

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205474Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	October 20, 2014
<b>From</b>	Satjit Brar, Pharm.D., Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	205474
<b>Supplement#</b>	
<b>Applicant</b>	Sovereign Pharmaceuticals, LLC
<b>Date of Submission</b>	January 14, 2014
<b>PDUFA Goal Date</b>	November 14, 2014
<b>Proprietary Name / Established (USAN) names</b>	Hydrocodone Bitartrate and Guaifenesin Oral Solution / hydrocodone bitartrate and guaifenesin
<b>Dosage forms / Strength</b>	Oral Solution (Immediate release) 2.5 mg hydrocodone bitartrate / 200 mg guaifenesin per each 5 ml
<b>Proposed Indication(s)</b>	Symptomatic relief of cough and to loosen mucus associated with common cold.
<b>Recommended Action:</b>	Approval

### 1. Introduction

This submission by the Applicant dated January 14, 2014, is a 505(b)(2) New Drug Application (NDA 205474) for use of a hydrocodone bitartrate and guaifenesin combination oral solution with a proposed indication is for “the symptomatic relief of (b) (4) cough (b) (4)

Initially proposed for adults (b) (4)

This NDA is comprised of a clinical pharmacology program that assesses the bioequivalence of their proposed product with the following reference listed drugs (RLDs) and OTC Monograph in their original NDA submission: 1) Hycodan (Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mg/1.5 mg per 5 mL), NDA 05-213, and 2) 21 CFR 341.18 for guaifenesin. As the Hycodan syrup manufactured by Endo Pharmaceuticals was discontinued from the market (not for reasons of safety or efficacy), the Applicant conducted the clinical pharmacology study using the hydrocodone bitartrate/homatropine methylbromide syrup developed by Hi-Tech Pharma as the reference drug for hydrocodone. Hi-Tech Pharma’s product is a generic drug (ANDA 40-613). This clinical pharmacology program also investigated the food-effect potential of their product.

The bioavailability study submitted by the Applicant has established the bioequivalence of each component of their cough/cold combination oral solution test drug product, hydrocodone

bitartrate and guaifenesin, to each of the respective reference drugs. As such, the recommended action for this NDA is approval. This review will summarize the Division's assessments of the application, most notably the demonstration of bioequivalence between the Applicant's proposed combination product oral solution and each of the individual reference drug products, hydrocodone and guaifenesin. Summaries will also be provided for applicable discipline-specific sections.

## 2. Background

This 505(b)(2) application is to market a combination product containing hydrocodone bitartrate and guaifenesin, as an immediate release oral solution containing 2.5 mg and 200 mg, per 5 mL, respectively. Guaifenesin is an expectorant, and hydrocodone is a semi-synthetic opioid derived from codeine used as a narcotic analgesic and as an antitussive.

This product is one of the hydrocodone-containing cough/cold products belonging to a group of formerly illegally marketed products. According to the Agency's Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], all manufacturers of hydrocodone-containing products had to discontinue manufacturing these products by December 31, 2007. Moreover, the Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. In response to this FDA action, Sovereign submitted IND 101683 on February 26, 2009 for a fixed-dose combination product of hydrocodone bitartrate and guaifenesin.

The clinical development program for this application is based on the demonstration of bioequivalence to the reference ingredients of the combination product. Since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the Applicant carries out a satisfactory clinical pharmacology program.

Of note is that Hycodan (Endo Pharmaceuticals) was the hydrocodone reference product agreed upon and used in the clinical pharmacology study submitted in first review cycle. During the initial review cycle, the manufacturer of Hycodan (Endo Pharmaceuticals) discontinued marketing Hycodan solution; however, the discontinuation was not because of safety or efficacy concerns. The Orange Book now lists the hydrocodone product from Hi Tech Pharma (ANDA 040613) as the RLD for hydrocodone bitartrate syrup. Subsequently, the Applicant used Hi-Tech Pharma's product as the reference for hydrocodone in their bioavailability studies upon the advice of the Agency since Hycodan solution was no longer

available, however Hycodan is still the reference drug for reliance for safety and efficacy of hydrocodone.

The Applicant cites OTC Monograph (21 CFR 341.18) to support guaifenesin and uses an OTC guaifenesin product as the RLD for guaifenesin component of the combination product.

