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December 21, 2007

Via Hand Delivery - Date Stamped Return Receipt Requested

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

PETITION FOR RECONSIDERATION AND STAY OF ACTION
DOCKET NO. 2007N-0353

The undersigned submits this petition on behalf of the GRAS/E Coalition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. 2007N-0353 or in the alternative, stay the effective date of this matter.

A. Decision Involved

On October 1, 2007, the Food and Drug Administration ("FDA" or "the Agency") issued a notice in the Federal Register announcing its intention to take enforcement action against unapproved drug products containing hydrocodone bitartrate, or any other salt or ester of hydrocodone (hereinafter collectively "hydrocodone"), and persons who manufacture or ship these products in interstate commerce.[1] The Agency stated that it would not take enforcement

[1] Drug Products Containing Hydrocodone; Enforcement Action Dates, Docket No. 2007N-0353, 72 Fed. Reg. 55,780 (Oct. 1, 2007).

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action against a person based solely on the manufacturing or otherwise introducing or delivering for introduction into interstate commerce certain hydrocodone products unless such a person is still manufacturing or shipping such products on or after October 31, 2007, with a label or labeling that, as of October 1, 2007, indicates any use for children under six years of age.[2] In addition, the Agency stated that it did not intend to take action against a person manufacturing or shipping certain hydrocodone products that are not labeled for use in children unless that person is still manufacturing these products on or after December 31, 2007, or shipping these products on or after March 31, 2008.[3]

B. Action Requested

We respectfully request that the Agency reconsider its plan to take enforcement action against those persons who manufacture or ship liquid cough/cold hydrocodone products that are not labeled for use in children under six years of age. In the alternative, we respectfully request that the Agency stay its enforcement action against manufacturers and shippers of liquid cough/cold hydrocodone products in a manner consistent with its previous actions (*e.g.*, levothyroxine, pancreatic insufficiency drug products, etc.) by extending the grace period for two years until December 31, 2009, and within this period allowing manufacturers who have submitted a drug application to continue to market liquid cough/cold hydrocodone products while FDA reviews these applications.

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[2] Id. at 55,783.

[3] Id.

C. Statement of Grounds

FDA should grant this petition for reconsideration because the Agency did not adequately consider the possibility that liquid hydrocodone cough/cold products were Generally Recognized as Safe and Effective ("GRAS/E") and therefore did not need an approved application to be on the market. These liquid hydrocodone cough/cold products have a long history of safe and effective use, have few reported adverse events, have adhered to compendial standards, have been manufactured in accordance with good manufacturing practices, and have a dosage form that poses no bioequivalence problems. In addition, it appears that the Agency would not require any additional information from manufacturers other than chemistry, manufacturing, and controls data, which are basically current Good Manufacturing Practices ("cGMPs") information, to support an approved application for liquid hydrocodone cough/cold products because there have been findings of safety and effectiveness and there would be no requirement for bioavailability data for these products in true solutions, which makes the entire concept of demanding approved applications for these products irrational.

If FDA does not grant this petition for reconsideration, then, in the alternative, FDA should stay its enforcement action and extend the grace period for two years until December 31, 2009, and within this period allowing manufacturers who have submitted a drug application to continue to market liquid cough/cold hydrocodone products while FDA reviews these applications. Otherwise manufacturers of liquid hydrocodone cough/cold products will suffer irreparable injury, and FDA will have exercised its authority in an arbitrary and capricious manner by providing manufacturers in previous similar situations, *e.g.*, the Agency's treatment of manufacturers of levothyroxine, and pancreatic insufficiency drug products, with a longer grace period than the manufacturers in the current situation. Additionally, refusing to grant this

petition will pose unnecessary costs on third party payors, manufacturers, patients, and FDA without providing a countervailing benefit to the public health.

I. Legal Requirements for Petitions for Reconsideration and Stay

Under its regulations, the Commissioner shall grant a petition for reconsideration when all of the following apply: (1) the petitioner demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting the reconsideration; and (4) reconsideration is not outweighed by public health or other public interests.[4] Additionally, the Commissioner shall grant a petition for stay if all of the following apply: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting the stay; and (4) the delay resulting from the stay is not outweighed by public health or other public interests.[5]

The regulations regarding both the petition for reconsideration and the petition for stay state that if a petition is submitted later than 30 days after the date of the decision involved, then the Commissioner will deny the petition as untimely unless the Commissioner permits otherwise.[6] The regulations further state that in the case of a decision published in the Federal Register the date of the publication of the Federal Register will be considered to be the date of the decision involved for determining the timeliness of a petition.[7] In the current situation, we

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[4] 21 C.F.R. § 10.33(d).

[5] 21 C.F.R. § 10.35(e).

[6] 21 C.F.R. § 10.33(g); 21 C.F.R. § 10.35(g).

[7] 21 C.F.R. § 10.33(b); 21 C.F.R. § 10.35(b).

are asking for the Agency to reconsider or stay an action that was first announced in a notice in the Federal Register on October 1, 2007. While this petition is submitted more than thirty days after the notice was published in the Federal Register, we believe that this petition is timely because we are not objecting to the enforcement action against manufacturers of hydrocodone products that were marketed for children under the age of six that was set to commence on or after October 31, 2007. Instead, we are only petitioning on those aspects of the notice that deal with the enforcement actions against manufacturers and shippers of liquid cough/cold hydrocodone products that are set to go into effect on December 31, 2007, and March 31, 2008. Therefore, this petition is submitted within 30 days of the relevant decisions going into effect and should not be dismissed as untimely due to submission of the petition after October 31, 2007. Nevertheless, if the Commissioner decides that the relevant date of the decision for this petition was October 1, 2007, and that petitions should have been filed within 30 days of that date, then we respectfully request that the Commissioner permit this petition to go forward based upon the irreparable injury to our client and the public policy interests in support of our position as explained further below.

Because both the requirements for reconsideration and the conditions for stay apply in the current situation, FDA should grant our petition for reconsideration or alternatively, our petition for stay.

II. Legal Status of Hydrocodone Products

A. Regulatory History

Historically, there was no requirement that drugs be proven to be safe and effective before being allowed to enter the market in the United States. In 1938, the newly enacted Federal Food Drug and Cosmetic Act ("FFDCA" or "the Act") required that before a "new drug"

could enter the market FDA had to approve a New Drug Application ("NDA") for the product that demonstrated that the drug was safe.[8] A new drug was defined by the FFDCA as a drug that was not generally recognized as safe among scientific experts ("GRAS").[9] During the period from 1938 to 1962, FDA generally considered any new drug that was identical, related or similar ("IRS") to a drug that had an FDA-approved NDA to be GRAS and thus, the manufacturer did not need to submit an NDA for a drug that was IRS to an approved product.[10]

In 1962, the Kefauver-Harris Drug Amendments required that, in addition to showing that a new drug product was safe, a manufacturer also had to demonstrate to the Agency that its "new drug" was effective before it could enter the market.[11] Under this revised law, a "new drug" was defined by the FFDCA as one that was not generally recognized as safe and effective among scientific experts, *i.e.*, GRAS/E.[12]

The requirement that new drugs had to be proven effective applied retroactively, such that manufacturers of drugs previously approved between 1938 and 1962 with safety-only NDAs had to demonstrate that their drugs were effective to be able to remain on the market.[13] In order to deal with the large amount of drug products that had safety-only NDAs, the government

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[8] Federal Food Drug and Cosmetic Act, Public L. No. 75-717, 52 Stat. 1040 (1938).

[9] Id. at § 201(p), 52 Stat. 1040, 1041-42 ("The term 'new drug' means [a]ny drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . .").

[10] Prescription Drugs Marketed Without Approved New Drug Applications, 49 Fed. Reg. 38,190, 38,191 (Sep. 27, 1984) ("This policy led to a growing number of [NDAs] requiring agency review. To deal with this problem, which was aggravated by wartime staff shortages, the agency developed a policy of providing advice on the need for [NDAs] for [certain] products. Consequently, many products were introduced to the market without effective [NDAs] because FDA advised the manufacturers that the products were generally recognized as safe (*i.e.*, not new drugs). Such advice was often based on a determination that the products were identical, similar, or related to one or more drug products with effective [NDAs].").

[11] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

[12] Id. at § 102, 76 Stat. 780, 781.

[13] Id. at § 107, 76 Stat. 780, 788.

enlisted the help of the National Academy of Sciences ("NAS") and the National Research Council ("NRC") to review the effectiveness of all drugs that had received FDA approval for safety only from 1938 until 1962.[14] This review of previously approved drug products with safety-only NDAs or that were IRS to drug products with safety-only NDAs was known as the Drug Efficacy Study Implementation ("DESI" or "DESI I") program. The FDA also reviewed other drugs that were marketed before 1962 that did not have a safety-only NDA and were not IRS to a safety-only NDA drug. The review of these drugs was referred to as the DESI II program (also known as the "Prescription Drug Wrap-Up" program).[15] In general, drugs that were IRS to an active pharmaceutical ingredient ("API") evaluated by the DESI I program were encompassed by the findings for that drug product.[16] The FDA then reviewed and evaluated the reports created by the advisory committees of the NAS/NRC and published its findings in Federal Register notices.

Because FDA never finished its review of DESI products, FDA created Compliance Policy Guide ("CPG") 7132c.02 on September 23, 1976, to describe its enforcement policy against those APIs reviewed or under review by the DESI program that were still on the market without approved new drug applications.[17]

In 1984, FDA amended its CPG on marketed unapproved drugs due to serious adverse events associated with unapproved drug products that contain E-Ferol and that were marketed on the basis of being IRS to pre-1962 drug products. FDA's revised CPG stated that the Agency

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[14] Reports of Information for Drug Effectiveness, 31 Fed. Reg. 9426 (July 9, 1966).

[15] FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs - Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (June 2006) ("2006 Compliance Policy Guide") at 10, available at http://www.fda.gov/cder/guidance/6911fnl.pdf (last visited Dec. 17, 2007).

[16] 21 C.F.R. § 310.6.

[17] Marketed New Drugs Without Approved New Drug Applications, 41 Fed. Reg. 41,770 (September 23, 1976).

may immediately initiate regulatory action against any marketed unapproved new drug if: (1) the product is first marketed after November 13, 1984, or the drug product is changed after November 13, 1984; (2) the product differs from a prescription drug marketed before November 13, 1984, and the FDA has deferred enforcement action against that prescription drug pending a determination on its status; and (3) the difference between the two products is not due to compliance with compendial requirements or FDA requirements.[18] In addition to the revised policy guide, FDA enacted regulation 21 C.F.R. § 310.305 requiring manufacturers, packagers, and distributors of marketed prescription drug products that were not subject to an approved application to submit any adverse event reporting so that FDA could be quickly informed of any adverse events related to these products.[19]

On June 9, 2006, FDA issued a revised CPG that superseded the previous CPG.[20] FDA stated that the purpose of the revised CPG was to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.[21] The Agency stated that if the final DESI hearing classified a drug as being effective for its labeled indication, FDA will still "require[] approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new Abbreviated New Drug Applications ("ANDAs") or NDAs, as appropriate, for IRS drugs."[22] It should be noted that we believe that this position is contrary to FDA law. We believe that the correct interpretation of the law would be that those products that had safety-only NDAs or were IRS to

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[18] 49 Fed. Reg. at 38,192.

