plant *Cannabis sativa L.*, whether growing or not; the seeds thereof; the resin

extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

(B) The terms "marihuana" and "marijuana" do not include—

(i) hemp, as defined in section 1639o of title 7; or
(ii) the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

In implementing the hemp provisions from the 2018 Farm Bill, DEA clarified that the definition of "Tetrahydrocannabinols" under 21 CFR 1308.11(d)(31) does not include "any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o."[5]

The 2018 Farm Bill additionally had the effect of decontrolling many products containing predominantly cannabidiol (CBD) derived from hemp and containing no more than 0.3 percent Δ9-THC on a dry weight basis. This included the FDA-approved product Epidiolex, which contains plant-derived, highly purified CBD as its active ingredient and was approved by FDA in June 2018, just prior to the enactment of the Farm Bill. Prior to FDA approval of Epidiolex, CBD was a Schedule I substance, based on its derivation from marijuana. To address the Epidiolex approval, DEA placed "approved cannabidiol drugs" into Schedule V of the CSA in September 2018, under 21 CFR 1308.15(f),[6] and asserted that the placement was necessary to carry out United States obligations under the Single Convention. Notably, though, FDA's review of the NDA for Epidiolex, as well as the subsequent HHS 8FA, found that, "Based on the totality of the available scientific data, CBD does not have meaningful abuse potential. In support of this finding, the evidence for any abuse potential is also substantially less than that of all substances currently in Schedule V." Thus, the decontrol of FDA-approved drugs that contain CBD derived from cannabis with no more than 0.1 percent Δ9-THC on a dry weight basis is scientifically supported by preclinical and clinical study data. Products containing predominantly plant-derived CBD or marketed with the intent of offering consumers a plant-derived, CBD-containing product, will not be addressed in this scientific and medical evaluation of marijuana. It should be noted some hemp-derived CBD products may contain Δ9-THC or other cannabinoids in amounts sufficient to produce drug effects more associated with marijuana, and may or may not be legally within the definition of marijuana. (b)(5)

(b)(5)

It is important to note that, to date, FDA has not approved an NDA for a drug product containing botanical marijuana. However, two drug products containing Δ9-THC (as dronabinol, which is specifically the *(-)-trans*-Δ9-THC stereoisomer), the primary compound in marijuana that is

[5] 85 FR 51639, 51639-51645, August 21, 2020

[6] Under 21 CFR 1308.15(f): "Approved cannabidiol drugs. (1) A drug product in finished dosage formulation that has been approved by the United States Food and Drug Administration that contains cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols."

responsible for its abuse potential, have received FDA approval: Marinol and Syndros. Dronabinol is a Schedule I substance under the CSA unless it is contained in an FDA-approved drug product, as described below.

Marinol (dronabinol) capsules, 2.5, 5, and 10 mg, received FDA approval in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments. In 1992, FDA approved an additional indication for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Following the 1985 Marinol approval, DEA conducted a product-specific rescheduling in 1986 for "synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules," moving it from Schedule I into Schedule II. In 1999, DEA rescheduled "synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules" again, from Schedule II into Schedule III, based on low numbers of reports of abuse of Marinol relative to marijuana.

Syndros (dronabinol) oral solution 5 mg/ml received FDA approval in 2016 for the same indications as those approved for Marinol: nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS. Following FDA approval, DEA conducted a product-specific rescheduling in 2017 for "FDA-approved products containing dronabinol in an oral solution" from Schedule I into Schedule II.

Considerations for Scheduling of Marijuana

In considering the scheduling of marijuana in response to President Biden's request, the Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA, pursuant to 21 U.S.C. 811(b). The eight factors are the following:

1. Its actual or relative potential for abuse;
2. Scientific evidence of its pharmacological effect, if known;
3. The state of current scientific knowledge regarding the drug or other substance;
4. Its history and current pattern of abuse;
5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. Its psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled.

Following consideration of the eight factors, three findings need to be made to determine the schedule for a drug or substance under the CSA. The three required findings relate to a substance's abuse potential, CAMU in the United States, and safety or dependence potential (21 U.S.C. 812(b)).

In this document, the term "marijuana" will be used to refer to *Cannabis sativa L.,* to be responsive to language of the CSA definition of "marihuana" or "marijuana" and its listing as the Schedule I drug class that is subject of this evaluation. The present evaluation of marijuana discusses the scientific and medical information relative to each of the eight factors, presents

findings in the three required areas (abuse potential, CAMU, and safety or dependence liability) and makes a recommendation regarding the scheduling of marijuana.

It is important to note that this evaluation is necessarily limited in scope and depth to those preclinical, clinical, and epidemiological data that are directly related to determining the abuse potential, physical dependence, and CAMU of marijuana in response to the eight factors described in the CSA. As such, this assessment is comprehensive, but is not exhaustive or encyclopedic. Extensive reviews of marijuana and cannabinoids are publicly available in papers published in the scientific and medical literature, as well as from federal entities such as NIDA and the Congressional Research Service, from professional medical associations, and from the National Academies of Science, Engineering and Medicine (NASEM). The current review is largely focused on modern scientific considerations on whether marijuana has a CAMU and on new epidemiological data related to abuse of marijuana in the years since the 2015 HHS 8FAs on marijuana.

In the epidemiological analyses below regarding prevalence of marijuana abuse and associated harms, evaluations included comparators such as (b)(5) (b)(5) (b)(5) Each individual epidemiological database evaluated a specific group of drugs and not every comparator was evaluated under each database.

(b)(5)

After assessing all available preclinical, clinical, and epidemiological data, FDA recommends that marijuana (b)(5) (b)(5)

II. Evaluating Marijuana Under the Eight Factors

Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below.

FACTOR 1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

Under the first factor, the Secretary must consider actual or relative potential for abuse of marijuana. The CSA does not define the term "abuse." However, the CSA's legislative history suggests using the following criteria in determining whether a particular drug or substance has a potential for abuse[7]:

a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

b. There is a significant diversion of the drug or drugs containing such a substance from legitimate drug channels.

c. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

d. The drug or drugs containing such a substance so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

In the development of this scientific and medical evaluation for the purpose of scheduling, the Secretary analyzed considerable data related to the abuse potential of marijuana. Determining the abuse potential of a substance is complex with many dimensions, and no single test or assessment provides a complete characterization. Thus, no single measure of abuse potential is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a substance can include consideration of the following elements: chemistry, receptor binding, behavioral effects indicating that the substance is rewarding or is similar to another substance controlled under the CSA, pharmacokinetics, behavioral effects indicating that the substance produces physical or psychic dependence, and epidemiological data related to abuse of the substance regarding its pattern and duration of use, as well as the risk it presents to the public health.

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[7] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.

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FDA has not approved an NDA for a drug product containing botanical marijuana for any therapeutic indication. Thus, at the federal level, the only way an individual can use marijuana on the basis of medical advice through legitimate channels under federal law is by participating in research under an IND. (b)(5)

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Marijuana has been a Schedule I substance under the CSA since it was enacted in 1970. The primary compound in marijuana that is responsible for its abuse potential is Δ9-THC (also known as dronabinol, when specifically referring to the *(-)-trans*-Δ9-THC stereoisomer), which has agonist activity at cannabinoid CB_1 receptors. (b)(5)

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(b)(5) Additionally, FDA has approved two drug products containing dronabinol: Marinol (in 1985; Schedule III) and Syndros (in 2016; Schedule II). When these products were being developed, they underwent a systematic evaluation of their abuse potential based on animal and human behavioral studies, which showed that dronabinol has abuse potential. The abuse-related studies for Marinol and Syndros confirmed the abuse potential of Δ9-THC, the primary compound responsible for the abuse of marijuana. (b)(5)

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FACTOR 2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN.

Under the second factor, the Secretary must consider the scientific evidence of the pharmacological effects of marijuana, based on the effects of Δ9-THC, the primary compound responsible for the abuse potential of marijuana. This section includes a scientific evaluation of the neurochemistry, receptor pharmacology, animal abuse-related behavioral effects, and human behavioral and physiological effects of marijuana. The overview presented below relies upon the current scientific information available in the public domain.

Neurochemistry and Receptor Pharmacology of Marijuana

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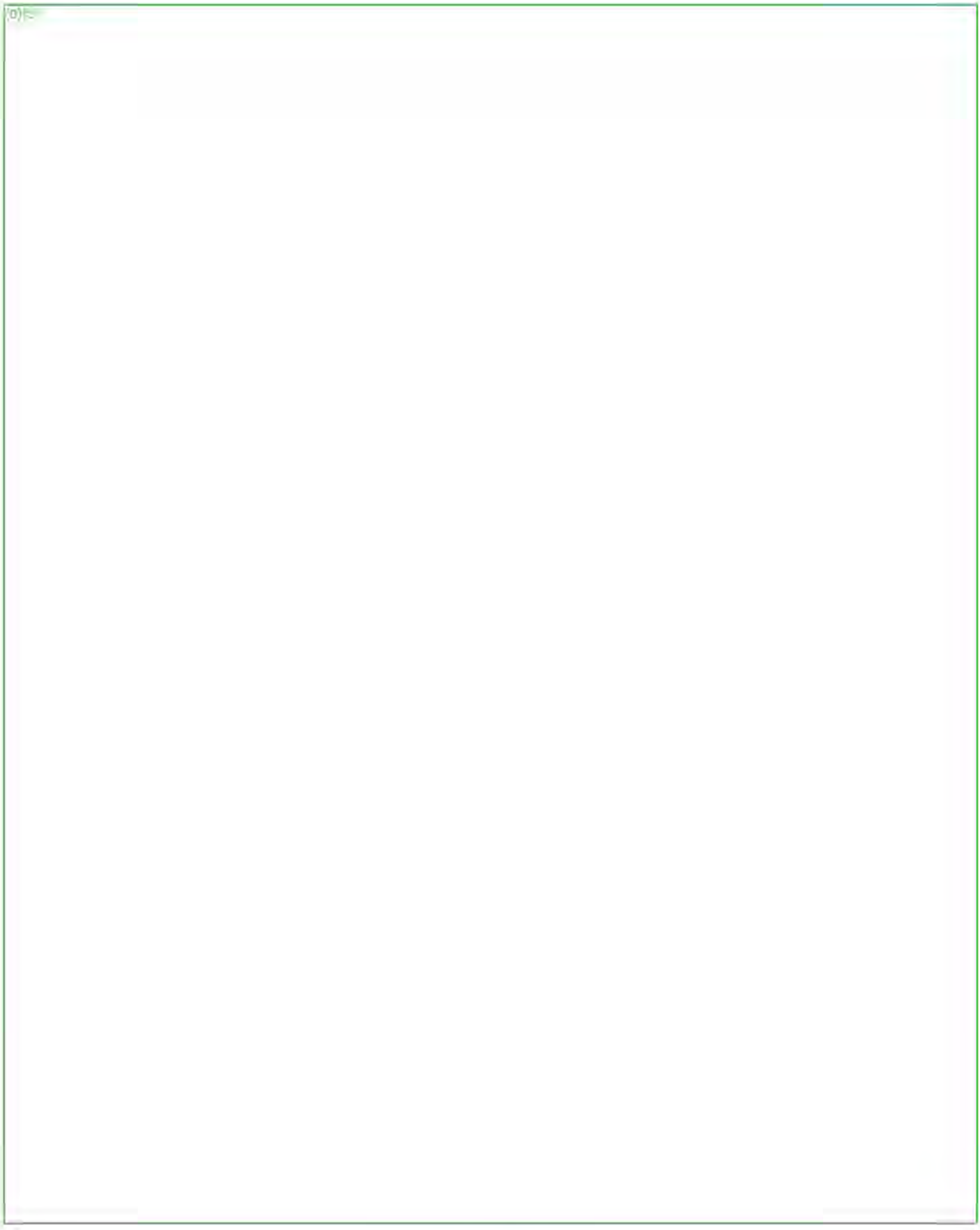

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Animal Abuse-Related Behavioral Effects

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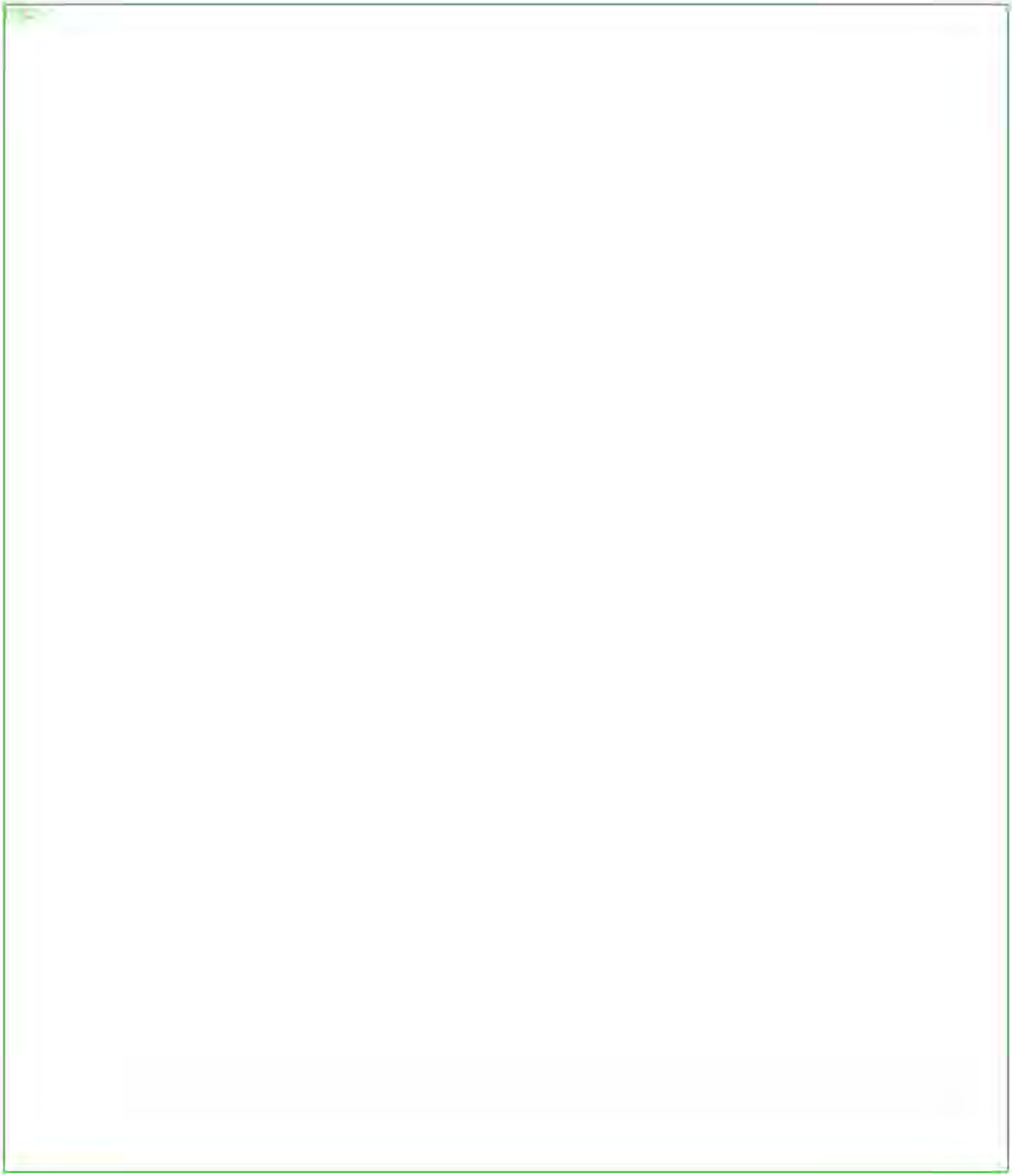
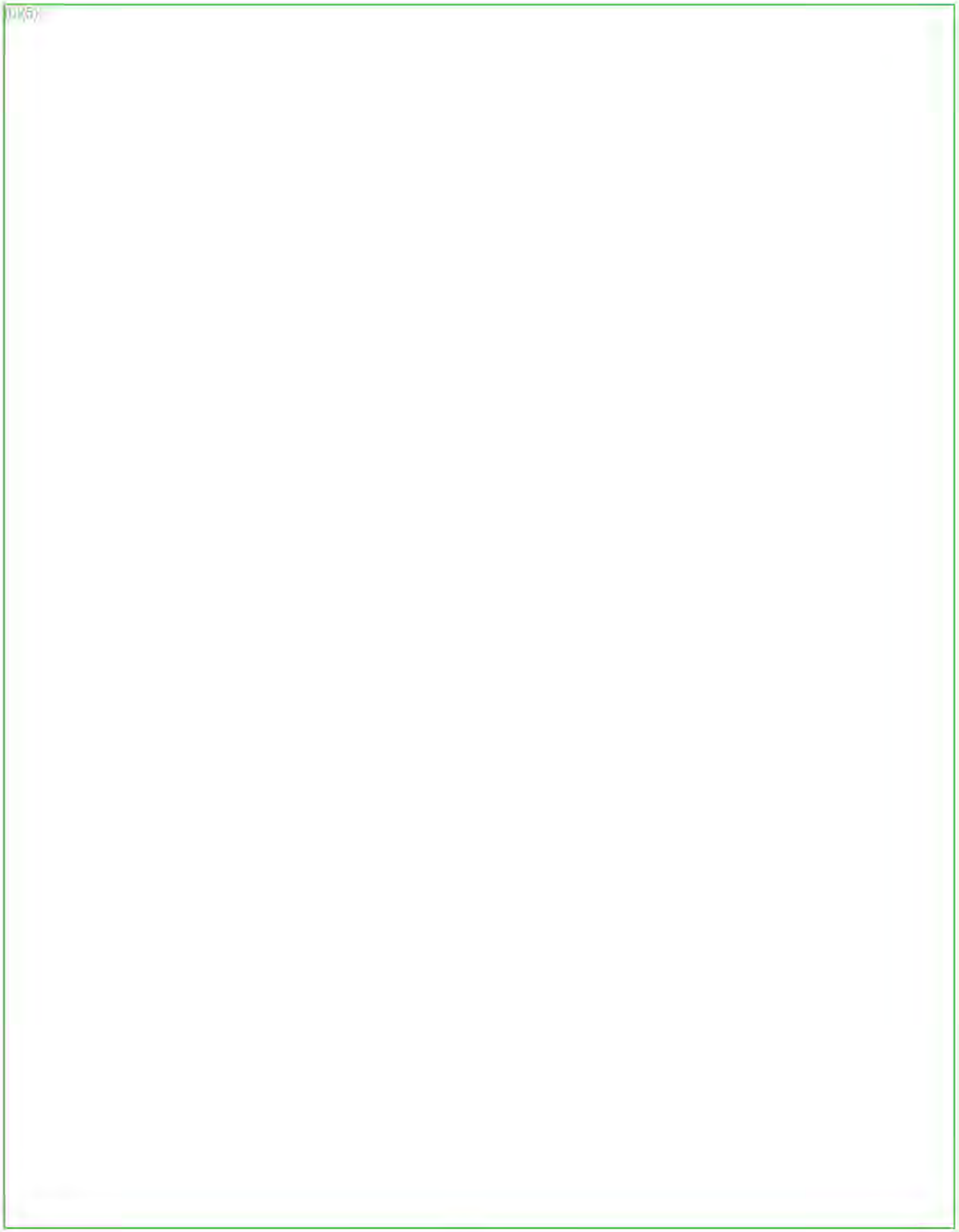


