CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209184Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 19, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209184
Product Name and Strength:	Inbrija (levodopa inhalation powder), 42 mg
Applicant/Sponsor Name:	Acorda Therapeutics Inc.
FDA Received Date:	December 13, 2018
OSE RCM #:	2017-1271-4
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container label for Inbrija (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation we made in a previous label and labeling memorandum.[a]

2 CONCLUSION

The revised container label for Inbrija is acceptable from a medication error perspective. We have no further recommendations at this time.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Whaley E. Label and Labeling Memo for Inbrija (NDA 209184). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 10. RCM No.: 2017-1271-3.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
12/19/2018

LOLITA G WHITE
12/20/2018

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 20, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products

From: Dominic Chiapperino, Ph.D., Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

Subject: **Secondary Review by CSS**
NDA 209184 /IND 115,750
Name: Inbrija (CVT-301**,** Levodopa Inhalation Powder**)**
Indication: Treatment of OFF periods in Parkinson's disease, as an adjunct to a carbidopa/levodopa regimen for use in adult PD patients
Dosage: Two 42 mg L-DOPA capsules that provide 84 mg L-DOPA (50 mg L-DOPA Fine Powder Dose, FPD) administered up to 5 times per day to deliver a maximum of 250 mg L-Dopa FPD
Company: Acorda Therapeutics

I. BACKGROUND AND DISCUSSION

This memorandum clarifies the final recommendations of the Controlled Substance Staff (CSS) to the Division of Neurology Products (DNP) related to Inbrija (CVT-301, powdered L-DOPA), NDA 209184.

Dr. Alicja Lerner, MD, PhD, Medical Officer in CSS, conducted a thorough review of this application and related FDA reviews, considering the extent to which there was evidence of abuse, misuse, or potential diversion in the clinical program for Inbrija. Dr. Lerner also considered the available data from a clinical evaluation of physical dependence in a subset of subjects in Study CVT-301-004E. In her review she draws many conclusions about the relevant data pertaining to potential abuse, misuse, diversion, and dependence, and offers recommendations to DNP, many of which we (signatories to this secondary memo) agree. However, there are some findings and recommendations with which we do not agree, and we will only elaborate on those specific findings and recommendations to clarify final CSS recommendations to DNP. The following areas were considered as warranting further comment.

1. Withdrawal Syndrome Indicative of Physical Dependence

There is little convincing evidence to conclude that a withdrawal syndrome occurs in PD subjects after discontinuation of Inbrija.

In the Sponsor's evaluation of physical dependence as part of Study CVT-301-004E, the following scales were used:

- Amphetamine Withdrawal Questionnaire (AWQ)
- Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC)
- Patient Health Questionnaire (PHQ-9)
- Epworth Sleepiness Scale (ESS)
- C-SSRS (self-report version)
- Movement Disorder Society - Unified Parkinson's Disease Rating Scale parts IB and II

Although there are indeed some gaps in data collection during the Sponsor's evaluation, as discussed at length in Dr. Lerner's review, the data available for review of dependence and withdrawal indicate that most, if not all, of the signs and symptoms reported after drug discontinuation are ubiquitous in patients with PD regardless of drug status.

Since Inbrija is prescribed as an as needed treatment for OFF periods in PD (up to 5 doses/day), very few of the PD patients exposed to the drug were on it consistently enough to speculate or conclude a withdrawal phenomenon. The majority of patients took the medication once, twice, or not at all in a single day.

Dr. Lerner's conclusion #2 (in her review at Page 4) and #4 (at Page 5) and recommendation #1 (in her review at Page 7) summarize deficiencies with the Sponsor's evaluation of dependence and recommends a Post Marketing Requirement (PMR) to further study withdrawal and physical dependence. With respect to this recommendation, we find that a PMR to further evaluate dependence and withdrawal in this patient population is unnecessary and perhaps unethical. Such a study would require a high daily maintenance dosage of Inbrija from which withdrawal might then be studied; however, such dosing is not consistent with the indicated use for this medication. We believe that DNP management may consider the results described in Dr. Lerner's review and in the overall clinical review conducted in DNP, particularly for the open label safety study extension, and determine whether any specific messages to prescribers are warranted in Inbrija product labeling pertaining to patient monitoring upon discontinuation of Inbrija medication or tapering of the medication based on how individual patients were using the medication prior to the decision to discontinue the drug. Also with respect to Dr. Lerner's conclusion #2, it should be clarified that although she mentions as a concern "the Sponsor's deleting and/or not providing data in the NDA," we have looked into this matter and consider this to be imprecise and problematic language to use in her review. Considering the seriousness of suggesting data deletion by the Sponsor, we must comment that there is no evidence of deletion or destruction of data associated with the evaluation of physical dependence that was conducted. There was only a rather protracted dialogue with the Sponsor to eventually obtain the available data that was of interest to Dr. Lerner for her review. In Dr. Lerner's review, she additionally characterizes her

concerns when discussing these data with DNP as being "dismissed" by DNP. We do not agree that the concerns raised in Dr. Lerner's (at that time preliminary) review of the dependence/withdrawal data were dismissed by DNP. There was discussion and differing views expressed, all of which were consistent with the intent of review team meetings for various review disciplines and senior management to share and discuss in-progress review findings.

Dr. Lerner has also, within the context of her review of the dependence/withdrawal evaluation, concluded (#4, at Page 5) that Inbrija may be leading to an unexpected level of worsening of the PD symptomology due to use of Inbrija and evidenced following drug discontinuation. However, there are no data to consider from a controlled evaluation of this possibility. Therefore, we conclude that this is speculative, based only on the data obtained from this subset of subjects. We would defer to DNP as to the time-limited efficacy of levodopa treatment in general to address PD symptomology, and whether additional data would be informative to distinguish expected worsening of PD symptomology after long-term treatment with levodopa from the possibility that Inbrija, as it will be indicated, may lead to a more rapid worsening of PD symptomology that would become evident upon discontinuation. Dr. Lerner's recommendation for labeling (#4, at Page 9) in section 9.3 is therefore not adequately supported to characterize observed worsening of some measures (motor and non-motor symptoms, depressive disorder, excessive daytime sleepiness) under a heading of withdrawal symptoms. This is not in other levodopa product labeling.

2. Dopamine Dysregulation Syndrome (DDS)

DDS is a rare (< 5%) consequence of patients taking levodopa and/or dopamine agonist drugs and may occur even in PD patients not taking greater doses than prescribed. Although many of the impulsive behaviors reported with DDS (compulsive gambling, hypersexuality, spending) may cause social and economic difficulties, they are uncommon and not medically significant enough to be added to the label's Warnings and Precautions section. Many of the most important findings in DDS, particularly impulse control disorder (ICD), psychosis and dyskinesia are already in Warnings and Precautions as class language. Lastly, in the Inbrija clinical program, an analysis of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson" (QUIP), designed to capture ICD symptoms seen in DDS, showed only rare, isolated, and insignificant evidence of intentional medication overuse.

3. Drug Accountability

Dr. Lerner, in her conclusion #8 (her review at Page 6), discusses Inbrija as possibly having a higher abuse potential than oral levodopa, based on pharmacokinetics of inhaled levodopa (Inbrija) as well as possible diversion of study drug, based on unreturned/unaccounted-for study medication. We are of the opinion that the observation of immediately higher levodopa concentration from Inbrija relative to orally administered levodopa is an intentional feature of the drug's therapeutic effect and does not lead us to a conclusion that Inbrija has a higher abuse potential. Levodopa is not known to have any abuse potential as a substance administered in a general population, and therefore a higher plasma concentration of levodopa by itself does not suggest that there are necessarily any different stimulant or other positive rewarding effects that follow. There is no documented evidence of other resulting pharmacology that may produce a

stimulant effect comparable to known drugs of abuse. Moreover, there is no significant evidence in the clinical program of higher rates of adverse events consistent with administration of a drug with stimulant or other effects or AEs typically observed with known stimulant drugs of abuse.

Regarding possible drug diversion, as described in Dr. Lerner's review in section 4.4.3 (beginning at Page 24), although unreturned study medication can often be an indication of study drug diversion for abuse purposes, there were no clear cases in these clinical studies to suggest this. In some cases there were more placebo capsules which were not returned than study drug. Additionally, given that this study population may have cognitive problems and each carton contained 92 capsules, simply forgetting to return unused medication might result in high numbers of unreturned medication without any suggestion of diversion.

II. RECOMMENDATIONS

The following recommendations reflect the above discussions and specify where CSS overall recommendations differ with respect to Dr. Lerner's recommendations (from DARRTS, review dated December 18, 2018):

1. We do not conclude that an additional clinical study of physical dependence and withdrawal is warranted as a PMR, based on the difficulty in designing and interpreting a subsequent study that would be ethically unacceptable to conduct if designed appropriately. We support the recommendation for enhanced pharmacovigilance (as described in Dr. Lerner's review at Page 7) of adverse events occurring in a context of treatment with Inbrija and discontinuation of Inbrija, and support future updates to Inbrija labeling if a pattern emerges to suggest that new warnings or other regulatory action are warranted that are specific to this levodopa formulation.

2. We support but will not require additional labeling messages to address the symptomology that may be related and overlapping among DDS and ICD. We believe this symptomology is more closely associated with underlying PD and is not considered in the more general context of a substance abuse potential. Therefore, CSS would defer to DNP and other affected OND divisions as to appropriate labeling for levodopa and other dopaminergic drug classes for which this may be applicable. We are glad to assist or advise if desired.

3. We do not recommend inclusion of section 9, Drug Abuse and Dependence, for Inbrija labeling, nor do we recommend other labeling sections that specifically discuss symptomology following Inbrija discontinuation as related to "withdrawal" from Inbrija (i.e., supplemental doses of levodopa for OFF periods). The observations from the dependence evaluation, as described in Dr. Lerner's review of the data collected from the 6 scales that were used following Inbrija discontinuation, may be considered by DNP along with their findings in the Phase 3 clinical program overall as to any statements in product labeling, e.g., in section 3 Dosage and Administration, or section 5. Warnings and Precautions, to advise patients and prescribers of best practices in tapering or discontinuing Inbrija medication. CSS is available to assist as necessary.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN S RUSINOWITZ
12/20/2018

DOMINIC CHIAPPERINO
12/20/2018

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Dec 17, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 209184 /IND 115,750**
Name: Inbrija (CVT-301**,** Levodopa Inhalation Powder**)**
Indication: treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen for use in adult PD patients (18+ years)

Dosage: two 42 mg L-DOPA capsules that provide 84 mg L-DOPA (50 mg L-DOPA Fine Powder Dose, FPD) administered up to 5 times per day to deliver a maximum of 250 mg LD FPD
Company: Acorda Therapeutics

Materials reviewed:
NDA is in DARRTS June 29, 2017
Meeting minutes from Type B PreNDA Oct 26, 2016
Review OSE/DPV1 by Dr. D. Croteau, July 11, 2018
Review OSE/DEPI by Dr. R.S. Swain, Aug 20, 2018
Response to IR # 1, Aug 23, 2018
Response to IR # 2, Oct 30, 2018
Response to IR # 3, Nov 18, 2018
Response to IR # 4, Nov 30, 2018

Table of Contents

I. BACKGROUND

This memorandum responds to a consult request from the Division of Neurology Products (DNP) to evaluate the abuse potential of INBRIJA (CVT-301, powdered L-DOPA) NDA 209184. This is a 505(b)(2) NDA submission with Sinemet® tablets, NDA 017555, as the reference listed drug (RLD).
Due to the disagreement with CSS team: Dr. D. Chiapperino, Dr. M. Rusinowitz and Dr. S. Calderon on the key conclusions and recommendations regarding Inbrija abuse potential, dependence and withdrawal this review constitutes my personal statements only. It is written in hope that maybe some points which I raise here and which were deleted from the official CSS review will be noted and reconsidered because they are critical for safety of patients with Parkinson's disease.

Levodopa is the precursor of the neurotransmitters dopamine, norepinephrine and epinephrine. Additionally, levodopa mediates release of neurotrophic factor in the central nervous system (CNS). Levodopa readily crosses the blood-brain barrier and then is converted to dopamine in the CNS by the enzyme aromatic L-amino acid decarboxylase (DOPA decarboxylase). Levodopa is used as pharmacologic treatment of Parkinson's diseases (PD). It is mainly a symptomatic treatment and provides replacement of striatal dopamine through the oral administration of levodopa (L-DOPA, LD). Levodopa is also used for treatment of dopamine-responsive dystonia (Segawa syndrome). There are currently multiple products on the market containing levodopa, including Sinemet, Rytary, Duopa, Stalevo (Drugs@FDA, FDA Approved Drug Products, August 14, 2018). The Sponsor is developing CVT-301 (levodopa inhalation powder) for the treatment of OFF periods in patients with PD as an adjunct to a maintenance carbidopa/levodopa regimen. CVT-301 is a drug combination product which includes L-DOPA capsules along with a breath-actuated inhaler device.

Idiopathic Parkinson's disease is traditionally considered a movement disorder with hallmark degeneration of neurons located in the substantia nigra pars compacta (SNpc). However, recent histopathological findings have established a newer view of PD as a multisystem disorder where symptoms of so-called "parkinsonism" arise as a late presentation of this neurodegenerative process. The motor symptoms of PD include tremor, rigidity, slowed movement (bradykinesia), impaired posture and balance, and difficulty walking. There are also numerous psychological and psychiatric symptoms, including depression, anxiety, sleep disturbances, amnesia, evening confusion, and difficulty thinking. Dementia may occur in the later stages of PD.

In this NDA, the Sponsor relies on FDA's previous findings of safety and efficacy for Sinemet oral tablets (NDA 017555) as the RLD, as well as original studies conducted by the Sponsor and relevant published literature.

The NDA has been resubmitted after receiving a refuse-to-file letter (RTF) on August 25, 2017, due to Chemistry, Manufacturing and Control issues, including manufacturing sites not being

ready for inspection, and deficiencies in the NDA proposed or actual master production record for the drug component (levodopa capsules). There were no CSS RTF issues**.**

The clinical development program for CVT-301 included:

- 6 phase 1 studies: CVT-301-001, CVT-301-006, CVT-301-007, CVT-301-010 in healthy volunteers, one study, CVT-301-008, in healthy volunteers with mild to moderate asthma and one study in PD patients, CVT-301-009
- 2 phase 2a and 2b studies in PD patients: CVT-301-002 and CVT-301-003
- 3 phase 3 studies in PD patients: CVT-301-004, extension CVT-301-004E, and CVT-301-005

As of December 20, 2017, 1103 subjects were enrolled in the CVT-301 clinical program, which included 951 PD patients. A total of 897 subjects received at least 1 dose of CVT-301 during all studies, including 754 subjects with PD.

Abuse, misuse, diversion, and dependence of levodopa

Levodopa products have generally been considered relatively safe and not having abuse potential. However, in the recent years a new syndrome of non-prescribed use of dopamine replacement products, mainly levodopa, has been described. It is called Dopamine Dysregulation Syndrome (DDS) or Hedonistic Homeostatic Dysregulation (Giovannoni et al., 2000, Pezzella et al., 2005; Cilia et al., 2013). DDS is manifested by overuse of levodopa products characterized by an addictive pattern of medication misuse with the intake of large doses of dopaminergic drugs in excess of that required to control motor symptoms (Beaulieu-Boire et al., 2015; Warren et al., 2017). The prevalence of DDS is reported as approximately 3-4% of patients treated for PD. The Agency's DEPI review (by Dr. R. S. Swain, Aug 20 2018) estimates a prevalence of levodopa misuse among Parkinson's patients to be 0-7.4%.

Diagnostic criteria for DDS have been described and include an excess of medication intake over that prescribed, symptoms of mania and hypomania related to dopamine replacement therapy (DRT), drug seeking behavior, impairment in social and occupational functioning, presence of a withdrawal syndrome including dysphoria, depression, irritability, and anxiety when reducing the level of DRT, and duration of at least 6 months (Giovannoni et al., 2000; Beaulieu-Boire and Lang, 2015). Table 3 is from Beaulieu-Boire, et al., 2015.

TABLE 3. Diagnostic criteria for dopamine dysregulation syndrome (DDS)

A. Parkinson's disease with documented L-dopa responsiveness
B. Need for increasing doses of DRT in excess of those normally required to relieve parkinsonian symptoms and signs
C. Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being 'on,' drug hoarding or drug seeking behavior, often consulting multiple neurologists, frequent visits to the emergency room, unwillingness to reduce DRT, absence of painful dystonia
D. Impairment in social or occupational functioning: fights, violent behavior, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family
E. Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT
F. Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT
G. Duration of disturbance of at least 6 months

Withdrawal in DDS

Patients with dopamine dysregulation syndrome (DDS), after abrupt discontinuation of levodopa, may experience withdrawal symptoms such as dysphoria, depression, irritability, anxiety, panic attacks, and suicidality. Somatic symptoms may include abdominal pain, palpitations, painful limbs, and profuse sweating. These symptoms may occur in the absence of off-period motor disability (Spigset et al., 1997; Giovannoni et al., 2000; Evans et al., 2004; Witjas et al., 2012; Beaulieu-Boire and Lang, 2015; Warren et al., 2017).

II. CONCLUSIONS

1. Levodopa is a long known drug used for the treatment of Parkinson's disease mainly as oral formulations such as Sinemet, Rytary, Stalevo and is not controlled under Controlled Substance Act.

2. Because a full evaluation of abuse potential and dependence of Inbrija was made impossible by the Sponsor through irregularities such as data deletion (AWQ, PHQ-9, DDS-PC), misleading explanations (related to absence of AWQ and to UPDRS conversion into MDS-UPDRS), the evaluation of abuse potential and dependence of Inbrija is not complete. Also, substantial portion of the requested data is or was missing in NDA, in fact:

- For Amphetamine Withdrawal Questionnaire (AVQ) up to s 26-32% LDOTs were missing
- For Patient Health Questionnaire-9 (PHQ-9) up to 38-40% LDOTs were missing in NDA (but then found and submitted on CSS request)
- For Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for part II and I B 100% LDOTs scores were missing, and the Sponsor claimed that

conversion from UPDRS (old scale) scores, which the Sponsor used during the clinical trials to MDS-UPDRS (new scale) which was used during withdrawal was impossible. However, DNP TL Dr. D. Podskalny informed CSS about existence of such conversion methods, which was then shared with the Sponsor who provided finally the full data.

*Importance of LDOT (Last day on treatment) lies in fact that withdrawal cannot be assessed without baseline which in this case is "last day on treatment".

Therefore, quality of abuse potential and dependence data is substandard and full extent of abuse potential and dependence is unknown.

The information on the irregularities related to the Sponsor's deleting and/or not providing data in NDA, or otherwise not reveling the critical for CSS data was conveyed to DNP however, this information was dismissed.

3. Abrupt discontinuation of Inbrija causes emergence of withdrawal symptoms which occur while still on the regular oral levodopa regimen.
   The evidence from partially only available withdrawal data for AWQ and full sets of PHQ-9 and EPS and MDS-UPDRS scales shows that withdrawal of Inbrija causes in at least 20-30% of PD patients moderate-to-severe symptoms which are partially stimulant-like withdrawal symptoms and include rebound, also include moderate-to-severe worsening of parkinsonian symptoms. Because both stimulant-like withdrawal syndrome and Parkinson's disease share many the same features such as slowness, tiredness, anxiety, sadness, agitation, and craving sleep the disentangling of these symptoms may be at times challenging. This Inbrija discontinuation results also in moderate-to-severe worsening of motor and non-motor aspects of experiences of daily living in up to 50%, and 25%, respectively. The motor worsening after Inbrija withdrawal in some patients is protracted and some worsening occurs still after 2 weeks. The syndrome also includes in up to 20% patients worsening or a new onset of moderate-to-severe depressive disorder and in some patients increased excessive daytime sleepiness.. The most intriguing aspect of this withdrawal syndrome is the fact that this rather serious worsening of motor and non-motor aspects of experiences of daily living, depression, and AWQ scores occurs in the presence of the full daily oral levodopa regimen.

4. The partially available MDS-UPDRS withdrawal data seems to suggest a possibility of worsening of symptoms of Parkinson's disease after Inbrija treatment in some patients. This conclusion is based on unexpectedly severe sometimes worsening of scores for Part II. Motor Aspects of Experiences of Daily Living (the only available for CSS part of MDS-UPDRS) during the Inbrija discontinuation period where the scores in some patients increased by up to 19 points, and the average worsening was 7.1-8.2 points only for part II. Of note is that average annual worsening of Parkinson's disease for all 3 parts (I, II, and III) is ~7.45 (SD=11.6) (Simuni et., al., 2018)). Therefore, a thorough evaluation of status of Parkinson's disease after discontinuation of Inbrija is critical to clarify this issue. Another explanation of these results might be that Inbija causes unusual withdrawal in some patients. Thus, PMR is recommended which will use all parts of MDS-UPDRS at weekly intervals for 6 weeks. At this point a discussion with DNP on the significance of the increased MDS-UPDRS withdrawal scores would be helpful.

5. Because: 1) of the major clinical safety implications and seriousness of the presence of withdrawal symptoms, 2) a very small sample of PD patients evaluated, 3) only partially available scores for AWQ scores and MDS-UPDRS it is recommended that a full evaluation of Inbrija withdrawal as PMR will be performed in at least 100 of PD patients, with all scales as above, inclusion of the full MDS-UPDRS scales part I, II, II, and IV and duration of 6 weeks. The 6 weeks period was chosen, because in some patients scores seemed to be increasing even at weeks 3 and 4.

6. Due to the presence of withdrawal symptoms which develops immediately after abrupt withdrawal of Inbrija with likely disabling worsening of Non-motor and Motor Aspects of Experiences of Daily Living of MDS-UPDRS it is recommended that section 5. Warnings will include information about slow tapering of Inbrija possibly over 2 weeks.

7. In the recent years levodopa overuse and abuse was described that occurs in ~ 3-4% of Parkinson's patients treated mainly with levodopa and is called either Dopamine dysregulation syndrome (DDS) (Evans et al., 2004; Witjas et al., 2012; Warren et al., 2017) or Hedonistic homeostatic dysregulation (Giovannoni et al., 2000; Pezella et al., 2005). Therefore, and according to the OSE/DPVI (Review DPVI by Dr. D. Croteau, July 11, 2018) recommendation Dopaminergic Dysregulation Syndrome should be included in the label, see Recommendations.

8. Inbrija seems to have much higher abuse potential than oral levodopa formulations likely due to its PK characteristic (very high rise of levodopa in CNS within minutes after administration in Parkinson's patients which is 36 x higher then oral levodopa) and "pulsatile" type of levodopa exposure (Hinkle et al., 2018). The increased abuse potential of Inbrija is evidenced by:

- unusually high number of diverted drug product in some cases up to 1284 (Section 4.4.3)
  - In the Study # CVT-301-004 there were 7 patients that did not return 129 to 320 capsules, and there were 3 placebo patients that did not return from 98 to 327 capsules.
  - In the Study # CVT-301-004E there were 9 patients that did not return 240 to 960 capsules.
  - In the Study # CVT-301-005 there were 9 patients that did not return 240 to 1284 capsules.