[19] Adverse Drug Experience Reporting Requirements for Marketed Prescription Drugs Without Approved New Drug or Abbreviated New Drug Applications, 51 Fed. Reg. 24,476 (Jul. 3, 1986).

[20] Guidance on Marketed Unapproved Drugs; Compliance Policy Guide; 71 Fed. Reg. 33,466 (Jun. 9, 2006).

[21] 2006 Compliance Policy Guide at 4.

[22] Id. at 9.

safety-only NDA drug products, that had APIs that were found to be effective under the DESI review, that have been marketed subsequently for a material time and extent for over thirty years without any significant safety issues, and that have been allowed to remain on the market for over forty years due with FDA's implicit approval can be considered GRAS/E. We believe that hydrocodone liquid cough/cold solutions fall within this legal category. This position is further bolstered when one considers that the Drug Enforcement Agency ("DEA") has for over 30 years regulated the distribution of this API. Therefore, these products would not be required to obtain an approved application prior to marketing.

FDA also reiterated in the 2006 Compliance Policy Guide that products that are the subject of an ongoing DESI proceeding or an ongoing over-the-counter ("OTC") monograph proceeding would be permitted to remain on the market while that proceeding is pending, as well as for any extra time that is stated in that proceeding.[23]

In this revised CPG, FDA stated that consistent with its risk-based approach to the regulation of pharmaceuticals it would prioritize its enforcement actions and listed its highest enforcement priorities as the following: (1) unapproved marketed drugs that have potential safety risks; (2) unapproved marketed drugs that lack efficacy evidence; (3) unapproved marketed drugs that are health fraud drugs; (4) unapproved marketed drugs that "present direct challenges" to the OTC and new drug approval processes; (5) unapproved marketed drugs that are violative of the Act in other ways; and (6) unapproved marketed drugs that are reformulated to evade an FDA enforcement action.[24]

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[23] Id. at 4-5.

[24] Id. at 3-4.

Even after FDA has determined that a class of drug products is being marketed without approved applications and that they should have approved applications, the Agency stated that it may allow a grace period during which manufacturers could continue to market these products for a set period of time. In determining whether to establish a grace period for unapproved marketed drugs, FDA stated that it would consider the following factors: "(1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration."[25] FDA also stated that it will provide a grace period of roughly 1 year from the date of approval of a drug product before it will initiate enforcement action against marketed unapproved drugs of the same type.[26]

In the Appendix to this CPG, FDA acknowledged that it was possible that some unapproved drug products that were on the market could qualify as GRAS/E and therefore could remain on the market without an approved application.[27] Nevertheless, FDA expressed skepticism that any current unapproved marketed product could qualify as GRAS/E.[28]

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[25] 2006 Compliance Policy Guide at 5.

[26] Id. at 6.

[27] Id. at 11.

[28] Id.

We believe that the facts, when fairly reviewed, show that liquid hydrocodone cough/cold products are GRAS/E especially considering FDA's and DEA's four decade history of de facto support for the marketing of these products.

B. Overview of Hydrocodone Drug Products

Hydrocodone was first manufactured by Knoll Pharmaceuticals in the 1920s, and Knoll later produced an antitussive drug product containing hydrocodone named Dicodin Bitartrate.[29] The first approved use of hydrocodone as an antitussive in the United States occurred in 1943 when FDA approved Hycodan (NDA 5-213), which was manufactured by Endo Laboratories, Inc. ("Endo").[30] By 1961, Merrell Dow Pharmaceutical Inc. was producing a hydrocodone product named Mercodinone[31] and by 1967, Lemmon Pharmacal Company was also producing an antitussive hydrocodone product.[32]

Because there were several hydrocodone products on the market before 1962 with safety-only NDAs, FDA reviewed hydrocodone products under the DESI I program.[33] FDA first reviewed Hycodan – marketed as a syrup, tablet and powder – under the DESI program in April 1972, and concluded that the use of hydrocodone bitartrate in combination with homatropine methylbromide was "probably effective for the temporary relief of cough."[34] In July 1982, FDA reviewed Endo's Para Hycodan Tablets and Syrups, which contained hydrocodone bitartrate in

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[29] Physician's Desk Reference to Pharmaceutical Specialties and Biologics 419 (J. Morgan Jones et al. eds., 5th ed. 1951), Attachment A.

[30] 72 Fed. Reg. at 55,781.

[31] Remington's Practice of Pharmacy 66 (Eric W. Martin et al. eds., 12th ed. 1961), Attachment B.

[32] The United States Dispensatory and Physicians' Pharmacology 578 (Arthur Osol et al. eds., 26th ed. 1967), Attachment C. In addition to these drugs, there were also a number of other hydrocodone drug products listed on the DESI II list. FDA, Compliance Report for DESI-2 at 258-259, Attachment D.

[33] FDA, FDA Interim Trade Name Index to All Prescription Drugs in the Drug Efficacy Study-Cumulative Up to March 1, 1983, at 41, 109-110, Attachment E (listing Coditrate and Hycodan as DESI I drugs).

[34] DESI 5213, 37 Fed. Reg. 7827 (Apr. 20, 1972).

combination with hydrocodone telephthalate, homatropine terephthalate, and pentylenetetrazol, for use as an antitussive.[35] FDA concluded that there was not enough substantial evidence to show that the Para Hycodan products were effective as an antitussive, and so the Agency found these products ineffective.[36] In March 1982, FDA reviewed Coditrate Syrup (hydrocodone and potassium guaiacolsulfonate) under the DESI program.[37] Under this review, FDA found that the applicant had not presented evidence to show that guaiacolsulfonate was effective in the combination product, and as a result, FDA withdrew approval of the NDA for Coditrate Syrup on May 18, 1982.[38]

In June 1982, FDA again reviewed Hycodan Syrup, Tablets, and Powder under the DESI program and reclassified these products from probably effective to effective for the symptomatic relief of cough.[39] Under this review, FDA also classified Hycodan products as "new drugs" and stated that Endo needed to obtain an NDA, or a supplement to its NDA in order to continue to market its Hycodan line of products. Furthermore, FDA stated that anyone that was making products IRS to any Hycodan product also needed to obtain an approved application for its product. [40] FDA stated that if anyone objected to this decision, they could request a hearing from the Agency regarding this issue.[41] Since that DESI review and for the last twenty-five years, FDA has permitted hydrocodone antitussive drugs to be marketed without the need for an approved application. During this twenty-five year period, manufacturers of these drug products

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[35] DESI 7240, 37 Fed. Reg. 14,825 (Jul. 25, 1972).

[36] Id.

[37] DESI 5914 and 6514, 47 Fed. Reg. 11,973 (March 19, 1982).

[38] DESI 5914 and 6514, 47 Fed. Reg. 21,301 (May 18, 1982).

[39] DESI 5213, DESI 6290, DESI 6303, DESI 8658, and DESI 11935, 47 Fed. Reg. 23,809, 23,810 (June 1, 1982).

[40] Id.

[41] Id.

have registered their facilities with FDA, been routinely inspected for compliance with cGMPs, listed these drug products with the FDA under 21 C.F.R. § 207.20, and filed adverse event reports ("AERs") for these products. Accordingly, FDA through its continued inaction for the past forty years has de facto recognized their GRAS/E status.

In addition to the review of hydrocodone under the DESI system, hydrocodone was also submitted to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products for review as an API.[42] The OTC panel determined that hydrocodone was safe and effective but that it should be a prescription-only drug and should not be sold OTC.[43] According to the panel, hydrocodone was categorized as not GRAS/E for OTC use because of its abuse potential.[44] The panel stated that hydrocodone "is safe for prescription use but that its addiction potential and other adverse reactions, including respiratory depression, are so serious that it is not appropriate for OTC use."[45] The panel added that "the activity of [hydrocodone] in chronic and serious diseases make it a valuable drug for use under proper medical supervision and for that reason [the panel] recommends that its availability continue to be restricted to prescription use only, under the Federal Controlled Substances Act."[46]

Thus, hydrocodone was found to be a safe and effective drug under the DESI review, and the OTC Advisory Committee implied in its findings that hydrocodone was GRAS/E for prescription use. Merely because the OTC Advisory Committee found hydrocodone not

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[42] Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, Advance Notice of Proposed Rulemaking, 41 Fed. Reg. 38,312, 38,342 (September 9, 1976).

[43] Id.

[44] Id.

[45] Id.

[46] Id.

GRAS/E for OTC use does not mean, legally, that the drug is a new drug. Rather, it can be GRAS/E for prescription use, which is what we argue in this petition.

As well as being regulated by FDA as an API, hydrocodone is also regulated by the DEA as a controlled substance on an API basis. Under DEA regulations, hydrocodone used in bulk or single entity products is a Schedule II controlled substance[47] and is classified as a schedule III controlled substance when used in combination with non-narcotic active ingredients.[48] Because of the increasing abuse of hydrocodone products, DEA has been reviewing a proposal to move hydrocodone combinations from Schedule III to Schedule II.[49]

Currently, there are several hydrocodone products that have obtained an NDA and are on the market as prescription antitussive products.[50] There are also many other products that utilize hydrocodone in combination with analgesics for use as a prescription painkiller.[51] Ever since they have been on the market, both the manufacturers of these approved hydrocodone products and the manufacturers of the marketed hydrocodone products without approved applications have been required to report all adverse events to FDA on an API basis without the requirement for an approved application.

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[47] 21 C.F.R. § 1308.12(b)(1)(11).

[48] 21 C.F.R. § 1308.13(e)(1)(iii), (iv).

[49] DEA, Hydrocodone, Legislation (stating that the DEA "is currently reviewing a petition to increase the regulatory controls on hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act (CSA).") at http://www.usdoj.gov/dea/concern/hydrocodone.html (last visited Dec. 18, 2007).

[50] FDA, Questions and Answers About FDA's Enforcement Action Regarding Unapproved Hydrocodone Drug Products at http://www.fda.gov/cder/drug/unapproved_drugs/hydrocodone_qa.htm (last visited Dec. 18, 2007) (stating that the following hydrocodone products have approved applications with antitussive indications: Tussicaps, Tussionex Pennkinetic, Hydrocodone Compound, Mycodone, Homatroprine Methylbromide and Hydrocodone, Bitartrate, Hycodane, and Tussigon).