Human Behavioral and Physiological Effects



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FACTOR 3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE

Under the third factor, the Secretary must consider the state of current scientific knowledge regarding marijuana. (b)(5)

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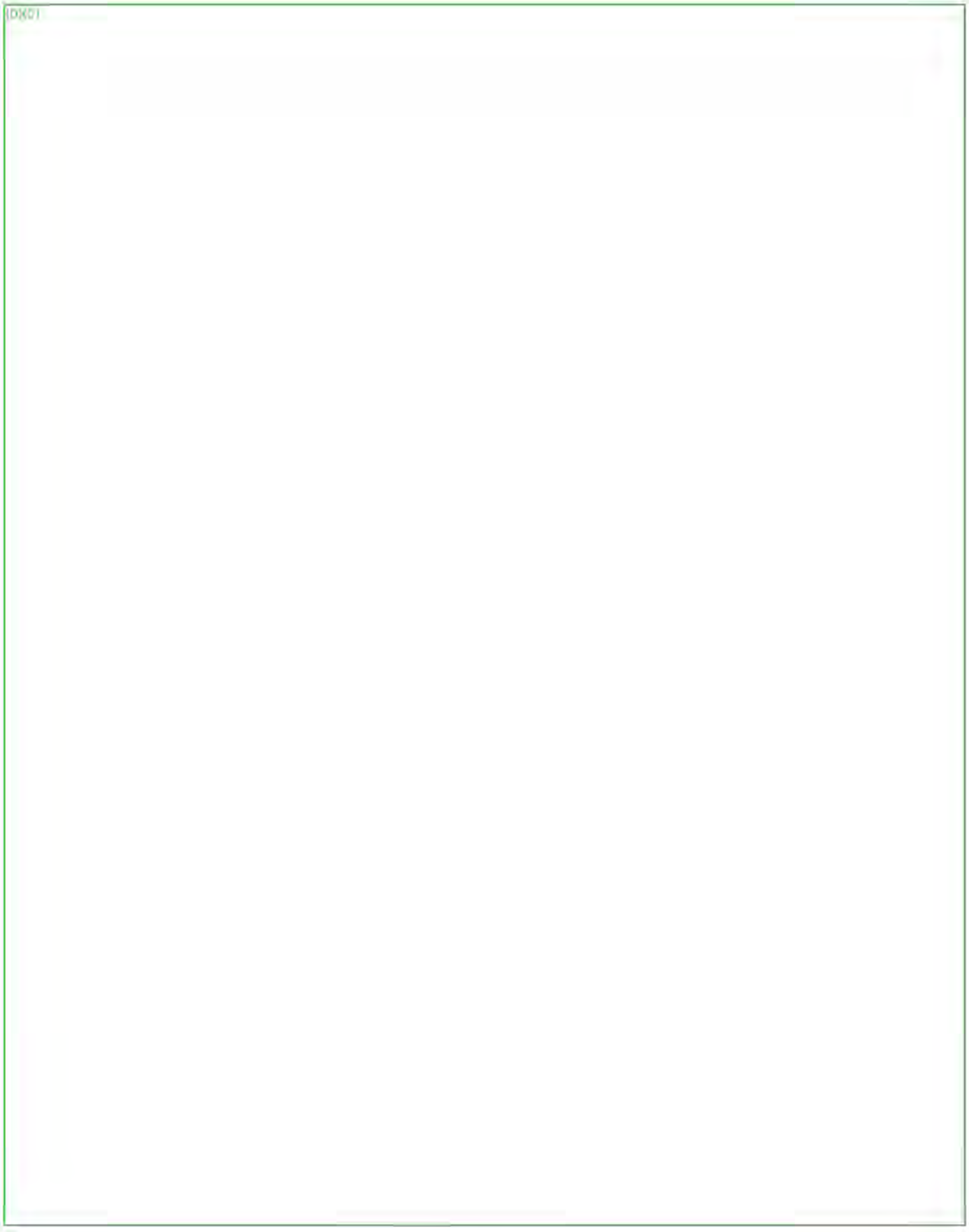

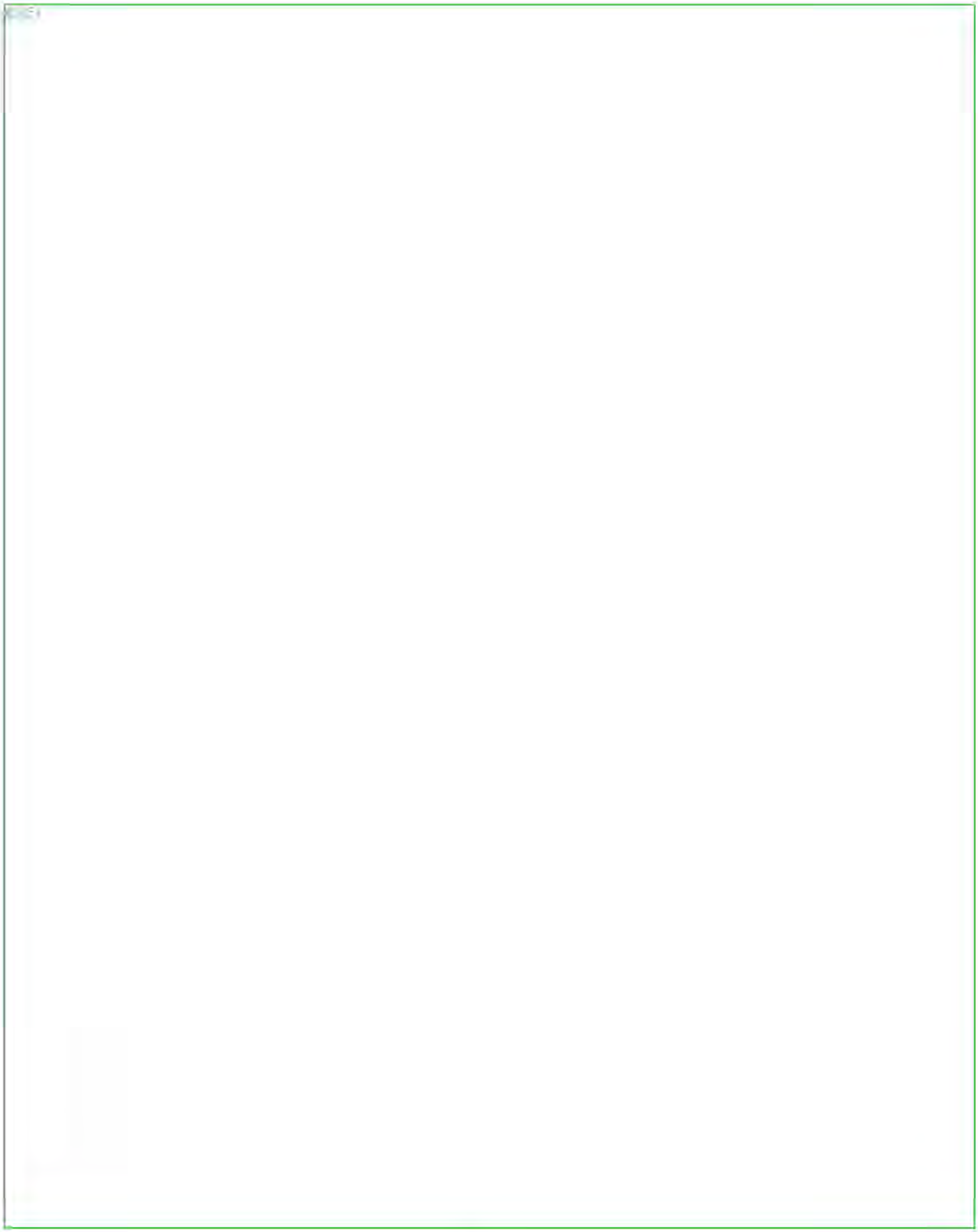

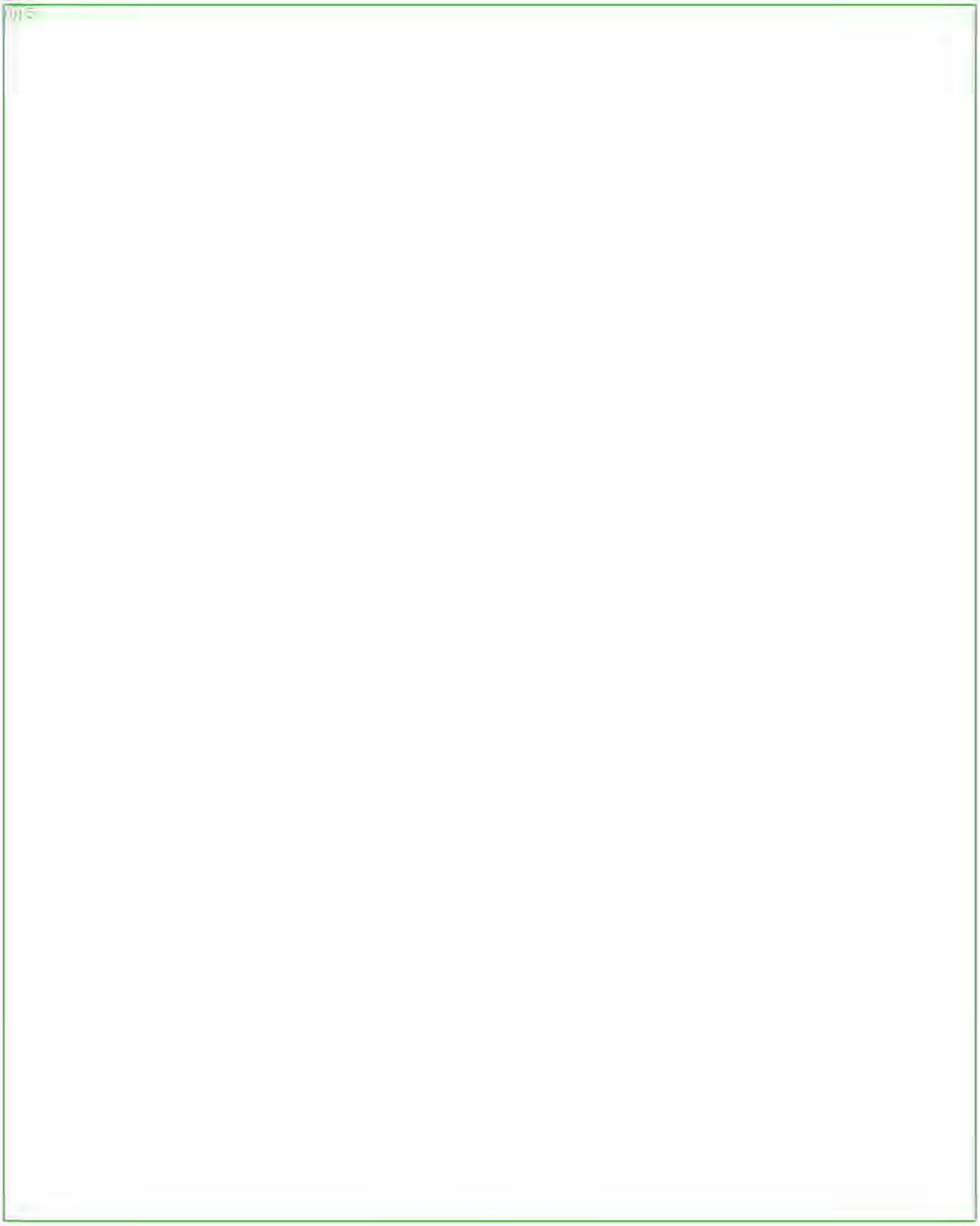

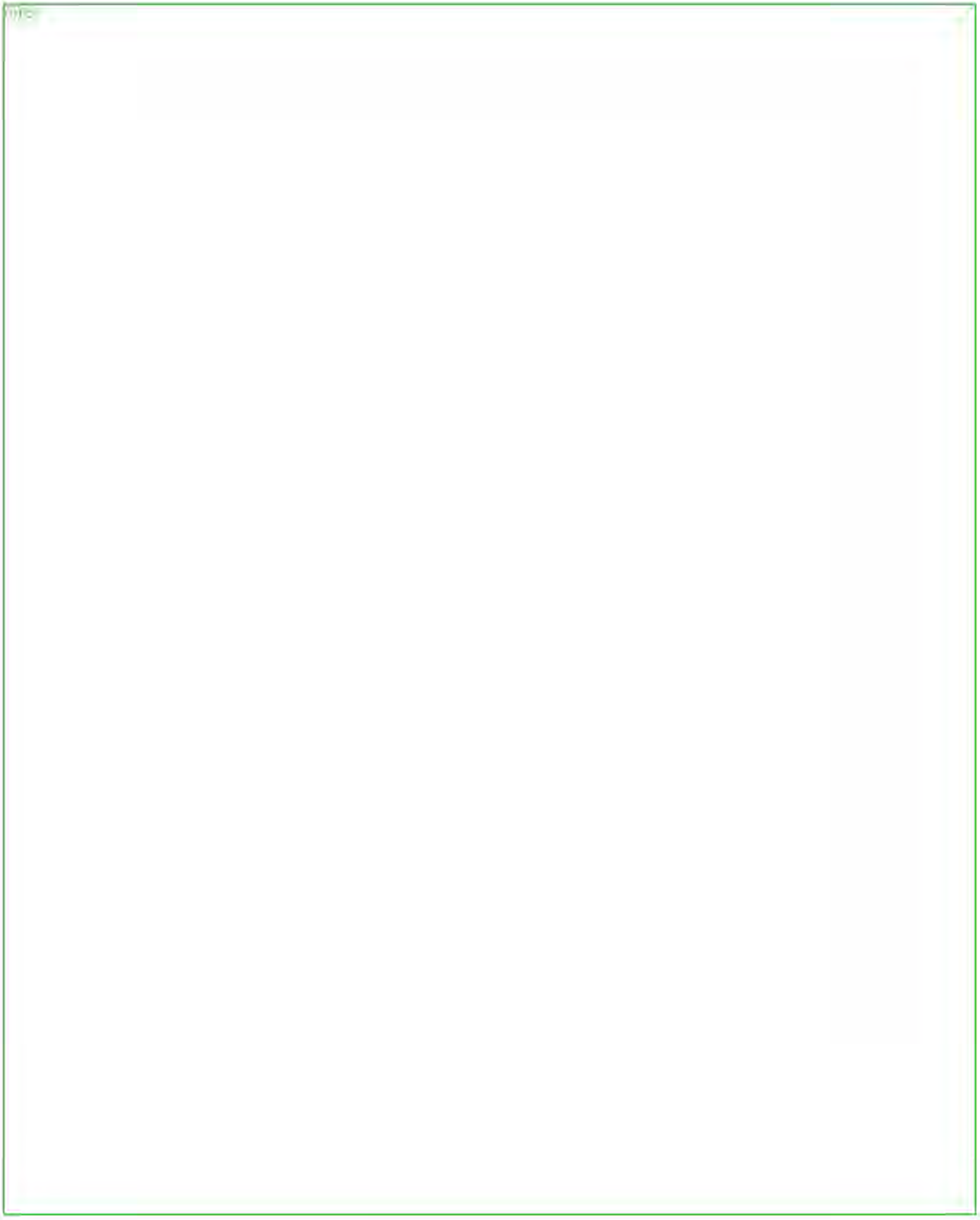

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Currently Accepted Medical Use of Marijuana

To inform its scheduling recommendation, HHS has conducted an evaluation of whether marijuana has a CAMU for purposes of scheduling under the CSA, 21 U.S.C. § 812(b). Such an evaluation is one of the findings relevant to the placement of a substance in one of five drug control "schedules" set forth in 21 U.S.C. § 812(b).