The Applicant proposed a dosing regimen of 10 mL oral solution (5 mg hydrocodone bitartrate/400 mg guaifenesin) given every 4 hours in adults (b) (4)

### 3. CMC/Device

The proposed product is an aqueous oral solution containing hydrocodone bitartrate USP 2.5 mg and guaifenesin USP 200 mg, per 5 mL, as an immediate release formulation. Inactive ingredients (excipients) include citric acid, potassium sorbate, potassium citrate, saccharin sodium, (b) (4) glycerin, propylene glycol, and methylparaben and propylparaben (b) (4)

(b) (4). The proposed product has two flavors, (b) (4) Cherry (b) (4) and Raspberry (b) (4). The formulation will be available in both 4 and 16 oz. white HDPE bottles with a child-resistant closure as the commercial product. The two active substances are USP ingredients that have been previously assessed to support other NDA applications in the past.

With respect to impurities, noticeable extractable and leachable impurities were found in the drug product for some of the materials used in the drug manufacturing system. The Applicant replaced components used in the manufacturing system that were not compatible with the drug product solution, which was deemed an acceptable approach and resolved the issue.

The manufacturing of the drug product and drug substance and manufacturing/testing site inspections have been judged as acceptable. Standard pharmaceutical grade excipients were used, and all excipients met applicable compendial standards. Stability data support a 24 month expiry. There are no outstanding product quality issues.

### 4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application. However, the safety of extractables of the hydrocodone bitartrate and guaifenesin oral solution was evaluated. The proposed drug product is formulated in (b) (4). A study was conducted to evaluate potential extractables from the HDPE container closure system for the proposed product. Extractables belonging to 3 chemical classes were identified following isopropanol and hexane extraction including higher alkanes, fatty acids, and (b) (4). No extractables were detected following water extraction.

No further nonclinical studies are warranted based upon the extractables identified as they are not considered to pose a safety concern. Moreover, since none of the identified extractables are water soluble and it is not expected to be found in the aqueous drug product.

## 5. Clinical Pharmacology/Biopharmaceutics

The Applicant has submitted 4 clinical pharmacology study reports. The pivotal studies that support labeling of this product are Study 11244403 and Study 92001. The general attributes of all the submitted studies are summarized in Table 1 below.

**Table 1 List of Four Phase 1 Single-dose Studies in Healthy Volunteers in NDA 205474**

Study ID	Objectives of the study	Study Design*	Fasted	# of subjects	Reference listed drug
R08-0467	Comparison of sponsor's hydrocodone with RLD	R, OL, 2-way Crossover	Fasted	20	HYCODAN®
92001	Food effect of proposed product	R, OL, 2-way Crossover	Fasted or fed	25	Proposed product
92002	Comparison of proposed product with 3 RLDs	R, OL, 4-way Crossover	Fasted	34	Hydrocodon + Homatropine (Hi Tech), extemporaneous Guaifenesin
11244403	Comparison of proposed product with 3 RLDs	R, OL, 4-way Crossover	Fasted	60 (56 completed all periods)	Hydrocodon + Homatropine (Hi Tech), Liquituss GG®

\* R: Randomized; OL, Open-Labeled. (Source: reviewer's summary based on 5.2 Tabular listing of clinical reports)

**Study 11244403** was a randomized, single-dose, open-label, 4-way crossover, comparative bioavailability study in 56 healthy volunteers 18 years of age and older designed to compare the relative bioavailability of the proposed drug product with reference drugs hydrocodone bitartrate solution, guaifenesin solution, and hydrocodone bitartrate solution plus guaifenesin solution. The study subjects were randomized to receive a single dose of the following 4 treatments after an overnight fasting:

Treatment A: Single 10 mL dose of guaifenesin 200 mg/ 5 mL, hydrocodone bitartrate 2.5mg/5 mL, for a total dose of 400 mg guaifenesin and 5 mg hydrocodone bitartrate (Sovereign Pharmaceuticals, LLC)

Treatment B: Single 5 mL dose of hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/1.5 mg per 5 mL, for a total dose of 5 mg hydrocodone bitartrate (Hi-Tech Pharmcal Co., Inc.)

Treatment C: Single 10 mL dose of Liquituss GG expectorant liquid (guaifenesin oral solution 200 mg/ 5 mL), for a total dose of 400 mg guaifenesin (Capellon Pharmaceuticals, LLC)

Treatment D: Co-administration of a single 5 mL dose of hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/ 1.5 mg per 5 mL (Hi-Tech Pharmacal Co., Inc.), and a single 10 mL dose of Liquituss GG expectorant liquid (guaifenesin oral solution 200 mg/ 5 mL) (Capellon Pharmaceuticals, LLC), for a total dose of 5 mg hydrocodone bitartrate and 400 mg guaifenesin.