[51] Drugs at FDA listing for hydrocodone (listing Vicodin® and other hydrocodone/acetaminophen combination products) at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last visited Dec. 18, 2007).

In summary, the use of hydrocodone as an antitussive API for liquid cough/cold products has been reviewed under both the DESI and OTC review and found to be safe and effective for prescription use for almost half a century. FDA has also approved various prescription hydrocodone products for use as an antitussive. The Agency has been collecting adverse events on hydrocodone products for about forty years from both approved and unapproved marketed drug products. These drug products have been listing with the FDA under the regulations, and have been subject to decades of FDA cGMP inspections. In addition, hydrocodone products have also been closely regulated by the DEA as a controlled substance on an API basis. During its use in the market for over forty years, there has been no evidence that there are any inherent issues related to the safety or efficacy of this API that would require the whole class of drugs to be removed from the market. In addition, there has been no evidence that having an approved application for prescription versions of hydrocodone products has reduced the abuse potential for these drugs.

III. FDA Did Not Adequately Consider Relevant Information in Its Federal Register Notice

A FDA Did Not Consider Whether Hydrocodone Products Are GRAS/E for Prescription Use

In deciding whether to take action enforcement against manufacturers of hydrocodone products, FDA did not consider whether liquid cough/cold hydrocodone products could qualify for GRAS/E prescription status and therefore, would not require approved applications in order to stay on the market.

Our position is that FDA should consider products GRAS/E, in part, based upon the criteria that the Agency has followed for more than thirty years in evaluating the GRAS/E status

of OTC drugs by API[52], and the criteria that the Agency uses to establish that a drug is the therapeutic equivalent of an approved drug product.[53] Therefore, our position is that a product should be considered GRAS/E when: (1) there is a long history of safe API usage as a prescription drug product; (2) the products are marketed in the same basic dosage form; (3) the labeling among the products is adequate to describe safe and effective use; and (4) the products comport with the applicable compendial criteria, are manufactured in compliance with cGMPs, and report applicable AERs to the Agency.

Liquid cough/cold hydrocodone products on the market should qualify for GRAS/E status under the FFDCA because: (1) there is a long history showing that these products are safe and effective as antitussives; (2) these hydrocodone products are marketed in the same basic dosage form as versions found to be safe and effective; (3) the labeling for these hydrocodone products is similar to versions found to be safe and effective; and (4) these hydrocodone products comport with the applicable compendial criteria, are manufactured in compliance with cGMPs, and are required to have all adverse events regarding their use reported to the Agency.

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[52] In general, an OTC drug product will be considered GRAS/E when: (1) the API is covered under a monograph; (2) the drug product is labeled in accordance with the standards set in the monograph; and (3) the drug product is formulated in accordance with compendial standards and manufactured in accordance with cGMPs. 21 C.F.R. Part 330.

[53] FDA, Approved Drug Products with Therapeutic Equivalence Evaluations, 7 (27th ed. 2007) ("FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.") available at http://www.fda.gov/cder/orange/obannual.pdf (last visited Dec. 18, 2007).

1. Hydrocodone Has a Long History of Safe and Effective Use as an Antitussive

Prescription liquid cough/cold hydrocodone products have been on the market as antitussives since the 1940s, and physicians and pharmacists have widely recognized the benefits of these products. This wide-spread and long-term use demonstrates that hydrocodone has been seen to be a safe and effective drug for a material time and to a material extent.

The use of hydrocodone in liquid cough/cold products as an antitussive has been found to be safe and effective under the DESI program, which was specifically designed to determine whether pre-1962 drugs could be considered effective. In addition, the OTC review, which was designed to determine whether drugs qualified as GRAS/E and could therefore be sold without a prescription, found hydrocodone to be "safe for prescription use" and effective as "an active antitussive."[54] While the OTC Panel classified this product as not GRAS/E for OTC use, the Panel's statements clearly indicate that it recognized hydrocodone as safe and effective for prescription use. In fact, the Panel explicitly stated that "the activity of [hydrocodone] in chronic and serious diseases make it a valuable drug for use under proper medical supervision and for that reason [the panel] recommends that its availability continue to be restricted to prescription use only, under the Federal Controlled Substances Act."[55] An OTC panel is not restricted from making a finding that a substance is GRAS/E for prescription purposes, and we contend that this is exactly what the OTC panel implicitly did when reviewing hydrocodone. Because hydrocodone has been found to be safe and effective by both the DESI review and OTC panel as an antitussive, FDA should also acknowledge the GRAS/E status of hydrocodone.

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[54] 41 Fed. Reg. at 38,342.

[55] Id.

Moreover, FDA has presented scant evidence of any safety risks associated with hydrocodone use as an antitussive. According to FDA, from 1969 until 2005 FDA received more than 400 spontaneous serious AERs associated with antitussive hydrocodone-containing products.[56] Thus, over the course of thirty-six years, FDA has averaged between 11 and 14 serious spontaneous adverse events related to antitussive hydrocodone products per year. Given the widespread and long-term use of this product, 400 spontaneous AERs is a small number, especially when compared to the AERs described in FDA's proposal to include ibuprofen tablets in the OTC monograph for GRAS/E internal analgesics.[57] Additionally, FDA's calculation of AERs associated with antitussive prescription hydrocodone includes situations related to drug abuse and intentional overdose, which have nothing to do with the safety profile of API hydrocodone as an antitussive.[58] Therefore, the small number of AERs for prescription antitussive hydrocodone products for thirty-six years supports the assertion that liquid cough/cold hydrocodone products have a long history of safe and effective use.

While it is true that hydrocodone products have been abused and misused in recent years, this fact does not mean that certain liquid cough/cold hydrocodone products could not be considered GRAS/E. Instead, it simply means that hydrocodone products should continue to be restricted to sale as prescription products and controlled substances so that physicians and DEA

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[56] 72 Fed. Reg. at 55,782 ("As of 2005, FDA has received more than 400 spontaneous reports of serious adverse events associated with all antitussive hydrocodone-containing products. While significant under-reporting of adverse events from spontaneous sources in the general population occurs, the adverse event categories most often reported in association with such hydrocodone-containing products involve: (1) The central nervous system, including psychotic behavior and drug abuse; (2) the gastrointestinal tract, including nausea, vomiting, and constipation; (3) the cardiopulmonary system, including cardiac arrest and respiratory depression; (4) hypersensitivity, including pruritis, dermatitis, and pharyngeal edema; and (5) intentional and unintentional overdose.").

[57] Proposed Amendment of the Tentative Final Monograph, and Related Labeling, 67 Fed. Reg. 54,139, 54,146 (Aug. 21, 2007) (listing a total of 8,168 case reports associated with 16,627 adverse events attributed to the use of single-ingredient, nongeneric OTC ibuprofen over a twelve year time period).

[58] Id.

can ensure that these drug products are not further abused or inappropriately prescribed. Although FDA wants to require liquid cough/cold hydrocodone products to have approved applications, there is scant evidence to support that marketing under an approved application will have any impact on the abuse of these products. All hydrocodone products marketed for pain-relief are required to have an approved application, and according to DEA, these are the hydrocodone products that are typically abused.[59] Because of this fact, a required application will not reduce abuse of these products. Therefore, the fact that hydrocodone tablets for pain are widely abused should not affect the status of hydrocodone as GRAS/E for prescription use in liquid cough/cold products as an antitussive.

2. Hydrocodone Products Are in the Same Dosage Form

Liquid cough/cold hydrocodone products are in the same dosage form that have been on the market for decades and in the same dosage forms which FDA found to be safe and effective. FDA stated in the DESI review that hydrocodone was found to be effective in liquid form.[60] Specifically, FDA stated that Hycodan (containing hydrocodone and homatropine methylbromide) was effective in syrup, tablet, and powder form.[61] Additionally, FDA has recognized that drug products that are sold as true solutions generally do not have any bioequivalence or bioavailability issues when compared to other true solutions.[62] Therefore, there should be no bioavailability issues between the liquid cough/cold hydrocodone product that

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[59] DEA, Hydrocodone ("Hydrocodone has been encountered in tablets, capsules and liquid form in the illicit market. However, tablets containing acetaminophen are the most frequently encountered products . . . . In 2006, the Monitoring the Future Survey . . . reported that 3%, 7% and 9.7% of 8th, 10th, and 12th graders, respectively, reported non-medical use of Vicodin® in the previous year.") at http://www.usdoj.gov/dea/concern/hydrocodone.html (last visited Dec. 18, 2007).

[60] 47 Fed. Reg. at 23,810.

[61] Id.

[62] 21 C.F.R. §§ 320.22(b)(2), (c).

FDA reviewed in its DESI proceedings and current liquid cough/cold hydrocodone products. FDA's previous finding of effectiveness for liquid cough/cold hydrocodone products and the agency's acknowledgement that true solutions present no bioavailability problems support the conclusion that liquid cough/cold hydrocodone products should be a suitable form for a GRAS/E hydrocodone product.

3. Certain Hydrocodone Products Have the Same or Similar Labeling to GRAS/E products

The labeling for certain hydrocodone products is similar to versions found to be safe and effective. FDA already created labeling standards for hydrocodone products in its DESI review of hydrocodone. FDA stated that the applicable indication for hydrocodone products would be for "the symptomatic relief of cough" and that the labeling should contain a general warning against dispensing without a prescription.[63]

In its recent Federal Register notice, FDA stated that one of its major concerns with hydrocodone products without approved applications was the variations and omissions in labeling information for these products.[64] The Agency also stated that the "lack of uniformity in the labeling of unapproved [hydrocodone] products (particularly for unapproved products labeled for use in young children)" was one of the reasons why the Agency wanted to take quick enforcement action.[65] But the Agency did not acknowledge that FDA is free to set further standards for GRAS/E labeling of hydrocodone products simply through the use of Federal Register notices.[66] Additionally, using Federal Register notices to set uniform labeling for all

[63] 47 Fed. Reg. at 23,810.

[64] 72 Fed. Reg. at 55,782.

[65] Id.

[66] FDA's ability to remove only timed-release guaifenesin products illustrates the Agency's ability to remove products without an approved application based on deviations from what it considers to be GRAS/E. Timed-Release

hydrocodone products without an approved application would be easier than ensuring that each approved application for a hydrocodone product has consistent labeling within the entire class of products along with also trying to update approved labeling with new safety and efficacy information.

If FDA believes the current labeling for hydrocodone products without an approved application is inadequate to ensure against misuse and prescribing confusion, then the appropriate course of action would be for the Agency to adjust these standards – not to require all manufacturers of hydrocodone products to obtain an approved application to institute the Agency's desired labeling reforms.

Thus, the current labeling for certain liquid cough/cold hydrocodone products is similar to products that have been found to be safe and effective, and any issues related to the labeling of these products can be addressed by the Agency by creating new standards focused to address this problem.