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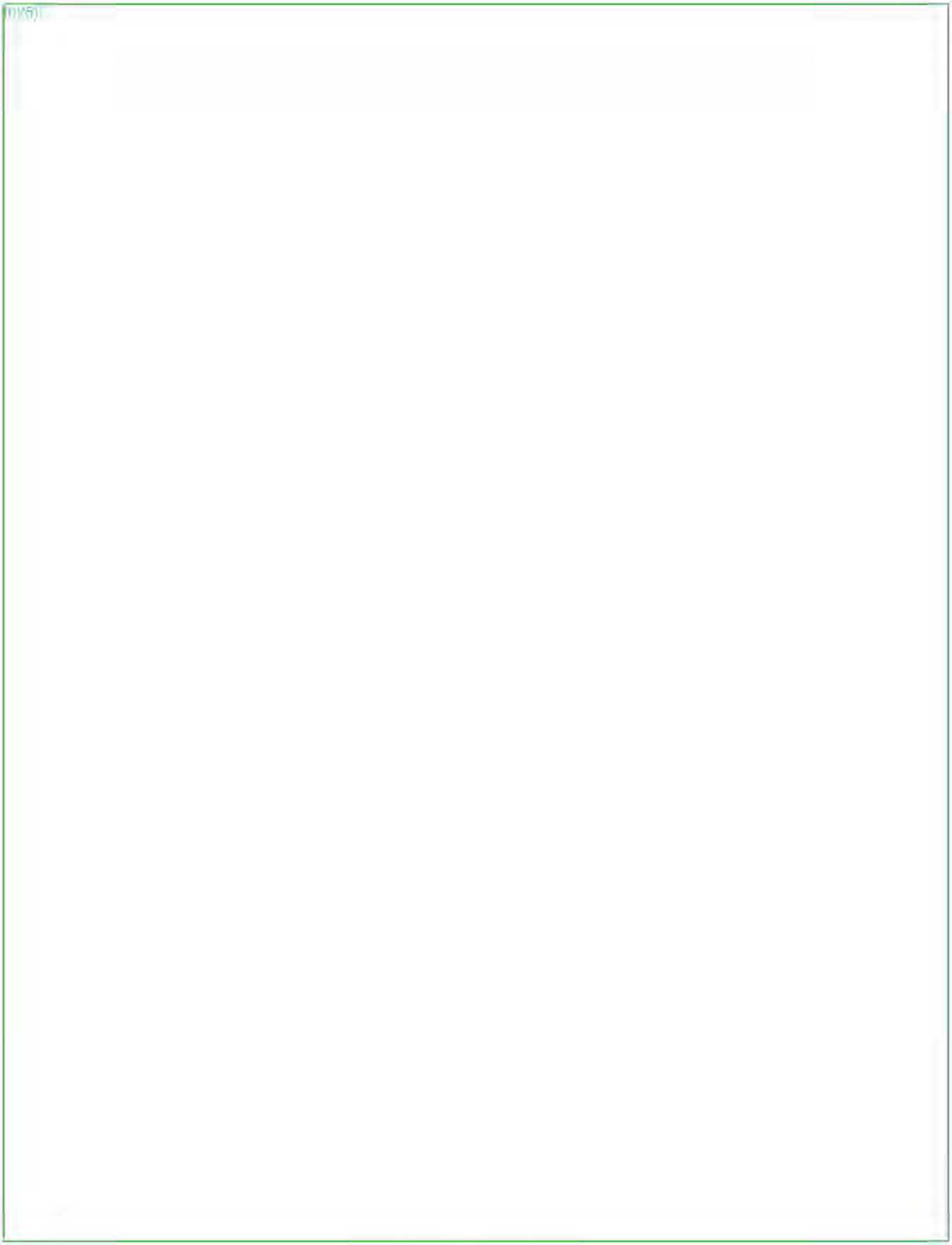

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Conclusions of CAMU

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FACTOR 4. ITS HISTORY AND CURRENT PATTERN OF ABUSE

Under the fourth factor, the Secretary must consider the history and patterns of marijuana use, including in relation to relevant comparator substances that are abused. (b)(5)

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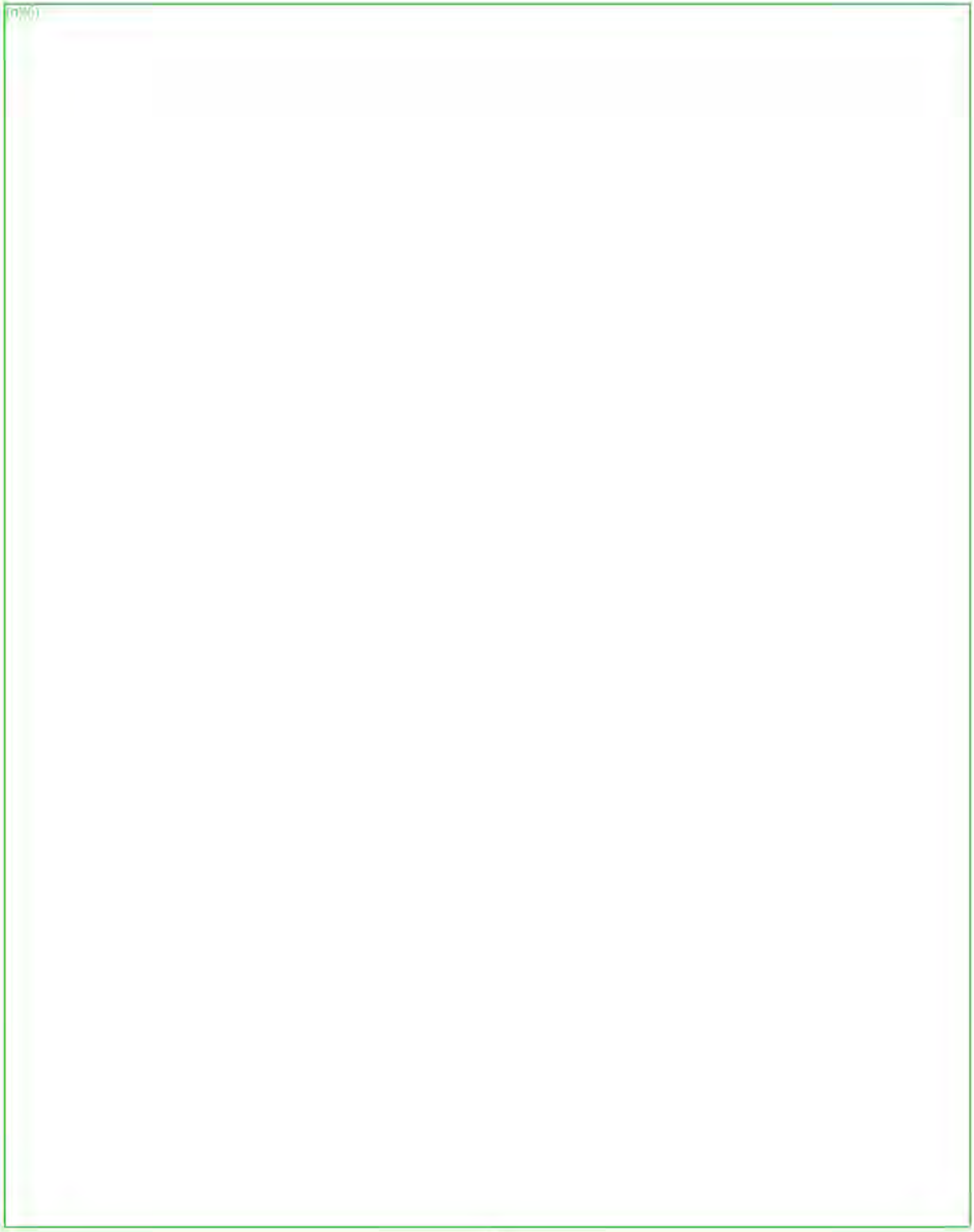


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Marijuana Use in the United States Since Passage of the CSA

Since 1970 when the CSA was passed, marijuana use has vacillated over time. As stated in the 2017 NASEM report *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*:

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Current Patterns of Use and Abuse of Marijuana

In analyzing current patterns of use and abuse of marijuana and marijuana-derived products, epidemiological databases were analyzed from 2015 to the most recent years of available data (which varies among data sources). A wide variety of epidemiological databases provide necessary data for our analyses. These include the NSDUH, BRFSS, RADARS, NMURx, MTF, YRBSS, and ICPS. A description of each data source and a summary of the data from each source follows below.

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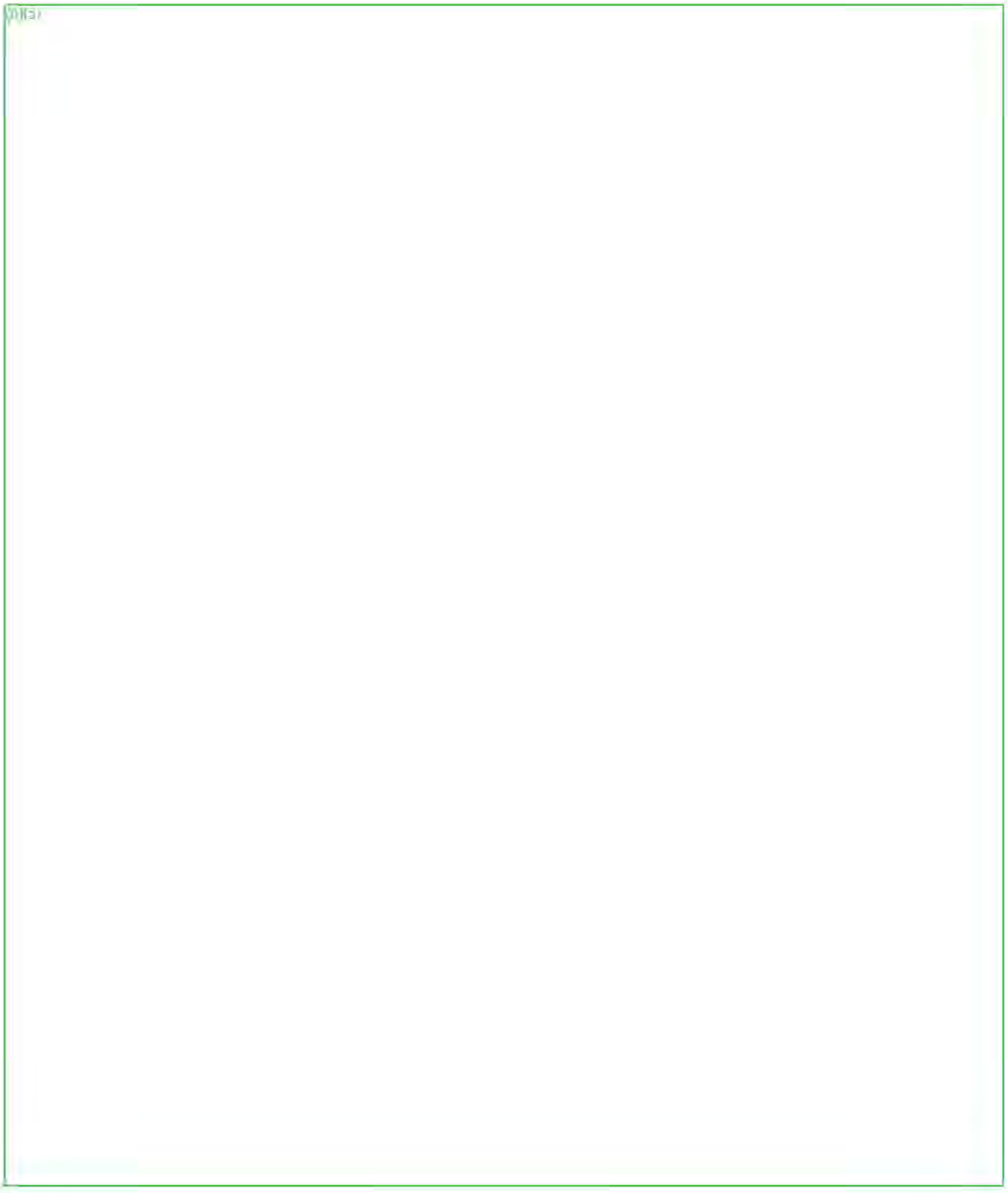

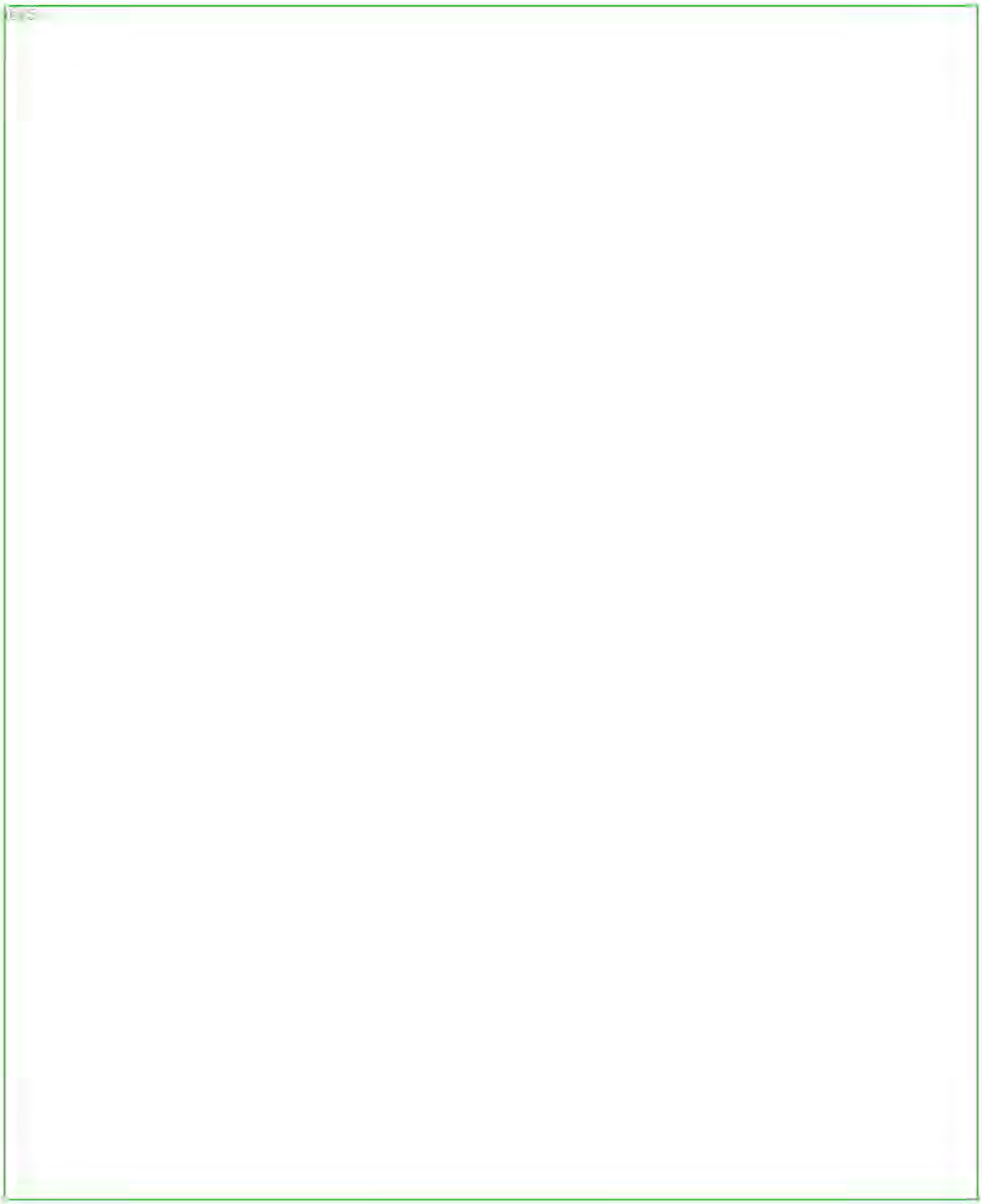

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Conclusions

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FACTOR 5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Under the fifth factor, the Secretary must consider the scope, duration, and significance of marijuana abuse, including in relation to relevant comparator substances that are abused.