- a development of new DDS symptoms or worsening of present DDS scores as detected with positive responses (at least one "yes") on part C. Medication Use of QUIP scale, in PD patients during the phase 2 and 3 clinical studies who were on the stable, long term oral levodopa regimen (see section 4.4.1)
  - In the Study # CVT-301-004 lasting 12 weeks in the population of patients N =227 exposed to Inbrija 20 (8.8%) of PD patients developed new DDS symptoms at some point or had worsening of pre-existing ones; 13 (5.7%) patients developed for the first time symptoms of DDS, 11 (4.8%) had already noted DDS symptoms before starting Inbrija 4 (1.7%) of them remained stable but 7 (3%) patients had at some points worsening of DDS symptoms noted as increased number of "yes" responses.

- In the Study # CVT-301-004E of duration of 12 months in the population of PD patients N =295 exposed to Inbrija, 23 (7.9%) patients developed for the first time some symptoms of DDS, 4 (1.3%) had worsening of pre-existing DDS symptoms, and one patient remained stable. Some (4) patients in this study developed more severe DDS answering majority of questions "yes" during the study.
- In the Study # CVT-301-004 of duration of 12 months in the population of N =271 PD patients exposed to Inbrija, 16 (5.9%) patients developed for the first time some symptoms of DDS, and 9 (3.3%) had already noted DDS symptoms before starting Inbrija: 8 (2.9%) of them remained stable and 1 (0. 3%) patient experienced at some points worsening of DDS symptoms. Total population of PD patients who developed new DDS symptoms at some point or had worsening of pre-existing ones is 17 (6.3%).
  Some (4) patients in this study developed more severe DDS answering majority of questions "yes" during the study.

- Because of discussed above increased abuse potential of Inbrija certain precautions are recommended and full description of DDS to include in the clinical section in 5. Warnings; the recommended language is provided in the section LABEL.

9. It is known that drugs which exhibit non-physiological "pulsatile" stimulation of dopamine receptors such as other short acting rescue medications (apomorphine injections) produce enhanced ventral striatal sensitization which plays a crucial role in the emergence of non-motor complications encountered in PD patients, including DDS (Giovannoni et al., 2000; Evans et al., 2004; Katzenschlager, 2011; Hinkle et al., 2018, Bereau et al., 2018). Therefore, a language should be included in section 5. Warnings to advice physicians to prescribe Inbrija with caution to PD patients with a current or past history of dopaminergic dysregulation syndrome, and to patients with history of drug abuse which is a risk factor for DDS development.

III. RECOMMENDATIONS

1. To be requested as PMRs:

2. There are some additional precautions and label changes that are recommended, see label recommendations:

- Class changes in the levodopa label section *5*. Warnings or section 9. Abuse potential to include information on DDS. CSS agrees with DPV recommendation to add Dopamine dysregulation syndrome to the label of levodopa drugs.

- Inbrija should be used in caution in PD patients with current or past history of dopaminergic dysregulation syndrome, and patients with history of drug abuse which is a risk factor for DDS in the label section 5. Warnings.

- Description of Inbrija withdrawal symptoms in section 9.3 Dependence or section 5. Warnings

IV. LABEL RECOMMENDATIONS

1. For the clinical section *5. Warnings and Precautions or section 9. Abuse:*

Dopamine Dysregulation Syndrome (DDS)
Abuse of levodopa has been observed in patients with Parkinson's disease and is called Dopamine Dysregulation Syndrome or Hedonistic Homeostatic Dysregulation. DDS is considered an overuse and abuse of levodopa products characterized by an addictive pattern of medication use with the intake of large doses of dopaminergic drugs in excess of that required to control motor symptoms. Diagnostic criteria for DDS include findings of a levodopa dose increase in excess of normally required to control PD symptoms, drug seeking behavior, impairment in social and occupational functioning, adverse events of euphoria, mania, hypomania, craving, psychosis (delusion and/or hallucinations), aggression, insomnia, psychomotor agitation and dyskinesis sometimes severe, and presence of a withdrawal syndrome on reducing the level of levodopa which consists of dysphoria, depression, irritability, and anxiety.

2. For the clinical section *5. Warnings and Precautions*

Inbrija should be used in caution in PD patients with current or past history of dopaminergic dysregulation syndrome, and patients with history of drug abuse which is a risk factor for DDS development.

3. For the clinical section *5. Warnings and Precautions*

Due to the presence of Inbrija withdrawal symptoms (see section 9.3. Dependence) a slow tapering of Inbrija possibly over 2 weeks is recommended.

4. For the section *9. Drug Abuse and Dependence* or section 5. Warnings

9.3. Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Inbrija withdrawal symptoms may include stimulant-like withdrawal symptoms such as such as slowness, tiredness, anxiety, sadness, agitation, vivid dreams, and craving sleep. There is also worsening of parkinsonian motor and non-motor symptoms which may include rebound. The withdrawal symptoms may include worsening or a new onset of depressive disorder and in some patients increased excessive daytime sleepiness.

V. REFERENCES

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VI. APPENDIX 2. Review of data related to abuse potential and dependence of Inbrija

1. Chemistry

1.1 *Substance Information*

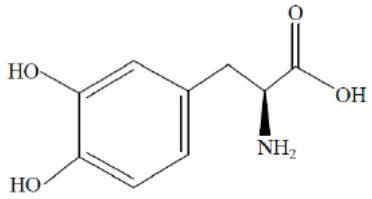
Drug Substance

Levodopa (L-DOPA, L-dopa)

Chemical Properties

Chemical name (2S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid
Molecular weight: 197.19 g/mol
Molecular formula: $C_9H_{11}NO_4$

Structural Formula:



Drug Product

CVT-301 is a device combination product which includes powder-filled capsules (dry powder formulation of L-DOPA) for oral inhalation and inhaler device. The proposed commercial dose of CVT-301 is two 42 mg LD capsules to provide a dose of 84 mg LD which can be administered up to 5 times per day, to deliver a maximum of 250 mg LD FPD (Fine Powder Dose).

CVT-301 dry powder formulation of L-DOPA
The formulation also contains the inactive ingredients sodium chloride (NaCl) and synthetically produced dipalmitoyl phosphatidylcholine (DPPC). The composition of CVT 301 formulation is presented in Table 1 (from Abuse Potential Evaluation Report for CVT-301, page 13).
CVT-301 capsules are packaged in a foil-foil blister to be stored at room temperature.

Table 1: Composition of CVT-301 (Levodopa Inhaled Powder)

Component	Ingredient (dry w/w)
Therapeutic Agent	(b) (4) levodopa, EP/USP
(b) (4)	(b) (4) DPPC
	(b) (4) NaCl, USP

USP = United States Pharmacopeia, DPPC = dipalmitoyl phosphatidylcholine
NaCl = Sodium chloride, w/w = Weight for weight

CVT-301 Inhaler

CVT-301 is delivered to the lung through a capsule-based, breath-actuated inhaler (Figure 1, page 14). The inhaler is approximately five inches long. For drug administration, the capsule is placed into the inhaler, punctured during a simple actuation process, after which the subject inhales the contents of the encapsulated drug product through the mouthpiece. The inhaler is reusable so that a single inhaler can be loaded, operated and unloaded multiple times.

2. Clinical Pharmacology

2.1 Pharmacokinetics in healthy subjects

Evaluation of PK parameters of CVT-301 was conducted in the Study CVT-301-001 in healthy volunteers.

Part A: single ascending-dose drug of four dose levels (10, 20, 30 and 50 mg) were administered. All subjects were pretreated with a standard dose of oral carbidopa (CD). Oral CD/LD doses were administered either a fasted or fed state, whereas CVT-301 was administered by inhalation in the fasted state.

Part B: aimed carbidopa pre-treatment evaluation, and was a two-period crossover study of a single inhaled dose of CVT-301 with and without pre-treatment with CD. Subjects received two single doses of CVT-301 40 mg LD FPD, with and without CD pretreatment.

Table 2 provides the summary of PK results.

Table 2: Summary of CVT-301 PK parameters based on study CVT-301-001 (from study # CVT-301-001, table 9, page 31).

Dose mg*	C_{max} ng/mL	C_{max}/Dose ng/mL/mg	AUC ng-min/mL	AUC/Dose ng-min/mL/mg	$T_{1/2}$*** min
CVT-301**					
10	196 ± 60	19.60 ± 5.99	23,374 ± 4,656	2,337 ± 466	120
20	393 ± 137	19.67 ± 6.83	44,150 ± 8,504	2,208 ± 425	122
30	576 ± 95	19.19 ± 3.17	66,914 ± 6,185	2,230 ± 206	108
50	884 ± 249	17.69 ± 4.99	106,011 ± 21,234	2,120 ± 427	101
Oral					
100(fasted)	1,317±558	13.17±5.58	156,598±26,921	1,566±269	101
100(fed)	637±144	6.37±1.44	159,042±30,544	1,590±305	114

*Dose: levodopa dose; **Refers to estimated fine particle dose; *** Median value

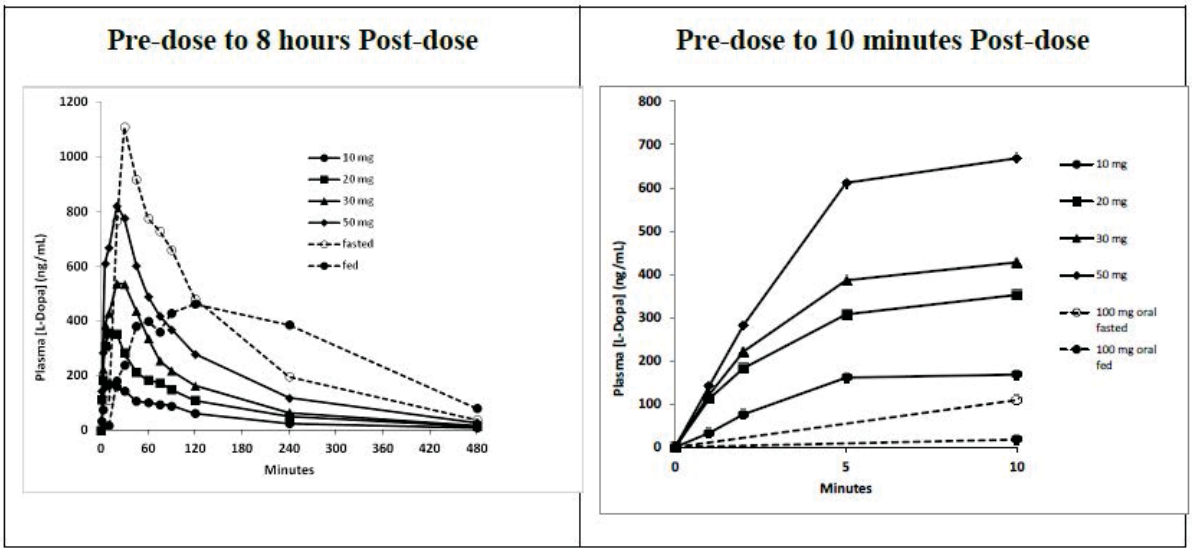
Of note is that plasma levodopa concentrations following CVT-301 inhalation **increased much faster** than following oral administration in the fasted condition and much faster than those under fed conditions (Figure 2, Table 3). Within only 5 min of inhalation of CVT-301, at doses 20 to 50 mg LD FPD, plasma concentrations reached levels 400 - 500 ng/mL or greater.
Also, peak plasma concentrations achieved following CVT-301 administration of LD FPD were compared to those observed following oral CD/LD (25 mg/100 mg) dosing.

Table 3: Summary of PK parameters for levodopa exposure after CVT-301 inhalation or oral levodopa administration **within 10 min** of drug administration (from study # CVT-301-001, table 10, page 36).

Dose (mg)	Mean ± SD $C_{max,\ 10m}$ (ng/mL)	Mean ± SD $AUC_{0\text{-}10m}$ (ng-min/mL)	Median T_{Cmax50} min	Median T_{max} min
CVT-301				
10 mg	187 ± 58	1240 ± 391	3.08	10
20 mg	368 ± 148	2590 ± 1283	2.64	10
30 mg	456 ± 59	3176 ± 769	2.90	30
50 mg	729 ± 265	4824 ± 1896	4.10	20
Oral levodopa				
100 mg oral fasted	109 ± 99	561 ± 477	18.32	45
100 oral fed	18 ± 21	124 ± 95	39.84	120

Inhaled CVT-301 for 50 mg dose is within 10 first min 7 times higher than oral fasted dose of 100 mg of levodopa, and 14 times higher if comparing the same dose level. This increase in availability of levodopa is even more dramatic for oral fed condition being 80 times higher than oral levodopa.

Figure 2: Mean levodopa plasma concentrations following CVT-301 inhalation and following a 100 mg LD FPD oral dose under fed and fasted conditions from Study CVT-301-001.



Reviewer's comment
The last figure emphasizes the fact that L-DOPA as CVT-301 formulation achieves very quickly formulation higher drug levels in comparison to oral L-DOPA, in fact within 5 min, which makes it comparable to abused stimulant type drugs such as cocaine and amphetamine. This fact may have an impact on drug abusability in stimulant users.

2.2. Pharmcokinetics in patients with PD

Study # CVT-301-002: A randomized, placebo-controlled, Phase 2 study of the safety, pharmacokinetics, and pharmacodynamics of CVT-301 (levodopa inhalation powder) in patients with Parkinson's disease and motor response fluctuations (OFF episodes)

Doses:
- CVT-301: 25 mg and 50 mg levodopa fine particle dose [FPD]
- Active control: open-label oral treatment with a standard oral carbidopa/levodopa (CD/LD) dose (25 mg/100 mg) that was administered during the first treatment visit of the dosing period.
- Placebo: inhaled placebo powder.

Population: 23 patients Parkinson's disease (PD) patients experiencing OFF episodes completed the study

Duration:
The dosing period consisted of 4 separate in-clinic visits over a 2- to 6-week period. Patients received a total of 4 treatments; 1 treatment was administered per visit day. Treatment visits were to be separated by at least 2 days.

Results:

Table 4: Median LD Plasma PK Parameters Immediately Following Dosing

Treatment Median	$C_{max\ 0-10}$ ng/mL	$C_{max\ 0-30}$ ng/mL	AUC_{0-10} ng-min/mL	AUC_{0-30} ng-min/mL	$T_{Cmax\ 50}$ Min	T_{max} min
CVT-301*						
25 mg	271	345	1890	7240	4.04	15
50 mg	500	549	3147	12515	3.99	15
Oral**	28	234	71	3092	47.3	66
Placebo	20	23	85	213	3.81	45

*Refers to estimated levodopa fine particle dose
** Oral CD/LD 25 mg/100 mg

Similar like with in healthy volunteers immediate levels of levodopa after the administration of CVT-301 spray 50 mg is rising **36 times higher** than oral carbidopa/levodopa 25/100 mg, and **Tmax is 4 times shorter**.

3. 1 Absorption, Distribution, Metabolism, Elimination (ADME)

Only summaries from literature review provided.

4. Clinical Studies

The clinical development program for CVT-301 included total of 11 studies, 5 studies in healthy volunteers and 6 studies in PD patients, see below table 5 (table 5, Mod 2.7.4, page 53).

As of December 20, 2017, 1103 subjects were enrolled in the CVT-301 clinical program, which included 951 PD patients. A total of 897 subjects received at least 1 dose of CVT-301 during all studies, 754 patients with PD and 145 healthy volunteers.

Healthy volunteers

Table 5. List of studies conducted in Healthy Volunteers (Mod 2.7.4, table 5, page 53).

Study (Phase)	Population	Number of Subjects Enrolled	Number of Subjects Exposed to CVT-301	Levodopa FPD (mg)	Route and Duration of Treatment
Clinical Pharmacology and Special Populations Studies					
CVT-301-001 (Phase 1)	Healthy Volunteers	26	26	10, 20, 30, 40, 50	Inhalation Single dose
CVT-301-006 (Phase 1)	Healthy Volunteers	13	12	50, 70, 105	Inhalation Single dose
CVT-301-007 (Phase 1)	Smokers / Non-smokers	63	56	50	Inhalation Single dose
CVT-301-008 (Phase 1)	Asthmatic Adults	26	25	50	Inhalation 3 doses in 1 day
CVT-301-010 (Phase 1)	Healthy Volunteers	24	24	35, 50	Inhalation Single dose
Total CVT-301 Exposure in Clinical Pharmacology Studies			**143**		

Patients with Parkinson's disease

Table 6. List of studies conducted in Parkinson's patients (Mod 2.7.4, table 5, page 53).

Study (Phase)	Population	Number of Subjects Enrolled	Number of Subjects Exposed to CVT-301	Levodopa FPD (mg)	Route and Duration of Treatment
Parkinson's Disease Patient Studies					
CVT-301-009 (Phase 1)	PD Patients	36	36	50	Inhalation Single dose
CVT-301-002 (Phase 2a)	PD Patients	24	24	25 and 50	Inhalation 2 doses
CVT-301-003 (Phase 2b)	PD Patients	89	43	35 and 50	Inhalation 4 weeks
CVT-301-004 (Phase 3)	PD Patients	351	227	35 or 50	Inhalation 12 weeks
CVT-301-004E[a] (Phase 3)	PD Patients	325	153[b]	35 or 50	Inhalation 12 months
CVT-301-005 (Phase 3)	PD Patients	408	271[c]	50	Inhalation 12 months
Total CVT-301 Exposure in PD subjects			**754**		

Sponsor's pooling data strategy

The sponsor presented the safety data in the ISS using various pooling strategies:
POOL 1: includes studies CVT-301-003 and CVT-301-004.
POOL 2 includes CVT-301 groups from studies CVT-301-004E and CVT-301-005.
POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005), that is combines exposure from Pool 1 and Pool 2.

For the population of PD patients the data from the pool 3 which encompasses majority of studies in PD patients will be used for the evaluation of abuse potential.

4.1 Human Abuse Potential Studies

No human abuse potential study was conducted.

4.2.1 Abuse Potential Adverse Events in Phase 1 Studies in Healthy Volunteers

Abuse potential AEs are reviewed for the selected studies.

1. *Study # CVT-301-001: A phase 1 study of the safety and pharmacokinetics of single ascending doses of cvt-301 (levodopa inhalation powder) in healthy, adult subjects.*

Study consisted of part 1A with 18 HV and SAD doses of Inbrija 10, 20, 30 and 50 and part B with 8 HV.

There were 4 neuropsychiatric AEs of 3 dizziness and 1 headache in part A with Inbrija and 1 AE of dizziness in part B (Inbrija and carbidopa).

2. *Study Report: CVT-301-010*: *A phase 1 single dose pharmacokinetic bridging study to compare two dose strengths of cvt-301 (levodopa inhalation powder) with an oral dose of sinemet® (carbidopa-levodopa) tablets*

This was a bridging study with Inbrija doses of 60 and 85 mg and in HV with 24 subjects in each group.
The only abuse potential AE was 1 (4.2%) somnolence at dose 84 mg.

In the studies #CVT-301-007 and CVT-301-008 no abuse potential AEs were reported.

4.2.2 Clinical Studies Phase 2/3 in Parkinson's Patients

A phase 2 and 3 controlled studies are presented as safety data from pool 1, 2 and 3 that includes 4 studies placebo-controlled studies CVT-301-003 and CVT-301-004, and long-term studies CVT-301-004E and CVT-301-005.
Data on number of subjects enrolled in these studies is provided in the table 6 and below. The duration and general design of these long-term studies is as follows:

- CVT-301-003: duration – 4 weeks, double blind, placebo-controlled
- CVT-301-004: duration – 12 weeks, double blind, placebo-controlled
- CVT-301-004E: duration -52 weeks, dose-level blinded
- CVT-301-005: duration - 52 weeks, OL

Patients with Parkinson's disease
The pooling for PD patients did not include safety data for study CVT-301-009 (phase 1, single dose) and study CVT-301-phase 2a, 2 doses).

Description of safety data is based on Mod 2.5, and Mod. 2.7.4.

In the pool 3 (total of pool 1 and 2) N=705 there were 489 (69.4) PD patients who reported AEs, including severe AEs 77 (10.9%) and serious AEs 83 (11.8). The number of patients discontinued due to AEs N=57 (8.1%). There were also 2 deaths (0.3%), one patient died of completed suicide, and one patient died of hypoxic-ischemic encephalopathy, subsequent to drowning.

In the pool 1 (drug N=270, placebo N=155) of placebo-controlled studies (# CVT-301-003 and # CVT-301-004), most frequent AE with CVT-301 and placebo, respectively, included cough (37 [13.7%] vs 3 [1.9%]), dyskinesia (10 [3.7%] vs 1 [0.6%]), upper respiratory tract infection (9 [3.3%] vs 3 [1.9%]), throat irritation (9 [3.3%] vs 1 [0.6%]), and nausea (9 [3.3%] vs 3 [1.9%]).

In the pool 2 of long-term studies (# CVT-301-304E and CVT-301-005) the most frequently reported AE was cough 80 (13.7%), fall 56 (9.6%), upper respiratory tract infection 32 (5.5%), dyskinesia 32 (5.5%), nasopharyngitis 29 (5.0%), back pain 22 (3.8%), and throat irritation 20 (3.4%).

Short summary of studies included in poolings:

Study # CVT-301-003

- Phase 2b. Safety and efficacy. Randomized, double-blind, placebo-controlled.
- Treatments: CVT-301 35 mg FPD, inhaled up to 3 times daily.
- Population: Patients with Parkinson's disease: CVT-301: 44; Placebo: 45
- Duration: 4 week

Study # CVT-301-004

- Phase 3, Safety and efficacy. Randomized, double blind, placebo-controlled
- Treatments: CVT-301 60 mg, inhaled up to 5 times daily; CVT-301 84 mg, inhaled up to 5 times daily; Placebo, inhaled up to 5 times daily, maintained standard carbidopa/levodopa (CD/LD) therapy
- Population: Patients with Parkinson's disease. Total - 351 randomized: CVT-301 60 mg - 115; CVT-301- 84 mg: 120; placebo-116
- Duration: 12 weeks

Study # CVT-301-004E

- Phase 3, Safety and efficacy. Dose-level blinded
- Treatments: CVT-301 60 mg, inhaled up to 5 times daily; CVT-301 84 mg, inhaled, up to 5 times daily
- Population: Patients with Parkinson's disease. 390 planned
- Duration: 52 weeks

Study # CVT-301-005

- Phase 3. Safety study.Open-label, randomized , observational control.
- Treatments: CVT-301 84 mg, inhaled up to 5 times daily; CVT-301 60 mg, inhaled up to 5 times daily (if dose reduction was necessary due to tolerability); Standard of care for Parkinson's patients in the observational cohort

- Population: Patients with Parkinson's disease - CVT-301 80 mg: 278; Observational Control: 130
- Duration: 52 weeks

Discontinuations From the Study and Adverse Events Leading to Study Discontinuation

For the total population of PD patients treated with CVT-301 N=705 (pool 3) there were 197 (27.9%) patients who discontinued the study, the most common reason for study discontinuation was withdrawal by subject 96 (13.6%); and the second reason were AEs.
In all studies in pool 3 there were 57 (8.1%) in N=705 of patients treated with CVT-301who discontinued studies due to AEs. The most frequent AEs leading to permanent study drug discontinuation was cough (13 [1.8%]), hallucination (including visual) (4 [0.6%]), dyskinesia and throat irritation (each, 3 [0.4%]), blurred vision, bronchitis, dry throat, dyspnea, euphoric mood, and upper respiratory tract irritation (each, 2 [0.3%]). Other AEs that lead to study drug discontinuation were reported by 1 (0.1) patient. (based on table 27, Mod 2.7.4, page 91) included completed suicide, visual hallucinations, dopamine dysregulation syndrome, intentional product misuse, paranoia.