4. Unapproved Hydrocodone Products Still Must Adhere to Compendial, cGMPs, and AER Requirements

Even though some hydrocodone drug products may not have an approved drug application, they are still required to meet certain requirements as set by the Agency regarding compendial requirements, cGMP requirements, and adverse event reporting requirements.

All drug products marketed in the U.S. must comport with applicable compendial standards. The U.S. Pharmacopeia ("USP") sets comprehensive specifications for drugs in individual ingredient-specific "monographs". The USP monographs set the following standards: drug name; definition; packaging, storage and labeling requirements; testing procedures; and

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Drug Products Containing Guaifenesin, 72 Fed. Reg. 29,517 (May 29, 2007). The Agency should use this power to issue labeling standards for GRAS/E hydrocodone products if it believes that the current labeling on these products is inadequate.

testing acceptance criteria to ensure that products will have the stipulated strength, quality, and purity. Failure to adhere to the applicable monograph means that a drug product will be classified as adulterated and misbranded under the FFDCA[67], regardless of whether that drug is considered a "new drug" or has achieved GRAS/E status.[68] Specifically, under the Act, any drug that "purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium" is considered to be adulterated.[69] Any drug that "purports to be a drug the name of which is recognized in an official compendium [is considered misbranded], unless it is packaged and labeled as prescribed therein."[70] Thus, even though a hydrocodone product is on the market without an approved application, it still must meet the requirements set forth in the USP.

In addition to the compendial requirements, hydrocodone products without an approved application must also be manufactured according to FDA's cGMPs. Under the law, all drugs are required to be manufactured according to cGMPs even if they do not have an approved application.[71] cGMPs are an extremely comprehensive set of methodologies and procedures that must be followed in the "manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."[72] Drugs

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[67] FFDCA §§ 501(b), 502(g).

[68] FFDCA §§ 501, 502.

[69] FFDCA § 501(b).

[70] FFDCA § 502(g).

[71] FFDCA § 501(a)(2)(B).

[72] 21 C.F.R. § 210.1(a).

that fail to conform to cGMPs are considered to be adulterated under the FFDCA,[73] and the drug itself, "as well as the person who is responsible for the failure to comply, [will] be subject to regulatory action."[74] In addition, because manufacturing facilities are required to register with FDA under cGMPs, FDA inspects the manufacturing of drug products to ensure that they are produced in accord with compendial standards and cGMPs even if the manufacturers do not have an approved application for their product.[75]

Finally, manufacturers of hydrocodone products without an approved application still must report any adverse events related to their product to the Agency as required under 21 C.F.R. § 310.305.[76] These regulations ensure that manufacturers of unapproved prescription drug products provide the Agency with sufficient data on the safety of these unapproved marketed drug products. The adherence to these requirements shows that these products are high quality drug products that must maintain high standards even though they are not subject to an approved application.

The information presented above demonstrates that the Agency already has evidence that: (1) liquid cough/cold hydrocodone products are safe and effective; (2) that there would be no bioequivalence issue with these products; (3) that there is acceptable labeling standards for these products or the Agency is able to revise the current labeling standards through Federal Register notices; and (4) that manufacturers of these products are already required to follow compendial requirements, cGMP requirements, and adverse event reporting requirements. Based on the wealth of available information on these products, it is unclear in this situation what further

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[73] FFDCA § 501(a)(2)(B).

[74] 21 C.F.R. § 210.1(b).

[75] FFDCA § 510; 21 C.F.R. Part 207.

[76] 21 C.F.R. § 310.305.

information the Agency would require to support an approved application for liquid hydrocodone cough/cold products other than chemistry, manufacturing, and controls data. Because FDA already has the information necessary to make a finding of safety and effectiveness, the entire concept of demanding approved applications for these products seems unnecessarily costly.

For the reasons stated above, FDA should reconsider its previous decision and find that certain liquid cough/cold hydrocodone products are considered GRAS/E and do not need approved applications to stay on the market.

IV. Hydrocodone Manufacturers Will Suffer Irreparable Injury If Petition for Reconsideration and Petition for Stay Is Denied

Even if FDA decides that it does not need to reconsider its previous decision, FDA should grant a stay of its enforcement action because FDA's enforcement action will cause irreparable injury to those manufacturers marketing hydrocodone products without an approved application.

FDA's notice only provides manufacturers with three months before it stated that the Agency would take enforcement action against these manufacturers. If a manufacturer of a hydrocodone product wanted to stay on the market under the Agency's position, it would have to conduct the necessary studies, file an NDA, and receive FDA approval within that three-month time period. No manufacturer can realistically meet this timeline. The alternatives are that a manufacturer will be forced to shut down production of that product until his application is approved or continue to market the product at his own risk.

While FDA may feel that its actions are fair considering that these products do not have approved applications, the Agency is partially responsible through its own actions and inactions for attracting manufacturers to this market. The reviews under the DESI and OTC monograph

program found hydrocodone to be safe and effective.[77] Furthermore, FDA's inaction over the past forty years has demonstrated to manufacturers that they did not need to obtain an NDA to enter the market. In fact, manufacturers would have had to bear substantial costs to get an NDA approved and even after approval, they would have still faced competition against other manufacturers of unapproved products that FDA had allowed to remain on the market.

In addition, FDA's 2006 Compliance Policy Guide would seem to give assurances that FDA would not take action against manufacturers of hydrocodone products because they do not qualify as a high priority risk. FDA states in its notice that it is taking action at this time against hydrocodone products in accordance with its 2006 CPG because (1) "hydrocodone is a drug with significant safety risks", and (2) "there are FDA-approved drug products containing hydrocodone" and thus "the continued marketing of unapproved versions is a direct challenge to the drug approval process."[78]

As discussed above, there have been relatively few reported serious adverse events – only an average of 11 to 14 per year – for prescription hydrocodone antitussive drug products over the past thirty-six years.[79] In addition, many of the safety risks mentioned in FDA's notice are most closely linked to abuse, medication error associated with formulation changes, and inappropriate and confusing labeling. These are not problems with hydrocodone drugs, but instead are problems associated with irresponsible manufacturers, doctors, and patients. If FDA knows of manufacturers who have inappropriately labeled or changed their products, then the Agency should take enforcement action against those manufacturers for selling products that are misbranded and/or adulterated. FDA should not, however, punish those responsible

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[77] See supra pp. 17-19.

[78] 72 Fed. Reg. at 55,783.

[79] See supra 18.

manufacturers that have been producing and selling hydrocodone for decades without incident by forcing them to obtain an approved application in an unrealistic time period. Furthermore, this petition does not object to FDA's outlawing of labeling that indicates that hydrocodone products can be used in children under six. We believe that this prohibition will address many of FDA's safety concerns, and FDA can address any other appropriate concerns through further labeling restrictions or regulations.

It is, however, true that other manufacturers have obtained an NDA for hydrocodone products, but FDA should still, at a minimum, provide a longer and more realistic grace period so that hydrocodone manufacturers are able to obtain NDAs during this period. FDA stated in its CPG that the Agency will generally provide a year grace period after the date of approval of an NDA for a product that has been marketed as an unapproved drug.[80] In the current situation, many hydrocodone products with NDAs have been on the market for a long time, and some have been approved as far back as 1983.[81] Nevertheless, we believe that FDA should generally set a preliminary grace period of at least a year based upon the date that FDA provided notice of its intention to take enforcement action against manufacturers. This action would be the only fair treatment given the fact that otherwise these manufacturers would not have any ability to enter the market lawfully in the grace period provided.

FDA also stated in its recent CPG that it would take into account the following factors when establishing a grace period for unapproved marketed drugs: "(1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to

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[80] 2006 Compliance Policy Guide at 6.

[81] FDA, Approved Drug Products with Therapeutic Equivalence Evaluations, ("Electronic Orange Book") entry for Mycodone at http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=088008&TABLE1=OB_Rx (last visited Dec. 18, 2007).

meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration."[82]

The wholesale removal of hydrocodone products without an approved application from the market will have a large impact on patients and their health. While it is true that there are approved hydrocodone drug products that will still remain on the market, the decreased supply will drive up prices for the remaining products to a point that patients may not be able to afford these drug products. Second, manufacturers of hydrocodone products would have a very difficult time of conducting the required studies and preparing an application in time to be able to remain on the market by the December 31 deadline. Third, as stated above, the removal of these products will have a huge effect on those manufacturers that have been selling these products for decades. Many of these companies rely on these products and the removal of these products from the market will have a material impact on the financial viability of these companies. Fourth, the Agency is currently facing much more pressing public health issues than those presented by liquid cough/cold hydrocodone products that has been on the market for over forty years and that have been extensively shown to be safe and effective.

Additionally, there is precedent for staying enforcement actions against marketed unapproved drug products so as to allow manufacturers an opportunity to navigate a lawful way onto the market. In the case of pancreatic insufficiency drug products, FDA originally provided a four year grace period during which manufacturers of pancreatic insufficiency drugs could

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[82] 2006 Compliance Policy Guide at 5.

continue to market their products before FDA would take any enforcement action against these manufacturers.[83] FDA recently extended this grace period for two more years for any manufacturer that obtained an investigational new drug application ("IND") and later submitted an NDA to FDA on these products.[84]

FDA also provided a similar grace period for levothyroxine sodium drug products. On August 14, 1997, FDA announced that drug products containing levothyroxine sodium were considered new drugs and thus, manufacturers would have to obtain approved applications to stay on the market.[85] FDA provided manufacturers three years during which they could continue to market their products.[86] On April 26, 2000, FDA extended this grace period for an additional year, until August 14, 2001, because the FDA concluded that manufacturers might need additional time to conduct studies and to prepare their applications.[87]

The short grace period that FDA has provided to hydrocodone manufacturers is arbitrary and inconsistent with the past grace periods it has provided to manufacturers of pancreatic insufficiency and levothyroxine sodium drug products.[88] Therefore, FDA should stay its enforcement action against liquid cough/cold hydrocodone products in a manner consistent with its previous actions by extending the grace period for two years and thereafter allowing

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[83] Exocrine Pancreatic Insufficiency Drug Products, 69 Fed. Reg. 23,410 (Apr. 28, 2004) (stating that the Agency would not take regulatory action against unapproved prescription pancreatic drug products until after April 28, 2008).

[84] Exocrine Pancreatic Insufficiency Drug Products, 72 Fed. Reg. 60,860 (Oct. 26, 2007) (extending the deadline to April 28, 2010 if the manufacturers have INDs on active status on or before April 28, 2008, and have submitted NDAs on or before Apr. 28, 2009).

[85] Prescription Drug Products; Levothyroxine Sodium 62 Fed. Reg. 43,535 (Aug. 14, 1997).

[86] Id.

[87] Prescription Drug Products; Levothyroxine Sodium; Extension of Compliance Date, 65 Fed. Reg. 24,488 (Apr. 26, 2000).