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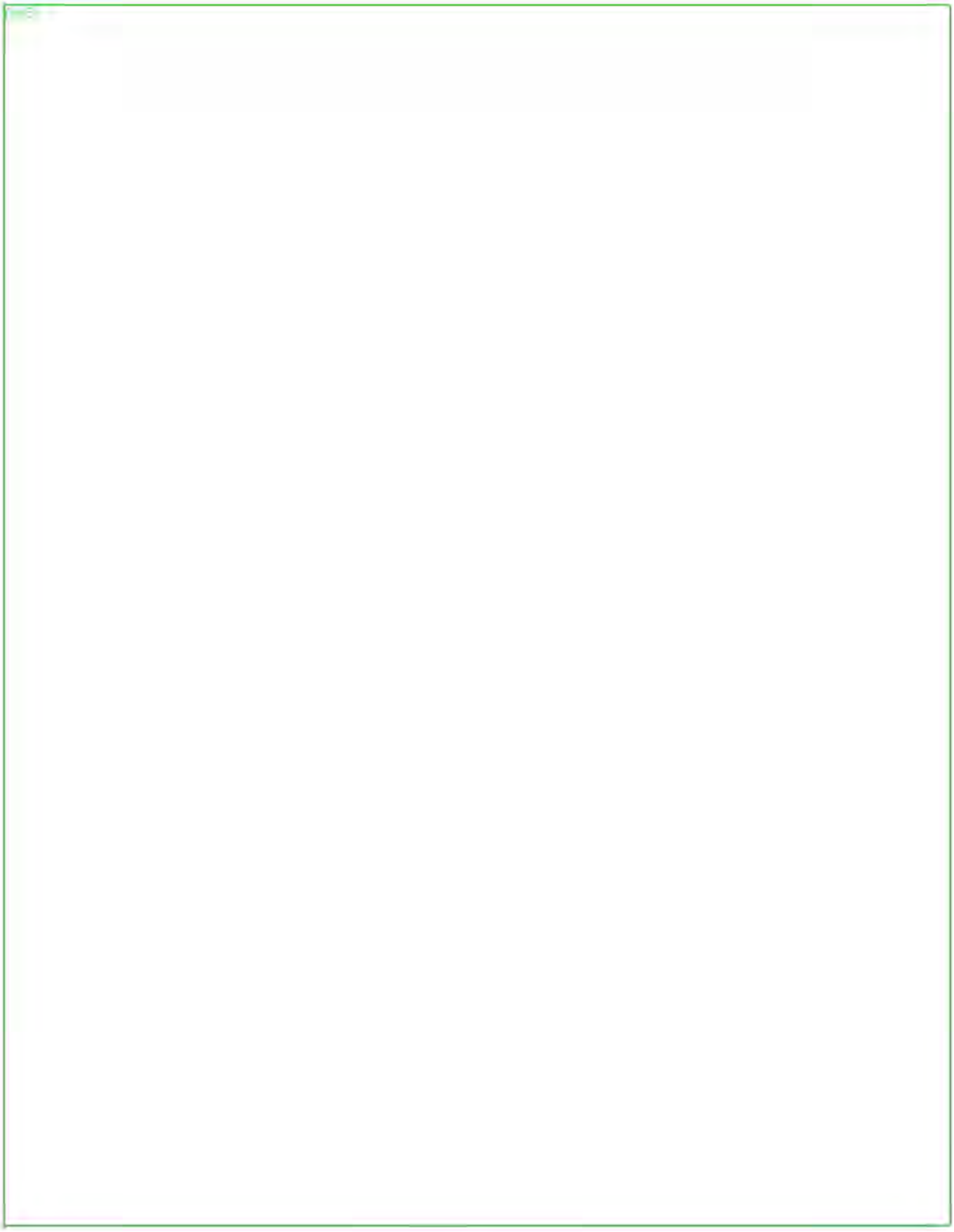