Reviewer's comment
Hallucinations are second most frequent reason leading to permanent study drug discontinuation, although hallucinations are to some extent also one of the Parkinson's disease symptoms, it appears that CVT-301 either exacerbates this symptom in PD or just causing emergence of hallucinations due to its effect on dopaminergic system.
Additionally, some clearly related to abuse potential adverse events lead to study drug discontinuation, such as euphoric mood, dopamine dysregulation syndrome, intentional product misuse, paranoia, which were maybe not very frequent but certainly concerning for higher abuse potential of CVT-301 than usual oral levodopa formulations.

Adverse Events Reported on First Dose Day
Due to very high Cmax achieved by CVT-301 levodopa formulation during first 10 min CSS requested in the meeting minutes IND 115750, Oct 27, 2016 an examination of abuse-related AEs collected within the first 10 minutes of drug exposure. However, the Sponsor did not provide this data citing not consistently captured the time of AEs in the database, and provided only AEs that occurred on that day in general. This renders this data essentially useless in terms of assessment of abuse potential.

Table 7. Abuse potential related AEs that occurred on the first dose day.

	POOL 1		POOL 2	POOL 3	Observational cohort N=127 n (%)
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)	
Any event	4 (1.5)	3 (1.9)	6 (1.0)	10 (1.4)	
Dizziness	3 (1.1)	3 (1.9)	3 (0.5)	6 (0.9)	
Agitation	1 (0.4)			1 (0.1)	
Euphoric mood			1 (0.2)	1 (0.1)	
Feeling abnormal			1 (0.2)	1 (0.1)	
Hallucination, visual			1 (0.2)	1 (0.1)	
Somnolence		1 (0.6)			

Few neuro-psychiatric AEs occurred on the first dose day including euphoric mood, 2 AEs, hallucination, visual, 1 AE, agitation, 1AE, and other most common that occurred were cough 62, throat irritation 17, dizziness 6 and dyskinesia 5. Although a number of the abuse related AEs in not frequent their occurrence at the first dose of the levodopa product is highly unusual.

Abuse Potential Related Adverse Events During the Clinical Studies in Parkinson's Patients

Abuse potential related adverse events are summarized in the table 8.

Table 8. Abuse potential related adverse events in PD patients in Phase 2/3 (pool 3) studies based on Table 29, Mod 2.7.4 p 97 and ISS table 3.3.1.1 page 3189. Only pool 1 and 3 are provided to show placebo group.

Adverse Event PT	POOL 1 CVT-301 (N=270) n (%)	POOL 1 Placebo (N=155) n (%)	POOL 3 CVT-301 (N=705) n (%)
Any event	14 (5.2)	9 (5.8)	46 (6.5)
Hallucinations (with visual)	4 (1.5)	2 (1.3)	18 (2.5)
Euphoric mood			2 (0.3)
Anxiety	3 (1.1)	1 (0.6)	12 (1.7)
Insomnia/initial	5 (1.9)	1 (0.6)	15 (2.1)
Depression	2 (0.7)	2 (1.3)	10 (1.4)
Depressed mood	2 (0.7)	1 (0.6)	6 (0.9)
Suicidal ideation			4 (0.6)
Completed suicide	1 (0.4)		1 (0.1)
Impulse-control disorder	1 (0.4)		3 (0.4)
Hypersexuality			2 (0.3)
Decreased appetite	1 (0.4)		5 (0.7)
Abnormal dreams			4 (0.6)
Somnolence	2 (0.7)		3)0.4)
Nightmare			3 (0.4)
Feeling abnormal			1 (0.1)
Dopamine dysregulation synd.			1 (0.1)
Intentional product misuse			1 (0.1)

Disturbance in attention			1 (0.1)
Agitation	1 (0.4)		1 (0.1)
Altered state of consciousness			1 (0.1)
Paranoia	1 (0.4)		1 (0.1)
Psychotic disorder			1 (0.1)
Delirium			1 (0.1)
Delusion			1 (0.1)
Irritability	1 (0.4)		1 (0.1)
Cognitive disorder			1 (0.1)

Reviewer's Comment
The PD patients population treated with CVT-301 shows some AEs of concern such as increased frequency of hallucinations, occasional euphoric mood, and more worrisome are psychiatric disorders such as delusion, delirium, paranoia, and suicidality. Although these disorders occur as a part of Parkinson's disease, there is a notable difference between placebo group which continues only oral levodopa regimen and population of Inbrija plus oral levodopa. Of note is that impulse-control disorders were also reported, and included hypersexuality and dopaminergic dysregulation syndrome.

2.4 Evidence of Abuse, Misuse Diversion and Overdose in Clinical Trials

4.4.1 Evidence of Abuse – Data on presence of Dopamine dysregulation syndrome based on Analysis of Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (QUIP)

Dopamine Dysregulation Syndrome (DDS)
DDS is considered a substance use disorder involving levodopa according to DSM-5 (Warrant et al., 2017). There is evidence that some DDS were found not only in AEs data base table 8, (1 case of DDS) but also using Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP) which is a standard questionnaire that evaluates the spectrum of Impulsive-Compulsive Disorders, including DDS, encountered during the levodopa treatment of Parkinson's disease.
In the CSS IR # 2 (Oct 30, 2018) QUIP data was requested but only the section for Medication Use, which was designed to capture DDS. However, in this received data set there are still missing multiple evaluations from different treatment visits including results from the screening visit or the first visit, so the results presented below likely underestimate frequency of DDS during the Inbrija treatment.

Below are listed QUIP questions which were designed to capture DDS (according to Dr. Daniel Weintraub who developed this questionnaire):

C. MEDICATION USE
1. Do [Did] you or others (including your physicians) think that you consistently take [took] too much of your Parkinson's medications? __Yes __No
2. Have [Had] you over time increased on your own, without medical advice, your overall intake of Parkinson's medications for psychological reasons, such as improved mood or motivation? __Yes __No

3. Have [Had] you over time increased on your own, without medical advice, your overall intake of Parkinson's medications because you only feel fully "on" when you are dyskinetic? __Yes __No
4. Do [Did] you have difficulty controlling your use of Parkinson's medications (such as experiencing a strong desire for more medication, or having worse mood or feeling unmotivated at a lower dosage)? __Yes __No
5. Do [Did] you hoard or hide your Parkinson's medications to increase the overall dosage? __Yes __No

The strategy to evaluate the number of PD patients in the clinical studies who developed or experienced worsening of symptoms related to DDS during the Inbrija treatment.

- To evaluate a number of PD patients who developed symptoms of DDS during Inbrija treatment for the first time the number of patients who provided positive responses to any of above listed QUIP questions but stated 'No" at the screening visit was counted.
- Also, included were the patients who responded to more questions with "Yes" comparing to the screening visit (worsening of DDS).
- Additionally, as separate category of patients were counted who responded with"Yes" at the screening visit (patients who developed DDS symptoms on the oral levodopa).

Study # CVT-301-004

During the study duration of 12 weeks in the population of patients N =227 exposed to Inbrija, 13 (5.7%) patients developed for the first time some symptoms of DDS, 11 (4.8%) had already noted DDS symptoms before starting Inbrija 4 (1.7%) of them remained stable but 7 (3%) patients had at some points worsening of DDS symptoms as detected by higher "yes" responses to the questionnaire. Total population of PD patients who developed new DDS symptoms at some point or had worsening of pre-existing ones is 20 (8.8%).
In fact, it seems that one patient in this study developed more severe DDS answering majority of questions "yes" during the study this includes patient # CVT-301-004-(b) (6)(Qs with "yes": at TV4: 2, 3, 4),

Study # CVT-301-004e

During the study duration of 12 months in the population of PD patients N =295 exposed to Inbrija, 23 (7.9%) patients developed for the first time some symptoms of DDS, and 4 (1.3%) had worsening of pre-existing DDS symptoms, and one patient remained stable.
Some patients in this study developed more severe DDS answering majority of questions "yes" during the study, this includes:

- patient # CVT-301-005 (b) (6) CVT-301-004E (b) (6) (Qs with "yes" at TV5: 2, 3, 4, 5)
- patient # CVT-301-005 CVT-301-004E (Qs with "yes" at TV5: 1, 2, 3, 4)
- patient # CVT-301-004 (Qs with at TV2: 2, 3, 4, and at TV6: 2, 4)
- patient # CVT-301-004 (Qs with "yes" TV5: 2, 3; TV6: 4, 5).

<u>An example of higher QUIP scores in Medication use section for a patient in the study # CVT-301-004e (CSS IR # 2, p 150)</u>

Listing PH 8.1.1
Listing of Subjects who Responded Yes to At Least One QUIP Medication Use Question
Safety Population

Unique Subject ID	Study	Subject ID	Treatment	Visit	Medication Use 1	2	3	4	5
CVT-301-005-(b) (6)	CVT-301-004E	(b) (6)	CVT 301 DL1	SV2	No	No	No	No	No
				TV1	No	Yes	No	Yes	No
				TV2	No	No	No	No	No
				TV3	No	No	No	No	No
				TV4	Yes	Yes	Yes	Yes	No
				TV5	No	Yes	Yes	Yes	Yes

SV2-Screening visit 2
TV-Treatment visit

Study # CVT-301-005

During the study duration of 12 months in the population of patients N =271 exposed to Inbrija, 16 (5.9%) patients developed for the first time some symptoms of DDS, and 9 (3.3%) had already noted DDS symptoms before starting Inbrija: 8 (2.9%) of them remained stable and 1 (0. 3%) patient experienced at some points worsening of DDS symptoms. Total population of PD patients who developed new DDS symptoms at some point or had worsening of pre-existing ones is 17 (6.3%).

Additionally, it is noted that some (4) patients in this study developed more severe DDS answering majority of questions "yes" during the study, this includes:

- patient # CVT-301-005-(b) (6) (Qs with "yes": TV6: 2, 3, 4),
- patient # CVT-301-005- (Qs with "yes" at TV4: 2, 3, 4),
- patient # CVT-301-005- (Qs with "yes" at TV6: 1, 2, 3),
- patient # CVT-301-005- (Qs wit "yes" at TV6: 3, 4, 5).

*TV-Treatment visit

Explanation of the data analysis:

- Observational cohort was not included and counted.
- These numbers are likely an understatement as in the multiple cases the QUIP reports start at TV2, or TV3, which is already a second or third treatment visit.

During the studies with Inbrija one case of DDS was diagnosed: CVT-301-005 (b) (6) and the drug was withdrawn.

Reviewer's comment

It seems that Inbrija has a higher potential to induce emergence of dopamine dysregulation syndrome in PD patients than oral levodopa formulations. Therefore, the warning language will be recommended to use Inbrija with caution in PD patients with past or current history of DDS or substance use disorder which is a high risk factor for development of DDS.

4.4.2 Overdose accidental and intentional

Cases of overdoses were summarized in Abuse section "1.7.2. Cases of Overdose in Phase 3 Studies, p 38.
Overdose was evaluated in studies CVT-301-004, CVT-301-004E CSR and CVT-301-005 by reviewing Inhaled Dosing Logs and to identify the patients who used 8 or more doses on any given day.
During these studies, 11 subjects (2 subjects on CVT-301 60 mg, 9 subjects on CVT-301 84 mg and none on placebo) used 8 or more inhaled doses on at least 1 study day and 6 of them reported AEs (1 subject in CVT-301 004 (b) (6); 2 subjects in CVT-301 004E (b) (6); and 3 subjects in 005 (b) (6)). The Sponsor states that provided narratives for these subjects, however the description of AEs related to overdose could not be located.

4.4.3 Study Drug Accountability

Patients received study drug kits for administration at home during the one Phase 2b study # CVT-301-003 and three Phase 3 studies (Studies # CVT-301-004, CVT-301-004E, CVT-301-005).
Below are presented table showing drug accountability expressed as kits dispensed and returned and capsules dispensed and returned.

Study CVT-301-003 -Accountability

Table 9. CVT-301-003 Drug Accountability based on Table 58, Mod 2.7.4, page 162

	Placebo (N=43) n (%)	**CVT-301 (N=43) n (%)**
Kits Dispensed	161	162
Entire Kits Returned	143 (88.8)	144 (88.9)
Partial Kits Returned	17 (10.6)	14 (8.6)
Kits Not Returned	0 (0.0)	0 (0.0)
Kits Not Reconciled*	1 (0.6)	4 (2.5)
Subjects with All Capsules Returned	31 (72.1)	31 (73.8)
Subjects with Capsules Not Returned	12 (27.9)	11 (26.2)
< 10% Capsules	12 (27.9)	11 (26.2)
10% to < 20%	0 (0.0)	0 (0.0)
>20%	0 (0.0)	0 (0.0)

In both arms Inbrija and placebo there was a similar number of capsules not returned.

Study CVT-301-004 -Accountability

Table 10. CVT-301-004 Drug Accountability based on Table 59, Mod 2.7.4, page 163

	Placebo (N=112) n (%)	DL1 (N=113) n (%)	DL2 (N=114) n (%)
Kits Dispensed	1251	1252	1287
Entire Kits Returned	1121 (89.6)	1131 (90.3)	1152 (89.5)
Partial Kits Returned	100 (8.0)	111 (8.9)	108 (8.4)
Kits Not Returned	9 (0.7)	10 (0.8)	9 (0.7)
Kits Not Reconciled*	21 (1.7)	0 (0.0)	18 (1.4)
Subjects with All Capsules Returned	60 (54.1)	54 (47.8)	57 (50.0)
Subjects with Capsules Not Returned	51 (45.9)	59 (52.2)	57 (50.0)
< 10% Capsules	45 (40.5)	52 (46.0)	49 (43.0)
10% to < 20%	3 (2.7)	3 (2.7)	4 (3.5)
20% to < 30%	0 (0.0)	2 (1.8)	2 (1.8)
30% to < 40%	1 (0.9)	0 (0.0)	2 (1.8)
40% to < 50%	0 (0.0)	0 (0.0)	0 (0.0)
>= 50%	2 (1.8)	2 (1.8)	0 (0.0)

In this CVT-301-004 study there was noted some difference in capsules not returned between Inbrija and placebo. Number of patients with capsules not returned was 6.3% (52.2%-45.9%) and 4.1% (50%-45.9%) for DL1 (60 mg) and DL2 (84 mg) groups, respectively, and as such was higher than placebo. Also, in both drug arms vs placebo, there were higher number of patients with not returned capsules in range of <10 and 10-20-30-40% of capsules.

Additional clarification on number of not returned capsules data was requested by CSS and received IR # 2 (Oct 30 2018, page 160) shows that a number of patients (7) did not return Inbrija capsules >100 whereas in placebo group there were only 3 such cases. In fact, some patients did not return 129 to 320 capsules, however there were placebo patients who did not return from 20 to 327 capsules.

Table 11. CVT-301-004 Drug Accountability based on summary of accountability presented as % of not returned capsules (CSS IR # 2, Oct 30 2018, page 160)

Listing PH 9.1
Listing of Subjects With >=20% of Capsules Not Returned
(Safety Population)

Group	Unique Subject ID	Subject ID	Treatment	Capsules Dispensed	Capsules Returned	Capsules Not Returned	% Capsules Not Returned
20% to <30%	CVT-301-004 (b) (6)	(b) (6)	CVT 301 DL1	960	759	201	20.9
	CVT-301-004		CVT 301 DL1	960	754	206	21.5
	CVT-301-004		CVT 301 DL2	560	431	129	23.0
	CVT-301-004		CVT 301 DL2	960	718	242	25.2
30% to <40%	CVT-301-004		CVT 301 DL2	960	671	289	30.1
	CVT-301-004		Placebo	320	222	98	30.6
	CVT-301-004		CVT 301 DL2	80	52	28	35.0
40% to <50%	No subjects in this study						
>=50%	CVT-301-004- (b) (6)	(b) (6)	Placebo	640	320	320	50.0
	CVT-301-004-		Placebo	640	313	327	51.1
	CVT-301-004-		CVT 301 DL1	320	0	320	100
	CVT-301-004-		CVT 301 DL1	320	0	320	100

Study CVT-301-004E -Accountability

Table 12. CVT-301-004E Drug Accountability based on Table 60, Mod 2.7.4, page 165

	CVT-301 DL1 (N=153) n (%)	CVT-301 DL2 (N=159) n (%)
Kits Dispensed	4467	5208
Entire Kits Returned	4070 (91.1)	4662 (89.5)
Partial Kits Returned	336 (7.5)	428 (8.2)
Kits Not Returned	40 (0.9)	77 (1.5)
Kits Not Reconciled*	21 (0.5)	41 (0.8)
Capsules Dispensed	355680	413360
Capsules Returned	349256 (98.2)	403067 (97.5)
Capsules Not Returned	6424 (1.8)	10293 (2.5)
Subjects with All Capsules Returned	48 (31.4)	45 (28.3)
Subjects with Capsules Not Returned	105 (68.6)	114 (71.7)
< 10% Capsules	101 (66.0)	104 (65.4)
10% to < 20%	1 (0.7)	4 (2.5)
20% to < 30%	1 (0.7)	5 (3.1)
30% to < 40%	0 (0.0)	1 (0.6)
40% to < 50%	1 (0.7)	0 (0.0)
>= 50%	1 (0.7)	0 (0.0)

In this study it seems more patients did not return the study drug. To translate better the number in the above tables it looks that: # 1) more patients did not return drug than returned 105 (68%), in lower dose group (60 mg) and 114 (71.7%) in higher dose group (84 mg), and # 2) in the lower dose group 105 patients “lost” total of 6424 capsules, and higher dose group 114 patients did not return 10293 capsules..
At this point accidental loss is probably not a best explanation and significant drug diversion has to be considered, which indicates higher abuse potential of Inbrija than oral levodopa formulations.

Additional clarification on number of not returned capsules data is provided in CSS IR # 2 (Oct 30 2018, p 161).

Table 12. CVT-301-004E Drug Accountability based on summary of accountability presented as % of not returned capsules (CSS IR # 2, Oct 30 2018, page 161)

Listing PH 9.2
Listing of Subjects With >=20% of Capsules Not Returned
(Safety Population)

Group	Unique Subject ID	Subject ID	Treatment	Capsules Dispensed	Capsules Returned	Capsules Not Returned	% Capsules Not Returned
20% to <30%	CVT-301-004E- (b) (6)	(b) (6)	CVT 301 DL2	3840	3039	801	20.9
	CVT-301-004-		CVT 301 DL2	1280	985	295	23.0
	CVT-301-004-		CVT 301 DL2	4160	3200	960	23.1
	CVT-301-004-		CVT 301 DL2	3520	2701	819	23.3
	CVT-301-004-		CVT 301 DL1	960	720	240	25.0
	CVT-301-004-		CVT 301 DL2	960	680	280	29.2
30% to <40%	CVT-301-004- (b) (6)		CVT 301 DL2	1920	1172	748	39.0
40% to <50%	CVT-301-004-		CVT 301 DL1	1920	1140	780	40.6
>=50%	CVT-301-004E		CVT 301 DL1	720	160	560	77.8

The table clarifies the issue of lost capsules, there is unusually high diversion of Inbrija in range of 240 to 960.

Table 13. CVT-301-005 Drug Accountability based on Table 61, Mod 2.7.4, page 166

	CVT-301 (N=271) n (%)
Kits Dispensed	7692
Entire Kits Returned	7019 (91.3)
Partial Kits Returned	561 (7.3)
Kits Not Returned	99 (1.3)
Kits Not Reconciled*	13 (0.2)
Capsules Dispensed	614320
Capsules Returned	601670 (97.9)
Capsules Not Returned	12650 (2.1)
Subjects with All Capsules Returned	111 (41.0)
Subjects with Capsules Not Returned	160 (59.0)
< 10% Capsules	144 (53.1)
10% to < 20%	7 (2.6)
20% to < 30%	6 (2.2)
30% to < 40%	1 (0.4)
40% to < 50%	0 (0.0)
>= 50%	2 (0.7)

Again, like in the previous table it seems that majority of 12650 capsules not returned were lost by few patients in this case 16 patients, 2 patients lost >50% of the drug received, which is >1133 capsules.

Additional clarification on number of not returned capsules data is provided in CSS IR # 2 (Oct 30, 2018, p 162).

Table 14. CVT-301-005 Drug Accountability based on summary of accountability presented as % of not returned capsules (CSS IR # 2, Oct 30 2018, page 162)

Listing PH 9.3
Listing of Subjects With >=20% of Capsules Not Returned
(Safety Population)

Group	Unique Subject ID	Subject ID	Treatment	Capsules Dispensed	Capsules Returned	Capsules Not Returned	% Capsules Not Returned
20% to <30%	CVT-301-005-(b) (6)	(b) (6)	CVT-301 50 mg	2320	1814	506	21.8
	CVT-301-005-		CVT-301 50 mg	2480	1878	602	24.3
	CVT-301-005-		CVT-301 50 mg	960	720	240	25.0
	CVT-301-005-		CVT-301 50 mg	2400	1797	603	25.1
	CVT-301-005-		CVT-301 50 mg	1120	830	290	25.9
	CVT-301-005-		CVT-301 50 mg	4320	3036	1284	29.7
30% to <40%	CVT-301-005-		CVT-301 50 mg	2720	1839	881	32.4
40% to <50%	No subjects in this study						
>=50%	CVT-301-005-(b) (6)		CVT-301 50 mg	1920	959	961	50.1
	CVT-301-005-		CVT-301 50 mg	1520	627	893	58.8

The table clarifies the issue of lost capsules, there is unusually high diversion of Inbrija in range of 240 to 1284 capsules.

Reviewer's comment
Drug accountability indicates high drug diversion especially in long-term studies with striking indeed numbers in range of 280 to 960 in the study CVT-301-004e and 240 to 1284 in the study CVT-301-005. This indicates high abuse potential of Inbrija in Parkinson's patients population.