[88] 5 U.S.C. § 706(2)(A) (A court can hold unlawful and set aside agency action found to be arbitrary and capricious).

manufacturers to continue to market products for which they have submitted a drug application while FDA reviews their applications. Because FDA has permitted grace periods in analogous situations, failing to permit this grace period here would be arbitrary and capricious agency action.

V. Petition Is Not Frivolous and Is Pursued in Good Faith

This petition is not frivolous and is being pursued in good faith. As the evidence above demonstrates manufacturers of liquid cough/cold hydrocodone products have a strong interest in ensuring that their products are recognized by FDA as GRAS/E or alternatively, are provided enough time in which to obtain an approved application.

VI. Sound Public Policy Grounds Support This Petition and the Suggested Remedy Is Not Outweighed by Public Health or Other Public Interests

There are several sound public policy grounds to support this petition and there are no public interests that outweigh the proposed remedy.

First, the removal of hydrocodone products without an approved application from the market will hurt patients and third party payors. The removal of these products will greatly affect the supply and price of the remaining hydrocodone products. By restricting the supply of hydrocodone products, FDA will in turn decrease competition overall for antitussive products, which will allow remaining sellers of antitussive products to raise their prices to higher levels. This increase in price will result in increased costs to patients and third party payors for medical bills. If, instead, FDA allowed certain hydrocodone products to remain on the market as GRAS/E based on the Agency's previous findings that these products are safe and effective or if the Agency stayed its enforcement action until more manufacturers could obtain an approved application, then FDA would encourage more entry into the market and help lower health care costs.

Second, requiring manufacturers to submit applications to the FDA will unnecessarily hurt drug manufacturers that have been selling these products for decades. The costs of obtaining an NDA for these products may be too high for many small manufacturers to bear, and they will be forced to leave the marketplace. Those that could submit an NDA will be unnecessarily forced to do so in a hurried fashion if they want to remain on the market lawfully.

Third, requiring FDA to review NDAs for GRAS/E hydrocodone products needlessly diverts needed funds and manpower both from reviewing applications for other drug products and from other efforts needed to ensure the public health. Hydrocodone has been shown to be safe and effective for decades, and requiring FDA officials to examine applications that prove its effectiveness is an inefficient and unwise use of Agency resources.

Although patients, third party payors, manufacturers, and the FDA will all have to bear a large cost for the removal of hydrocodone products without approved applications, this cost could be theoretically offset if there were large enough benefits to the public to support these restrictions. Unfortunately, in the current situation, the benefits derived from the Agency's demands are all benefits that could be achieved in a cheaper and more efficient fashion.

FDA states several public health reasons why it has decided to institute these restrictions on manufacturers and sellers of hydrocodone products without approved applications.

First, FDA stated that there are serious adverse event reports associated with hydrocodone. Many of the adverse events as stated by FDA are related to the abuse and misuse of hydrocodone products by patients.[89] The abuse and misuse of these products does not support the need to require all manufacturers to obtain an approved application. The manufacturer of a hydrocodone product has no ability to influence the correct prescribing or administration of

[89] 72 Fed. Reg. at 55,782.

hydrocodone products. This task can only be accomplished by a physician and the patient. If FDA wants to help reduce the abuse of hydrocodone products, then it should work with the DEA to solve this problem. Nevertheless, requiring manufacturers to obtain an application will not decrease the abuse of hydrocodone. It should also be noted that at no point does FDA conclude that hydrocodone is not safe and effective for its indication as an antitussive product due to these AERs. If FDA did find hydrocodone to be unsafe or ineffective, then it should restrict the sale of all hydrocodone products and not just those that can be considered GRAS/E.

Second, FDA stated that there are serious adverse event reports associated with hydrocodone without approved applications due to unregulated formulation changes and similarity of proprietary names.[90] FDA already has the ability to regulate formulation changes and labeling problems through its power to regulate false and misleading labels as misbranded.[91] If FDA knows of products that have false or misleading labels based on AERs, then the Agency should take action now against those products instead of requiring all manufacturers to obtain an approved application. FDA has clearly demonstrated its ability to regulate the labeling of unapproved products through its restriction against labeling any hydrocodone products for use in children under six years of age.[92] This labeling restriction is the type of focused regulation that is more efficient at solving the present issues with hydrocodone prescription products than the Agency's proposed action, which will lead to unnecessary costs.

Lastly, FDA states that unapproved hydrocodone products pose a risk to the public health because they have neither demonstrated adequate bioavailability of their ingredients nor

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[90] Id. ("[T]he agency has received reports of medication errors associated with formulation changes, such as changing the strength of the active ingredient, and reports of confusion based on similarity between the proprietary names of unapproved hydrocodone-containing antitussive products and other drug products.").

[91] FFDCA § 502.

[92] 72 Fed. Reg. at 55,782.

demonstrated the adequacy of their chemistry, manufacturing, and controls specification.[93] While we believe that there would be no bioavailability issues for liquid cough/cold hydrocodone products because they are sold as true solutions and the Agency already has the ability to monitor the cGMPs of unapproved products, we would not object to the Agency increasing inspections of GRAS/E manufacturers or requiring certain evidence be submitted regarding the product's ingredients or manufacturing. Nevertheless, such a course of action does not lead to the conclusion that FDA needs to require manufacturers to submit an NDA to remain on the market.

Because the large costs to patients, third party payors, manufacturers, and FDA will not be offset in gains to the public health, we believe that sound public policy grounds support this petition and that the suggested remedy is not outweighed by any public benefit.

VII. Conclusion

The Agency should grant our petition for reconsideration to evaluate whether liquid hydrocodone cough/cold products can qualify as GRAS/E under the FFDCA. FDA should not take any enforcement action against makers of liquid hydrocodone cough/cold products before deciding this issue. As shown in the petition above, liquid hydrocodone cough/cold products have been shown to be safe and effective under both the DESI program and the OTC monograph system. Furthermore, these products have a long history of safe use, have only a relatively small number of adverse events related to them over the course of thirty-six years, and have adhered to all other regulations regarding compendial requirements and manufacturing cGMPs. While

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[93] Id. ("Finally, even the expected risks associated with use of approved products that contain hydrocodone are potentially greater for unapproved products because the quality, safety, and efficacy of unapproved formulations have not been demonstrated to FDA. For example, the ingredients and bioavailability of unapproved products have not been submitted for FDA review, nor has FDA had the opportunity to assess the adequacy of their chemistry, manufacturing, and controls specifications.").

certain liquid hydrocodone cough/cold products may fall outside the scope of being GRAS/E due to issues relating to labeling or formulation, FDA should address this problem by simply stating what labeling and formulation it would consider to be GRAS/E under the law.

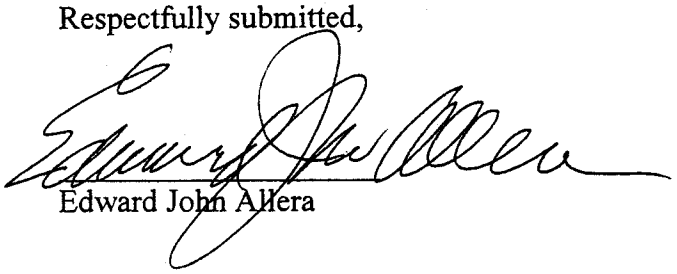
Alternatively, FDA should grant this stay its enforcement action against liquid hydrocodone cough/cold products to provide manufacturers an opportunity during which they could obtain an approved application for their product. FDA's previous guidance and statements support an extension of this grace period. Failure to provide such a grace period would be arbitrary and capricious given the Agency's treatment of other similarly situated manufacturers (*e.g.*, levothyroxine, pancreatic insufficiency drug products) and would cause irreparable injury to manufacturers of liquid hydrocodone cough/cold products.

Refusing to grant either the petition for reconsideration or the petition for stay will create unjustified expenses for FDA, manufacturers and the public without providing any benefit to the public welfare that could not be achieved in a less costly manner.

* * * *

Based on the forgoing, we respectfully request that the Agency reconsider its previous decision to take enforcement action against manufacturers or shippers of liquid cough/cold hydrocodone products not indicated for children under six years of age, or in the alternative, stay its enforcement action against manufacturers and shippers of liquid cough/cold hydrocodone products in a manner consistent with its previous actions by extending the grace period for two years until December 31, 2009, and thereafter allowing manufacturers to continue to market products for which they have submitted a drug application while FDA reviews these applications.

Respectfully submitted,



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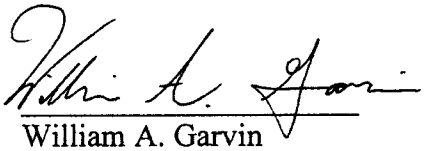

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Attachment A

PHYSICIANS' DESK REFERENCE TO PHARMACEUTICAL SPECIALTIES AND BIOLOGICALS

PDR

1951

Fifth Edition

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Compilation and printing mechanics require our using an arbitrary page numbering plan. Section One starts on 101, Section Two on 201, Section Three on 301, Section Four on 401 and Section Five on 601.

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ALPHABETICAL INDEX

SECTION II (Yellow)
DRUG, CHEMICAL and PHARMACOLOGICAL INDEX

SECTION III (Blue)
THERAPEUTIC INDICATIONS INDEX

SECTION IV (White)
PROFESSIONAL PRODUCTS INFORMATION

SECTION V (Green)
GENERAL PROFESSIONAL INFORMATION

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ous Suspension: A crystalline testoster- m designed for pro- ct. *rbs":* Specially pre- testosterone designed ual administration. For subcutaneous im- ained and prolonged

S: In the Male: As in eunuchism, eunu- ic, etc.; to produce ac- vth in cases of dwarf- me, etc.; as a protein treatment of debilitat- es, osteoporosis, etc. onal uterine bleeding, ociated with inhibition rhea, the menopausal nd the treatment of rtain selected cases.

AND DOSAGE: *s Suspension:* 25 mg. three times weekly sponse of the patient *rbs":* 3 mg. to 6 mg. ily. The "Lingusorb" l pouch or under the

ntinued on next page

Ayerst, McKenna, & Harrison—Cont.

Testosterone Pellets: When 75 mg. weekly of Testosterone by injection is required, 4 to 6 pellets are implanted (300 mg. to 450 mg.). With lower requirements, the number of pellets is reduced accordingly. Implantation technics are outlined in package insert.

PRECAUTIONS: Sexual precociousness may be induced by prolonged therapy in the preadolescent male patient. Androgens should be administered with care to elderly patients with cardiovascular impairment, and should be contraindicated when prostatic carcinoma is present or suspected. When treating women with androgens, it is suggested that under ordinary circumstances the total monthly dosage should not exceed 300 mg. by injection or from 500 mg. to 600 mg. by the buccal or sublingual route.