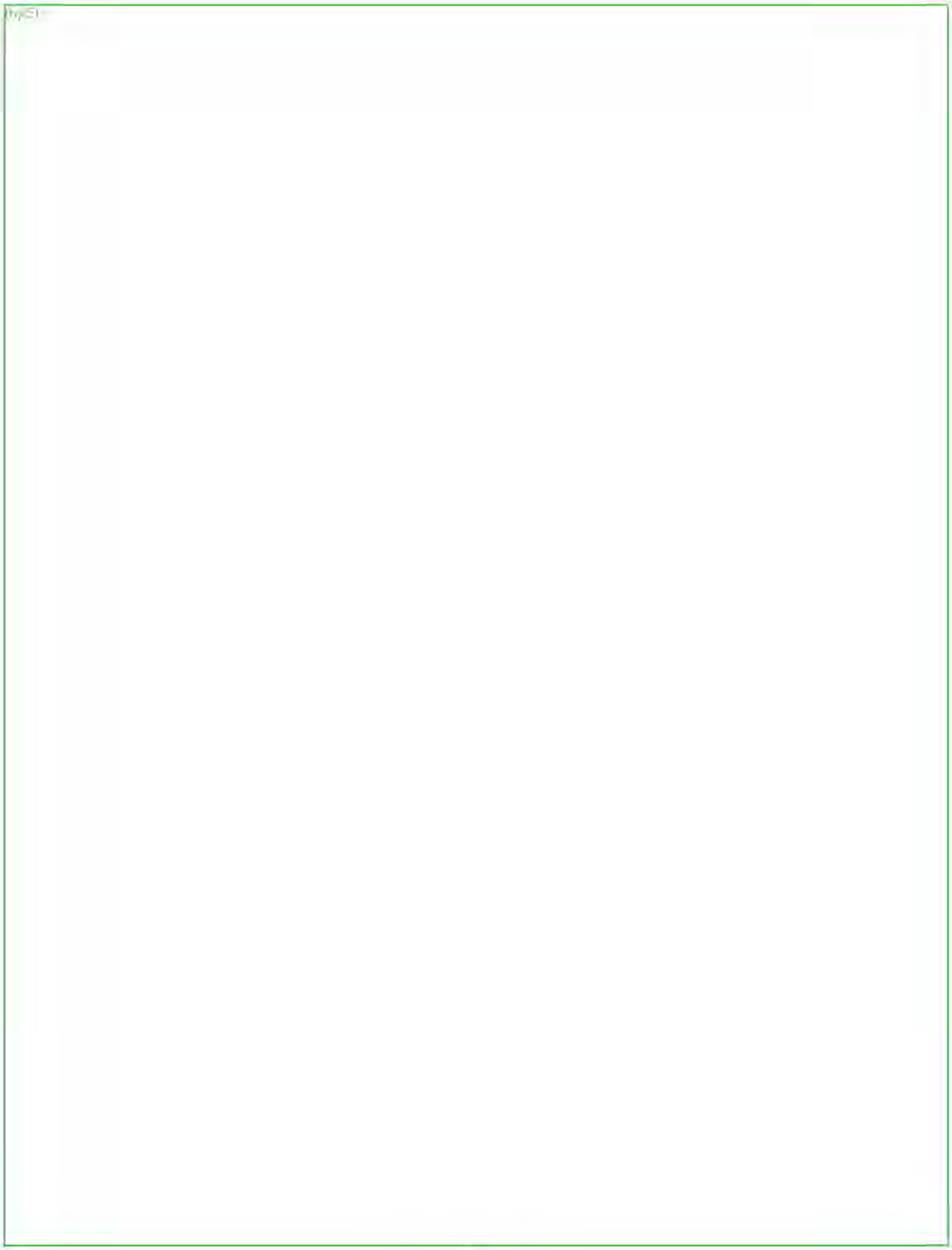

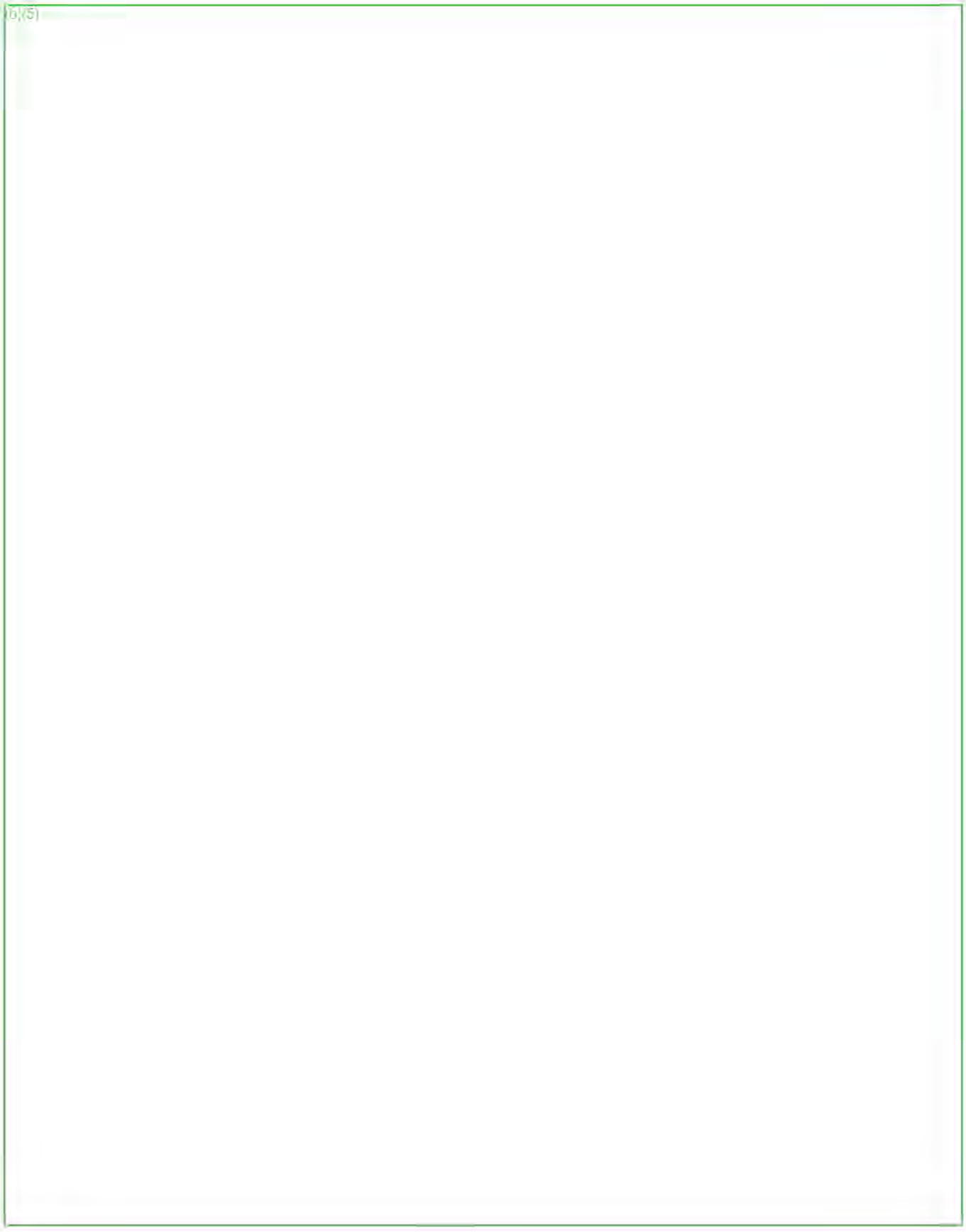

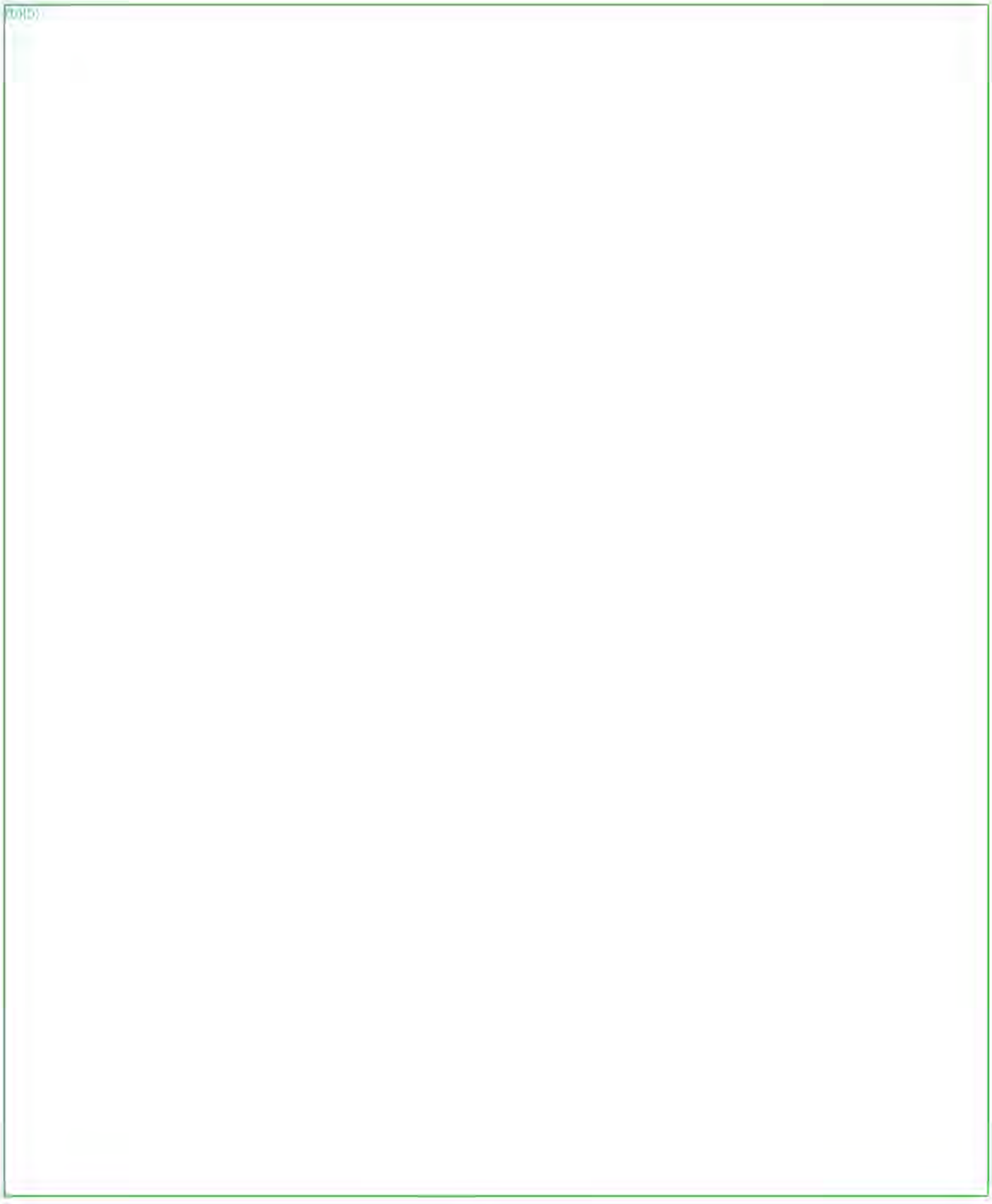

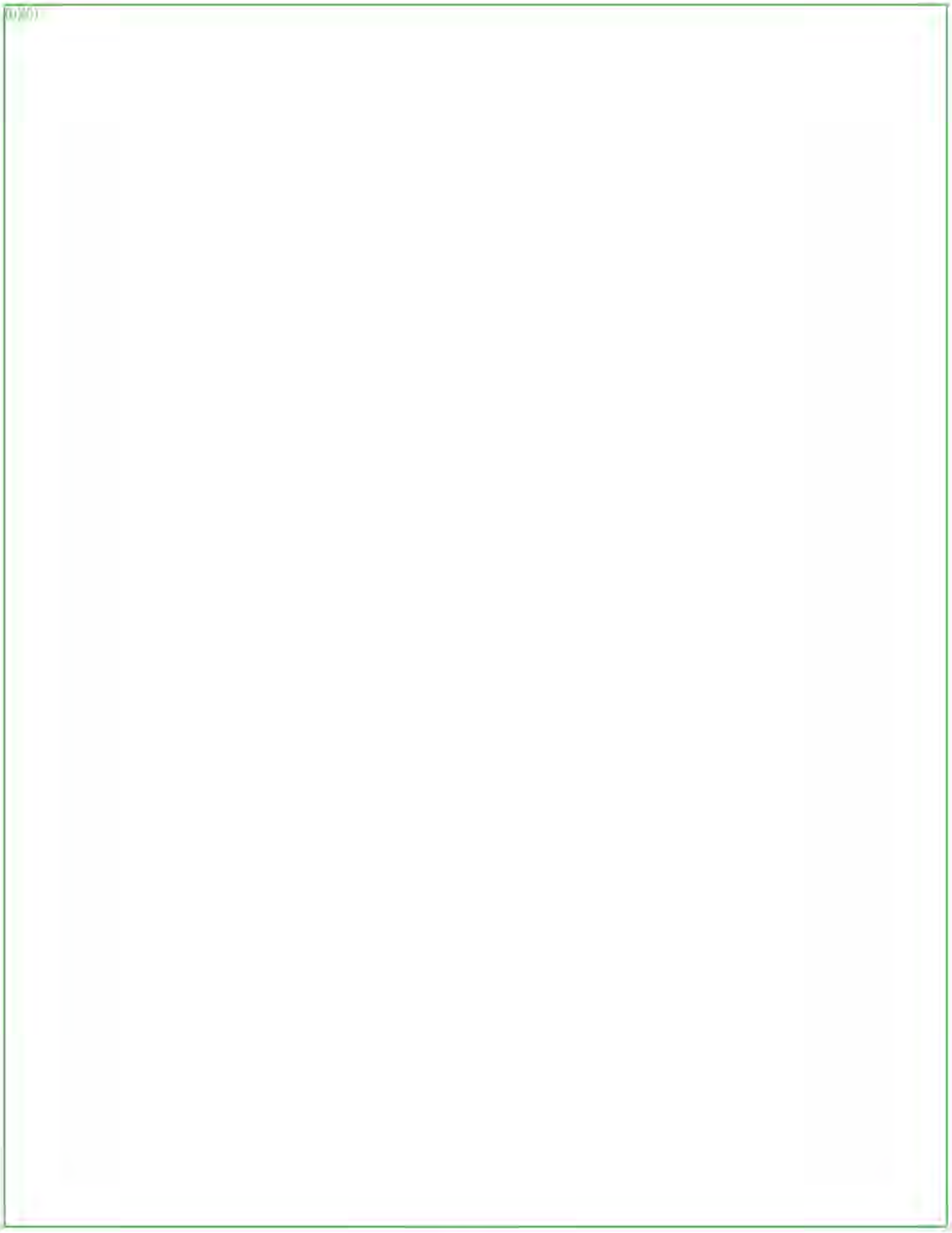

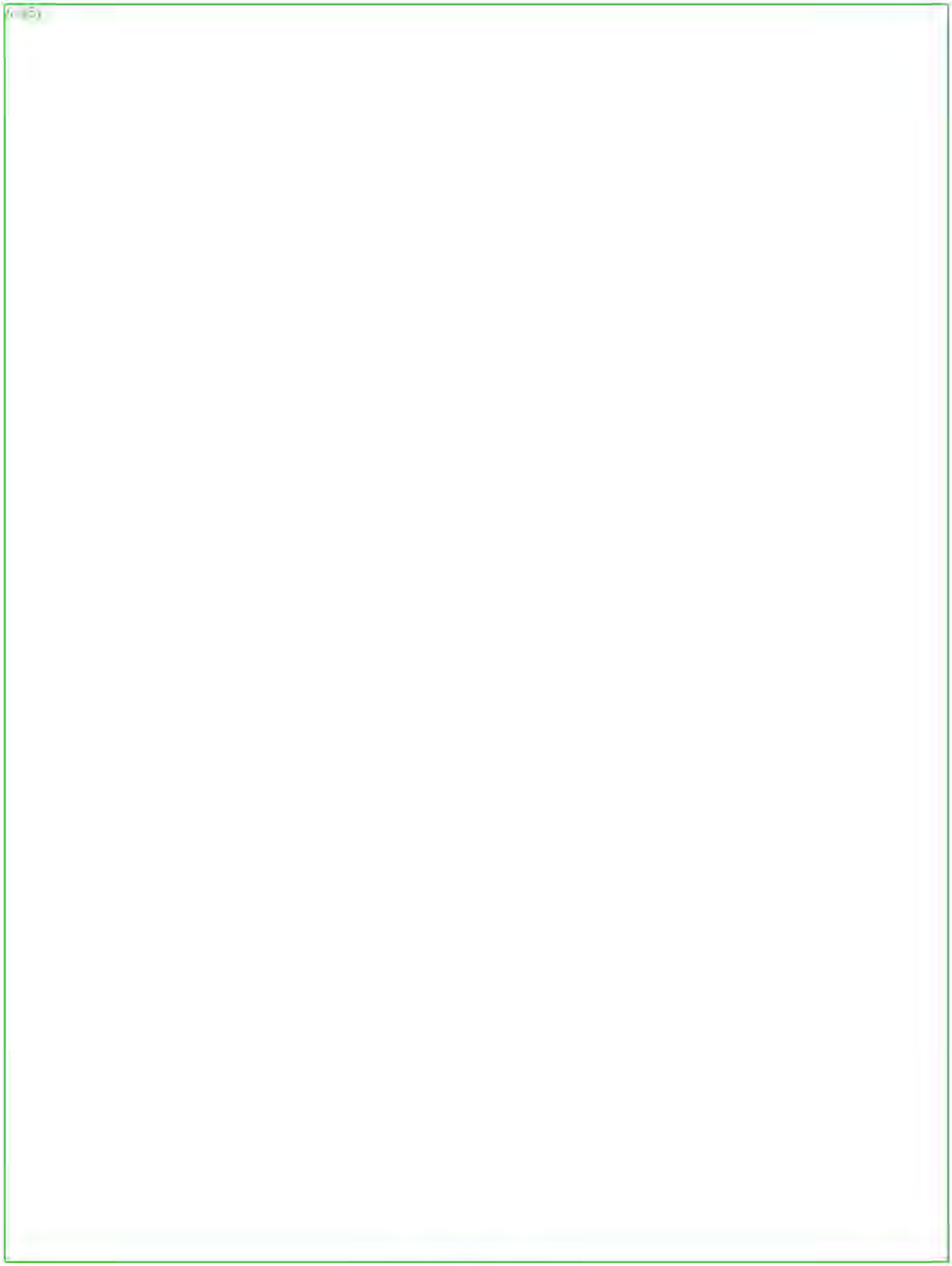

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Conclusions

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FACTOR 6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

Under the sixth factor, the Secretary must consider the risks posed to the public health by marijuana. Previous factors have provided data that contribute to an understanding of this issue.

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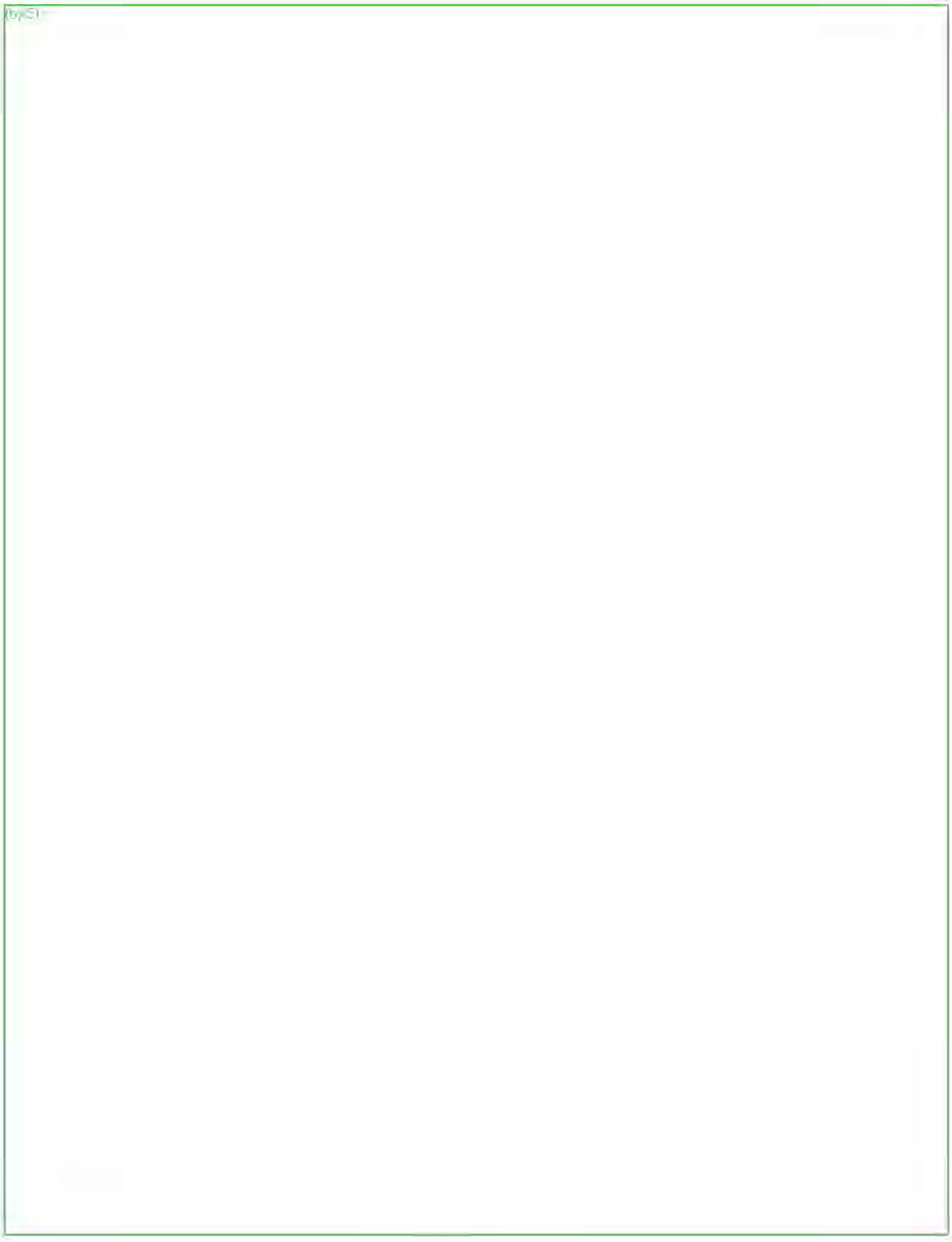