The treatment phases were separated by washout periods of at least 7 days. The following pharmacokinetic variables were calculated for each treatment: AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub>, T<sub>max</sub>, and t<sub>1/2</sub>. The results of Study 11244403 are shown in the table below.

**Table 2. Pharmacokinetics Results of Study 11244403 – Comparative Bioavailability Assessment for Hydrocodone and Guaifenesin**

PK parameters	AUC <sub>0-inf</sub> (pg.hr/mL) Geometric Mean	AUC <sub>0-t</sub> (pg.hr/mL) Geometric Mean	C <sub>max</sub> (pg/mL) Geometric Mean	T <sub>max</sub> (hr) Mean	T <sub>1/2</sub> (hr) Mean
<b>Test Drug</b>					
Hydrocodone	80186	75373	12501	1.25	4.81
Guaifenesin	4222	4202	3711	0.333	0.855
<b>Reference</b>					
Hi-Tech's Hydrocodone	80630	75922	13351	1.00	4.78
<b>Reference</b>					
Guaifenesin	4070	4050	3593	0.333	0.865
<b>Reference</b>					
Hydrocodone + Guaifenesin	83272 4373	78402 4352	13415 3593	1.00 0.333	4.78 0.865
<b>Ratio of Test vs Reference (90% CI)</b>					
Hydrocodone (A vs B)	0.99 (0.96 – 1.03)	0.99 (0.96 – 1.03)	0.94 (0.90 – 0.98)	----	----
Guaifenesin (A vs C)	1.04 (0.99 – 1.09)	1.04 (0.99 – 1.09)	1.03 (0.94 – 1.13)	----	----

Results of the comparison show that the 90% confidence intervals of the ratios for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> for two components in Hydrocodone Bitartrate and Guaifenesin Oral Solution and reference drugs are within the 80 – 125% bounds for bioequivalence. There was no evidence of significant drug interaction between the immediate release guaifenesin and hydrocodone doses administered in this study.

**Study 92001** was a single-center, randomized, open-label, two-period, two-sequence, 2-way crossover, comparative bioavailability and food effect study. A single-dose of 10 mL oral solution of 5 mg hydrocodone/400 mg guaifenesin either under fasting or fed conditions was administered in each study period. The treatment phases were separated by a washout period of 7 days. A total of 25 healthy adults completed the 2-period study. The following pharmacokinetic variables were calculated for each treatment: AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub>, T<sub>max</sub>, and t<sub>1/2</sub>. The results of Study 92001 are shown in the table below.

**Table 3. Pharmacokinetics Results of Study 92001 – Food Effect Assessment for Hydrocodone and Guaifenesin**

PK parameters	AUC <sub>0-inf</sub> (pg.hr/mL) Geometric Mean	AUC <sub>0-t</sub> (pg.hr/mL) Geometric Mean	Cmax (pg/mL) Geometric Mean	Tmax (hr) Mean	T1/2 (hr) Mean
<b>Test Drug, Fed</b>					
Hydrocodone	81158	77609	10958	1.43	5.17
Guaifenesin	2529	2495	1658	0.364	0.953
<b>Test Drug, Fasted</b>					
Hydrocodone	70109	67323	12450	0.94	5.19
Guaifenesin	4821	4789	5295	0.330	0.901
<b>Fed/fasted, ratio (90% CI)</b>					
Hydrocodone	1.158 (1.12 – 1.19)	1.153 (1.12-1.18)	0.880 (0.82 – 0.94)	----	----
Guaifenesin	0.525 (0.45 – 0.60)	0.521 (0.44-0.60)	0.313 (0.16 – 0.46)	----	----

Based on the results from study 92001, the bioavailability of hydrocodone is comparable between the fed and the fasted status, although hydrocodone median T<sub>max</sub> was 30 minutes later under the fed condition than the fasted condition.

Conversely, food significantly reduced the bioavailability of guaifenesin (AUC and C<sub>max</sub> of fed status are a half and one-third of those of fasted status, respectively). However, the effect of food on guaifenesin absorption is not expected to impact on the efficacy and safety of the proposed drug product. The efficacy of guaifenesin is supported by OTC Monograph [21 CFR 341.72] with the specified guaifenesin dose ranging from 200 to 400 mg every 4 to 6 hours. If the proposed drug product is being administered with food at the proposed dose (i.e., 400 mg every 4 to 6 hours), a decreased absorption of 50% would result in an exposure that is still effective, per OTC Monograph.

**Study R08-0467** was a pilot study designed to assess the bioavailability of their hydrocodone bitartrate solution in comparison with that of the reference drug Hycodan® Syrup. As the test drug hydrocodone bitartrate solution is not the proposed drug product in this NDA submission, the data from this study is not assessed in this memo.