HOW SUPPLIED: Testosterone in Aqueous Suspension: No. 544—25 mg. per cc., 10 cc. vials; No. 545—100 mg. per cc., 5 cc. vials.

Testosterone "Lingusorbs": No. 591 — 3 mg. per "Lingusorb"; No. 592 — 6 mg. per "Lingusorb." Bottles of 30, 100, 500, and 1,000.

Testosterone Pellets: No. 596 — 75 mg. in each pellet. Supplied in sterile, aluminum foil envelopes. Packages of 1 and 3 envelopes.

LITERATURE AVAILABLE: Yes.

Barnes, A. C. Company

NEW BRUNSWICK, N.J.

ARGYPULVIS®

COMPOSITION: Contains finely milled ARGYROL in a kaolin-lactose base, in two forms: as an insufflation powder in 7-gram bottles fitting the Holmspray or equivalent vaginal insufflator, and as a vaginal insertion capsule containing 2 grams.

ACTION AND USES: The two dosage forms of ARGYPULVIS make possible a combined home and office treatment of Trichomonas vaginalis vaginitis assuring continuity of treatment and efficient control.

ADMINISTRATION AND DOSAGE: Insufflation—A speculum is put in place. A 7-gram bottle of ARGYPULVIS is attached to the insufflator and a gentle stream of the powder directed into the fornices until from one third to one half of the bottle has been transferred. Capsule insertion—Following a nightly douche of 2 quarts of warm water containing 4 tablespoonfuls of white vinegar, the patient inserts 1 or 2 capsules of ARGYPULVIS high in the vaginal vault. This is done for 6 successive nights. On the 7th night the patient uses only the douche and returns to the physician for reexamination the following day. Repeat for a 2nd and 3rd week after which treatment usually can be discontinued, with continuing precaution vs. contamination and reinfection and return for checkup after 1, 4, 7, 10 and 22 weeks.

HOW SUPPLIED: Physician's Package, Carton of three 7-Gram bottles. Patient's Package, Bottle of twelve 2-Gram capsules.

LITERATURE AVAILABLE: Mailed to physicians on request. Also, sample.

ARGYROL®

COMPOSITION: A stable, colloidal preparation containing 20% of silver combined with protein to give solutions with a silver ion concentration near 10^{-8}, a pH near 9 and a particle diameter between 1/10th and 1/100th that of Staph. aureus.

ACTION AND USES: ARGYROL is used mainly on mucous membrane, as a bacteriostatic anti-infective, mild astringent, detergent and demulcent, effective against both Gram-positive and Gram-negative bacteria.

Barnes—Cont.

ADMINISTRATION AND DOSAGE: Nose: Tampons of 10% ARGYROL, as described by Dowling and Haseltine; drops of 10 to 20% solution, 1 to 3 to each nostril, at intervals of 2 to 4 hours.

Eyes: 1 to 3 drops of 10 to 20% solution at intervals of 2 to 4 hours.

Cervix: Tampons of 20% ARGYROL in glycerin, as described by Balas.

Genito-urinary: Acute Gonorrhea: 1.5 cc of 5% solution sealed in the anterior urethra once a day for 4 days, together with sulfathiazole orally, as described by Ballenger, McDonald and Coleman. Prophylaxis: 10% solution, into the urethra, within one hour after exposure.

HOW SUPPLIED: Bottles of 1-oz. and 4-oz. Crystals.

Original Packages for compounding 5, 10, 15, 20 and 25% solutions in ¼, ½, 1, 2, and 4-oz. sizes.

Tablets 0.2 Gm.—Bottles of 37—Packages of 3 Bottles.

LITERATURE AVAILABLE: Mailed to physicians on request. Also, sample.

OVOFERRIN®

COMPOSITION: A colloidal solution of iron, stabilized by protein and containing 8% of alcohol as a preservative; elementary iron content 0.4% (64 mg. per tablespoonful); practically non-ionized (ionic iron content below that producing irritant or astringent effect on mucous membrane); pH near 6.

ACTION AND USES: OVOFERRIN provides iron in a form which can be assimilated and utilized for hemoglobin production by persons with iron deficiency, without disturbing digestion, causing constipation or affecting the teeth.

ADMINISTRATION AND DOSAGE: 1-2 tablespoonfuls in water or milk, before or after meals and at bedtime; children, 1 or 2 teaspoonfuls in water or milk.

HOW SUPPLIED: Bottles of 11 ounces.

LITERATURE AVAILABLE: Mailed to physicians on request. Also, sample.

PDR SECTIONS

PINK

Alphabetical Index: Firms and Products

YELLOW

Classified Index—Drugs, Chemicals Pharmacological Designations

BLUE

Classified Index—Therapeutic Indications

WHITE

Professional Products Information

GREEN

General Professional Information

Bilhuber-Knoll Corp.

377 CRANE ST.
ORANGE, N.J.

BROMURAL-BILHUBER

COMPOSITION: Alpha mono-brom-isovaleryl carbamide; is neither a bromide nor a barbiturate.

ACTION AND USES: A quick-acting somnifacient. Direct action lasts 3 to 4 hours. An efficient daytime sedative in nervousness, nervous exhaustion, excitability and irritability; is non-cumulative. For use as sedative in circulatory neuroses, neurasthenia, menopausal hypertension; in asthma, whooping cough and for preliminary sedation in anesthesia. As mild hypnotic for insomnia.

ADMINISTRATION AND DOSAGE: As a sedative—1 tablet several times daily. For hypnosis—2 or 3 tablets at bedtime or during the night. Children in proportion.

HOW SUPPLIED: Tablets, 5 grain, bottles of 100 and 500. Powder, bottles of 1 oz.

DICODID® BITARTRATE

COMPOSITION: Dihydrocodeinone bitartrate. A white crystalline powder freely soluble in water.

ACTION AND USES: Same as codeine or morphine; a powerful analgesic and cough sedative; quick acting and well tolerated. For the relief of pain and as a sedative in various types of irritative coughs.

ADMINISTRATION AND DOSAGE: For cough—1/12 gr. For pain—1/6 gr.

CONTRAINDICATIONS: Same as for morphine or codeine, observing same precautions in respect to respiratory depression and habit formation. Note smaller dosage.

HOW SUPPLIED: DICODID bitartrate oral tablets (soluble) 5 mgm. (1/12 grain), tubes of 10. Powder, vials of 15 grains.

DILAUDID® HYDROCHLORIDE

COMPOSITION: Dihydromorphinone hydrochloride, a white crystalline powder, freely soluble in water.

ACTION AND USES: For relief of severe pain in inoperable carcinoma; in surgery, obstetrics, urological procedure; in renal colic and for cardiac pain. As an opiate cough sedative.

ADMINISTRATION AND DOSAGE: For pain relief 1/32 to 1/20 grain hypodermically. (1/20 grain Dilaudid HCl is considered equivalent to ¼ grain morphine sulfate in analgesic power). Orally, 1/24 grain, as tablets or solution of the powder; increase dose as required. Rectally, 1/24 grain in suppository. For cough—smaller doses, best given in a palatable opiate-free cough vehicle, ½ grain to 4 or 6 oz. vehicle, in teaspoonful doses.

CONTRAINDICATIONS: Same as for morphine, observing same precautions in respect to respiratory depression and habit formation. Note much smaller dosage.

HOW SUPPLIED: DILAUDID hydrochloride (N.N.R.)—Tablets, oral, 1/24 grain, tubes of 10, bottles of 100. Tablets, hypodermic, 1/64, 1/48, 1/32, 1/20, 1/16 grain, tubes of 20, bottles of 100. Suppositories, 1/24 grain, boxes of 6. Ampules 1 cc. 1/32 and 1/20 grain, 6's. Powder, vials of 15 grains.

EURESOL, EURESOL PRO CAPILLIS

COMPOSITION: A synthetic organic compound; a viscid amber-colored liquid readily soluble in alcohol and acetone, insoluble in water; miscible with ointment bases.

ACTION AND USES: Astringent, stimulant, readily penetrating, non-irritating and less toxic than resorcin. For use in the treatment of eczema, itching dermatoses, dandruff, alopecia and seborrhea.

ADMINISTRATION AND DOSAGE: Scalp—Euresol pro capillis, as inunction, or as a 3% alcoholic solution. For dry scalp,

Continued on next page

Attachment B

Remington's
PRACTICE OF PHARMACY

A treatise on the manufacturing, standardizing, and dispensing of pharmaceutical products, with biological and chemical properties and tests, assays, uses, and doses; also a guide to the legal obligations of the pharmacist and the professional services rendered in helping to maintain community health . . . A textbook and reference guide for pharmacists, physicians, and other medical scientists

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Eric W. Martin E. Fullerton Cook

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John E. Hoover

With the cooperation of more than 250 assistant editors and contributors

OVER 1,000 ILLUSTRATIONS

TWELFTH EDITION

MACK PUBLISHING COMPANY

EASTON, PENNSYLVANIA / 1961

Library of Congress Catalog Card No. 60-53334

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

Specialty Containing Opium Alkaloids

Pantopon (Roche)—Ampuls, each ml. containing 20 mg. of a mixture of the hydrochlorides of the opium alkaloids in approximately the same proportion as they occur in Turkish opium. Also available as hypodermic tablets, oral tablets, and powder. *Uses:* narcotic analgesic. *Dose:* 20 mg., used where 10 to 15 mg. of morphine would be required.

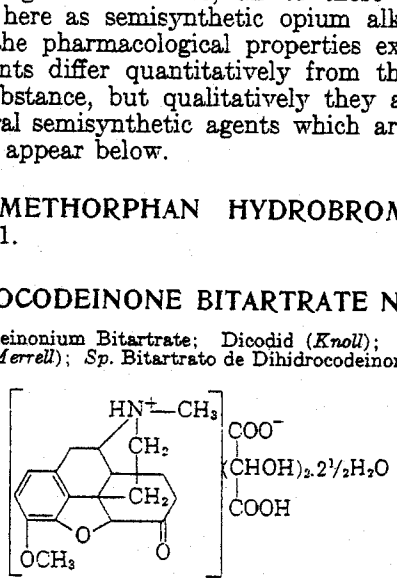
Semisynthetic Opium Alkaloids

In an effort to obtain an agent which would possess the advantages of morphine or codeine without their disadvantages, chemists have modified the structure of these natural alkaloids of opium. Some of these modifications, *e.g.*, dihydrocodeinone, dihydromorphinone, ethylmorphine, nalorphine, etc., result from making minor chemical alterations in the natural alkaloids, the iminoethanophenanthrene nucleus (see page 647) remaining intact. Others, *e.g.*, dextromethorphan, levorphanol, levallorphan, etc., are truly synthetic compounds constructed around the nonopiate morphinan nucleus (see page 647) which is readily synthesizable from coal tar derivatives. For pharmacologic convenience, all of these agents are classified here as semisynthetic opium alkaloids. In general, the pharmacological properties exhibited by these agents differ quantitatively from those of the parent substance, but qualitatively they are similar. The several semisynthetic agents which are clinically employed appear below.