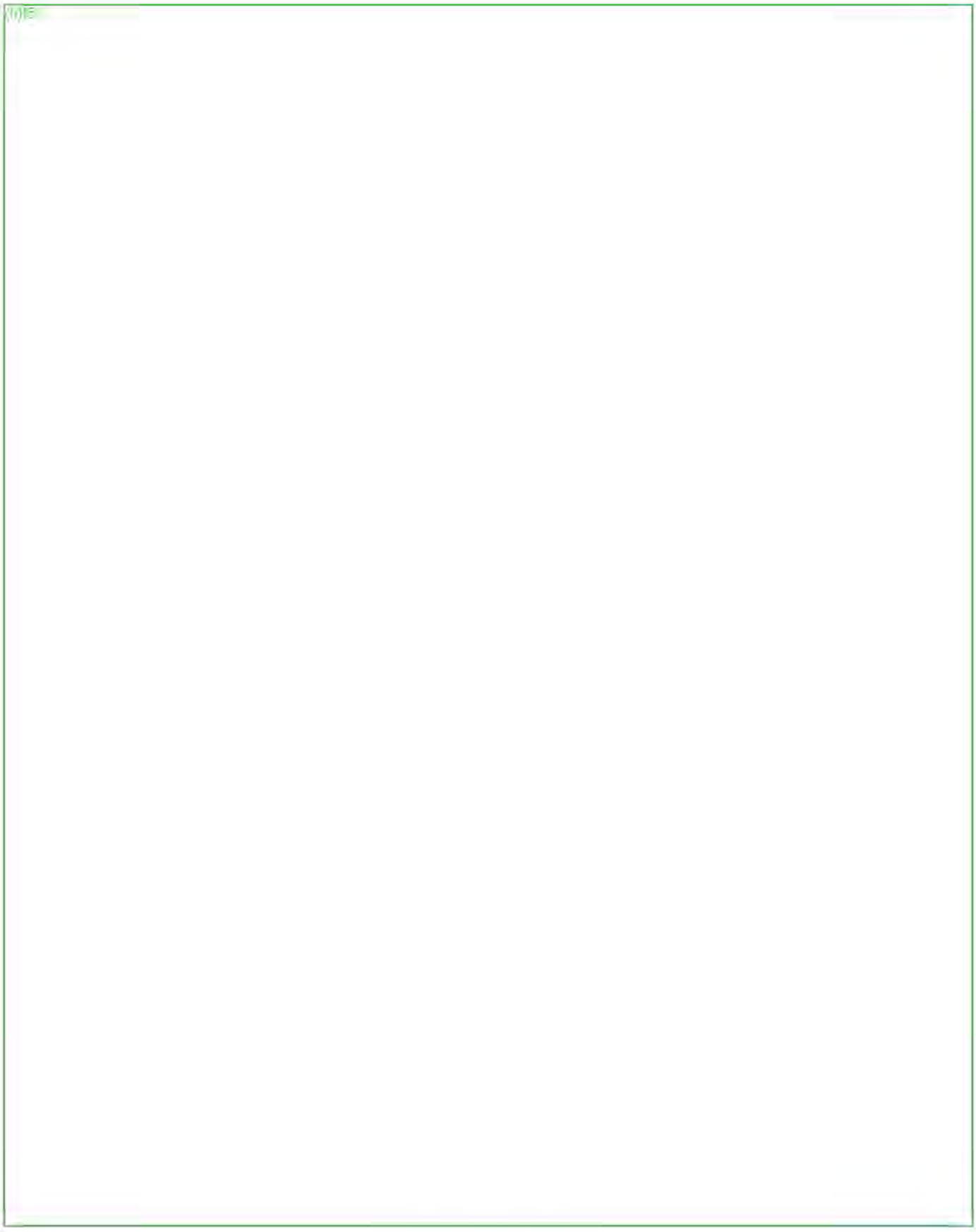

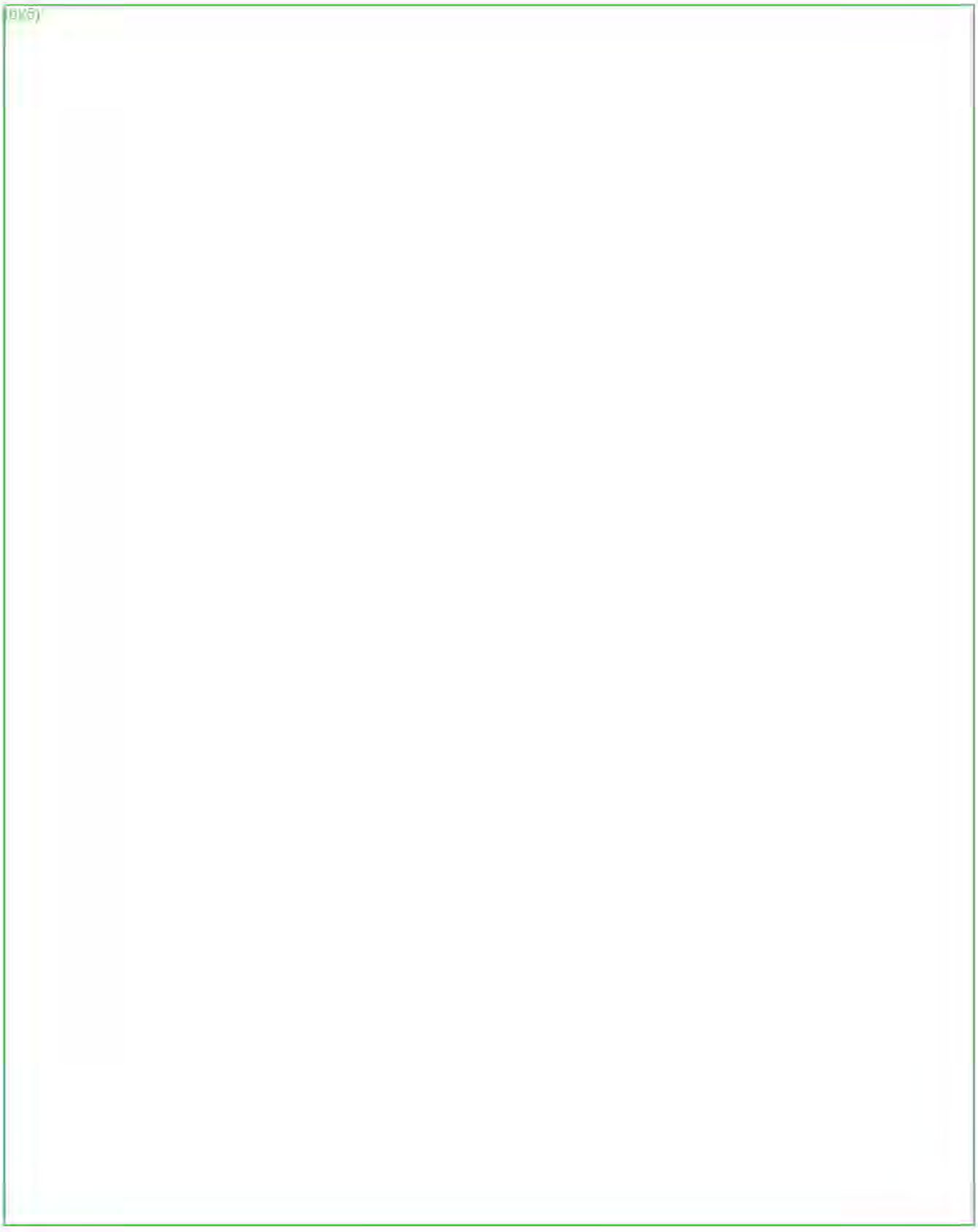

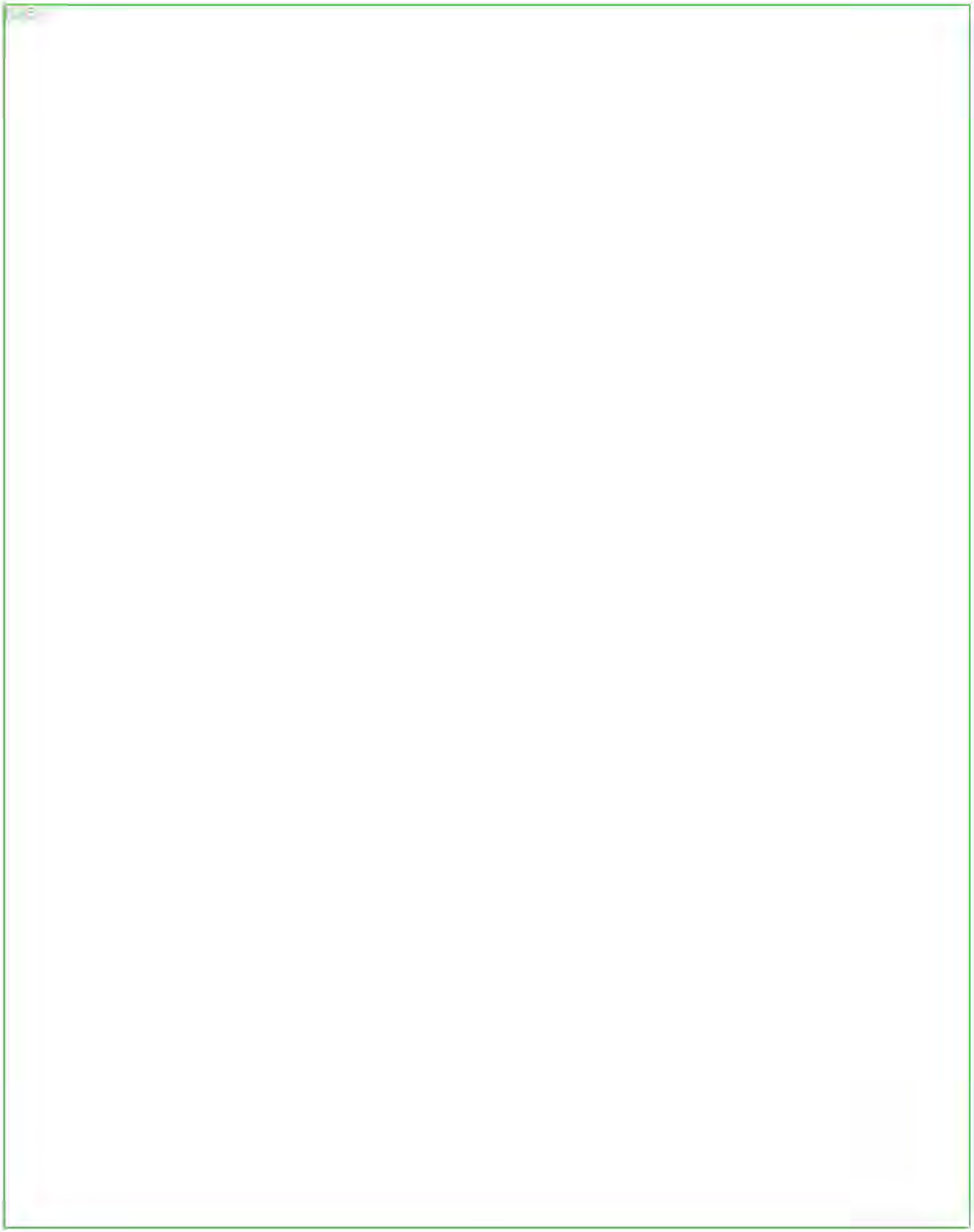

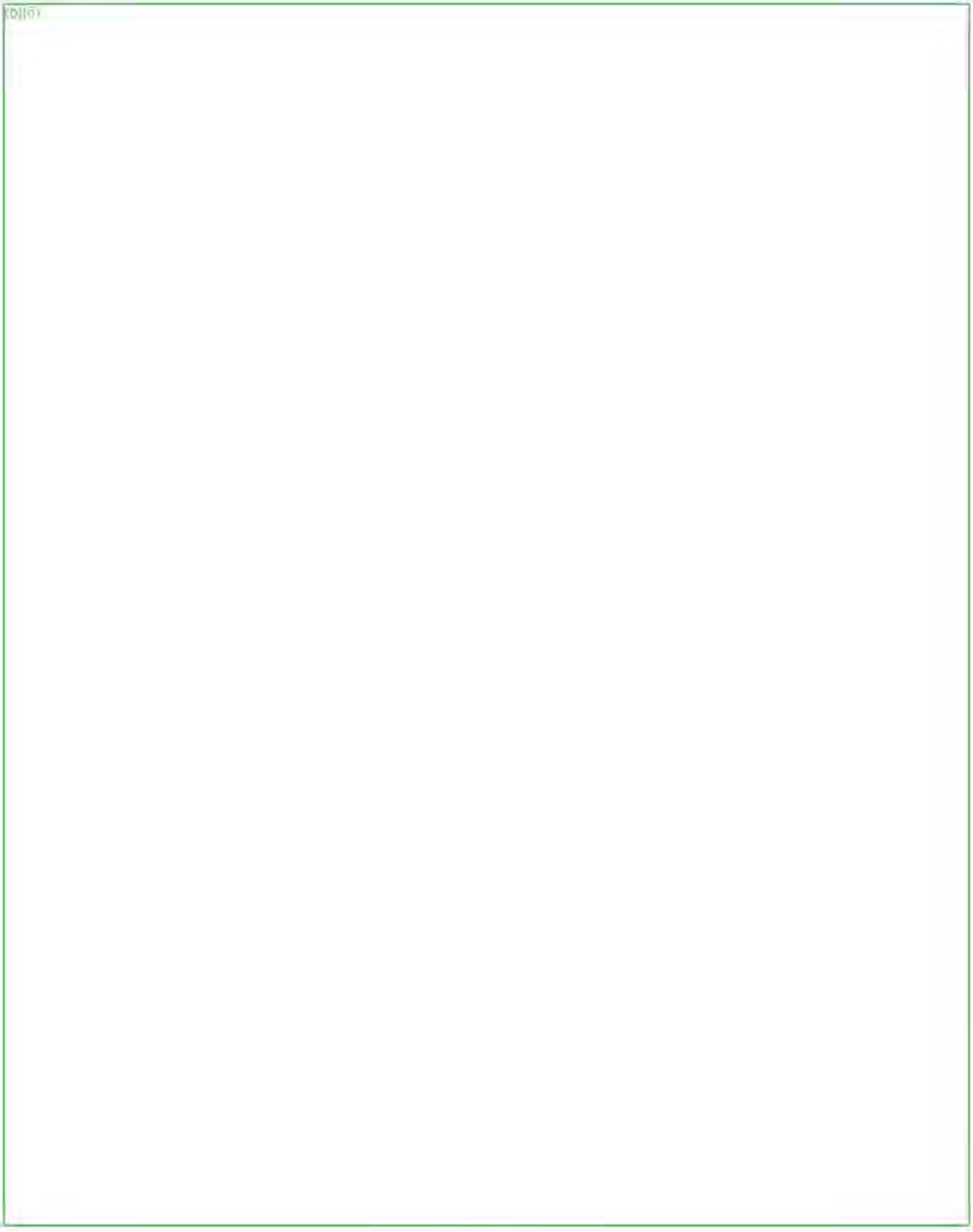

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Conclusions

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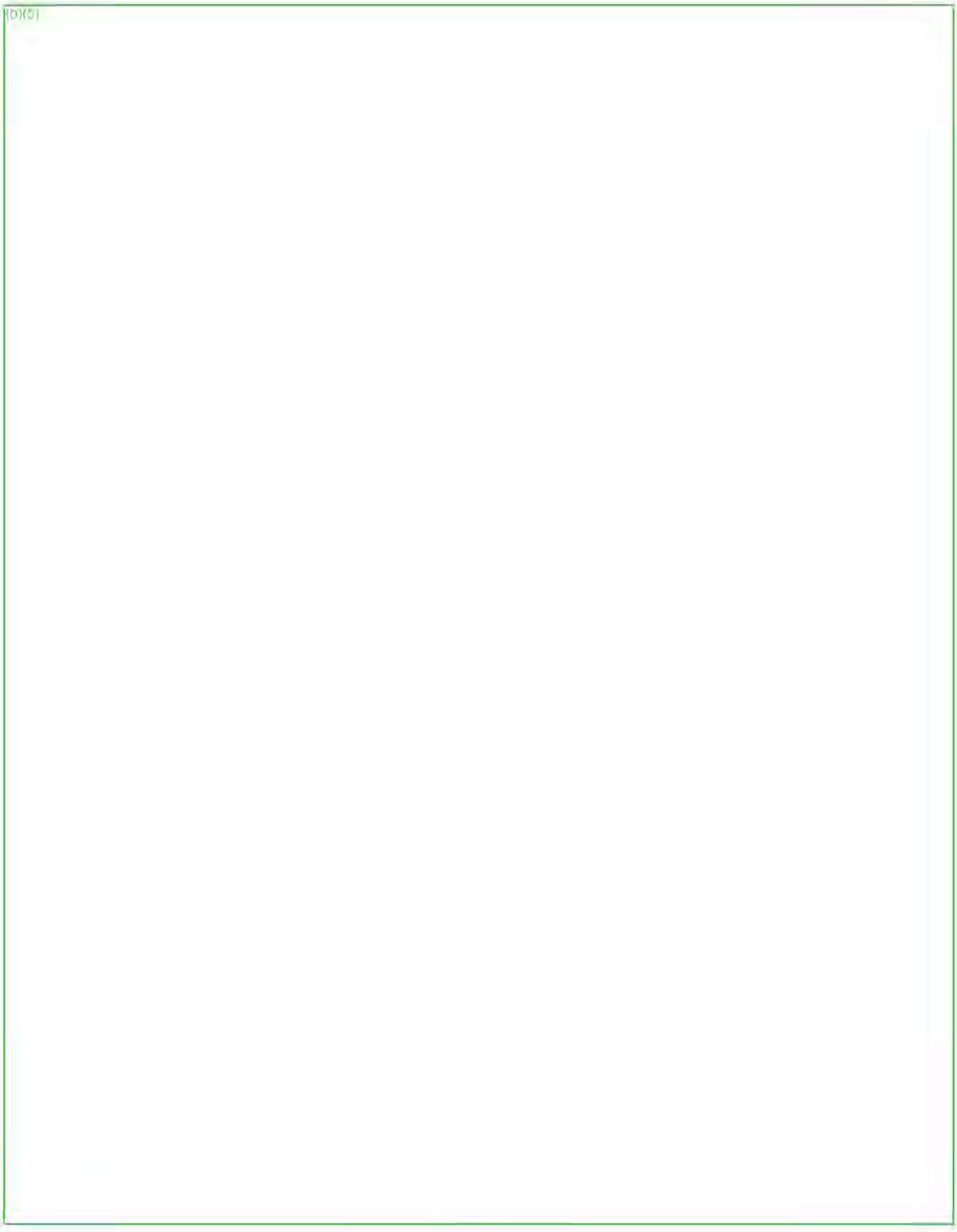
FACTOR 7. ITS PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY

Under the seventh factor, the Secretary must consider the psychic or physiologic dependence liability of marijuana.

Psychic Dependence

The term "psychic or psychological dependence" has been used to convey a similar state to that of addiction (O'Brien, 1996). For diagnosis purposes, the DSM-V has combined "abuse" and "drug dependence" (i.e., addiction) previously specified in the DSM's Fourth Edition into a single "substance use disorder," which may occur in a broad range of severity, from mild to severe (Hasin et al., 2013).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(b)(5)

Physical Dependence

Physical dependence is a state of adaptation, manifested by a drug-class specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Although physical dependence is often associated with addiction, it can be produced by repeated administration of drugs both with and without abuse potential.