**Study 92002** was a randomized, single-dose, open-label, 4-way crossover, comparative bioavailability study in 34 healthy volunteers to compare the relative bioavailability of the proposed drug product with reference drugs hydrocodone bitartrate solution, guaifenesin solution, and hydrocodone bitartrate solution plus guaifenesin solution. Results showed that the guaifenesin component of the proposed drug product was not bioequivalent to the reference guaifenesin solution (extemporaneously prepared by the Applicant) with the guaifenesin of the test drug having a significantly higher bioavailability (189% in C<sub>max</sub> and 162% in AUC) than that of the Applicant prepared guaifenesin solution. The Applicant concluded that the formulation effect of their own guaifenesin solution reference resulted in the higher C<sub>max</sub> and AUC of guaifenesin in the proposed drug product. The Applicant then re-conducted the study (Study 11244403) with a commercially available Guaifenesin Solution (manufactured by Capellon Pharmaceuticals) as the reference drug for guaifenesin component of the proposed drug product.

## 6. Clinical Microbiology

This is a non-sterile solution product for oral ingestion. The product contains methylparaben and propylparaben at target concentrations of (b) (4) % w/v, respectively, which were found to be adequate (b) (4) effectiveness. There are no unresolved microbiology issues with the formulation.

## 7. Clinical/Statistical- Efficacy

The application relies on a bioavailability comparison of the proposed drug product to that of approved reference products Hycodan (the actual hydrocodone product used was a generic version of Hycodan since that product is no longer marketed) and the OTC monograph for guaifenesin. No clinical efficacy studies were conducted.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the proposed product to the approved reference products. In addition, the Applicant provided a Summary of Clinical Safety including a literature survey and the safety data from the clinical pharmacology studies.

A total of 146 subjects from three clinical pharmacology studies received a single dose of the test drug Hydrocodone Bitartrate and Guaifenesin Oral Solution. No death or serious adverse events occurred in these studies. The most common adverse events were headache, somnolence, dizziness, and nausea. These events were balanced between the test drug and reference hydrocodone and guaifenesin. Adverse events observed in the clinical pharmacology studies did not reveal any new safety signals.

The proposed drug product was marketed as an unapproved drug product under the name of (b) (4) in the U.S. from February 2006 through October 2007. During that period approximately (b) (4) size were distributed. No adverse event reports were received by the Applicant from any source for the proposed drug product.

In addition, the Applicant conducted a review of the literature, and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from October 2007 through March 2008. For this submission, the Applicant submitted a 120-day safety update dated April 10, 2014. These searches did not reveal any new safety signals.

## 9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. The two active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications.

## 10. Pediatrics

(b) (4)

This partial waiver was requested because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. It is appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. Nevertheless, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression raises the concern of the most appropriate dose for the pediatric population from 6 to less than 18 years of age.

Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children, with several cases being related to overdose. The collective safety information led to revision of the labeling in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. Hence, in view of this dose-related safety concern, it is appropriate to require the Applicant to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Therefore, pharmacokinetic data to establish appropriate dose selection, and safety data are needed in the pediatric population.

(b) (4)

The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to fewer than 18 years of age, post-approval.

The Applicant submitted a pediatric study plan that was discussed at the Pediatric Review Committee (PeRC) PREA Subcommittee meeting on May 7, 2014. PeRC agreed with the Division to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies from 6 to under 18 years of age until post-approval because adult studies are completed and the product is ready for approval in adults. The agreed upon post-approval pediatric studies, along with timelines, are as follows:

- Conduct a study to assess the pharmacokinetics of each active component in proposed drug product in (b) (4) children ages 6–17 years with symptoms of (b) (4)

(b) (4)

The timelines of protocol submission, study initiation, and final report submission dates for the study are set to be March 2015, September 2015, and March 2017, respectively.

- Conduct a study to assess the safety of the proposed drug product in [REDACTED] (b) (4)  
children 6–17 years of age with symptoms o [REDACTED] (b) (4)

Although this study is primarily a safety study, the effectiveness of the proposed drug will be assessed. The secondary endpoints will include changes of symptom scores from baseline. The timelines of protocol submission, study initiation, and final report submission dates for the study are set to be September 2018, March 2019, and September 2022, respectively.

The dosing of guaifenesin in the proposed combination product is the same as the dosing in the Agency’s approved OTC cough/cold monograph. Since the Agency is not aware of any new safety concerns with these ingredients at these doses and the current monograph is still in effect, the proposed dose for guaifenesin in this combination solution is acceptable.