DEXTROMETHORPHAN HYDROBROMIDE—See page 821.

DIHYDROCODEINONE BITARTRATE N. F., Ph. I.

[Dihydrocodeinonium Bitartrate; Dicodid (*Knoll*); Mercodinone (*Merrell*); *Sp.* Bitartrato de Dihidrocodeinona]



Dihydrocodeinone Bitartrate contains not less than 98 per cent and not more than 102 per cent of $C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$ (494.51).

Preparation—This synthetic alkaloid is prepared either by catalytic rearrangement of codeine or by hydrolysis of dihydrothebaine.

Description—Fine white crystals or a fine white crystalline powder. It is affected by light. The N. F. provides tests for *Identification* and *Purity*.
Solubility—One Gm. dissolves in 16 ml. of water. It is slightly soluble in alcohol and insoluble in ether and in chloroform.
Assay—Dihydrocodeinone (base) is liberated and isolated from a sample and reacted with an excess of standard sulfuric acid. The surplus acid is then titrated with standard sodium hydroxide solution using methyl red as the indicator. See page 1455.
Storage—Preserve in tight, light-resistant containers.

Uses—This alkaloid possesses the *antitussive* and *analgetic* activity of *Codeine* (page 1072). It is a narcotic which causes addiction, and is controlled by the *Harrison Narcotic Act*.

Dose—*Usual*, 10 mg.

Dihydrocodeinone Bitartrate Syrup N. F.

[*Sp.* Jarabe de Bitartrato de Dihidrocodeinona]

Dihydrocodeinone Bitartrate Syrup contains not less than 90 per cent and not more than 110 per cent of the labeled amount of $C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$. Dihydrocodeinone Bitartrate Syrup may be prepared according to the following formula:

Dihydrocodeinone Bitartrate	2.5 Gm.
Purified Water	50 ml.
Cherry Syrup, a sufficient quantity,	
To make	1000 ml.

Dissolve the dihydrocodeinone bitartrate in the water by warming gently and add sufficient cherry syrup to make the product measure 1000 ml.

Alcohol Content—From 1 to 2 per cent of C_2H_5OH.
Assay—The method described above for *Dihydrocodeinone Bitartrate* is adapted to the Syrup.
Storage—Preserve in well-closed, light-resistant containers.

Uses and Dose—See *Dihydrocodeinone Bitartrate*.

The Syrup contains 12.5 mg. of the alkaloidal salt in 5 ml. (1/8 grain per fluidram.)

Dihydrocodeinone Bitartrate Tablets N. F.

[Dicodid Bitartrate Tablets (*Knoll*); (*Endo*); *Sp.* Tabletas de Bitartrato de Dihidrocodeinona]

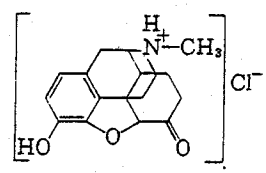
Dihydrocodeinone Bitartrate Tablets contain not less than 90 per cent and not more than 110 per cent of the labeled amount of $C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$.

Description—The N. F. provides tests for *Identification* and requirements for *Disintegration* and *Weight variation*.
Assay—The method described above for *Dihydrocodeinone Bitartrate* is adapted to the Tablets.
Storage—Preserve in tight, light-resistant containers.

Uses and Dose—See *Dihydrocodeinone Bitartrate*.

DIHYDROMORPHINONE HYDROCHLORIDE U. S. P., Ph. I.

[Dihydromorphinoni Hydrochloridum; Hydromorphone Hydrochloride; Dihydromorphinonium Chloride; Dilaudid (*Knoll*); Hymorphan Hydrochloride (*Endo*); *Sp.* Clorhidrato de Dihidromorfinona]



Preparation—Dihydromorphinone hydrochloride [$C_{17}H_{19}NO_3.HCl$(321.81)] is made by passing hydrogen into a solution of morphine hydrochloride in the presence of palladium as a catalyst.

Description—A fine, white, odorless, crystalline powder, affected by light. Specific rotation: $-136°$ to $-139°$. Its aqueous solution is practically neutral or only slightly acid to litmus. The U. S. P. provides tests for *Identification* and *Purity*.
Solubility—One Gm. dissolves in about 3 ml. of water. It is sparingly soluble in alcohol, and nearly insoluble in ether.
Storage—Preserve in tight, light-resistant containers.
Incompatibilities—Reactions characteristic of alkaloids are generally applicable to this substance. See page 668.

Uses—Dihydromorphinone (Dilaudid) is allied both chemically and pharmacologically to morphine and has the same general actions and uses as morphine. However, it differs in certain respects. It is more analgetic and more toxic on a weight basis and hence is given in doses one-fourth as large as for morphine. The duration of analgesia is definitely shorter than for morphine

Attachment C

26th Edition

THE UNITED STATES DISPENSATORY

and Physicians' Pharmacology

ARTHUR OSOL, PH.D., LL.D.

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Director of Medical Service, Wyeth Laboratories, Inc.; Clinical Professor of Medicine, Temple University School of Medicine

PHILADELPHIA & TORONTO

J. B. LIPPINCOTT COMPANY

Entered, according to Act of Congress, in the year 1877,
By GEORGE B. WOOD, M.D.,
In the Office of the Librarian of Congress at Washington

The first twenty-five editions of this book were published under the title of *The Dispensatory of the United States of America*. These editions were published from 1833 to 1960 and the abridgment to the shorter title, *The United States Dispensatory*, has been first made with this edition.

Distributed in Great Britain by
PITMAN MEDICAL PUBLISHING CO., Limited, London

Library of Congress
Catalog Card Number
67-17443

Printed in the United States of America

1 3 5 6 4 2

fetor hepaticus, which are signs of impending hepatic coma.

When prescribed with potent antihypertensive drugs, especially ganglionic blocking agents, the dose of the latter should be reduced by one-half or more.

The possibility that thiazide drugs may decrease arterial responsiveness to levarterenol and other pressor amines and enhance the paralyzing action of tubocurarine in surgical patients suggests the advisability of discontinuing therapy with thiazides a week before elective surgery. It may be noted, however, that patients who have had emergency surgery while being treated with hydrochlorothiazide have rarely been subject to untoward effects.

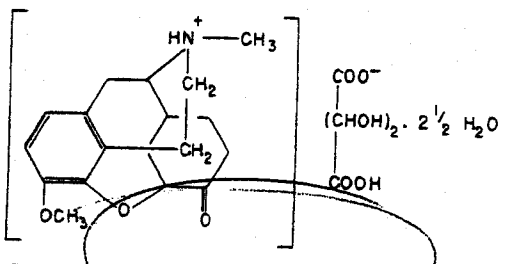
The possibility that electrolyte disturbances and neonatal thrombocytopenia may develop in the fetus and newborn infant requires careful use of thiazide diuretics in edema and toxemia of pregnancy.

Dose. — The initial dose of hydrochlorothiazide, when used as a diuretic for adults, is in the range of 25 to 200 mg. daily; the average maintenance dose is 75 to 100 mg. daily. As an antihypertensive the usual dose is 25 to 50 mg. once or twice daily, but as much as 200 mg., in divided doses, may be necessary. The dose for children is one-tenth that of chlorothiazide, which is 40 mg. per Kg. of body weight daily; thus the dose of hydrochlorothiazide is 4 mg. per Kg. daily, divided into 2 doses administered orally. The A.M.A. Council on Drugs, however, recommends for children a daily dose of 2 mg. per Kg., and for infants under 6 months of age, up to 3 mg. per Kg. daily, in each case given in 2 divided doses.

Dosage Forms.—Tablets containing 25 and 50 mg.

Hydrocodone Bitartrate

Hydrocodone bitartrate is dihydrocodeinone bitartrate and contains not less than 98 per cent of $C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$.



Dihydrocodeinone bitartrate; Codone (*Lemmon*); Dicodid (*Knoll*); Hycodan (*Endo*); Mercodinone (*Merrell*).

Dihydrocodeinone is a rearrangement product of codeine; it differs from codeine in containing a ketone group in place of hydroxyl and in having one double bond hydrogenated, thus leading to the same empirical formula for both compounds. Dihydrocodeinone may be prepared by catalytic rearrangement of codeine or by hydrolysis of dihydrothebaine (*J. A. Ph. A.*, **40**, 580, 1951).

Description.—Fine, white, crystalline powder; affected by light. One Gm. dissolves in about 16 ml. of water. Slightly soluble in alcohol; insoluble in ether and in chloroform.

Actions and Uses.—Hydrocodone bitartrate is essentially similar to codeine salts in its actions; when compared on the basis of equal content of the active moiety the hydrocodone salt is both more active and more prone to cause addiction.

Hydrocodone bitartrate is used primarily as an antitussive. It is a useful cough sedative in acute respiratory infections, laryngeal and pulmonary tuberculosis, acute and chronic bronchitis, and cough associated with heart disease. It is not considered to have any clearcut advantage over codeine.

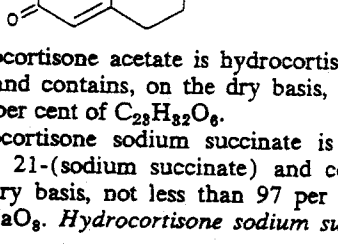
Untoward Effects.—The effects are similar to those of codeine. In therapeutic doses its effect on respiration is minimal; however, it is capable of producing respiratory depression similar to that of codeine when used in large doses. It is reported to be less constipating than either codeine or morphine. Hydrocodone has a greater addiction liability than codeine.

Dose.—The usual adult dose, given orally, is 5 mg., with a range of 5 to 10 mg., every 6 to 8 hours. The dose for children is 0.6 mg. per Kg. of body weight daily, divided into 3 or 4 portions.

Dosage Forms.—Syrup containing 5 mg. in 5 ml.; tablets containing 5 mg.

Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Sodium Succinate

Hydrocortisone is 11β,17,21-trihydroxypregn-4-ene-3,20-dione and contains, on the dry basis, not less than 97 per cent of $C_{21}H_{30}O_5$.



Hydrocortisone acetate is hydrocortisone 21-acetate and contains, on the dry basis, not less than 97 per cent of $C_{23}H_{32}O_6$.