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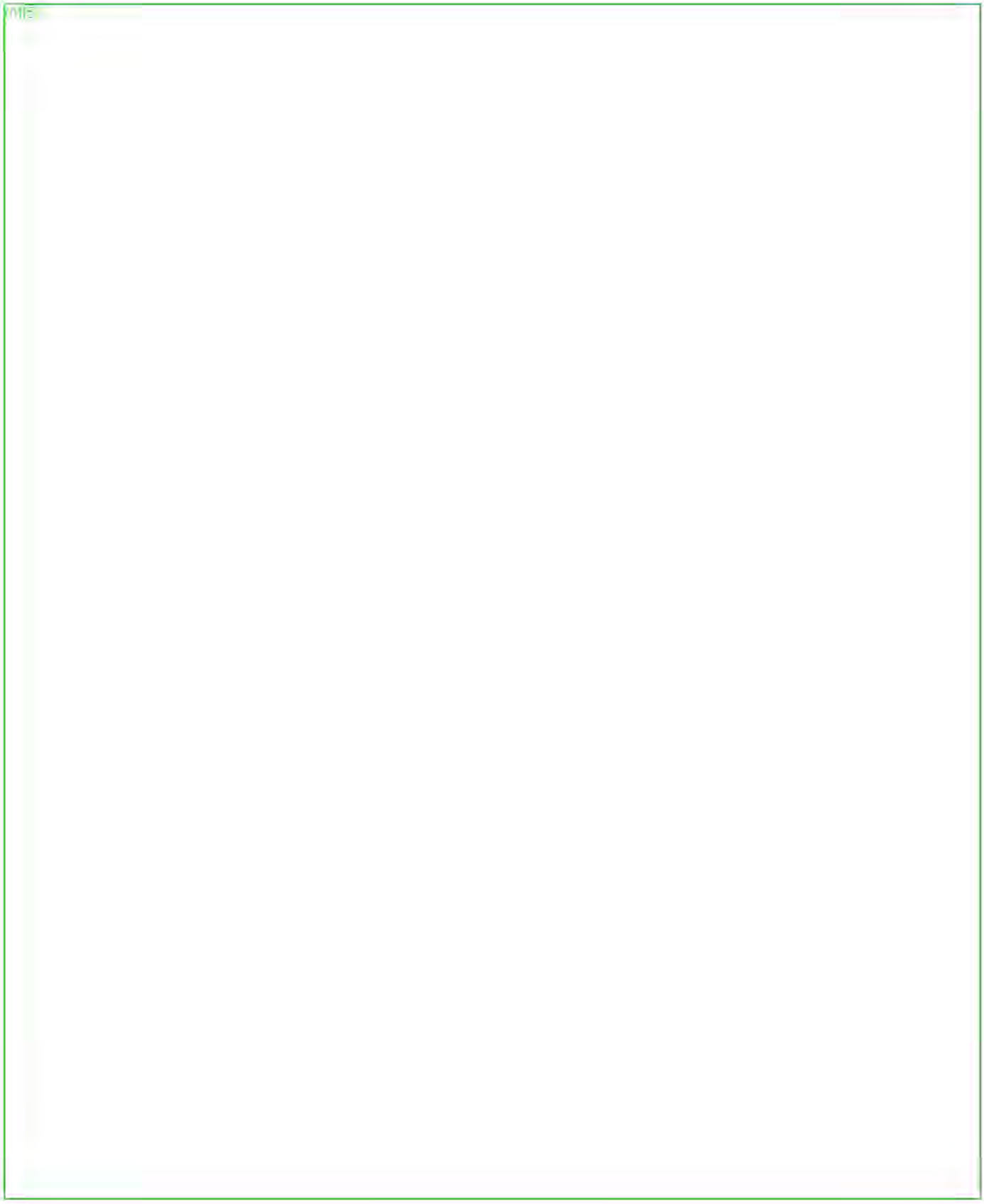

Conclusions

(b)(5)

FACTOR 8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS ARTICLE

Under the eighth factor, the Secretary must consider whether marijuana is an immediate precursor of a controlled substance. Marijuana is not an immediate precursor of another controlled substance.

III. RECOMMENDATION

Upon consideration of the eight factors determinative of control of a substance (21 U.S.C. 811(c)), FDA recommends that (b)(5)

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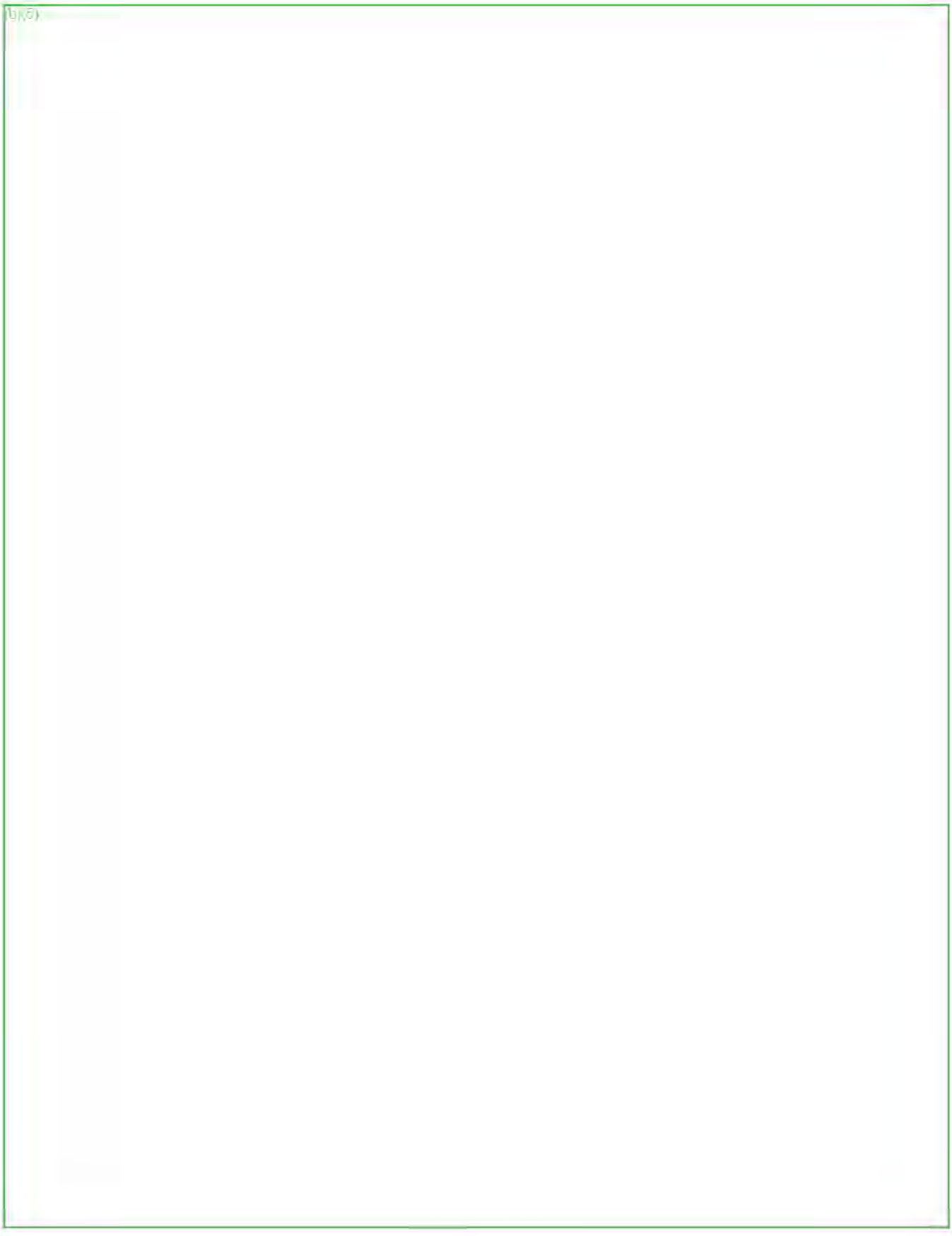