4.5 Evaluation of Dependence, Tolerance and Rebound in Clinical Studies

4.5.1 Dependence and Withdrawal

Dependence was evaluated during Study CVT-301-004E under the amendment to study protocol (Protocol version 5.0, 5.1, and 5.2) according to FDA recommendations (from the pre-NDA meeting, 28 September 28, 2017).
Following 6 withdrawal questionnaires were used:

- Amphetamine Withdrawal Questionnaire (AWQ)
- Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC)
- Patient Health Questionnaire (PHQ-9)
- Epworth Sleepiness Scale (ESS)
- C-SSRS (self-report version)

- Movement Disorder Society - Unified Parkinson's Disease Rating Scale parts IB and II

The withdrawal symptoms were evaluated over a 28 day period after abrupt discontinuation of CVT-301 (Inbrija). The collection of the withdrawal questionnaire was restricted to patients who had minimum of 6 months of study drug exposure. Majority study sites administered the 6 withdrawal assessment questionnaires at TV6 (protocol Version 5.0 and 5.1), except for selected US sites, where patients participated in the withdrawal symptom assessment at the end of TV4, TV5, or TV6, depending on which of the visits was the next scheduled one for the patient (protocol Version 5.2).

Total of 82 patients participated in the evaluation of withdrawal and dependence, 42 at dose level 60 mg LD (DL1 group) and 40 PD patients at dose level 84 mg LD (DL2 group). All patients received copies of the AWQ, the DDS-PC, PHQ-9, ESS, C-SSRS (self-report version), and the self-administered MDS-UPDRS Parts IB (non-motor) and 2 (motor) to complete at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after the treatment visit. Patients were also instructed to fill out the questionnaires during their first ON state (after the intake of their first scheduled dose of standard oral PD medication) on these days.
However, for unknown reasons many questionnaires from last day of treatment (LDOT)* were missing 40% for Patient Health Questionnaire – 9 (PHQ-9) (depression scale), up to 23% for Amphetamine Withdrawal Questionnaire (AWQ). But what is even more concerning that many of the missing questionnaire were missing in a very puzzling pattern, they were present for EPS but absent for AWQ and DDS-PC, as though the same patient selectively avoided/discriminated against AWQ and DDS-PC forms…

Following number of questionnaires was missing on the last day of treatment (LDOT) for different scales in the NDA:

- for Patient Health Questionnaire – 9 (PHQ-9) (depression scale); 38% for lower dose and 40% for higher dose (of note full set was requested as IR and received by CSS)
- for Amphetamine Withdrawal Questionnaire (AWQ): 23.8% for lower dose, 22.5% for higher dose (the full set of data was never received)
- for DDS – Patient and Caregiver Inventory: 23.5% for lower dose and 25% for higher dose
- for Epworth Sleepiness Scale (ESS); none were missing for both doses
- for MDS-UPDRS the 100% LDOT values were missing because the Sponsor used a different scale in the clinic (old UPDRS) and different scales were used at home (new MDS-UPDRS) and the Sponsor **further claimed that they are not comparable**….which was proven to be not true and at the meeting with DNP on Nov 26 2018 it was clarified that the UPDRS scale can be converted into MDS-UPDRS scale.
- Also, for some specific scales AWQ and PHQ-9 and DDS-PC many questionnaires were missing from home evaluations however on the same days none or only sporadic questionnaires are missing for UPDRS and EPS.

*The importance of last day of treatment (LDOT) values lies in the fact that it is used to evaluate extent of withdrawal. The highest score is obviously used to diagnose the severity of withdrawal, but LDOT is needed to see what was the patients baseline score.

Analysis of the data

Score increases of "1" only in the below presented scales were not considered in any the analysis, only score increases of =/>2.
The withdrawal score was counted as the difference between highest achieved withdrawal score on the scale and last day on treatment (LDOT).

Amphetamine Withdrawal Questionnaire (AWQ)

The analysis was performed in only 32 of 42 patients in DL1 and 31 of 40 patients in DL2 as the rest of the data did not have last day of treatment values (LDOT). There were 23.8% LDOT missing for lower dose, 22.5% LDOTs were missing for higher dose for reasons not well explained by the sponsor.
In the group of 62 patients with available LDOTs 37 (59.6%) patients: 21 (65.6%) in DL1 and 16 (51.6%) in DL2, had an increase of AWQ score above the LDOT on any day of the withdrawal period.
Score increase >10 is diagnostic of amphetamine withdrawal and is comparable to the lowest scores of the first 5 days of acute methamphetamine withdrawal (McGregor et al., 2005, cited by the sponsor, see below). The score increase >10 was seen in the lower dose group DL1 in 13 (40.6%) and in higher dose DL2 in 9 (29%) patients. In this group some patients had already at LDOT score >10, 6 (18.7%) and 5 (16.1%), in DL1 and DL2, respectively, however during the withdrawal their scores worsened significantly.

Example of sudden worsening of AWQ scores within 1-3 days of Inbrija withdrawal from CSS IR # 1, p. 21):

Listing PH 1.1
Amphetamine Withdrawal Questionnaire (AWQ) Total Score
Safety Population - Subjects with an Increase in Withdrawal Period Score Compared to LDOT

Treatment Group: CVT 301 DL1

Subject ID	Visit/Day After LDOT	Date of Assessment	Total Score
(b) (6)	TV6 (LDOT)	2017-10-20	7
	TV6/Day 1	2017-10-21	19*
	TV6/Day 3	2017-10-23	19*
	TV6/Day 6	2017-10-26	19*
	TV6/Day 14	2017-11-03	
	TV6/Day 17	2017-11-06	
	TV6/Day 24	2017-11-13	19*

In the data requested in CSS IR # 2 (Oct 30, 2018), which included AWQ scores without LDOT, at least 3 more patients in lower dose group and 1 patient in the higher dose group had scores >10 comparable to acute methamphetamine/amphetamine withdrawal syndrome.

TABLE 15. AWQ scores during the Inbrija withdrawal period measured with Amphetamine Withdrawal Questionnaire (AWQ) and with the interpretation based on use of AWQ in methamphetamine withdrawal study (McGregor, 2005A and B)

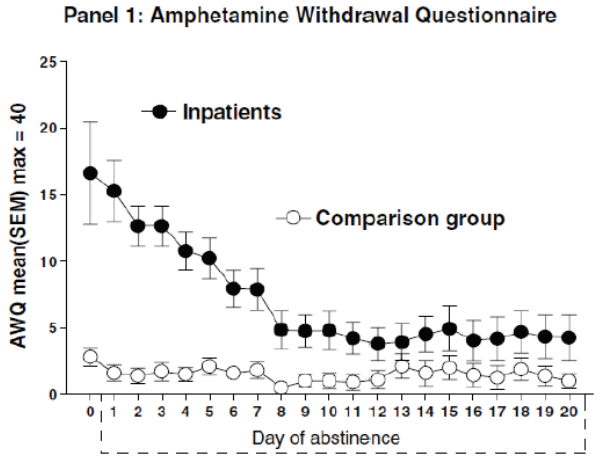
AWQ scores-Interpretation	DL1 group 60 mg N=32 (%)	DL2 group 85 mg N=31 (%)	Total N=63 (%)
Patients with any score increase	21 (65.6)	16 (51.6)	37 (59.6)
Score increase (< 10),	7 (21.8)	4 (12.9)	15 (17.4)
Range of score increases	2- 7	2-4	
Score increase (=/> 10*)	13 (40.6)	9 (29)	22 (34.9)
LDOT < 10	7 (21.8)	4 (12.9)	11 (17.4)
LDOT> 10**	6 (18.7)	5 (16.1)	11 (17.4)
Range of score increases	2-20	4-18	
Range of final scores	10-25	10-34	

*10 -was chosen as it represents the lower score seen during first 5 days of acute methamphetamine withdrawal (McGregor et al., 2005A), below. Also, score 10 was used to diagnose amphetamine withdrawal in amphetamine dependent subjects (McGregor et al., 2015B).
**Of note is that some patients had already higher AWQ scores (>10) at LDOT, those patients' scores increased significantly during the withdrawal.

This data is indicative of stimulant-type of withdrawal in PD patients after abrupt withdrawal of Inbrija. However, it was noted that some patients had already scores > 10 at the beginning of the withdrawal. Taking into consideration that the most frequent symptoms depicted by AWQ with > 3 points on 40 point scale during the abrupt withdrawal of Inbrija were: 1) slowness, 2) tiredness 3) anxiety, 4) sadness, agitation, vivid dreams, 5) craving sleep (IR # 2, Oct 30, 2018), it may be considered that Inbrija withdrawal can be also seen as moderate-to-severe worsening of parkinsonian symptoms with some stimulant withdrawal like features.
The question may arise how to distinguish stimulant-like withdrawal symptoms due to Inbrija discontinuation from worsening of PD symptoms such as depression, anxiety, sleepiness. The withdrawal symptoms by definition are transient so decrease of scores after initial increase would be expected, whereas PD symptoms either will increase or stay relatively stable.

Figure 3. Results of the methamphetamine withdrawal using AWQ (McGregor et al., 2005).

Figure 8: Amphetamine Withdrawal Questionnaire (from Mcgregor et al, 2005)



Patient Health Questionnaire – 9 (PHQ-9), a depression scale

According to the sponsor of the 82 patients who had available LDOT values 45 (54.8%) of patients had an increase of PHQ-9 score above the LDOT during the withdrawal period 23 (54.7%) in DL1 group, 22 (55%) in DL2 group.
*It is important to clarify that the large portion of LDOT scores which were not present in Abuse section at the NDA submission, but then were found and provided upon CSS request in CSS IR # 1, (Aug 23, 2018)
According to University of Michigan Health System interpretation of PHQ-9 scoring system in this population 7 (8.5%) patients experienced mild depression, 11 (13.4%) patients experienced moderate depression (score 10-14), 7 (8.5%) patients experienced moderately severe depression (score 15-19), and 2 (2.4%) patients experienced severe depression (score 20-27), table 16.
In a number of patients 10 (12.1%) scores increase of at least 4 points (up to 11) would happen during the first 3 days.

TABLE 16. Depression scores during the Inbrija withdrawal period measured with Patient Health Questionnaire – 9 (PHQ-9) and interpreted according to University of Michigan Health System Depression Guideline, August 2011.

Depression scores-Interpretation	DL1 group 60 mg N=42 (%)	DL2 group 85 mg N=40 (%)	Total N=82 (%)
Patients with any score increase	23 (54.7)	22 (55)	45 (54.8)
Mild depression (5-9)	5 (11.9)	2 (5)	7 (8.5)
Moderate depression (10-14)	5 (11.9)	6 (15)	11 (13.4)
Moderately severe depression (15-19)	5 (11.9)	2 (5)	7 (8.5)
Severe depression (20-27)	1 (2.3)	1 (2.5)	2 (2.4)

Summarizing the findings on evaluation of depression it can be said that 20 (24.3%) patients developed or their symptoms worsened resulting in moderate-to-severe depression during the Inbrija withdrawal in spite of still being on their routine oral levodopa treatment.

Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale has 8 questions with the score 0-3 and maximal score of 24 and measures daytime sleepiness.
In total of 82 patients (42 in DL1, 40 in DL2) with LDOT scores, 45 patients, 22 (52.3%) in DL1 and 23 (57.5%) in DL2, had an increase of ESS score above the LDOT value on any day of the withdrawal assessment period.
According to the interpretation of M. Johns, the developer of ESS, in this population the 6 (7.3%) patients experienced higher normal daytime sleepiness, 6 (7.3%) patients experienced mild excessive daytime sleepiness, 4 (4.8%) patients experienced moderately excessive daytime sleepiness and 6 (7.3%) patients experienced severe excessive daytime sleepiness, table 17.
In a number of patients 10 (12.1%) scores increase of at least 3 points (up to 7) would happen during the first 3 days.

Summarizing this finding it can be said that 10 (12.1%) patients developed or their symptoms worsened resulting in moderate-to-severe daytime sleepiness during the Inbrija withdrawal in spite of still being on their routine levodopa treatment.

TABLE 17. Daytime sleepiness scores during the Inbrija withdrawal period measured with Epworth Sleepiness Scale (ESS) and interpreted according to Murry W Johns, The Epworth Sleepiness Scale.

Sleepiness scores-Interpretation	DL1 60 mg N=42 (%)	DL2 85 mg N=40 (%)	Total N=82 (%)
Patients with any score increase	22 (52.3)	23 (57.5)	45 (54.8)
Higher Normal Daytime Sleepiness (6-10)	2 (4.7)	4 (10)	6 (7.3)
Mild Excessive Daytime Sleepiness (11-12)	2 (4.7)	2 (5)	6 (7.3)
Moderately Excessive Daytime Sleepiness (13-15)	4 (9.5)	0	4 (4.8)
Severe Excessive Daytime Sleepiness (16-24)	5 (11.9)	1 (2.5)	6 (7.3)

Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDS-PC)

This scale is not a withdrawal scale per se, it was supposed to be used to capture a possible increase of drug hoarding and symptoms of DDS during and after the study.

However, in the provided data it was not exactly clear what scoring system the sponsor used, so, the scale was not analyzed.

Movement Disorder Society-Unified Parkinson's Disease Rating Scales (MDS-UPDRS) only Part IB and II

To clarify further this issue it has to be stated that CSS originally requested the evaluation of all aspects of Parkinson's disease (non-motor and motor) after the abrupt withdrawal of Inbrija using UPDRS (old version) which was administered during the clinical studies. CSS initially requested all parts of UPDRS that is Part I: Non-motor Experiences of Daily Living, Part II: Motor Experiences of Daily Living, Part III: Motor examination and Part IV: The Complications of Therapy. But later the Sponsor informed CSS that only part 1B and 2 can be completed at home and only as MDS-UPDRS new version will be used.
However, then the sponsor claimed that these both scales are not interchangeable, thus initially in the NDA the sponsor did not provide LDOT for any of these scales rendering this data essentially useless and uninterpretable. However, later during the review it became clear that part II UPDRS (Motor Experiences of Daily Living) can be converted into MDS-UPDRS. This data was requested (on Nov 27, 2018, and received soon after) however unfortunately only Part II could be only converted into MDS-UPDRS.

UPDRS-Part II-Motor Aspects of Experiences of Daily Living

The part II of the MDS-UPDRS scale assesses the motor impact of Parkinson's disease on patients' experiences of daily living such as speech, chewing, eating, writing, walking, balance and freezing and it has 13 questions that are rated 0-1-2-3-4.

The table 18 shows MDS-UPDRS with LDOT scores analyzed. The data shows that during Inbrija withdrawal 42.6% patients experienced moderate motor deterioration and 12% experienced severe motor deterioration. Some patients initially (at LDOT) had scores already in range of moderate of severe scores but they additionally worsened during the withdrawal. It is important to emphasize that rise of the scores means for the patients being more disabled in most basic functions of daily living.

Additionally, what seems to be unique to Inbrija withdrawal is that some patients were still experiencing motor deterioration during the 3rd and 4th week of withdrawal, even though it is known that motor deterioration after abrupt withdrawal of oral levodopa lasts only 12-14 days (Barbato et al., 1997; Hauser et al., 2002, The Parkinsonian Study Group, 2004). Also, it is important to note that all these patients were on their continuous daily regimen of oral levodopa…

TABLE 18. MDS-UPDRS Part II: Motor Aspects of Experiences of Daily Livings scores during the Inbrija withdrawal period and interpretation based on "Cut-off points of the MDS-UPDRS" table 4 (Martinez-Martin et al., 2015).

MDS-UPDRS Part II - scores-Interpretation	DL1 group 60 mg N=42 (%)	DL2 group 85 mg N=40 (%)	Total N=82 (%)
Patients with any score increase +/>2	28 (66.6)	22 (55)	50 (61)
Mild - Score increase (0-12)	**3 (7.1)**	**7 (17.5)**	**10 (12.2)**
Range of score increases	2-6	2-11	
Range of final scores	9-12	6-12	
Moderate -Score increase (13-29)	**20 (47.6)**	**15 (37.5**)	**35 (42.6**)
LDOT < 13	8 (19)	12 (30)	20 (24.3)
LDOT> 13	12 (28.5)	3 (7.5)	15 (18.3)
Range of score increases	2-19	3-14	
Range of final scores	13-29	13-26	
Severe -Score increase (=/>30)	**5 (12)**	0	**5 (12)**
LDOT < 13	1 (2.4)		1 (2.4)
LDOT < 30	2 (4.7)		2 (4.7)
LDOT> 30	2 (4.7)		2 (4.7)
Range of score increases	4-23		
Range of final scores	31-38		

Table 19. Mean MDS-UPDRS score increase in PD patients who experienced withdrawal measured as a difference between maximal worsening score and LDOT.

MDS-UPDRS Part II – mean scores	DL1 group 60 mg N=28	DL2 group 85 mg N=22	Total N=50
Mean MDS-UPDRS on LDOT	14.4	9	11.7
Mean MDS-UPDRS at the Maximal Withdrawal Score (worsening of motor score)	22.6	16.1	19.35
Difference between Maximal Withdrawal Score and LDOT	8.2	7.1	7.65

To put these scores in the proper perspective below is provided table (Martinez-Martin et al., 2015) which shows grading system for MDS-UPDRS scales, highlighted is Part 2 discussed above.
It shows that on average scores in lower dose increased from low moderate to medium moderate, while the scores in the high dose group changed from mild to moderate scores.

Table 4
Cut-off points of the MDS-UPDRS.

MDS-UPDRS	Method			Triangulation cut-off values
	Centile 90	ROC	OLR	
Part 1				
Mild/moderate	11/12	8/9	11.4/11.5	10/11
Moderate/severe	20/21	23/24	20.5/20.6	21/22
Part 2				
Mild/moderate	12/13	12/13	13.5/13.6	12/13
Moderate/severe	28/29	30/31	29.2/29.3	29/30

Rebound after abrupt Inbrija withdrawal

A number of patients had significant worsening of the scores within the first 1-3 days of Inbrija discontinuation, 12 (28.5%) and 10 (25%) with the maximal worsening of the scores within 1-3 days up to 21 and 14 points, in DL1 and DL2, respectively.

Many of these cases were identified as rebound 8 (19%) and 4 (10%) in DL1 and DL2, respectively.
Rebound is defined as a worsening of the symptoms of the treated disease in comparison with the baseline pretreatment condition after the abrupt drug discontinuation. However, in the case of progressive disorder such as Parkinson's disease where some deterioration over time is expected, the second aspect of rebound was considered that is decrease over time of symptoms after the initial rebound. This differentiates rebound from parkinsonian motor deterioration which first increases after oral levodopa discontinuation but then stabilizes in within ~ 2 weeks (Hauser et al., 2000, Parkinson study group, 2004). However, in case of Inbrija withdrawal, there were observed a number of cases where the motor deterioration still was increasing after 2 weeks, which actually raises a question if it is just parkinsonian symptoms deterioration similar to that seen in oral levodopa washout or Inbrija withdrawal causes protracted motor worsening?.
It was also observed that sometimes both withdrawal related rebound and motor deterioration co-exist. Usually first rebound would appear, then scores decrease but not to the baseline level but stabilize much higher (Table 20, part C).

Table 20. Adapted from Listing PH 3.4.1, Converted Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 2: Listing of Actual Treatment Group: CVT 301 DL1

Part A. Examples of rebound related to Inbrija withdrawal. After initial rebound the scores decrease to the levels in range of LDOT/baseline (CSS IR # 4, p 8, 9, 25)

Treatment Group: CVT 301 DL1

Unique Subject ID	Subject ID	Visit/Day	Date of Assessment	Total Score
CVT-301-004-(b) (6)	(b) (6)	TV1 (Baseline)	2016-01-14	10
		TV6 (LDOT)	2017-06-02	16
		TV6/Day 1	2017-06-03	29*
		TV6/Day 3	2017-06-05	20*
		TV6/Day 6	2017-06-08	20*
		TV6/Day 8	2017-06-10	18*
		TV6/Day 11	2017-06-13	17*
		TV6/Day 14	2017-06-16	18*
		TV6/Day 17	2017-06-19	20*
		TV6/Day 24	2017-06-26	19*
		TV6/Day 28	2017-06-30	19*
CVT-301-004-(b) (6)	(b) (6)	TV1 (Baseline)	2016-08-01	12
		TV4 (LDOT)	2017-04-13	9
		TV4/Day 1	2017-04-14	9
		TV4/Day 3	2017-04-16	15*
		TV4/Day 6	2017-04-19	13*
		TV4/Day 8	2017-04-21	11*
		TV4/Day 11	2017-04-24	12*
		TV4/Day 14	2017-04-27	12*
		TV4/Day 17	2017-04-30	14*
		TV4/Day 24	2017-05-07	14*
		TV4/Day 28	2017-05-11	13*

Part B. Examples of parkinsonian motor deterioration (IR # 4, p 16, 47)

Treatment Group: CVT 301 DL1

Unique Subject ID	Subject ID	Visit/Day	Date of Assessment	Total Score
CVT-301-004-(b) (6)	(b) (6)	TV1 (Baseline)	2016-07-18	13
		TV6 (LDOT)	2017-10-20	19
		TV6/Day 1	2017-10-21	26*
		TV6/Day 3	2017-10-23	26*
		TV6/Day 6	2017-10-26	23*
		TV6/Day 8	2017-10-28	23*
		TV6/Day 11	2017-10-31	26*
		TV6/Day 14	2017-11-03	26*
		TV6/Day 17	2017-11-06	26*
		TV6/Day 24	2017-11-13	26*
		TV6/Day 28	2017-11-17	26*

Treatment Group: CVT 301 DL2

Unique Subject ID	Subject ID	Visit/Day	Date of Assessment	Total Score

CVT-301-009-	(b) (6)	(b) (6)	TV1 (Baseline)	2016-10-27	11
			TV6 (LDOT)	2017-10-19	12
			TV6/Day 1	2017-10-20	20*
			TV6/Day 3	2017-10-22	22*
			TV6/Day 6	2017-10-25	22*
			TV6/Day 8	2017-10-27	26*
			TV6/Day 11	2017-10-30	25*
			TV6/Day 14	2017-11-02	25*
			TV6/Day 17	2017-11-05	26*
			TV6/Day 24	2017-11-11	26*
			TV6/Day 28	2017-11-15	26*

Part C. Two examples of the mixed symptoms of rebound and protracted motor deterioration, the scores after the rebound decrease over time but not to LDOT or baseline level (IR # 4, p 18-19, 37).