## 11. Other Relevant Regulatory Issues

### Inspections

The Division of Scientific Investigation (DSI) conducted an audit for the analytical sites used for this clinical pharmacology program. The inspection of analytical site was conducted at [REDACTED] (b) (4).

DSI did not identify any deficiencies during this inspection and subsequently issued a Memorandum on July 29, 2014, recommending that the analytical data generated in study 11244403 be accepted for the review. As such, the data for study 11244403 are judged as acceptable to support the clinical pharmacology program.

### Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

### Financial Disclosures

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The clinical investigator certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f).

## 12. Labeling

### Proprietary Name

At the time of this review, a proposed trade name has not been agreed upon by the Office of Prescription Drug Promotion (OPDP). If a proprietary name is not agreed upon by the PDUFA date, the product will be named Hydrocodone (b) (4) and Guaifenesin Oral Solution.

### Physician Labeling

In this submission, the physician labeling was reviewed and extensively revised by the review team and conveyed to the Applicant. Changes were made to the Indication section to reflect the population for which it would be used; symptomatic relief of cough and to loosen mucus associated with the common cold. The restriction of the age limit to adults (patients 18 years of age and older) only was included in the original label submitted by the Applicant.

As noted in section 10 (Pediatrics), PK and safety data should be obtained in the pediatric population before the product is labeled for this age group.

In this submission, the Applicant submitted a label in the Physician's Labeling Rule Format. During this review cycle significant revisions to the Adverse Reaction and Clinical Pharmacology sections were made as well as changes in format and grammar. In addition, prescribing language with regard to drug interaction information was added to be consistent with current prescription cough and cold product labeling. At the time of this review the final draft product labeling has not been agreed to by the Applicant and the Division. Final label discussions will continue at the time of finalizing the review.

### Carton and Immediate Container Labels

A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with DMEPA and DDMAC. At the time of this review, the final carton and container labels format is under discussion with the Applicant.

### Patient Labeling and Medication Guide

There is no separate patient labeling and medication guide for this product.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant submitted reports of their clinical pharmacology program which has established the bioequivalence of their proposed hydrocodone bitartrate 2.5 mg/ guaifenesin 200 mg per 5 mL oral solution to the individual reference products. In establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of

hydrocodone bitartrate and guaifenesin in the proposed combination product for symptomatic relief of cough (b) (4) associated with common cold when administered to adults 18 years of age and older at a dose 10 mL every 4 to 6 hours by mouth, not to exceed 6 doses (60 mL) in 24 hours. Therefore, the recommendation is for Approval for the adult population. As detailed in Section 10 (pediatrics) above, approval for children 6-17 years of age is dependent upon the results of adequately designed pharmacokinetic and safety studies to be performed as a PREA post-marketing requirement in that population.

- Risk Benefit Assessment

The overall risk and benefit assessment of the proposed hydrocodone and guaifenesin combination product, based on establishing bioequivalence to the individual reference products and literature and AERS database searches does not suggest an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population. Since dose-related respiratory depression associated with fatalities from the use of hydrocodone has been reported for the younger population (patients under 18 years of age) additional PK and safety data to support the appropriate dose in the pediatric population is necessary prior to extending the indication to the pediatric population.

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential thereby classifying it as a Schedule II controlled substance as a *single* ingredient (21 CFR 1308.12). According to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all hydrocodone *combination* products (analgesic and antitussive) are placed into Schedule II controlled substance as well (b) (4). Thus, this combination product as proposed will be labeled as a Schedule II narcotic and available by prescription only. At this time, the abuse potential can be managed by appropriate labeling. However, we will monitor for signals of abuse/misuse, overdose, and addiction post approval.

- Recommendation for other Postmarketing Study Commitments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. For this combination product we are waiving the requirement for children less than 6 years of age based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). Because of the safety concerns for the pediatric population, the Applicant will need to conduct PK and safety studies to evaluate the appropriate dose for patients less than 18 years of age. This issue was discussed with the Applicant during the this review cycle and a pediatric plan which included studies to assess the pharmacokinetics and safety of this product in children 6-17 years of age was submitted at the time of NDA submission. For the pharmacokinetics assessment, in children 6 – 17 years of age, the

timelines of protocol submission, study initiation, and final report submission dates for the study are set to be March 2015, September 2015, and March 2017, respectively. For the safety assessment, in children 6 – 17 years of age, the timelines of protocol submission, study initiation, and final report submission dates for the study are set to be September 2018, March 2019, and September 2022, respectively.

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/s/

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SATJIT S BRAR  
10/27/2014