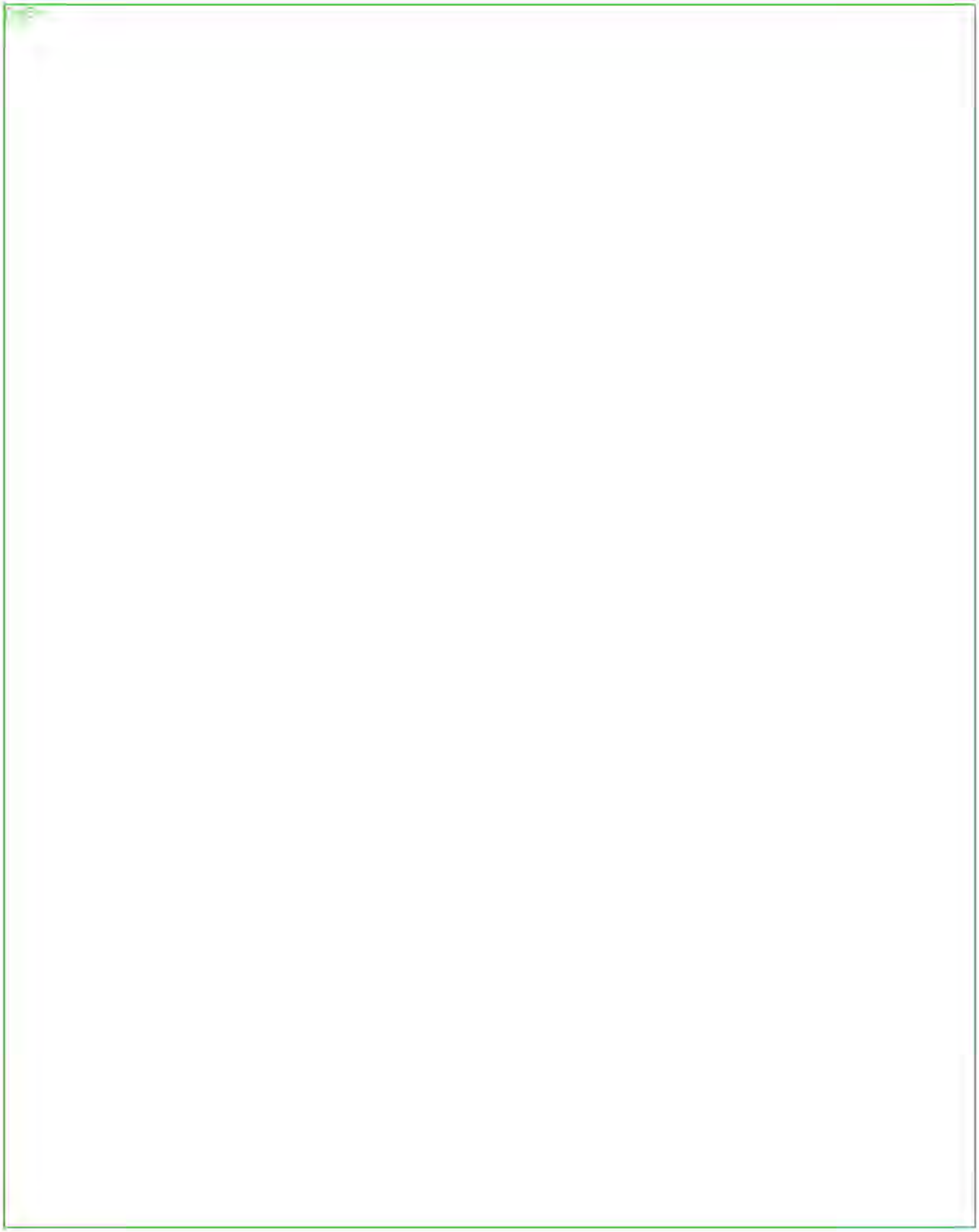


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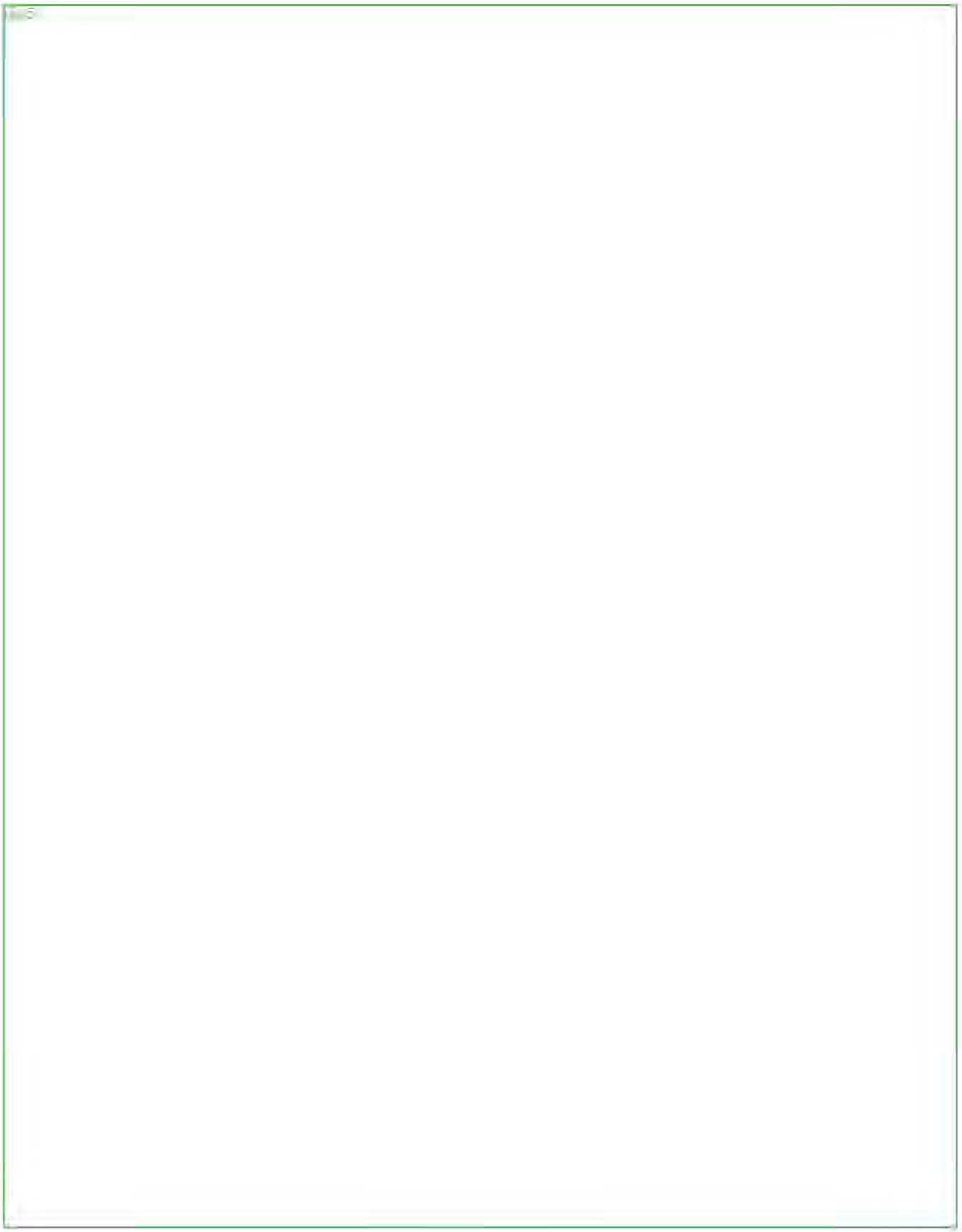
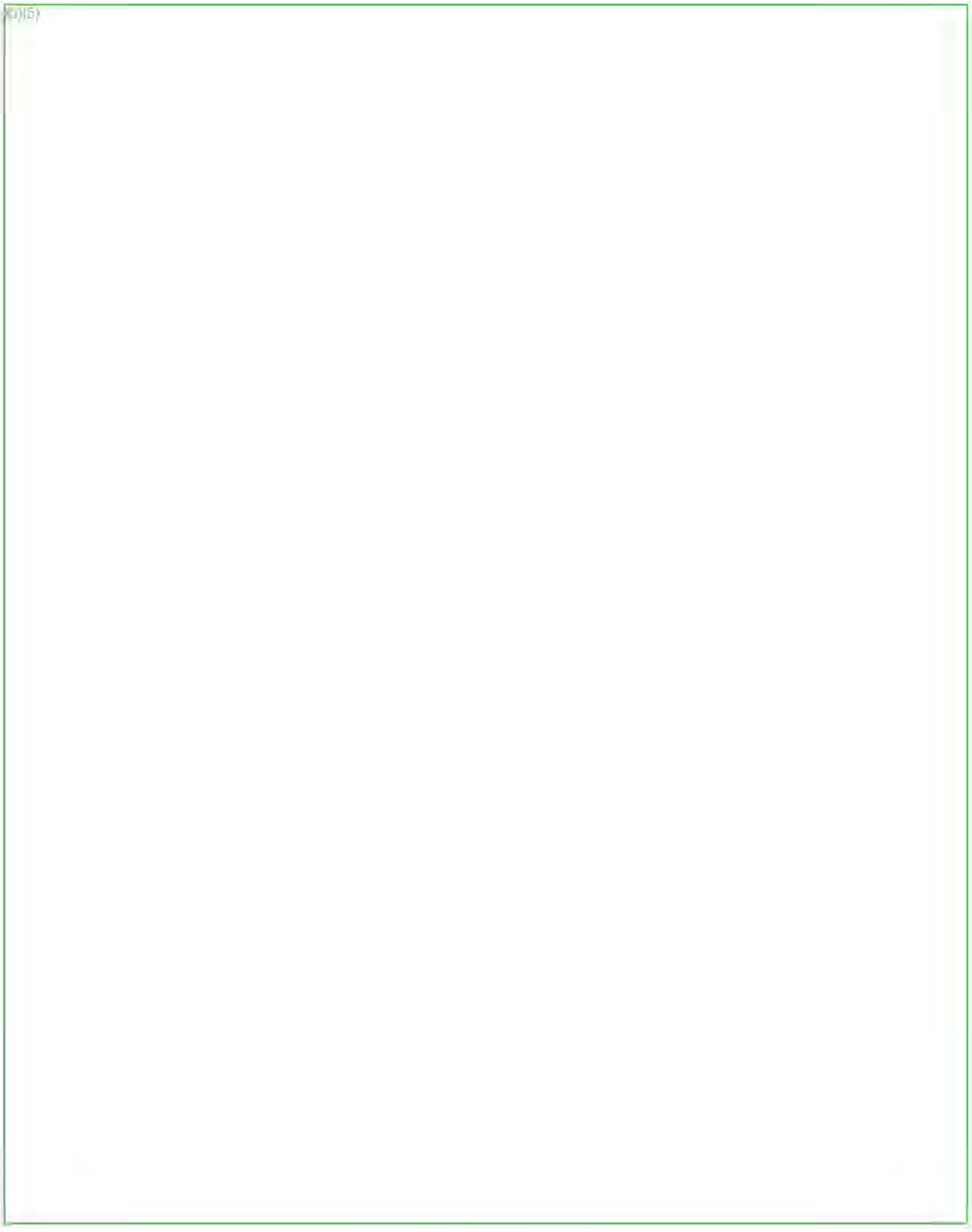
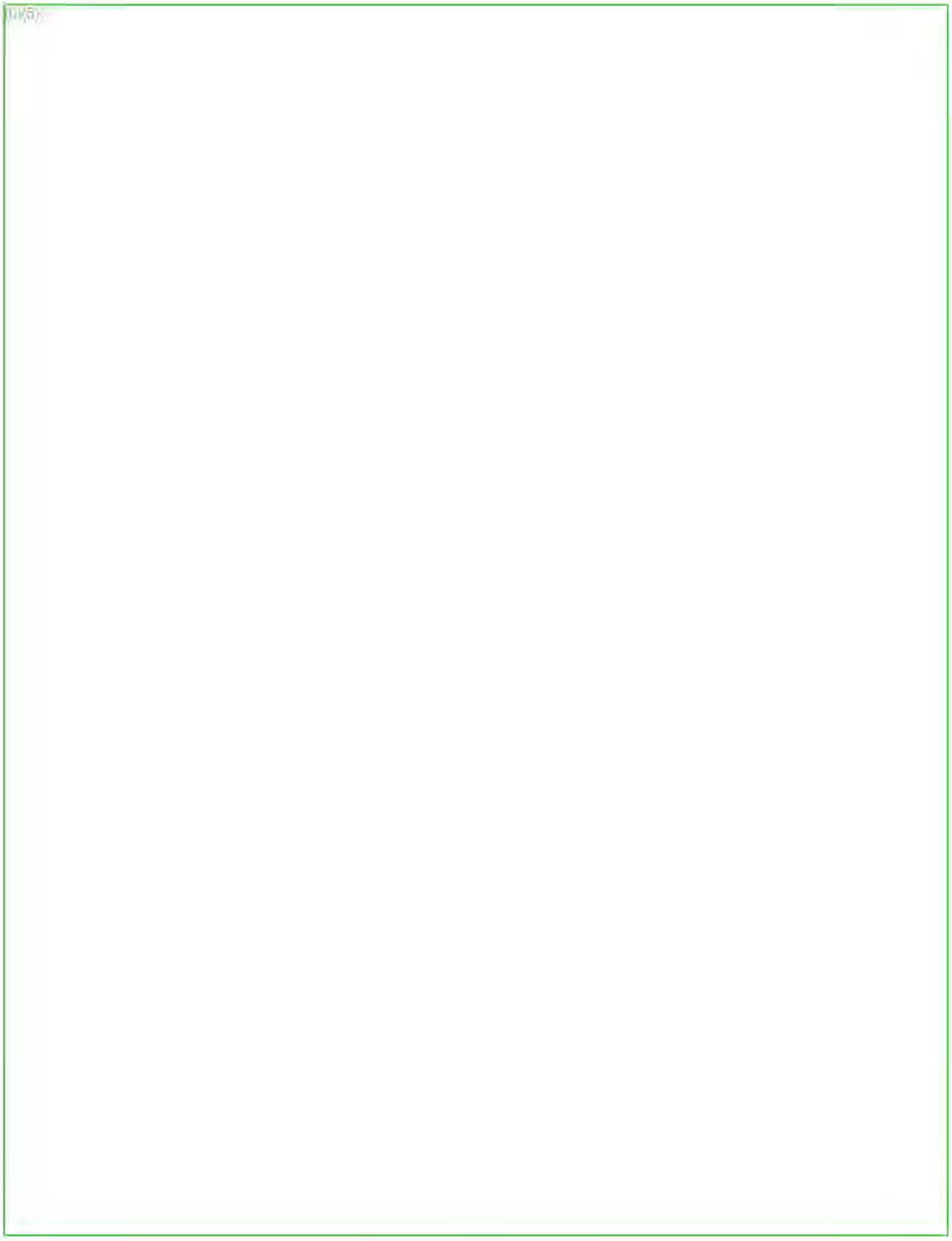
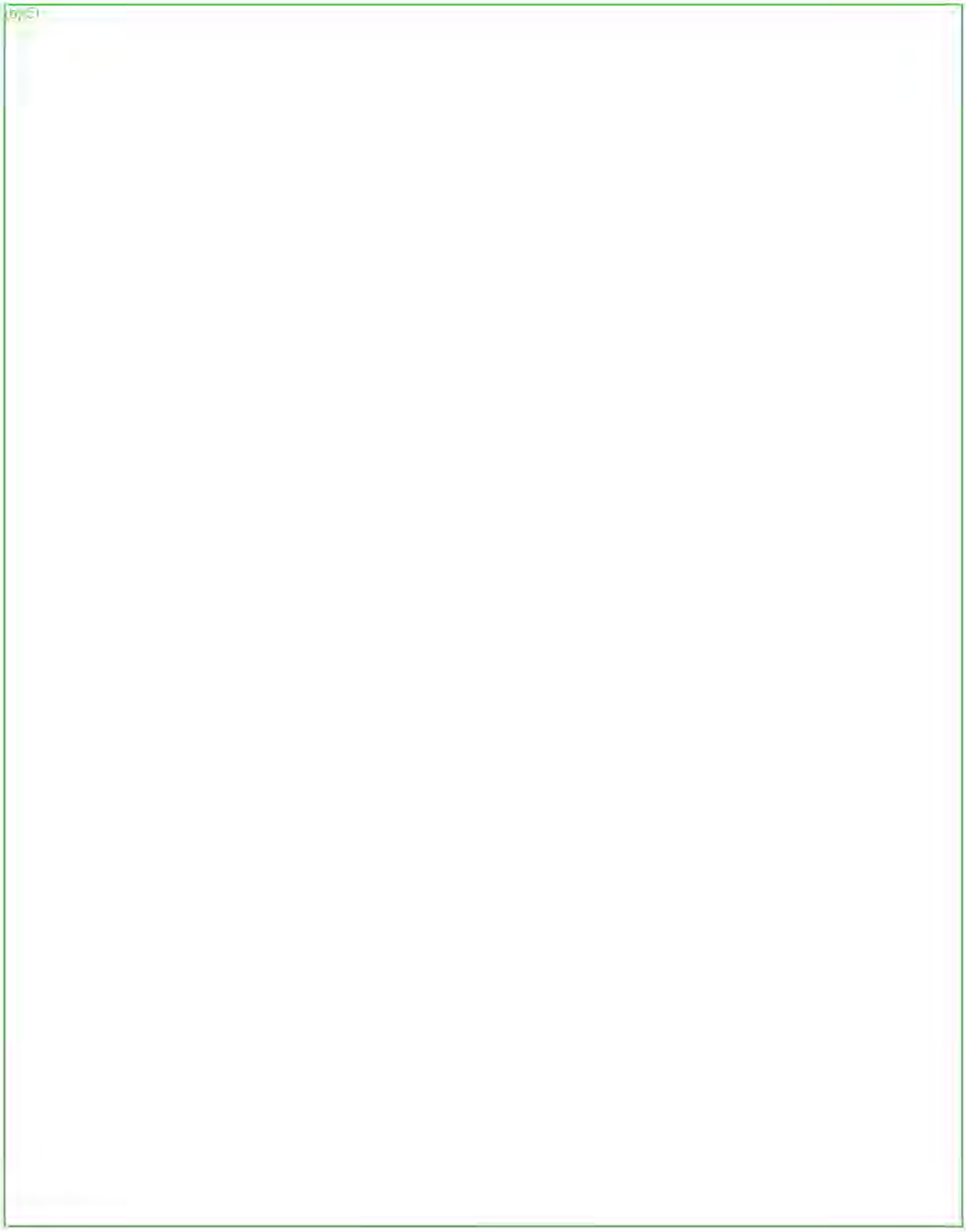
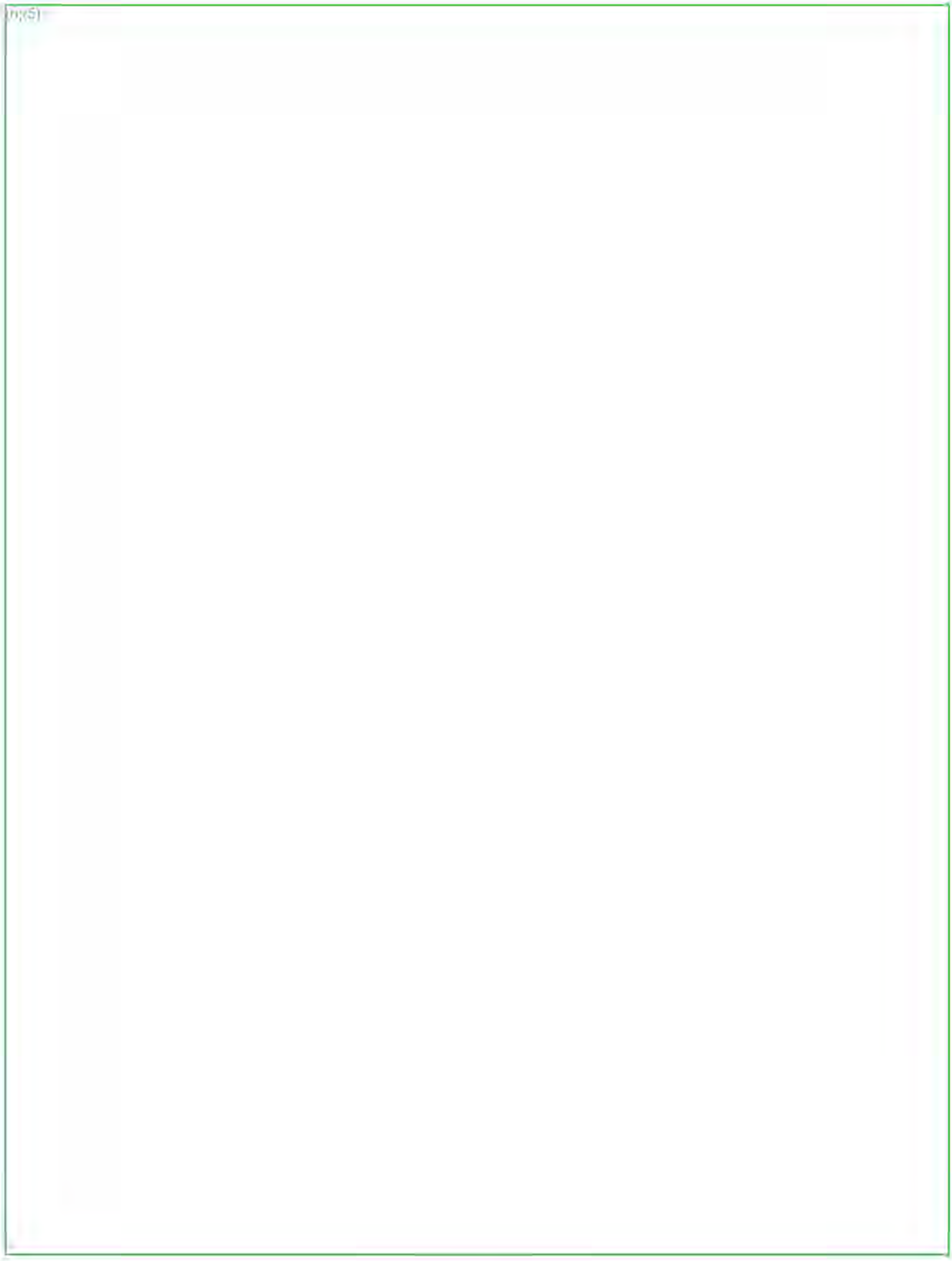
IV. REFERENCES







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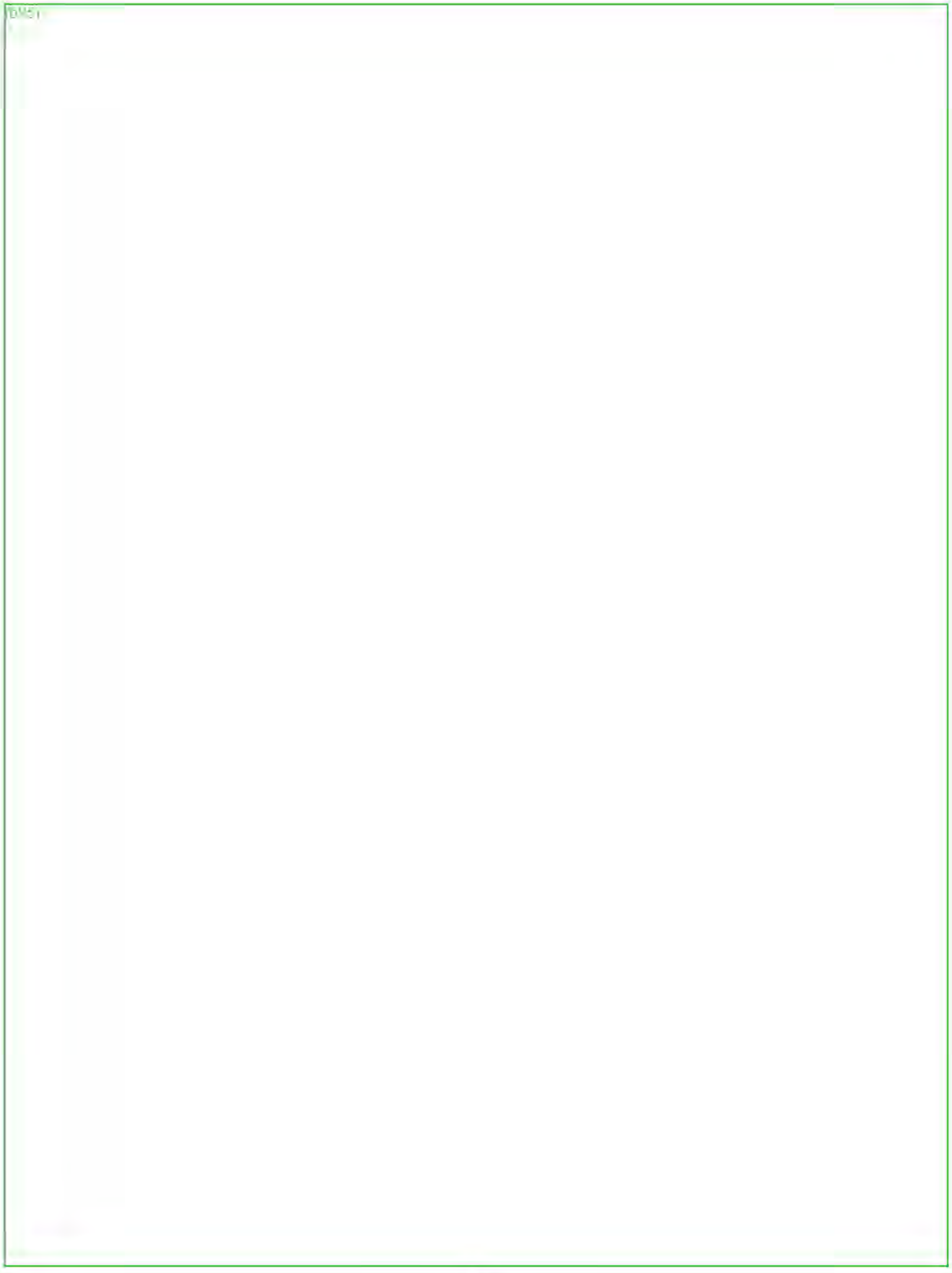


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