Treatment Group: CVT 301 DL1

Unique Subject ID	Subject ID	Visit/Day	Date of Assessment	Total Score	004 Study Record
CVT-301-004-	(b) (6)	(b) (6)	TV1 (Baseline)	2015-12-21	4
		TV6 (LDOT)	2017-03-29	15	
		TV6/Day 1	2017-03-30	20*	
		TV6/Day 3	2017-04-01	18*	
		TV6/Day 6	2017-04-04	22*	
		TV6/Day 8	2017-04-06	23*	
		TV6/Day 11	2017-04-09	17*	
		TV6/Day 14	2017-04-12	13	
		TV6/Day 17	2017-04-15	13	
		TV6/Day 24	2017-04-22	22*	
		TV6/Day 28	2017-04-26	23*	

Treatment Group: CVT 301 DL2

Unique Subject ID	Subject ID	Visit/Day	Date of Assessment	Total Score
CVT-301-004	(b) (6)	(b) (6)	TV1 (Baseline)	2016-04-12	9
		TV5 (LDOT)	2017-03-21	9
		TV5/Day 1	2017-03-22	23*
		TV5/Day 3	2017-03-24	17*
		TV5/Day 6	2017-03-27	17*
		TV5/Day 8	2017-03-29	18*
		TV5/Day 11	2017-04-01	20*
		TV5/Day 14	2017-04-04	18*
		TV5/Day 17	2017-04-07	23*
		TV5/Day 24	2017-04-14	22*
		TV5/Day 28	2017-04-18	22*

UPDRS-Part IB-Non-Motor Aspects of Experiences of Daily Living

The full part I of the MDS-UPDRS scale which includes part IA and IB assesses the non-motor impact of Parkinson's disease on patients' experiences of daily living and has 13 questions that are rated 0-1-2-3-4. Part 1A is administered by the rater (6 questions) and focuses on complex behaviors such as hallucinations, psychosis, DDS, cognitive impairment. Part 1B is a part of the self-administered Patient Questionnaire with 7 questions that address non-motor experiences of daily living such as sleep, fatigue, constipation, urination. Unfortunately, the sponsor did not provide responses to part IA only to part IB which makes the correct interpretation of the scores more difficult. However, in order to estimate the extent of worsening the numbers of grading

presented by Martinez-Martin and colleagues (2015) were adjusted to the number of 7 questions, which likely is an underestimate.

Of the 82 patients (42 in DL1, 40 in DL2) who had available Day 1 withdrawal scores, 56 patients (28 in DL1, 28 in DL2) had an increase of MDS-UPDRS Part 1B score above the Day 1 score on any day of the withdrawal period.

TABLE 19. MDS-UPDRS Part IB: Non-Motor Aspects of Experiences of Daily Livings scores during the Inbrija withdrawal period and interpretation based on "Cut-off points of the MDS-UPDRS", table 4 (Martinez-Martin et al., 2015), additional correction to the scores by was introduced as explained above.

MDS-UPDRS Part IB - scores-Interpretation	**DL1 group 60 mg N=42 (%)**	**DL2 group 85 mg N=40 (%)**	**Total N=82 (%)**
Patients with any score increase	28 (66.6)	28 (70)	56 (68.3)
Mild - Score increase (0-7)	**3 (7.1)**	**6 (15)**	**9 (11)**
Range of score increases	2-5	**2-4**	
Range of final scores	6-7	**2-7**	
Moderate -Score increase (8-11)	**4 (9.5)**	**3 (7.5**)	**7 (8.5**)
1st WD* < 8	3 (7.1)	2 (5)	5 (6)
1st WD> 8	1 (2.4)	1 (2.5)	2 (2.4)
Range of score increases	2-4	2-7	
Range of final scores	8-10	10-11	
Severe -Score increase (=/>12)	**9 (21.4)**	**7 (17.5)**	**16 (19.5)**
1st WD < 12	3 (7.1)	4 (10)	7 (8.5)
1st WD> 12	6 (14.2)	3 (7.5)	9 (11)
Range of score increases	2-7	3-7	
Range of final scores	12-25	12-19	

*1stWD – First Withdrawal Day (used instead of missing LDOT)

Obviously, the results presented are underestimation as the LDOT scores were not available only 1st withdrawal day served as a baseline.

Analysis of MDS-UPDRS part IB shows worsening during the withdrawal period with 8.5% of patients reaching moderate range of scores and 19.5% of patients reaching severe scores. Although adjustment was made to the scoring system due to lack of the first part IA (6 questions), the fact of such severe worsening of non-motor components of part IB (7 questions) during the withdrawal period is certainly very worrisome as it indicates that patients experienced disabling in most basic activities of daily living.

***Columbia-Suicide Severity Rating Scale (C-SSRS*)**
At the time of data cutoff, 42 patients in DL1 and 40 patients in DL2 completed the questionnaire during the withdrawal period.

During the withdrawal period 3 patients on a number of visits had suicidality thoughts and ideations and responded with "Yes" to items on the C-SSRS questions # 1 ("Have you wished you were dead or wished you could go to sleep and not wake up?") and # 2 ("Have you actually had any thoughts about killing yourself?"), in lower dose group DL1 patient # (b) (6) and # (b) (6) and in higher dose group DL2 patient # (b) (6). Of note, one of these patients # (b) (6) had previously had positive C-SSRS responses during the treatment period and had suicidal ideation throughout the withdrawal period and even responded to the question 4. "*Active Suicidal Ideation with Some Intent to Act, without Specific Plan*" with "Yes" on a number of days during the withdrawal. This indicate that 3 (3.7%) patients in the withdrawal population (N=82) had suicidal ideation.

Adverse events reported during the withdrawal period

During the 28-day withdrawal period 82 patients who participated in the evaluation of withdrawal 6 patients reported 7 AEs during the assessment period, 3 AEs might be related to the withdrawal and included: visual hallucinations, headache, nausea, fatigue.
Three other AEs were not related to withdrawal and include: upper respiratory infection, benign L breast mass, and periodontitis.

Reviewer's comments on Inbrija withdrawal symptoms

Abrupt discontinuation of Inbrija results in withdrawal symptoms even though the patients are still on oral levodopa regimen.
The evidence from partially only available withdrawal data for AWQ and MDS-UPDRS and full sets of PHQ-9 and EPS scales suggests that Inbrija withdrawal causes in at least 20-30% of PD patients moderate-to-severe stimulant-like withdrawal symptoms of slowness, tiredness, anxiety, sadness, agitation, vivid dreams, and craving sleep, that are typical symptoms of stimulant withdrawal. Although to some degree these symptoms overlap with worsening of Parkinson's symptoms. The withdrawal symptoms include also moderate-to-severe worsening of motor and non-motor aspects of experiences of daily living, and also include worsening or a new onset of moderate-to-severe depressive disorder and increased excessive daytime sleepiness in some patients.
Because 1) of the major clinical safety implications of the presence of Inbrija withdrawal symptoms, 2) a very small sample of PD patients evaluated, 3) only partially available scores for AWQ and MDS-UPDRS the full evaluation of Inbrija withdrawal as PMR is recommended which should be conducted in at least 100 of PD patients with all scales as above for 6 weeks and include all MDS-UPDRS scales part I, II, II, and IV. Additionally, withdrawal symptoms should be described in the label section 9. Abuse or section 5. Warning, there should be also information in the label to titrate this drug at the end of therapy.

Conclusions

1. Abrupt discontinuation of Inbrija even still on oral levodopa regimen causes withdrawal symptoms.

2. Dependence and withdrawal after discontinuation of Inbrija were not systematically evaluated in Phase 2/3 trials:
   - Only a very small subpopulation of 82 PD (~11%) patients at the end of phase 3 study # CVT-301-004E participated in evaluation of withdrawal, in total population of 754 of PD patients in the whole clinical program..
   - even in this already small group of PD patients a number of withdrawal questionnaires was missing up to ~30% of LDOTs for AVQ and DDS-PC and for UPDRS 100% LDOTs were missing
   - absence of MDS-UPDRS scores for part 1A and III and IV

3. The quality of dependence/withdrawal data is not acceptable therefore PMR should be requested to evaluate dependence/withdrawal either at any on-going or future study in 100 Parkinson's patients or in the human dependence study in Parkinson's patients, using all the same scales as before but additionally all 4 parts of MDS-UPDRS scales. This additional information is of critical importance due to already known motor and non-motor deterioration after Inbrija withdrawal.

5.2 Recommended Studies or Trials as Postmarketing Requirements (PMRs)

PMR s

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALICJA LERNER
12/18/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 209184 – Regulatory Device Consult

Date: October 8, 2018

To: Dahlia Walters (CDER/OPQ/OPRO/DRBPMI/RBPMBI)
Through: James Lee, PhD, Branch chief (CDRH/ODE/DAGRID/RPDB)
From: Brandon Blakely, PhD, Biomedical Engineer (CDRH/ODE/DAGRID/RPDB)

Applicant: Acorda Therapeutics
Product Name: Levodopa Inhalation Powder
Manufacturer: (b) (4)

Indication: CVT-30 is indicated for (b) (4) intermittent treatment of OFF symptoms in Parkinson's disease as adjunct to a stable carbidopa and levodopa Parkinson's medication regimen.

A. Executive Summary

Acorda Therapeutics has re submitted a 505(b)(2) NDA for CVT-301 (levodopa inhalation powder). This NDA contains original studies conducted by the applicant and published literature, and relies upon FDA's previous findings of nonclinical safety and clinical safety and efficacy for Sinemet oral tablets (NDA 017555) as the listed drug.

The sponsor has submitted an investigational new drug (IND 115750) application in support of this product. The sponsor then held a Type B and Type C meeting in a Pre-NDA for this product in 2016. The Lead Reviewer for these prior interactions for the CDRH team was Derya Coursey (CDRH/ODE/DAGRID/RPDB).

CDRH Review Team:

Brandon Blakely (CDRH/ODE/DAGRID/RPDB)	Lead Reviewer
BiFeng Qian (CDRH/ODE/DAGRID/INCB)	Device Biocompatibility
Christopher Dugard (CDRH/ODE/DAGRID/INCB)	Cleaning/Disinfection

Human factors (HF) consults were initially requested from Shannon Hoste and Hanniebey Wiyor. However, the HF review was provided by DMEPA, so no further CDRH HF review was conducted.

Additional information was requested from the sponsor regarding their device through

Information Request Letter. The dates of the IR sent, sponsor response received and area of deficiencies are shown below.

IR sent	IR response received	Area
5/8/2018	5/28/2018	Device Biocompatibility, Reprocessing
6/26/2018	7/9//2018	Device Biocompatibility, Reprocessing
8/1/2018	9/5/2018	VOC/PM2.5 Testing
9/5/2018	9/10/2018	VOC/PM2.5 Testing
8/1/2018	9/11/2018	E&L Testing and Toxicological Risk Assessment
9/11/2018	9/27/2018	E&L Testing and Toxicological Risk Assessment

The sponsor provided information through interactive review. However, there were still outstanding biocompatibility issues remaining. In the sponsor's initial response, dated July 9, 2018, the sponsor requested additional time to respond to the biocompatibility concerns (until "early September") since the PDUFA date was in October. I deferred to CDER, but the lead center indicated that this timing was not acceptable. Therefore, I initially recommended not approval for this combination product from a device perspective in my Lead Memorandum sent to CDER on August 1, 2018. During interactive review through the month of September, the sponsor provided additional biocompatibility reports that addressed our concerns.

RECOMMENDATION: There are no longer any outstanding device-related deficiencies. Therefore, the product is recommended for **approval** from a device perspective.

B. Intended Use

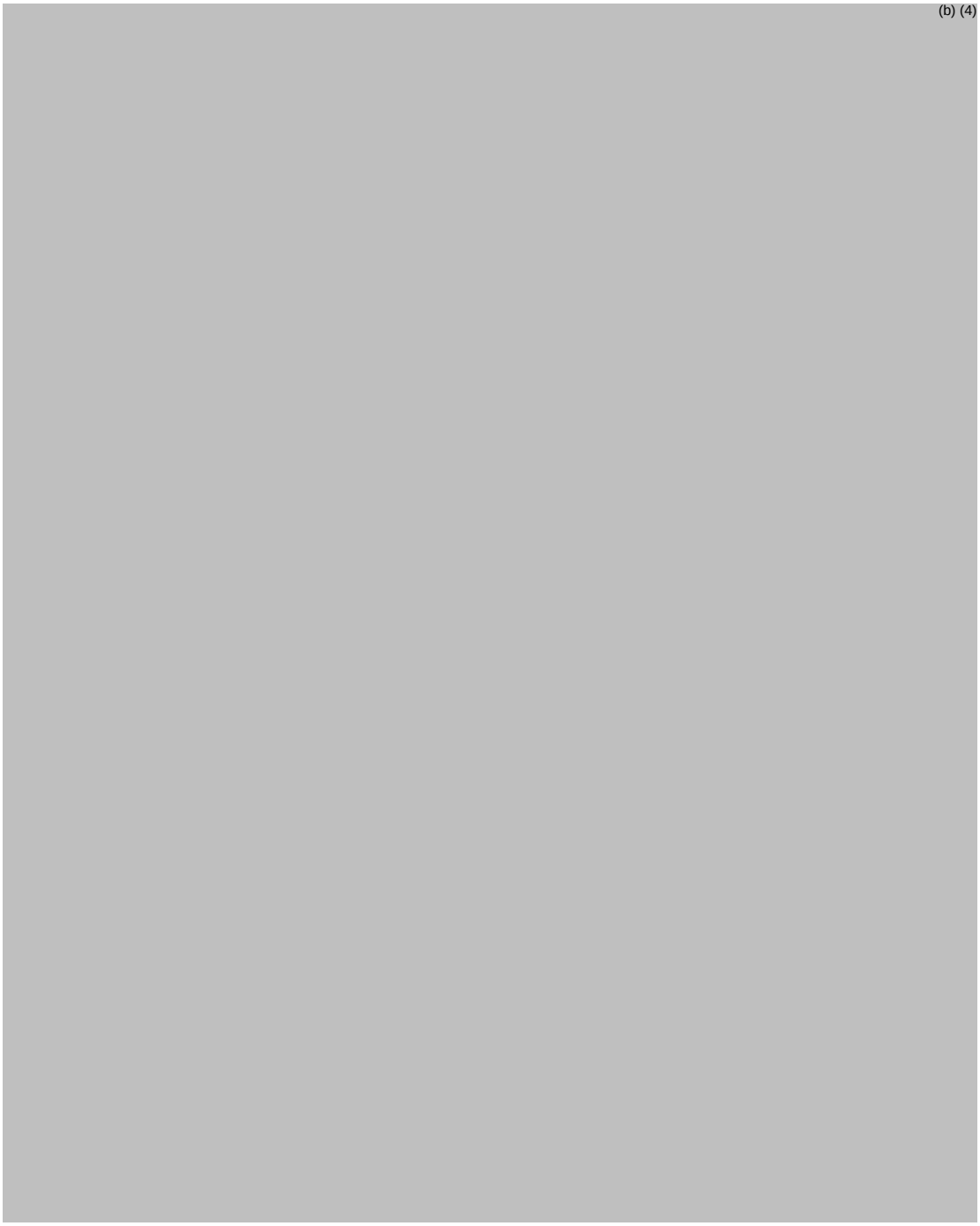
CVT-30 is indicated for (b) (4) intermittent treatment of OFF symptoms in Parkinson's disease as adjunct to a stable carbidopa and levodopa Parkinson's medication regimen.

C. Device Description

The following is excerpted from Subsection 1 of Section 3.2.R.1 of the submission, shown below in *italics*:

CVT-301 is a combination product composed of CVT-301 (levodopa inhalation powder) filled capsules and the CVT-301 dry powder inhaler. The dry powder inhaler is manufactured independently from the capsules. The two components (strips of foil-foil blistered CVT-301 capsules and one CVT-301 inhaler) are co-packaged in a carton to form the final drug product.

CVT-301 (levodopa inhalation powder) is delivered to the lung using a proprietary breath-actuated inhaler, CVT-301 inhaler. The CVT-301 inhaler is approximately 5 inches long (b) (4) *. The general outer appearance of the inhaler is provided in Figure 1, Figure 2, Figure 3, and Figure 4. A schematic diagram showing all components is provided in Figure 4. The inhaler components are listed in Table 1 below. There are no accessories for the inhaler.*



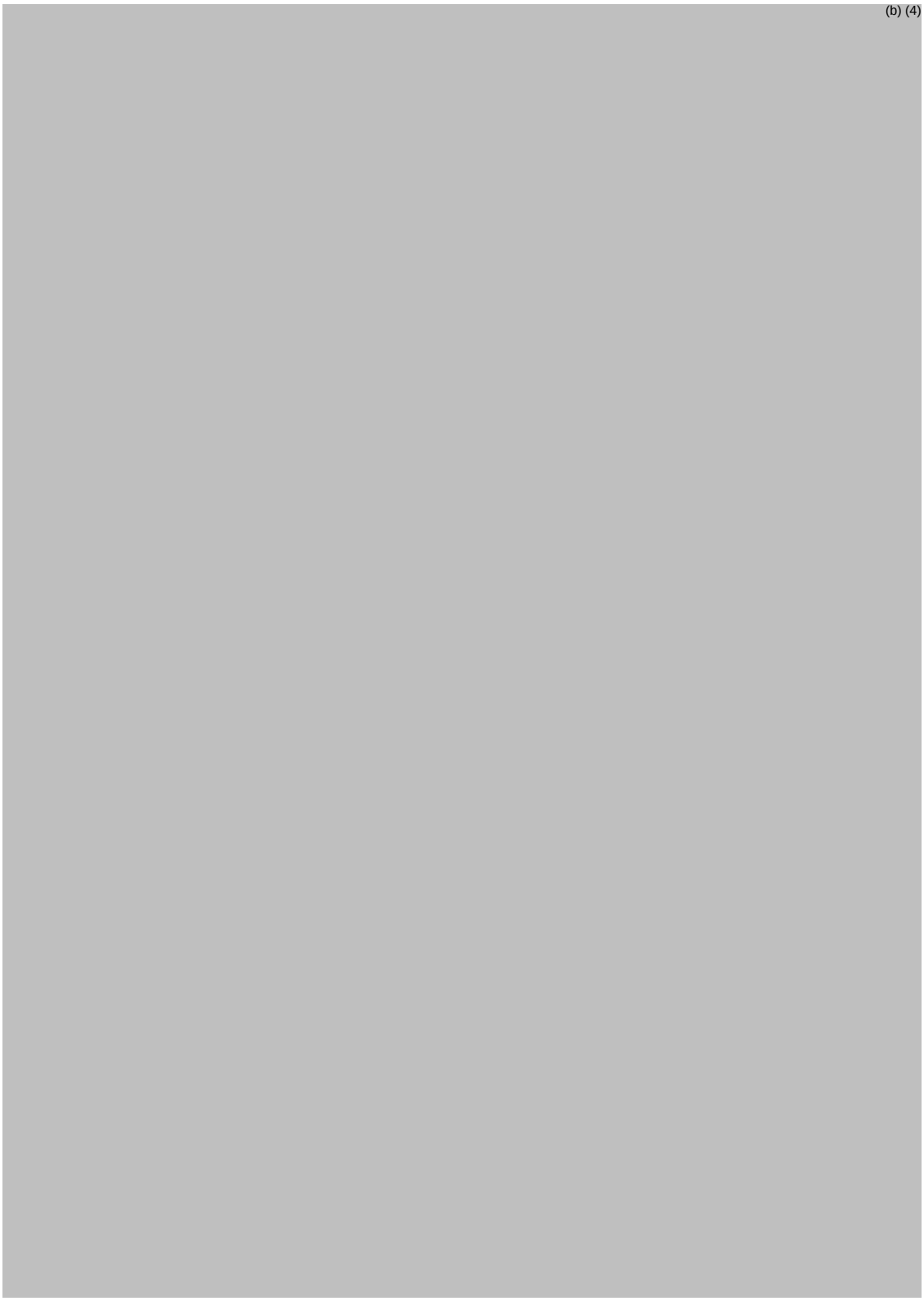
The CVT-301 inhaler is designed to puncture and disperse the levodopa inhalation powder from a CVT-301 capsule. A capsule is placed into the inhaler's aerosolization chamber and is punctured as the inhaler is compressed during Mouthpiece attachment. The patient inhales the drug powder through the holes in the Mouthpiece.

The aerosolization chamber is comprised of the components surrounding the capsule, which are the Staple Guide (distal), Body (medial), and Mouthpiece (proximal). An illustration is provided in Figure 5 with the aerosolization chamber identified by a yellow trace.

The components that come in contact with the drug powder are the Tines during capsule puncture, and the aerosolization chamber components (Mouthpiece, Body, and Staple Guide) during inhalation. An illustration of these components during capsule puncture is provided in Figure 6.

The air flow path through the aerosolization chamber is illustrated by an orange trace in Figure 7. The components that are part of the air flow are the Mouthpiece, Body, and Staple Guide.

Component coloring in these figures is for illustrative purposes only. The white CVT-301 capsule, loaded by the user at time of dosing, is shown for context.



The sponsor provided the following table summarizing previous FDA requests for data in support of the subject NDA submission during previous rounds of review (Table 20 from Subsection 1.7 of Section 3.2.R.1):

Section	Study	FDA Request
Section 1.7.1	Biocompatibility, extractables, and leachables testing (Inhaler Safety qualification)	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 2
Section 1.7.2	Routine Returns: In vitro testing of at least 100 inhalers from patients dosed with active treatment in the Phase 3 clinical studies	07Aug2014 End of Phase 2 (Type B) FDA Memorandum of Meeting Minutes; Meeting Discussion of Question 4i.
Section 1.7.3	Particulate Analysis per EPA PM2.5	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 2
Section 1.7.4	Inhaler Aerosol Performance	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, Comment 3
Section 1.7.5	MDI/DPI Drug Product Characterization Studies Includes: 1) Evidence that inhaler performance is not effected by i) varying inhalation flow rates; ii) drug build up with continuous use; iii) orientation held during inhalation; iv) moisture level; and v) simulated lifetime use 2) Assessment of Device robustness and Reliability 3) IEC-60601-1 Cleaning Studies 4) Surface charge of the gas path	1) 26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 4b-f 2) 26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 5 3) 26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 5 with agreement to testing only IEC 60601-1 drop and cleaning in the 7Oct2016 FDA Type C Meeting Request Written Responses and 7Nov2016 FDA Division email 4) 27Jan2014 FDA Written-Responses to Type C Meeting Request (13Nov2013) (surface charge of the gas path)
Section 1.7.6	IEC 60601-1 Inhaler Drop Testing	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 5 with agreement to testing only IEC 60601-1 drop and cleaning in the 7Oct2016 FDA Type C Meeting Request Written Responses and 7Nov2016 FDA Division email.
Section 1.7.7	Mouthpiece Removal Force	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 6
Section 1.7.8	Whirl Sound over Flow Rate Range and Effect	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 7
Section 1.7.9	Device Performance (Dose Delivery) is not Effected by Air Flow Resistance	26Sept2016 Pre-NDA (Type B) FDA Meeting Preliminary Comments, CDRH Comment 4a
Section 1.7.10	Nonintegrated device	14Oct2014 End-of-Phase-2 (Type B) CMC FDA Meeting Minutes, Response to Question 5 (Human Factors), Comment 1
Section 1.7.11	Multi-lot confirmation of consistent dose	26Dec2012 Pre-IND (Type B) FDA Meeting Minutes, CDRH Comment 3

D. Cleaning, Disinfection, Maintenance

Section 6.1 of Section 2.3.R states, "The inhaler is intended for single-patient use for the quantity of capsules supplied in the carton as directed by the Instructions for Use" (page 37 of 2.3.R).