Hydrocortisone sodium succinate is hydrocortisone 21-(sodium succinate) and contains, on the dry basis, not less than 97 per cent of $C_{25}H_{33}NaO_8$. *Hydrocortisone sodium succinate*

Attachment D

COMPLIANCE CODE: B04

000065-0311 ALCON LABORATORIES INC.	ISOPTO HOMATROPINE 2%		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	OPTHALMIC	2 %
		2 %HV	
000998-0311 ALCON (PUERTO RICO) INC.	ISOPTO HOMATROPINE		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	OPTHALMIC	2 %
		2 %HV	
000065-0315 ALCON LABORATORIES INC.	ISOPTO HOMATROPINE 5%		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	OPTHALMIC	5 %
		5 %HV	
000065-0712 ALCON LABORATORIES INC.	HOMATROPINE HYDROBROMIDE		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	INTRAOCULAR	5 %
		5 %HV	
000998-0315 ALCON (PUERTO RICO) INC.	ISOPTO HOMATROPINE		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	OPTHALMIC	5 %
		5 %HV	
010719-*254 MAURRY BIOLOGICAL COMPANY, INC.	HOMATROPINE HYDROBROMIDE		
HOMATROPINE HYDROBROMIDE	SOLN(NONINJ)	OPTHALMIC	5 %
		5 %HV	
050732-*650 LUCHEM PHARMACEUTICALS INCORP.	NALEX DH		
	LIQUID	ORAL	
HYDROCODONE BITARTRATE		1.67 MG	
PHENYLEPHRINE HYDROCHLORIDE		5 MG	
000056-0246 DU PONT PHARMACETICALS	HYCOMINE		
	SYRUP	ORAL	
HYDROCODONE BITARTRATE		5 MG	
PHENYLPROPANOLAMINE HYDROCHLORIDE		25 MG	
000056-0247 DU PONT PHARMACETICALS	HYCOMINE PEDIATRIC		
	SYRUP	ORAL	
HYDROCODONE BITARTRATE		2.5 MG	
PHENYLPROPANOLAMINE HYDROCHLORIDE		12.5 MG	

COMPLIANCE CODE: B04

000131-5034 CENTRAL PHARMACAL CO., THE	CODICLEAR DH			
	SYRUP			
HYDROCODONE BITARTRATE		ORAL		
POTASSIUM GUAIACOLSULFONATE		5 MG		
		300 MG		
000068-0042 MERRELL-DOW PHARMACEUTICALS, INC.	TUSSEND			
	TAB,PC			
HYDROCODONE BITARTRATE		ORAL		
PSEUDOEPHEDRINE		5 MG		
		60 MG		
000068-1018 MERRELL-DOW PHARMACEUTICALS, INC.	TUSSEND LIQUID			
	LIQUID			
HYDROCODONE BITARTRATE		ORAL		
PSEUDOEPHEDRINE HYDROCHLORIDE		5 MG		
		60 MG		
000178-0959 NATIONAL PHARMACEUTICAL MFG., CO.	DETUSSIN LIQUID			
	LIQUID			
HYDROCODONE BITARTRATE		ORAL		
PSEUDOEPHEDRINE HYDROCHLORIDE		5 MG		
		60 MG		
010235-1031 CHEMRICH LABORATORIES	CORTISOL			
	LOTION			1 %
HYDROCORTISONE		TOPICAL		
		1 %HV		
000077-0715 BARNES-HIND INC	BARSEB THERASPRAY			
	AEROSOL,SPRAY			
HYDROCORTISONE		TOPICAL		
SALICYLIC ACID		360 MG		
		288 MG		
053653-8331 NESTAR DENTAL, INC.	THIXO-GEL			
	GEL			
HYDROFLUORIC ACID		TOPICAL		
PHOSPHORIC ACID		.34 GM		
		1 GM		
000273-0129 LORVIC CORPORATION, THE	KARIDIUM THIXOTROPIC TOPICAL GEL-CHERRY FLAVOR			1.2 %
	GEL			
HYDROFLUORIC ACID		DENTAL		
PHOSPHORIC ACID		NS		
		NS		

Attachment E

PRODUCT NAME	M W	NDA/E NUMBER	DESI NO.	A N T	FIRM NAME	DOSAGE /RTE ADMIN	ORIG PUB. DATE	ORIG PUB. PAGE	ORIG PUB. CLASS	MILE STONE DATE	EXM CAT	CURRENT, HIGH CLASS	F I N
CO-HYDELTRA		10372/011	09414		MSD	TAB/ORAL	72/07/11	566	1000	72/02/08 72/07/11		INEFFECTIVE	F
CO-PYRONIL		08305/022	07366		DISTA PRODUCTS	CAP/ORAL	71/08/19	128	1200	72/12/14 78/02/17 82/08/17	15	INEFFECTIVE	F
		09234/011	07366		DISTA PRODUCTS	SUS/ORAL	71/08/19	128	1200	82/09/15 82/10/18 83/01/07 72/12/14 78/02/17 82/08/17 82/09/15 82/10/18 83/01/07	15	INEFFECTIVE	F
CO-PYRONIL PEDIATRIC		08305/021	07366		DISTA PRODUCTS	CAP/ORAL	71/08/19	128	1200	72/12/14 78/02/17 82/08/17 82/09/15 82/10/18 83/01/07	15	INEFFECTIVE	F
COCO-DIAZINE		06317/051	04054		LILLY	SUS/ORAL	69/06/17	464	1204	69/06/17 69/08/30 70/11/20 77/04/22 78/05/12		EFFECTIVE	F
COCO-SULFONAMIDES TRIP		06317/011	02053		LILLY	SUS/ORAL	69/09/11	299	1000	70/05/20 70/10/15		INEFFECTIVE	F
CODITRATE		06529/011	06514		CENTRAL PHARCA	SYR/ORAL	73/02/09	006	1000	73/02/09 73/12/14 78/02/17 82/03/19 82/05/18	15	INEFFECTIVE	F
COGENTIN		09193/011	01403		MSD	TAB/ORAL	70/11/07	211	0004	-		EFFECTIVE	F

PRODUCT NAME	M W	NDA/E NUMBER	DESI NO.	A N T	FIRM NAME	DOSAGE /RTE ADMIN	ORIG PUB. DATE	ORIG PUB. PAGE	ORIG PUB. CLASS	MILE STONE DATE	EXM CAT	CURRENT, HIGH CLASS	F I N
HIWOLFIA RED		09276/011	08867		BOWMAN PHARM	TAB/ORAL	71/04/28	984	1204	76/08/05		EFFECTIVE	F
		09276/013	08867		BOWMAN PHARM	TAB/ORAL	71/04/28	984	1204	71/04/28 76/08/05		EFFECTIVE	F
HORMOTONE T 1000 1U		00758/012	00758		CARNRICK	TAB/ORAL	70/08/29	802	1000	71/02/18		INEFFECTIVE	F
HORMOTONE T 5000 1U		00758/011	00758		CARNRICK	TAB/ORAL	70/08/29	802	1000	71/02/18		INEFFECTIVE	F
HUMACORT		50204/011	50204	A	PD	ONT/TOP	70/09/23	799	0200	71/10/23 72/02/12		INEFFECTIVE	F
HUMATIN		12790/011	12019		PD	SYR/ORAL	70/05/13	465	1204	71/07/03		EFFECTIVE	F
HUMATIN 250MGCAP		12019/011	12019	A	PD	CAP/ORAL	70/05/13	465	1204	71/07/03		EFFECTIVE	F
HUMORSOL 1.25 MG/ML		11860/011	00654		MSD	SOL/OPH	70/06/25	392	0004	-		EFFECTIVE	F
HUMORSOL 2.5 MG/ML		11860/012	00654		MSD	SOL/OPH	70/06/25	392	0004	-		EFFECTIVE	F
HY-COR ACETATE		09786/011	07110		GOLD LEAF	SUS/IA	72/02/19	775	1234	72/02/19 77/03/01		EFFECTIVE	F
		09786/012	07110		GOLD LEAF	SUS/IA	72/02/19	775	1234	77/03/25 77/06/07 72/02/19 77/03/01 77/03/25 77/06/07		EFFECTIVE	F
HYAZYME		07933/011	06343		ABBOTT	PWR/SC	70/09/23	800	1234	70/09/23 72/06/23 76/12/10		EFFECTIVE	F
HYCODAN		05213/011	05213		ENDO	SYR/ORAL	72/04/20	827	0030	73/12/14 78/02/17 82/06/01	15	EFFECTIVE	F
		05213/012	05213		ENDO	PWR/ORAL	72/04/20	827	0030	82/07/01 73/12/14 78/02/17 82/06/01	15	EFFECTIVE	F

PRODUCT NAME	M W	NDA/E NUMBER	DESI NO.	A N T	FIRM NAME	DOSAGE /RTE ADMIN	ORIG PUB. DATE	ORIG PUB. PAGE	ORIG PUB. CLASS	MILE STONE DATE	EXM CAT	CURRENT, HIGH CLASS	F I N
HYCODAN		05213/012	05213		ENDO	PWR/ORAL	72/04/20	827	0030	82/07/01	15	EFFECTIVE	F
		05213/013	05213		ENDO	TAB/ORAL	72/04/20	827	0030	73/12/14	15	EFFECTIVE	F
										78/02/17			
										82/06/01			
										82/07/01			
HYDANTAL		06008/021	05694		SANDOZ	TAB/ORAL	70/11/05	069	0030	72/06/01		INEFFECTIVE	F
HYDELTRA	5MG	10051/011	07750		MSD	TAB/ORAL	70/10/21	425	1234	70/10/21		EFFECTIVE	F
										77/03/01			
										78/05/12			
HYDELTRA 2.5MG		10051/002	07750		MSD	TAB/ORAL	70/10/21	425	1234	-		EFFECTIVE	F
HYDELTRA-T B A		10562/011	07110		MSD	SUS/0110	72/02/19	775	1234	72/02/19		EFFECTIVE	F
										77/03/01			
										77/03/25			
HYDELTRASOL		10639/011	07913		MSD	SOL/OPH	71/10/22	451	1034	71/10/22		EFFECTIVE	F
										76/08/13			
		11028/011	07913		MSD	ONT/OPH	71/10/22	451	1034	71/10/22		EFFECTIVE	F
										76/08/13			
		11583/011	07110		MSD	SOL/0116	72/02/19	775	1234	72/02/19		EFFECTIVE	F
										77/03/01			
										77/03/25			
HYDERGINE		08119/011	08119		SANDOZ	SOL/0090	73/01/30	780	1200	74/08/06		INEFFECTIVE	F
		09087/011	08119		SANDOZ	TAB/BUCC	73/01/30	780	1200	75/03/21 74/08/06		EFFECTIVE	F
										75/03/12			
HYDRIN-2	2PCT	10231/011	09130		BROEMMEL	SUS/OPH	70/08/26	605	1204	70/08/26		EFFECTIVE	F
										76/08/13			
HYDROCORTISONE		09018/031	07913		MSD	ONT/0100	71/10/22	451	1034	71/10/22		EFFECTIVE	F
										76/08/13			
		09658/011	07750		COOPER	TAB/ORAL	70/10/21	425	1234	70/10/21		EFFECTIVE	F