Biorisk Reviewer (Christopher Dugard) Comment:
The device is intended to be single patient and is only used for the duration of treatment (i.e., until 1 carton which contains the inhaler and drug capsules is completely used). Based on this, the inhaler is not likely to present a challenge to cleaning. Since the device will only be wiped using a tissue or cotton swab and the device will be disposed following treatment, use-life is not a concern. There is a concern, however, that the potential buildup of drug on the outside or within the mouthpiece may impact dosing. For this reason, the sponsor should revise the instructions to instruct the end-user to ensure all powder is removed following dosing. **Deficiency.**

E. Shelf & Use Life

The following shelf-life and storage information is excerpted from Subsections 1.8-9 of Section 3.R.2 of the submission, shown below in *italics*:

1.8_Storage
The inhaler is intended to be stored at 15-30°C (59-86°F).

1.9_Expiry Dating

A 39-month expiry for the inhaler is supported by the data below. The inhaler date of manufacture is defined as the start date of final assembly (see manufacturing flow diagram Figure 2). For the co-packaged combination drug product, the expiry of the carton will be defined by the component with the shortest shelf life. Additional co-packaging information is provided in Section 3.2.P.7 Container Closure).

1.9.1._Justification of Expiry

The ongoing stability program for the CVT-301 inhaler consists of three lots of inhalers that were also used in the Phase 3 clinical program (oldest lots at time of study commencement). Inhalers were stored at ambient conditions until selected for the stability program. Lot 1045-009 is the first Phase 3 GMP lot from the validated manufacturing process. The design of the stability study is summarized in Table 4. If supported by data, the CVT-301 inhaler expiry will be extended in 12 month intervals and the change will be communicated in an Annual Report.

Table 4: CVT-301 Inhaler Stability Study Protocol

Lot No.	Storage Condition	Testing Interval (Months)							
		Initial	6	12	20	24	36	48	60
1045-009	25°C/60%RH	X	--	--	X	X	X	X	X
1045-009	40°C/75%RH	X	X	X		X	--	--	--
1045-016		X	X	--	--	--	--	--	--
1045-018		X	X	--	--	--	--	--	--

X = Inhalers tested for Resistance, Capsule Puncture, Mean Emitted Dose, and Emitted Dose Uniformity (%TDD)

Lead Reviewer Comments:
The sponsor has justified the 39-month expiry date for the inhaler using both real-time and accelerated aging.

F. Biocompatibility

In 2.3.R Device Summary, pages 16-19, the sponsor states:

Air flow path components were tested according to category External Communicating Device-Tissue contact, prolonged exposure (>24 hours to 30 days) □□these tests were inclusive for Mouthpiece mucosal contact testing. Inhaler components with non-mucosal, skin contact (Body, Insert, Housing, and Cap) were evaluated according to Surface-contacting Device-Intact Skin with prolonged contact. As shown in Table 6 below, all CVT-301 inhaler components tested met all of the biological test requirements.

Table 6: CVT-301 Inhaler – ISO-10993 Biological Evaluation Results

Test	*Body + Mouthpiece + Staple Guide1*	*Body*	*Staple Guide (Mouthpiece)*	*Housing (Insert & Cap)*
Cytotoxicity	*Pass*	*--2*	*--2*	*Pass*
Intracutaneous Irritation	*Pass*	*--2*	*--2*	*Pass*
Sensitization	*Pass*	*--2*	*--2*	*Pass*
Systemic toxicity	*Pass*	*--2*	*--2*	*N/A*
Implantation	*--2*	*Pass*	*Pass*	*N/A*
Genotoxicity – Bacterial reverse mutation	*Pass*	*--2*	*--2*	*N/A*
Genotoxicity – Mouse lymphoma assay	*Pass*	*--2*	*--2*	*N/A*
Genotoxicity – Mouse peripheral blood micronucleus study	*Pass*	*--2*	*--2*	*N/A*
Material-Mediated	*Pass*	*--2*	*--2*	*N/A*

1 One test article was created that consisted of all three components: 1 Body, plus 1 Mouthpiece, plus 1 Staple Guide.
2 Test performed under other column in the table.

Extractable / Leachable Studies with Toxicological Evaluation
Extraction studies were performed to quantitatively and qualitatively assess and characterize any volatile organic compound that may contaminate the dry gas path and any residues that could contaminate the gas path of the inhaler. Exhaustive extraction studies (ISO-10993-18) and Controlled extraction studies (PQRI, 2006) were conducted on the Mouthpiece, Body, Staple Guide, and Tines, using various polarity solvents over several time periods. Extracts were analyzed for organic compounds and elemental analysis. Exhaustive extraction and Controlled extraction (PQRI, 2006) chemical evaluations produced complementary results:

- *No detectable levels of Volatiles were found for any of the inhaler components.*
- *Elemental evaluation did not produce any metals of concern (i.e. no Class 1, 2, or 3 elements).*
- *Mouthpiece and Staple Guide extracts contained:* (b) (4)
- (b) (4)

Toxicological evaluation was performed on maximum estimated extractables levels for the compounds listed above. The safety evaluation determined that the exposure of patients to each extractable compound from the inhaler would pose negligible risk.
Inhaler Tines were not part of the biological testing plan, since they are not part of the air flow path and there is no direct patient contact. Tine safety was independently confirmed from chemical controlled extraction test results in which no organic residues were found.

A simulated leachables extraction from the Mouthpiece was performed using (b) (4) *at 40ºC for up to 16 hours. No semi-volatiles and no non-volatiles were observed; thus, there were no potential leachable compounds to toxicologically assess for patient safety.*
Based on the results of the chemical and biological evaluations performed, the materials used in the CVT-301 Inhaler are absent of harmful effects for user-contact device materials.

Biocompatibility (BiFeng Qian) Reviewer Comments:

1) The sponsor states that the biocompatibility testing was conducted, in response to 26Sep2016 Pre-NDA Type B FDA Meeting Preliminary Comments (Comment 2). [LEAD REVIEWER NOTE: This report has been located.]

2) Please see the recommended deficiencies in the sections below, regarding the patient contact classification, biocompatibility evaluation, and output gas assessment.

G. Software

Not applicable.

H. Electrical Safety and Electromagnetic Compatibility (EMC)

Not applicable. The device is not electrical.

I. Device Performance

In vitro Aerosol Characterization]

The aerosol characteristics were evaluated by CDER. The inhaler is a simple metered dose inhaler (MDI). Per the inter-center agreement between CDER and CDRH, MDI performance is reviewed by CDER.

Lead Reviewer Comments:
In FDA's response to the sponsor in the Pre-NDA, CDRH made the following comment:

An assessment of device robustness and reliability was not found in the present the submission. Please provide a complete assessment of the mechanical safety of the proposed device in accordance with applicable clauses of IEC 60601-1. While the proposed device does not contain electrical components, please note that test reports relating to drop, impact, stability, transportability, temperature, leakage, humidity preconditioning and cleaning are applicable to the proposed device.

Environmental Conditions Testing

The following is excerpted from Subsection 6.2.3.3 of Section 3.2.P.2 of the submission shown below in *italics*:

This study was designed to characterize dose delivery using the CVT-301 commercial system in a high temperature and humidity environment (40°C/75%RH) and a low temperature and humidity environment (20°C/10%RH). These conditions are representative of the range of high and low humidity environments observed throughout the year where the system could be used by a patient.
Inhaler/Capsule system performance was evaluated against the critical quality attribute of emitted dose.

Conclusion

- Dose delivery is not impacted when performed in a hot/humid or cool/dry environment. The system was determined to be robust across a wide range of humidity and temperature scenarios.
- No specific statement required in the CVT-301 Instruction for Use, regarding the
- temperature or humidity in which a patient must use the system.

Device Robustness Study

The following is excerpted from Subsection 6.2.7 of Section 3.2.P.2 of the submission shown below in *italics*:

The inhaler drop testing study was design was to evaluate the CVT-301 inhaler for primary inhaler functions (related to dose delivery) and secondary functions (related to the user interface and assembly) after drop from a distance that is representative of normal use. The test was performed per the recommendations in IEC 60601-1-1, chapter 15.3.4.1 as agreed to by FDA in the 7 October 2016 Type C Meeting - WRO (pre-NDA for CMC), written response to Question 4, and clarified in the 7 November 2016 FDA Division email (see above Section 6.2.2 FDA Requests and Agreements).
The IEC 60601-1-1, chapter 15.3.4.1 Drop Test states to test the sample by allowing the sample to fall freely once from each of three different starting orientations encountered during normal use, from a height at which the equipment is used or from a height of 1 meter whichever is greater, onto a hard wood board lying on flat on concrete (or similar rigid base).
Ten CVT-301 inhalers were dropped in six orientations onto a steel plate from 1 meter, which represents a sitting patient. Sixty (60) additional inhalers were dropped onto a hard wood board lying on concrete in three orientations from 1.5 meters, which represents a standing patient (see Figure 43). The CVT-301 inhaler selected for the study is inhaler iteration 3 (I3), which is the proposed commercial inhaler absent the commercial markings.
The six orientations for the 1 meter drop were as follows:

- *Vertical with mouthpiece down*
- *Vertical with mouthpiece up*
- *Horizontal with long axis parallel to the ground*
- *Horizontal with short axis parallel to the ground*
- *At approximately a 45 degree angle with mouthpiece down*
- *At approximately a 45 degree angle with mouthpiece up The three orientations for the 1.5 meter drop were as follows:*
- *Vertical with mouthpiece up*

- *Hoizontal with scalloped side down*
- *At approximately a 45 degree angle with mouthpiece down*

After drop testing, the system performance was evaluated for primary function (dose delivery) by the following tests: Capsule Puncture, Air Flow Resistance, Emitted Dose % and Fine Particle Mass. Inhalers were also evaluated for secondary function (user interface and assembly) by the following tests: Mouthpiece Twist off Torque, Mouthpiece Attachment and Snap Force (with and without capsules).

Device Performance During Simulated Use

The following is excerpted from Subsection 6.2.3.1 of Section 3.2.P.2 of the submission shown below in *italics*:

The study design focused on use of a commercial CVT-301 carton, which contains one inhaler and 92 capsules. Two frequencies of use were studied: (1) Nominal Frequency in which the carton was fully used in 23-days; and (2) Low Frequency in which the carton was fully used in 6 months. At nominal frequency, the commercial carton would be used at a rate of 2 doses or a total of 4 capsules per day. At low frequency, the commercial carton would be used at a rate of
2 doses or 4 capsules per week. These two scenarios bracket the anticipated majority of potential patient consumption rates for one commercial carton.
In addition, two inhaler cleaning techniques were evaluated (dry cotton swab and alcohol wipe):

- *Cleaning with a cotton swab was evaluated after each dose for half of the inhalers; the other half remained uncleaned. The study compared the system performance between cleaned and uncleaned inhalers for both Nominal Use and Low Frequency Use scenarios.*
- *Cleaning with an alcohol wipe was evaluated as a misuse scenario in case this common cleaning method was used. Cleaning was performed after every dose on half of the inhalers; the other half remained uncleaned by either the cotton swab or alcohol wipe. The wipe was used only on the outside of the mouthpiece after each dose emission. The study was performed only for the Low Frequency Use test arm. System performance between cleaned and uncleaned inhalers was compared.*

The study used 12 inhalers. Each inhaler was subjected to 92 capsule emissions. Six (6) of the inhalers were cleaned after each dose emission, the other 6 inhalers were not cleaned.
Inhaler/Capsule system performance was evaluated against the critical quality attributes of emitted dose, fine particle mass (FPM), and purity of the emitted dose.
The 'Whirl' of the capsule was evaluated by confirming the 'whirl' sound that the capsule makes in the inhaler as air flows during dose deliver testing and comparing the audible cue with the measured emitted dose. The test results are summarized in Section 6.2.9 Capsule 'Whirl' – Effect on Emitted Dose.
Inhaler performance was evaluated by measurement of Inhaler Resistance, Snap-on Force, and Twist-off Torque prior to dosing and after completion of dosing. Additionally, resistance was in after removing any powder residue on the inhaler mouthpiece.

Lead Reviewer Comments:

The testing performed in support of device durability is acceptable.

J. Interactive Review Logs for May 2018

The review team communicated interactive deficiencies to the sponsor via an email correspondence, dated May 8, 2018. The sponsor provided their responses via a PDF document attachment to an email correspondence, dated May 28, 2018. I am including these interactive review (IR) requests related to the CDRH consultation. To clarify, the CDRH deficiencies were numbered as "FDA CMC Request 5" through "FDA CMC Request 10" in the May 28, 2018 Letter, but they are numbered sequentially starting from one in this memorandum. The FDA request are shown below, and the sponsor's responses are shown below in *italics*.

1. In NDA209184, you claimed that the proposed CVT-301 dry powder inhaler can be used in all age groups. While it is understood that Parkinson's disease is primarily diagnosed in adults and is rare in pediatric population, you did not clearly identify the intended patient subpopulations. To proceed with the device biocompatibility review, please clearly identify the intended patient subpopulations, the lowest age and body weight.

Sponsor's May 28, 2018 Response:
Inbrija (levodopa inhalation powder) and the CVT-301 dry powder inhaler are indicated for the treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen. Inbrija should be taken when symptoms of an OFF period start to return, which could be motor or non-motor. The recommended dose of Inbrija is oral inhalation of the contents of two 42 mg capsules (84 mg) as needed for treatment of symptoms of OFF periods, up to 5 times a day. The maximum daily dose of Inbrija should not exceed 420 mg. Only one dose (2 capsules) is to be taken to treat an OFF period. The safety and effectiveness of
Inbrija in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended (see the proposed Inbrija USPI, Sections 1 Indication and Usage, 2 Dosage and Administration and 8.4 Pediatric Use in the NDA 209184 resubmission).
In the Phase 3 clinical program (see Reports CVT-301-004, Section 9.3; CVT-301-004E, Report 3, Section 9.3 and CVT-301-005, Section 9.3) the inclusion criteria specified male or female subjects age 30 to 85 years (86 years in Study CVT-301-004E). The studies' entry criteria did not specify a minimum weight or body mass index in the Phase 3 clinical program. In Study CVT-301-004 (see Report CVT-301-004, Table 14.1.3.1.2) the mean ± SD age, height and weight were 63.3 ± 8.7, 171.6 ± 9.6 cm, 81.0 ± 17.0 kg, respectively. In Study CVT-301-004E (see Report #3 CVT- 301-004E, Table 7) the mean ± SD age, height and weight were 63.4 ± 8.6, 171.6 ± 9.3 cm, 81.6
± 16.5 kg, respectively. In Study CVT-301-005 (see Report CVT-301-005, Table 6) the mean ± SD age, height and weight were 63.8 ± 8.3, 168.2 ± 9.0 cm (see Report CVT-301-005, Table 14.1.3.1.1) and 76.8 ± 15.8 kg, respectively.
The minimum age for subjects receiving CVT-301 in the Phase 3 program were 38 years, 39 years, and 37 years for studies CVT-301-004, CVT-301-004E, and CVT-301-005, respectively. The minimum body weight for subjects receiving CVT-301 in the Phase 3 program were 46.3 kg, 43.0 kg, and 44.0 kg for studies CVT-301-004, CVT-301-004E, and CVT-301-005, respectively. The minimum body weight of all subjects in the Phase 3 program was 40.0 kg in the observational cohort of CVT-301-005.

CVT-301 has not been tested in pediatric patients in the clinical program and there is no intention to do so. Acorda has requested a pediatric waiver in all age groups (see NDA 209184, Module 1.9 Pediatric Administrative Information).
Therefore, the intended subpopulations of Parkinson's disease patients for treatment with Inbrija are male and female adults. The entry criteria for the Phase 3 clinical program required a minimum age of 30 years and no minimum weight limitation, and the lowest age and weight in subjects exposed to CVT-301 in the Phase 3 program was 37 years and 43 kg, respectively.

Biocompatibility Reviewer (BiFeng Qian) Comments:
The response is deemed adequate to address the deficiency.

2. You classified that the proposed CVT-301 dry powder inhaler is a prolonged device (>24 hours to 30 days). However, this device is indicated for treatment of patients with Parkinson's disease, which is a chronic neurodegenerative disorder. Patients under this medical condition may continuously and repeatedly use the CVT-301 dry powder inhaler and its replacement.

   Due to considerations of the potential for cumulative exposure to the device and its replacements, FDA considers that the CVT-301 dry powder inhaler is a permanent contact device. Please be advised that the recently cleared similar devices with the same or similar intended use are also classified as permanent contact devices. The device components that will be contacting the aerosolized drug and patient's inhaled/exhaled gases are considered external communicating devices, tissue contact. Some device components may have more than one type of patient contact. For example, the Mouthpiece has both a direct surface contact and an indirect contact with tissue via gas. To support the biocompatibility of the CVT-301 dry powder inhaler, please revise the patient contact classification in this NDA and provide appropriate biocompatibility endpoints assessments based on the contact type and permanent contact duration, per Table A.1 of the FDA 2016 Guidance Document: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". This FDA Guidance Document can be obtained at the link below:

   http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Sponsor's May 28, 2018 Response:
At the Type B pre-NDA meeting held September 28, 2016, FDA requested clarification on the contact duration and provided direction on conduct of the CVT-301 biocompatibility program. From the meeting minutes:

"Please clarify whether the ultimate/cumulative exposure from repeated direct contact to the device is prolonged or permanent. For components of your device which are external communicating, tissue contacting (e.g. interior of the device or patient interface, tubing,), permanent duration, please conduct cytotoxicity, sensitization, genotoxicity, and implantation. For components with surface, mucosal contact, permanent duration, (e.g. the mouthpiece), please conduct cytotoxicity, sensitization, irritation, sub-chronic toxicity, and genotoxicity. For components of your device which

are surface, skin contact, please conduct cytotoxicity, sensitization, and irritation testing".

In accordance with FDA's Request 6 above, Acorda has re-categorized the inhaler components as permanent contact. As discussed below, the biocompatibility program completed to date complies with the requirements defined at the pre-NDA meeting.

The mouthpiece, body and staple guide components are external communication devices contacting tissue. For permanent contact duration, Table A.1 of the FDA 2016 guidance document *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1; Evaluation and testing within a risk management process"* recommends the ISO-10993 endpoints of cytotoxicity, sensitization, irritation (intracutaneous reactivity), acute systemic toxicity, subacute/subchronic toxicity, genotoxicity and implantation. In accordance with FDA feedback and recommendations from the pre-NDA meeting, Acorda has conducted all seven ISO 10993 studies, as well as material-mediated pyrogenicity. Except for implantation, a composite sample of the mouthpiece, body and staple guide was used for the biocompatibility evaluation. As summarized in Table 9 below (with links to the individual test reports), the mouthpiece, body and staple guide passed all biocompatibility evaluations.

With regard to the other user-contacting materials used in the inhaler, the housing, insert and cap components are surface devices contacting intact skin. For permanent contact duration, Table A.1 of the FDA 2016 guidance document *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1; Evaluation and testing within a risk management process"* recommends the ISO 10993 biocompatibility endpoints of cytotoxicity, sensitization and irritation (intracutaneous reactivity). All three components are composed of the same (b) (4) and are produced from the same (b) (4) process; thus, the housing was chosen as the representative component for these tests as it contains an additional pad-printed ink bearing the drug product name. As summarized in Table 10 below (with links to the individual test reports), the housing with pad print ink passed all biocompatibility evaluations.

Biocompatibility Reviewer (BiFeng Qian) Comments:
The response is deemed adequate to address the deficiency.

3. In Table 6 of 2.3.R Device Summary, you listed the biocompatibility testing conducted for the CVT-301 dry powder inhaler, including the testing for cytotoxicity, intracutaneous irritation, sensitization, systemic toxicity, genotoxicity, implantation, etc. However, the test reports are not provided in NDA 209184. To determine if your testing conducted is adequate and acceptable, please provide the complete test reports from the testing laboratory, dated and signed, for each of the referenced biocompatibility testing. Please include the following information in the test reports: a clear and detailed description of the test device, description of the sample preparation, the test systems (animals, cells, etc.), test procedures and test standards followed, appropriate controls, summary of the test results including the control test data, test criteria, and conclusions. Please ensure that the testing was conducted based on a worst case scenario and the final finished subject device (or components).

Sponsor's May 28, 2018 Response:

Test reports can be accessed via the links provided in Table 9 and Table 10 above. These reports provide a description of the test device, description of the sample preparation, the test systems (animals, cells, etc.), test procedures and test standards followed, appropriate controls, summary of the test results including the control test data, test criteria, and conclusions. Test methodology was carried out according to guidelines identified in ISO-10993 (appropriate subparts).

Test articles (Body, Mouthpiece, Staple Guide and Housing components) were manufactured

(b) (4)

[redacted]

device and are thus suitable as test articles for biocompatibility testing. To ensure a "worst case" assessment, the toxicological assessments of extractables (discussed in the response to FDA Request #8) assumed that total extracted quantity was administered in a single day rather than in some type of more protracted release.

Biocompatibility Reviewer (BiFeng Qian) Comments:

- The sponsor also states that they have performed testing for sensitization. However, the test report (14T_32829_07-08) cannot be located. The sensitization test report needs to be reviewed. [LEAD REVIEWER NOTE: This report was located and deemed adequate.]

- Chronic systemic toxicity endpoints are not adequately assessed. Chronic systemic toxicity endpoints assessments may be achieved by either animal testing or appropriate extractables and leachables (E&L) testing plus a toxicological risk assessment based on chronic inhalation exposure. In NDA 209184 and the interactive response, the sponsor does not provide any animal testing to assess the chronic systemic toxicity endpoints. The E&L testing and toxicological risk assessments provided do not adequately address the concerns for chronic systemic toxicity. Recommend that the sponsor provide revised E&L testing and chronic exposure and safety assessments or provide the chronic systemic toxicity testing based on ISO 10993-11.

4. To demonstrate the biocompatibility of the CVT-301 dry powder inhaler and the drug-device material compatibility, you stated that chemical extractable and leachable testing plus a toxicological risk assessment was conducted. However, the assessment reports are not included in NDA 209184. Please provide the chemical characterization test report from the testing laboratory, dated and signed. Please provide the toxicological risk assessment report for the chemical extractables and leachables identified.

a. Please clearly describe and justify the extraction method used for the chemical extractable and leachable testing, including the extraction temperature, time, surface area to extraction volume ratio, etc. We recommend that you follow the FDA- recognized test standard ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference materials for preparation of the test samples. As the CVT-301 dry powder inhaler is classified as a permanent contact device, we recommend that you use an exhaustive extraction method at 50°C or 50C° for 72 hours as a default for extraction of the test articles. The extraction solvents used should be adequate for a worst case extraction of both polar and non-polar chemical residues. Alternatively, the chemical extraction may be conducted based on a worst case drug solution or a surrogate chemical that has chemical properties similar to the drug solution. Please provide your scientific rationale and justification for your choice of the drug solution, surrogate, or solvents. In addition, please clarify whether the drug solution, surrogate, or solvents used were compatible with the tested device. If the drug solution, surrogate, or solvents used compromised the device's integrity and caused degradation, the chemical testing data may be invalidated.
b. Please clearly describe your analytical instruments and test methodologies used. The analytical instruments and test methodologies used should be adequate for detection and analysis of various types of chemical extractables and leachables, including the organics, inorganics, organometallics, metals, and other residues.
c. Please specify the concentrations per device system for each of the chemical extractables and leachables identified. Please provide a comprehensive risk assessment (exposure and safety assessment), based on the inhalation exposure route, intended patient population, and a worst case scenario. For analysis of the chemical residues and the allowable limits, please refer to the published toxicological literature and the inhalation protective values from the US based health organizations or WHO. For the risk assessment calculation, you may refer to the FDA-recognized standard ISO 10993- 17 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and to the TTC approaches described in the CDER ICH M7 guidance. Please include all your calculations in the risk assessment, such as the calculations for the margin of safety (MOS), the body weight, the reference doses (NOAELs or LOAELs), the limit of detections (LODs), the limit of quantifications (LOQs), the acute and chronic exposure assessments, etc. The body weight and daily inhalation rate (m3/day) used in the risk assessment calculations shall be appropriately justified, based on a worst case scenario and the published US NHANES and EPA data. In addition, please provide a clear rationale for the uncertainty values that are used in the safety assessment for each chemical.

Sponsor's May 28, 2018 Response:

A report summarizing the results of extraction studies was provided in the NDA (see RPT-2028).

A review of the studies conducted, including links to the individual assessment reports, is provided below. The review is divided into three parts:

1) *Exhaustive Extraction Studies*
2) *Controlled Extraction Studies*

3) Toxicological Assessment

Biocompatibility Reviewer (BiFeng Qian) Comments:

- Regarding 1): The extraction solvents used should be adequate for a worst case extraction of both polar and non-polar chemical residues. As the ethanol solvent degraded the device materials, the chemical testing data are considered invalidated.
- Regarding 2) The extraction solvents used should be adequate for a worst case extraction of both polar and non-polar chemical residues. As the ethanol solvent degraded the device materials, the chemical testing data are considered invalidated.
- Regarding 3) Recommend that the sponsor provide revised exhaustive E&L testing and toxicological risk assessments for review.

5. To support the quality of airs delivered through the CVT-301 dry powder inhaler, you indicated that you conducted the dry gas testing for volatile organic compounds (VOCs) and fine particles (PM2.5). However, the test reports are not provided for review. To demonstrate that the output airs delivered through the device are not adulterated with VOCs and PM2.5, please provide the output air quality test reports for review. In the test report, please clearly describe how the output airs delivered through the CVT-301 dry powder inhaler were collected and analyzed, including a clear description and justification for the testing and sampling conditions, with respect to the device set up, exposure temperature, flow rate, sampling time, volume of airs analyzed, etc. Please provide test data to demonstrate that the particulate matters released from the device do not exceed the acceptance limit, based on the published US EPA data for ambient air quality. Please clarify if the VOCs analysis was conducted based on the EPA TO-15 Compound List. If your VOCs screening analysis was limited only to selected target compounds, please provide a scientific justification for your selection. Please specify all VOCs identified in the output air samples and provide a comprehensive risk assessment (exposure and safety assessment) based on the inhalation exposure route, intended patient population, and a worst case scenario.

Sponsor's May 28, 2018 Response:

Assessment of volatile organic compounds (VOCs) was performed by Headspace GC-MS on individual device components that are within the air flow path of the inhaler. Approximately 1 gram of the test sample material was prepared in duplicate and placed into separate headspace vials (subdividing as necessary to fit), along with 1.0 mL of USP H2O and hermetically sealed. All samples were processed in a headspace sampling apparatus operated under the conditions shown in Table 20 *below and interfaced to a gas chromatograph injection port. The testing of individual components allowed capture of any volatiles unique to a specific material. The volatilization of any VOCs was promoted by use of accelerated conditions of temperature and humidity.*

Biocompatibility Reviewer (BiFeng Qian) Comments:

The testing provided was not designed to assess the output airs delivered through the CVT-301 dry powder inhaler. Recommend that the sponsor provide assessments for the output airs, based on the recently published ISO 18562 standards "Biocompatibility evaluation of breathing gas pathways in healthcare applications".

6. You state in the instructions for use "It is normal for some powder to remain on the inhaler; You do not need to clean the inhaler. You can use a dry cotton swab or tissue to wipe the outside of the inhaler". Buildup of powder between uses may impact dosing. For this reason, please revise the instructions for use to instruct the end-user to ensure no powder remains between uses. This will help prevent the risk of powder build-up.

Sponsor's May 28, 2018 Response:
As explained in the response to FDA Request #3 above, inhaler dosing after the initial dose is relatively consistent throughout the lifetime use of the inhaler and co-packaged capsules. Data presented in 3.2.P.2.6, Section 6.2.3.1 (42 mg) and Section 6.2.5.1 (30 mg) demonstrate that the dose differences between cleaned vs. uncleaned inhalers are relatively small and likely have a negligible impact on efficacy or safety.

Biorisk Reviewer (Christopher Dugard) Comments:
This response is acceptable.

K. Interactive Review Logs for June-September 2018

The review team communicated interactive deficiencies to the sponsor via an email correspondence, dated June 27, 2018. The sponsor provided their responses via a PDF document attachment to an email correspondence, dated July 5, 2018. I am including these interactive review (IR) requests related to the CDRH consultation. The FDA request are shown below, and the sponsor's responses are shown below in *italics*.

1. In the interactive response, you re-categorized the CVT-301 dry powder inhaler as an externally communicating device, tissue contact, permanent duration. In response to Deficiencies #6-8, you provided study reports for biocompatibility assessments and chemical characterization and risk assessments of the device. Based on the study reports provided, assessments for chronic systemic toxicity and drug-device material compatibility are considered inadequate. Chronic systemic toxicity endpoints assessments may be achieved by either animal testing or appropriate extractables and leachables (E&L) testing plus a toxicological risk assessment based on chronic inhalation exposure. In NDA 209184 and the interactive response, you did not provide any animal testing to assess the chronic systemic toxicity endpoints.

   We acknowledge that you provided test reports for chemical extractables and leachables. The initial exhaustive extraction studies were conducted using (b) (4). As the (b) (4). As the CVT-301 dry powder inhaler is intended for permanent use, the extremely short extraction time does not represent the worst clinical use condition and does not allow for adequate extraction and analysis of the chemical extractables and leachables.

   To address the safety concerns for chronic systemic toxicity and drug-device material compatibility, we believe that a revised exhaustive E&L testing using an adequate extraction

solvent that is compatible with the subject device, is necessary. The extraction solvent(s) used should be adequate for a worst case extraction of both polar and non-polar chemical residues. Alternatively, the chemical extraction may be conducted based on a worst case drug solution or a surrogate chemical that has chemical properties similar to the drug solution. We recommend that you use an exhaustive extraction method at 50°C or 50C° for 72 hours as a default for extraction of the test articles.

Please provide the revised E&L testing. Please provide your scientific rationale and justification for your choice of the drug solution, surrogate, or solvents. In addition, please clarify whether the drug solution, surrogate, or solvents used were compatible with the tested device. If the drug solution, surrogate, or solvents used compromised the device's integrity and caused degradation, the chemical testing data may be invalidated.

Please provide a revised, comprehensive risk assessment (exposure and safety assessment), based on the inhalation exposure route, intended patient population, and a worst case scenario. Please also refer to our original Deficiencies # 8a-c identified in the CDER Information Request letter dated May 8, 2018 for NDA 209184.

Sponsor's July 5, 2018 Response:
It is Acorda's position that the extraction conditions employed to date (specifically the solvents chosen and the time and temperature conditions employed) provided an adequate material characterization of the CVT-301 inhaler components. An exaggerated extrapolation of potential daily exposure to extractables was used to provide a very conservative assessment of the risks associated with the use of the CVT-301 inhaler; thus, it is highly unlikely that additional studies will identify any new risks (see justification discussion below). Therefore, Acorda believes that the data submitted to date provide an acceptable assessment of the risks and the safety of the CVT-301 inhaler and that this issue should not preclude approval of the NDA by the October 5, 2018 PDUFA date.
Nonetheless, Acorda agrees to conduct the requested E&L study at 50°C for 72 hours. This work has begun, and we anticipate that new E&L and toxicological assessment reports will be available in early September.

Biocompatibility Reviewer (BiFeng Qian) Comments:
The sponsor's justification for the extraction conditions is **inadequate**. The original deficiency stands.

Sponsor's September 11, 2018 Response:
The study report to fulfill this commitment is provided via the hyperlink shown below:

*CMC Request **1:** Extractables at 50°C for 72 Hours*
1) *RPT-4146 : CVT-301 Chemic Labs: Exhaustive Extraction Study for a CVT301 Dry Powder Inhaler*

The RPT-4146 report includes a toxicological assessment of all identified compounds that were found to be above the Threshold of Toxicological Concern (TTC) of 1.5 µg/day. The highest
levels of extractable compounds were determined to pose negligible risk to patients.

Lead Reviewer Comments:
The following interactive deficiency (drafted by BiFeng Qian) was sent to the sponsor via an email correspondence, dated September 11, 2018, shown below in red:

> You reported that multiple chemical compounds were identified in the extractable and leachable testing, in the test extracts of (b) (4). Based on the test data presented, many of the chemical extractables and leachables identified appear to be unknown compounds. However, you only provided safety assessments for the chemical compounds with known identity or structure. You did not provide any toxicological risk assessments for the unknown chemical compounds. Please provide a revised toxicological risk assessment for all chemical compounds identified, both known and unknown. Alternatively, please provide solid scientific rationales to justify why you believe that the identified unknown chemical compounds are not a safety concern.

The sponsor sent the cover letter of their response via an email correspondence, dated September 16, 2018. However, the content of their response was omitted. I requested that the project manager receive the rest of the sponsor's response. The complete response was received, via an email attachment in an email dated September 27, 2018.

Sponsor's September 27, 2018 Response:
Based upon the justification provided below, it is Acorda's position that the identified unknown chemical compounds are not a safety concern. The mouthpiece and body inhaler components have different types of patient contact and are discussed separately. A diagram of the CVT-301 inhaler is provided in Figure 1 for reference.

Figure 1: Diagram of the CVT-301 Inhaler

(b) (4)

Lead Reviewer Comments:
See the sponsor document for more details. Essentially, the sponsor argued that 1. (b) (4) extracts of the mouthpiece were more representative of patient risk for the intended use and 2. The unknowns for the body were from liquid extracts, while only volatile leachants would be a concern of the product during actual use since the body only contacts the gas pathway.]

Biocompatibility Reviewer (BiFeng Qian) Comments:
I have reviewed the sponsor's response to the CDER Information Request dated September 12, 2018 for NDA209184, regarding risk assessments for the unknown compounds identified from the chemical extractable and leachable testing of the CVT-301 dry powder inhaler.

In the response, the sponsor stated that that the identified unknown chemical compounds are not a safety concern. However, in their toxicological risk assessments, the sponsor only considered the surface areas of the device components that will be in direct contact patient body. The chemicals in the airflow path were not adequately assessed for their risks. The sponsor explained that the unknow chemicals were only detected in the HPLC-DAD testing for non-volatiles. No unknown peaks were observed in the semi-volatiles (GC-MS) or volatile (headspace GC) extractions. As the unknowns are limited to non-volatile compounds only, there is minimal risk of inhalation exposure to these unknown chemicals in the airflow path, due to their very low volatility.

I do not agree with the sponsor regarding this risk assessment strategy, because during clinical uses the proposed CVT-301 dry powder inhaler will be contacting the aerosolized drugs and patient's exhaled gases. Under the humidified conditions, liquid condensate can form on the gas pathway surfaces, which may leach or absorb other substances from the medical device. There is a concern that potentially hazardous substances in the condensate can be conveyed to the patient by the gas pathway. Therefore, it is our position that all chemicals that may potentially leach out or be present in the gas pathway should be assessed for their toxicological risks.

I acknowledge that the chemical extractable and leachable testing and associated toxicological risk assessments were provided to address the concerns for chronic systemic toxicity and drug-device material compatibility. Due to the following considerations, my overall risk concerns for the identified unknown chemical compounds are low:

- The proposed CVT-301 dry powder inhaler will be only used in adults. The subject device will not be used in more vulnerable pediatric patients including neonates and infants.

- The Mouthpiece and Body are the device components that will be contacting patient gas pathway. The materials used in the Mouthpiece and Body are commonly used respiratory device materials, with a history of safe use.

- The chemical extractable and leachable testing of the Mouthpiece and Body was conducted at 50°C for 72 hours. The extraction condition was far worse than the typical clinical use condition, with respect to the chemical leaching and daily exposure of the devices. Based on the extractable and leachable testing data presented, except one unknown chemical (unknown at RRT (b) (4)) that was detected at a level of (b) (4) ug/component in the (b) (4) of the Body, all chemicals identified in the (b) (4) extracts had a detectable level either below or marginally above 10ug/component. Based on the TTC approaches described in the CDER ICH M7 guidance, the acceptable daily intake for a chemical for a treatment duration of 1-10 years is 10 ug/day, and is 120 ug/day for a treatment duration of <30 days. Based on the recently published standard ISO 18562-1 Biocompatibility evaluation of breathing gas pathways in healthcare applications - Part 1: Evaluation and testing within a risk management process, for inhalation exposure of chemicals, the tolerable exposure level for adults is 360 µg/day for the first 24 hour period, 120 µg/day for the subsequent twenty-nine 24 hour periods, and thereafter 1.5 µg/day.

- Although the CVT-301 dry powder inhaler is indicated for permanent use, the daily treatment time will be only a few minutes. Therefore, for a10-year treatment duration, the cumulative use time of the device will be likely < 30 days.

- In addition to the extractable and leachable testing, the sponsor also provided biological testing for cytotoxicity, intracutaneous reactivity, sensitization, acute systemic toxicity, subacute/subchronic systemic toxicity, genotoxicity (two *in vitro* and one *in vivo*), 4-week implantation, and material-mediated pyrogenicity. All testing was completed by (b) (4) based on applicable FDA-recognized ISO 10993 test standards. According to the test results, the device tested did not indicate significant risks.

Based on the above assessments, I have **no significant biocompatibility concerns** for the CVT-301 dry powder inhaler, for the proposed use. Therefore, **no further questions will be raised**

2. In response to Deficiency #9 regarding the concerns for output air quality, you provided assessments for volatile organic compounds (VOCs) and particulate matters. For the VOCs assessment, 1 gram of test materials from individual device components was analyzed by headspace GC-MS. The particulate matter testing was conducted per USP <788> Particulate Matter in Injections. It is noted that the testing provided was not designed to assess the output airs delivered through the CVT-301 dry powder inhaler.

   To demonstrate that the output airs delivered through the subject device are not adulterated with VOCs and PM2.5, please provide assessments for the output airs. For the air quality testing, you may refer to the recently published ISO 18562 standards "Biocompatibility evaluation of breathing gas pathways in healthcare applications". Please specify all VOCs and other chemicals identified in the output air samples and provide a comprehensive risk assessment (exposure and safety assessment) based on the inhalation exposure route, intended patient population, and a worst case scenario. Please also refer to our original Deficiency #9.

Sponsor's July 5, 2018 Response:
It is Acorda's position that the approaches used to date (specifically the use of headspace-GC for VOCs and USP<788> for particulates) are adequate to characterize the output airs of the CVT- 301 inhaler and that it is highly unlikely that additional studies will identify any new risks (see justification discussion below). Therefore, Acorda believes that the data submitted to date provide an acceptable assessment of the risks and the safety of the CVT-301 inhaler and that this issue should not preclude approval of the NDA by the October 5, 2018 PDUFA date.
At the time this work was performed, ISO 18562 standards were not final. Now that these standards have been accepted, Acorda agrees to conduct testing of the output airs as per the ISO 18562-3 (VOCs) and ISO 18562-2 (Particulate Matter). This work has begun, and we anticipate that the new VOC, particulate and any required toxicological assessment reports will be available in early September.

Biocompatibility Reviewer (BiFeng Qian) Comments:
The sponsor's justification for the output air testing conditions is inadequate. The original deficiency stands.

Sponsor's September 10, 2018 Response:
The study reports to fulfill this commitment are provided via the hyperlinks shown below:

CMC Request 2: Output Airs Assessment per ISO 18562

1) RPT-4093: *CVT-301* (b) (4) *: Analysis of Inhaler Device for VOCs based on ISO 18562-3*
2) RPT-4112: *CVT-301 Inhaler Flow Path Particulate Matter Report*

The VOC study (RPT-4093) detected no volatile organic compounds above the threshold for toxicological concern (TCC); thus, no toxicological assessment was required. RPT-4112 on particulate matter includes a toxicological assessment, and the measured levels of particulates for PM2.5 and PM10 were determined to pose negligible risk to patients.

Lead Reviewer Comments:
The following interactive request for additional information was sent the sponsor via an email correspondence dated September 5, 2018, shown in red:

> You have provided an analysis of the particulate matter emitted from the dry gas flow through the subject product in RPT-4112. In Section 6.0 of this document, you described the test setup. You used a source airflow of 60 LPM for 2 minutes through the subject product, which was then directed to a Fluke 985 particle counter. However, it is not clear whether the Fluke 985 particle counter is specified to operate with this flow rate or whether the accuracy specifications cited in Section 14.2 of RPT-4112 are reflective of the particle counter performance at this high flow rate. This information is necessary to determine whether the testing described in RPT-4112 is adequate to determine the output air quality of the subject product per the ISO 18562 standards "Biocompatibility evaluation of breathing gas pathways in healthcare applications." Please provide scientific justification that the Fluke 985 particle counter accurately measures P2.5 at the 60 LPM flow rate used during the testing described in RPT-4112.

Sponsor's September 10, 2018 Response:
The Fluke 985 Airborne Particle Counter controls the airflow to 2.83 LPM (0.10 CFM) via a built-in impeller that drives the gas flow through the detection chamber during operation (see Fluke 985 Datasheet). In order to use the Fluke 985 for testing of the CVT-301 inhalers, a fractional sampling method had to be employed.
The particulate testing reported in RPT-4112 complies with ISO 18562-2 in that:

1) *The 60L/min flow rate represents "normal use" of the device in the Parkinson's patient population (as discussed ISO 18562-2, Section 5.5(c)).*
2) *A particle counter can be used instead of filter collection (as discussed in ISO 18562-2, Section 5.7 and Annex A-A.2-Subclause 5.7).*
3) *A "fractional sampling method" is allowed when the flow rate is too high to allow the entire stream to be analyzed directly (see discussion of Figure 2 in ISO 18562-2).*

The fractional sampling method employed by Acorda is compared to the fractional sampling method provided in ISO 18562-2 in Figure 1 below, with the Fluke particle counter replacing the 0.2µm filter in the ISO example.
As noted above, the design of the Fluke 985 controls the sampled airflow to 2.83 LPM. Thus by use of the fractional sampling setup, the Fluke Particle Counter is able to operate at its internally controlled flow rate, which is a factory calibrated operational parameter. The measured particulate

levels are then scaled by the ratio of the output airstream and the sampled airstream:

$$reported\ counts = measured\ counts \times \frac{output\ airsteam\ flow\ [60\ \pm 2\ LPM]}{sampled\ airstream\ flow\ [2.83\ LPM]}$$

To confirm that the Fluke 985 particle counter was operating as intended as utilized in the fractional sampling setup, a standard ISO dust was analyzed and recovery (mass balance) was calculated. Details of this assessment were provided in RPT-4122 - Attachment 2. The average recovery calculated for the 5 samples was 76%. Thus, a correction factor of 1.4x (based on the lowest determined recovery value of 70%) is used to calculate the final amount of emitted particulate (µg) to correct for any particulate that may have been retained on the mouthpiece or test apparatus that could otherwise be inhaled during use.
It is Acorda's position that the testing described in RPT-4112 is adequate to determine the output air quality per the ISO 18562-2 standard.

Lead Reviewer Comments:
The Biocompatibility Reviewer (BiFeng Qian) and I discussed the sponsor's reasoning. We agreed with the sponsor's rationale. The response is **adequate**.

L. Recommendation

The device is recommended for **approval** at this time from a device perspective. After the initial review the team found that the sponsor had yet to provide either animal testing or appropriate extractables and leachables (E&L) testing plus a toxicological risk assessment based on chronic inhalation exposure to address chronic systemic toxicity. In addition, the sponsor had yet to provide assessments for the output airs. These deficiencies were communicated to the sponsor in the interactive review request dated June 27, 2018. The sponsor provided the requested information during interactive review through September as documented in the interactive deficiency log section (Section K) above..

Digital Signature Concurrence Table	
Reviewer Sign-Off	Brandon L. Blakely -S Digitally signed by Brandon L. Blakely -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002107348, cn=Brandon L. Blakely -S Date: 2018.10.08 22:01:23 -04'00'
Branch Chief Sign-Off	

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/s/

DAHLIA A WALTERS
12/14/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 12, 2018
To:	William Dunn, M.D. Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	INBRIJA (levodopa inhalation powder)
Dosage Form and Route:	for oral inhalation use
Application Type/Number:	NDA 209184
Applicant:	Acorda Therapeutics Inc.

1 INTRODUCTION

On June 27, 2017, Acorda Therapeutics Inc. submitted for the Agency's review a New Drug Application (NDA) 209184 for CVT-301 (levodopa inhalation powder), for oral inhalation use. On August 25, 2017, Acorda Therapeutics Inc. received a Refusal to File (RTF) letter from the Agency indicating the application was insufficiently complete. On December 5, 2017, Acorda Therapeutics Inc. resubmitted the application addressing all the outstanding issues including Chemistry and Manufacturing and Control (CMC) deficiencies and an amended Human Factors Summative Validation Report. On March 5, 2018, the proprietary name of INBRIJA was granted. INBRIJA (levodopa inhalation powder), for oral inhalation use is indicated for (b) (4) intermittent treatment of OFF symptoms in Parkinson's disease as an adjunct to a stable carbidopa and levodopa Parkinson's medication regimen.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on March 2, 2018 for DMPP and OPDP to review the Applicant's proposed PPI and IFU for INBRIJA (levodopa inhalation powder), for oral inhalation use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU dated September 4, 2018 was completed.

2 MATERIAL REVIEWED

- Draft INBRIJA (levodopa inhalation powder) PPI and IFU received on December 5, 2017, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on December 3, 2018.
- Draft INBRIJA (levodopa inhalation powder) Prescribing Information (PI) received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 3, 2018.
- Approved DUOPA (carbidopa and levodopa) comparator labeling dated September 15, 2016.
- Approved XADAGO (safinamide) tablets, comparator labeling dated June 16, 2017.
- DMEPA Human Factors Results and Label and Labeling Review dated September 4, 2018.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as

Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we have:

- simplified wording or clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/12/2018

DHARA SHAH
12/12/2018

LASHAWN M GRIFFITHS
12/12/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 10, 2018

To: Gerald Podskalny
Division of Neurology Products (DNP)

Stacy Metz, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for INBRIJA™ (levodopa inhalation powder), for oral inhalation use

NDA: 209184

In response to the DNP consult request dated March 2, 2018, OPDP has reviewed the proposed product labeling (PI), Patient Information, Instructions for use (IFU), and carton and container labeling for the original NDA submission for INBRIJA™ (levodopa inhalation powder), for oral inhalation use (Inbrija).

PI: OPDP's comments on the proposed labeling are based on the draft PI received from DNP (Stacy Metz) on December 3, 2018 and are provided below.

Patient Information and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed patient labeling will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 6, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
12/10/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 10, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209184
Product Name and Strength:	Inbrija (levodopa inhalation powder), 42 mg
Applicant/Sponsor Name:	Acorda Therapeutics Inc.
FDA Received Date:	December 6, 2018
OSE RCM #:	2017-1271-3
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised carton labeling for Inbrija (Appendix A) to determine if it is acceptable from a medication error perspective. The sponsor did not submit a revised container label; however, we note the Agency provided a container label recommendation during a previous label and labeling review.[a] The sponsor also submitted a document describing their response to the Agency's carton labeling and container label recommendations.

2 CONCLUSION

The revised carton labeling for Inbrija is acceptable from a medication error perspective. However, the container label is unacceptable from a medication error perspective because the NDC format is not aligned with 21 CFR 207.33.

[a] Whaley E. Human Factors and Label and Labeling Review for Inbrija (NDA 209184). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 4. RCM No.: 2017-1271-2; 2017-1514-1.

3 RECOMMENDATIONS FOR ACORDA THERAPEUTICS INC

We recommend the following be implemented prior to approval of this NDA 209184:

A. Container (blister) label

1. The container label contains the following numeric code "(01)003 10144 342018". We acknowledge your clarification regarding which portion of this code corresponds to the NDC number (i.e. 10144 34201). However, the product label must contain the NDC number. The NDC number is currently a 10 or 11-digit number, in its FDA-assigned 3-segment format, that identifies the labeler, product, and trade package size. While industry's practice is to use a GTIN that may incorporate the digits of the NDC, the GTIN typically contains additional digits and is not in the 3-segment format by which the NDC is defined in FDA regulations (e.g. use of hyphens for the 5-3-2 format, XXXXX-XXX-XX). Moreover, FDA is concerned that use of the GTIN alone in the human-readable portion of the product identifier could lead to improper identification of the NDC and drug product. As such, we recommend you ensure the NDC number appears in the format aligned with 21 CFR 207.33. If the NDC is on the label in its FDA-assigned 3-segmant format, a company may also voluntarily affix or imprint the associated GTIN on the label.

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/s/

EBONY A WHALEY
12/10/2018

LOLITA G WHITE
12/10/2018

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 4, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209184
Product Name and Strength:	Inbrija (levodopa inhalation powder), 42 mg
Product Type:	Single-ingredient Combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Acorda Therapeutics Inc.
Submission Date:	July 9, 2018
OSE RCM #:	2017-1271-2; 2017-1514-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Neurology Products requested a consultative review of a supplemental human factors (HF) validation study results report and labels and labeling submitted under NDA 209184 for Inbrija (levodopa inhalation powder). This is a combination product with a proposed capsule-based dry powder oral inhaler device constituent part that is intended to treat symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen.

1.1 PRODUCT DESCRIPTION

The Inbrija user interface consists of an inhaler device and levodopa capsules; the contents of the capsules are orally inhaled using the inhaler device. The Inbrija inhaler is intended for administration by patients, caregivers and healthcare providers (HCPs) in the home or healthcare setting. Currently, there are no approved inhaled medications for treatment of Parkinson's disease. Inbrija is a 505(b)(2) product and the RLD is Sinemet (NDA 17555) oral tablets.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 5, 2017, the sponsor resubmitted NDA 209184 after a Refuse to File action. We reviewed the HF validation study results included in the submission, and we identified a methodological deficiency where the untrained patients were provided an overview of the Instructions for Use (IFU), which we consider a form of training.[a] Thus, we determined the results from the untrained patient group were not generalizable to the intended user population. We also identified areas for improvement in the IFU and container label. We recommended the sponsor complete a supplemental HF validation study in untrained patient participants and incorporate our labeling recommendations. DNP agreed with our assessment and submitted a Discipline Review letter to the sponsor on May 7, 2018.

On June 7, 2018, the sponsor submitted a supplemental HF validation study protocol, and our review of the protocol identified one area that the sponsor needed to address, which was to ensure the proposed education levels of participants are representative of the intended user population and also provided a container label recommendation.[b]

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[a] Whaley, E. Human Factors Results and Labeling Review for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 3. RCM No.: 2017-1271-1; 2017-1514.

[b] Whaley, E. Human Factors Protocol Review for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jun 7. RCM No.: 2017-1514-1.

On July 9, 2018, the sponsor submitted the supplemental HF validation study results report to the NDA.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C – N/A
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Tables 2 and 3), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The supplemental HF validation study included 15 untrained patient participants. In the first session, the participants were introduced to the product and were allowed to familiarize themselves with the product to the level they desired; however, the participants did not receive any training or instruction and did not perform dose preparation or administration. For the second session, participants returned the following day for simulated use testing, knowledge task questions, and reading comprehension questions.

3.2 RESULTS AND ANALYSES

Table 2 compares the initial HF validation study results with the supplement HF validation study results. Table 3 describes the supplemental HF validation study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Summary of objectives, methods, user groups, and results for the HF Validation Studies to support the use of Inbrija				
	HF Validation Study		**Supplemental HF Validation Study**	
Objective	Validate whether the drug-device, labeling, and associated instructions can be correctly, safely, and effectively used by the intended user populations (Parkinson's disease (PD) patients, caregivers, and healthcare providers) without observable patterns of preventable errors that would result in harm to a patient		Validate the effectiveness and usability of CVT-301 in PD patients within an untrained condition, without product demonstration or guided practice	
Participants	Total: n = 57 - Untrained patients (n=7)*, trained patients (n=20), untrained caregivers (n=8), trained caregivers (n=7), and trained HCPs (n=15) *Study methodology concern noted		Total: n = 15 - Untrained patients (n = 15)	
Participant key	Untrained patients = PU, trained patients = PT, untrained caregivers = CU, trained caregivers = CT, trained HCPs = HCP			
Task performance	**Failures**	**Close Calls/ Use Difficulties**	**Failures**	**Close Calls/ Use Difficulties**
Attach mouthpiece and compress to puncture capsule	n = 3 failures (PU x 3)	n = 1 close call (PT) n = 2 difficulties (CU x 1, PT x 1)	n = 2 failures (PU x 2)	n = 1 difficulty (PU)
Remove used capsule from inhaler	n = 1 failure (HCP)	None	None	n =1 difficulty (PU)
Repeat with second capsule	n = 1 failure (CU)	None	None	None
Identify what to do if device does not "whirl"	n = 1 failure (PU)	n = 1 close call (PU)	n = 1 failure (PU)	None

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija Supplemental HF Validation Study						
Critical Task	**Number of Use Errors and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Attach Mouthpiece and Compress to Puncture Capsule	n = 2 failures	n = 1 difficulty	**<u>Failures</u>** **One untrained patient participant (P113) failed this task with both capsules (for a total of 2 failures).** The participant compressed the mouthpiece more than 2 times and damaged the first and second capsules. The participant attempted to attach the mouthpiece but did not press until they heard the click; instead, the participant released the mouthpiece early each time. The participant stated they had difficulty "…getting the inhaler lined up" and that they just needed time (e.g. 1 dose) to get used to the attachment technique. At the end of the session, the participant successfully performed this task with an additional capsule. **<u>Use Difficulty</u>** **One participant (P112) noted difficulty with compressing the mouthpiece.**	Regarding the failure with this task, the sponsor noted that the participant was reading the IFU and attaching the mouthpiece at the same time, but did not look down at the mouthpiece while attempting to attach it. The sponsor also noted that the participant had the strength to do it complete the task, but their technique didn't allow the mouthpiece and inhaler body to touch and click before releasing the mouthpiece.	The sponsor determined that no mitigations are needed in response to the failures and use difficulty with this task.	We reviewed the use-related issues (e.g. failures and difficulties) associated with the task to attach the mouthpiece and compress to puncture capsule. According to the use-related risk analysis, if the mouthpiece is compressed more than three times, there is potential for underdose if the capsule is damaged. We note that the proposed IFU labeling is more restrictive in that it recommends that users compress the mouthpiece no more than once. We note that this product is intended for adjunctive treatment of OFF symptoms in patients already on a carbidopa-levodopa regimen. We also note that the draft PI indicates that (b) (4) [redacted]. In conversation with the medical officer for this product, we learned that an underdose or dose

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija Supplemental HF Validation Study						
Critical Task	**Number of Use Errors and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			The participant stated, "I had initial difficulty with the first compression." The participant successfully completed the task.			failure with this product would result in the patient remaining in the OFF state. Additionally, the medical officer noted that if a patient is uncertain of how much dose was delivered, the patient could administer an oral medication (e.g. carbidopa-levodopa) and then would have to wait for the oral medication to take effect which might extend the time for the patient would remain in the OFF state. As such, although there is risk of underdose and subsequent continuation of OFF symptoms, we find that in the event of an underdose users would have access to oral medication to treat the OFF symptoms. Our review of the instructions for use (IFU) finds the IFU labeling adequately describes how to attach the mouthpiece and what to do if the mouthpiece is compressed more than once. In addition, the study participants did not attribute the root

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija Supplemental HF Validation Study						
Critical Task	**Number of Use Errors and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						cause of their use-related issues to the labeling or instructions. As such, we agree with the sponsor's assessment and do not have recommendations at this time.
Remove Used Capsule from Inhaler	N/A	n = 1	**<u>Use difficulty</u>** **One untrained patient participant** (b) (6) stated they had difficulty removing the second capsule ("I had a little difficulty getting the second capsule out").	The sponsor did not provide a root-cause analysis for this use difficulty.	The sponsor did not propose mitigations in response to this use difficulty.	According to the use-related risk analysis, there is risk of re-using the same capsule for the second inhalation if users do not correctly identify that a used capsule was left in the inhaler from the first inhalation, which would result in underdose. As previously noted, although there is risk of underdose and subsequent continuation of OFF symptoms, we find that in the event of an underdose, users would have access to oral medication to treat the OFF symptoms. Our review of the IFU labeling finds that the IFU adequately informs users that the used capsule should be removed from the inhaler (e.g. Step 11 of the IFU). We agree with the sponsor that no mitigations are needed and do

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija Supplemental HF Validation Study						
Critical Task	**Number of Use Errors and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						not have recommendations at this time.
Identify What to Do if Device Does Not "Whirl"	n = 1	N/A	**<u>Failure</u>** **One untrained patient participant** (b) (6) did not hear a whirl sound after inhaling the contents of the first capsule ("…I heard the second one whirl but not the first one."). The participant indicated that they were aware that the capsule did not whirl and how to resolve it and noted "I thought that you should only use two capsules". At the end of the session, the participant successfully performed this task with an additional capsule.	The sponsor determined that the participant performed all the preparation steps correctly and inhaled deeply. The sponsor also noted determined that the participant knew they should have inhaled again but believed that for the purposes of the study, they should not try again. The sponsor attributed this failure to study artifact due to use of empty capsules in the simulated use scenario.	The sponsor determined that no mitigations are needed in response to the failure with this task.	According to the use-related risk analysis, if users fail to re-inhale if the device does not "whirl" during dose administration, there is risk of underdose. As previously noted, although there is risk of underdose and subsequent continuation of OFF symptoms, we find that in the event of an underdose, users would have access to oral medication to treat the OFF symptoms. We disagree with the sponsor's determination that the failure occurred due use of empty capsules in the HF validation study. Instead, we find that the failure occurred due to study artifact due to the artificial study environment (e.g. participant was aware that they did not hear the whirling noise and how to resolve; however, they believed they should only use two capsules).

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija Supplemental HF Validation Study						
Critical Task	**Number of Use Errors and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						Our review of the IFU labeling finds that the IFU adequately informs users that "Important: If you did not hear or feel the capsule "whirl" while inhaling you may need to take a deeper, longer breath. Start again from the beginning of Step 8 using the same capsule.". We also note the submitted root cause information does not suggest that the user interface contributed to the failures. As such, we agree with the sponsor's assessment and do not have recommendations at this time.

As part of our evaluation of this NDA, we considered the results from the HF validation study that was previously reviewed.[3] In light of the study methodology deficiency in the first HF validation study, we also considered the results of this HF validation supplemental study. As shown in table 2 above:

- In the initial HF validation study, study participants (excluding the untrained patient group) experienced failures, close calls, and use difficulties with the following critical tasks: attach mouthpiece and compress to puncture capsule, remove used capsule from the inhaler, and repeat procedure with second capsule.
- In the supplemental HF validation study, the untrained patient participants performed similarly on the aforementioned critical tasks; additionally, no new areas of concern requiring mitigation were identified.

When considering the totality of the data submitted, we find the residual risks acceptable.

3.3. LABELS AND LABELING

Table 4 below includes the identified medication error issues with the submitted container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Acorda Therapeutics Inc (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
Container Label			
1.	The NDC format is not clear.	The NDC is often used to facilitate identification of the product.	The container label contains the following numeric code "(01)003 10144 342018". It is unclear which portion of this code corresponds to the NDC number. Clarify the NDC number and ensure the NDC number appears in the format aligned with 21 CFR 207.33.

[3] Whaley, E. Human Factors Results and Labeling Review for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 3. RCM No.: 2017-1271-1; 2017-1514.

4 CONCLUSION AND RECOMMENDATIONS

We find the results of the HF validation studies acceptable. Our evaluation of the proposed container label identified an area of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the applicant/sponsor so that recommendations are implemented prior to approval of this NDA 209184.

4.1 RECOMMENDATIONS FOR ACORDA THERAPEUTICS INC.

We find the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed container label identified an area of vulnerability that may lead to medication errors. We have provided a recommendation in Table 4 and we recommend that you implement this recommendation prior to approval of this NDA 209184.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Inbrija that Acorda Therapeutics submitted on December 5, 2017.

Table 5. Relevant Product Information for Inbrija	
Initial Approval Date	N/A
Active Ingredient	levodopa
Indication	the treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen
Route of Administration	oral inhalation
Dosage Form	capsule
Strength	42 mg
Dose and Frequency	The recommended dose is oral inhalation of the contents of two 42 mg capsules (84 mg) as needed for treatment of symptoms of OFF periods, up to 5 times a day. The maximum daily dose of INBRIJA should not exceed 420 mg. Do not take more than one dose (2 capsules) per OFF period.
How Supplied	Inbrija contains foil blister strips of levodopa capsules with two black bands on the body and "A42" in black on the cap, and one Inbrija inhaler. - Carton containing 60 Inbrija capsules (15 blister cards containing 4 capsules each) and 1 INBRIJA inhaler: NDC 10144-342-60 - Carton containing 92 Inbrija capsules (23 blister cards containing 4 capsules each) and 1 INBRIJA inhaler: NDC 10144-342-92 Inbrija inhaler consists of a blue cap, blue handle with "INBRIJA" imprinted on it, and white mouthpiece covering the capsule chamber.
Storage	Store in a dry place at 25°C (77°F), excursions permitted to 15–30°C (59–86°F).
Container Closure	(b) (4)

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 16, 2018, we searched DMEPA's previous reviews using the terms, levodopa and Inbrija.

B.1.2 Results

Our search identified 5 previous reviews[defgh], and we note that our previous recommendations were considered or implemented.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

\\cdsesub1\evsprod\nda209184\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\off-periods\5354-other-stud-rep\rpt-2202\rpt-3944.pdf

[d] Whaley, E. Human Factors Protocol Review for CVT-301 IND 115750. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 6. RCM No.: 2016-1771.

[e] Whaley, E. Label and Labeling Memorandum for CVT-301 IND 115750. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 5. RCM No.: 2016-1771-1.

[f] Whaley, E. Human Factors Memorandum for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 8. RCM No.: 2017-1271.

[g] Whaley, E. Human Factors Results and Labeling Review for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 3. RCM No.: 2017-1271-1; 2017-1514.

[h] Whaley, E. Human Factors Protocol Review for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jun 7. RCM No.: 2017-1514-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Inbrija labels and labeling submitted by Acorda Therapeutics.

- Container label (blister) received on July 9, 2018
- Instructions for Use (image not shown) received on July 9, 2018

F.2 Label and Labeling Images

(b) (4)

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

EBONY A WHALEY
09/04/2018

LOLITA G WHITE
09/04/2018

QUYNHNHU T NGUYEN
09/10/2018

DANIELLE M HARRIS
09/11/2018

Clinical Inspection Summary

Date	07/30/2018
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Stacy Metz, Regulatory Project Manager Susanne Goldstein, M.D., Medical Officer Division of Neurology Products
NDA #	209184
Applicant	Acorda Therapeutics, Inc.
Drug	Levodopa inhalation powder
NME	No
Proposed Indication	Treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen
Consultation Request Date	1/22/2018
Summary Goal Date	8/5/2018
Action Goal Date	10/5/2018
PDUFA Date	10/5/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Goodman and Mickielewicz were inspected in support of this NDA. Subject # (b) (6) from Dr. Mickielewicz's site was enrolled in the study despite not meeting eligibility criteria. We therefore recommend that the review division conduct an exploratory analysis removing the data from this subject. Otherwise, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of both Dr. Goodman and Dr. Mickielewicz was No Action Indicated (NAI).

II. BACKGROUND

Levodopa inhalation powder is being developed by Acorda Therapeutics, under NDA 209184 (IND 115750), for the treatment of symptoms of OFF periods in Parkinson's disease (PD) as an adjunct to a carbidopa/levodopa regimen. The sponsor has submitted one Phase 3 study, CVT-301-004, in support of the efficacy and safety of levodopa inhalation powder for the treatment of symptoms of OFF periods in PD as an adjunct to a carbidopa/levodopa regimen.

Protocol CVT-301-004

Title: A phase 3, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of CVT-301 (levodopa inhalation powder) in Parkinson's disease patients with motor response fluctuations (OFF phenomena)

Subjects: 351 enrolled and randomized

Sites: 65 sites in 4 countries; United States (52 sites), Canada (4 sites), Poland (8 sites), and Spain (1 site)

Study Initiation and Completion Dates: 12/4/2014 – 12/6/2016

This was a randomized, double-blind, placebo-controlled, multicenter study comparing the efficacy and safety of inhaled levodopa powder with placebo in subjects with Parkinson's disease (PD) experiencing motor response fluctuations (OFF periods).

The study was comprised of three periods, a Screening Period, a 12-week double-blind Treatment Period, and a Follow-up Period (occurring one to two weeks after the treatment period). Subjects were randomized in a 1:1:1 ratio to the following study arms for the 12-week treatment period:

- Inhaled levodopa 60 mg as needed
- Inhaled levodopa 84 mg as needed
- Inhaled placebo as needed

Subjects self-administered inhaled study drug during clinic visits and as an outpatient when they experienced OFF periods (but not early morning OFF periods). Study drug could be used up to 5 times daily at home. The first dose of inhaled study drug was administered in the clinic at Visit 1.

Study visits occurred during Screening (SV1/SV2), Baseline (TV1), Treatment [at Weeks 4 (TV2), 8 (TV3), and 12 (TV4)], and Follow-up. Spirometry was assessed at all study visits. For SV1/SV2 and TV1 study visits, spirometry was assessed at the study site (usually a neurology clinic). After implementation of Version 4 of the protocol (7/10/2015), spirometry assessments for visits TV2, TV3, and TV4 were performed at pulmonary function facilities along with carbon monoxide diffusing capacity (DLco) assessments. Prior to Version 4 of the protocol, all spirometry assessments were performed at the study site.

The primary efficacy endpoint for the study was the change in the Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 motor score from predose to 30 minutes post-dose at Week 12 (TV4). A number of key secondary efficacy endpoints were assessed in this study in a hierarchical manner.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, numbers of adverse events, impact on primary efficacy endpoint, and prior inspectional history.

III. RESULTS

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Compliance Classification
Site #5044 **Ira Goodman, M.D.** Bioclinica Research 100 West Gore Street Suite 202 Orlando, FL 32806	CVT-301-004 Subjects: 35	20-23 Mar 2018	NAI
Site #5301 **Anatol Mickielewicz, M.D.** Medica Pro-Familia SA Marymoncka 14/1 Warsaw 01-868 Poland	CVT-301-004 Subjects: 12	7-10 May 2018	NAI

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.
VAI = Voluntary Action Indicated, deviation(s) from regulations.
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

1. Ira Goodman, M.D.

At this site for Protocol CVT-301-004, 59 subjects were screened, 35 subjects were randomized, and 29 subjects completed the study. The EIR did not specify reasons for the 6 subjects who discontinued the study. Per sponsor data listings, these subjects discontinued due to: withdrawal by subject (3), other (physician decision), other (change in Parkinson's Disease medication), and adverse event (drug inhalation-triggered cough).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, spirometry and diffusing capacity of the lungs for carbon monoxide (DLco) assessments, concomitant medications, protocol deviations, and primary efficacy endpoint data (UPDRS Part 3 motor score). Clinical trial monitoring was performed by (b) (4). Spirometry data collected by clinical sites was reviewed by a central spirometry laboratory, (b) (4)

The FDA field investigator was able to verify the primary efficacy endpoint data, the UPDRS Part 3 motor scores pre-dose and at 30 minutes post-dose at Treatment Visit 4. As requested by

the review division, spirometry and DLco assessments were also reviewed. The FDA field investigator noted a discrepancy in a DLco measurement in Subject (b) (6) According to the source document from the pulmonary function lab, the best of three trials for DLco prior to randomization was 17.5 mL/mmHg/min compared to the sponsor line listing of 17.15 mL/mmHg/min (the other two trials yielded DLco values of 16.8 and 16.1).

There was no evidence of under-reporting of adverse events. The FDA field investigator noted one instance in which a subject was not reconsented with an ICF addendum that had been updated with additional safety information. This subject was consented in August 2015 with Version 1 of the ICF. An ICF addendum with updated risk and discomfort information was approved by the IRB in September 2015. This subject was not reconsented with the ICF addendum and completed the study in January 2016. The ICF addendum included an updated section on most common side effects that "seem to be related to inhaling levodopa based on previous studies" including "cough, blackish color mucus when coughing, dryness of the throat, and tickling sensation in the throat or chest".

Reviewer's comment: The FDA field investigator noted a minor discrepancy in a DLco measurement (prior to randomization) in one subject. It is very unlikely that this discrepancy impacted the safety analyses. In addition, one subject was not reconsented with an ICF addendum describing updated safety information regarding levodopa administered by inhalation. This occurred in one subject and appears to be an isolated incident.

2. Anatol Mickielewicz, M.D.

At this site for Protocol CVT-301-004, 17 subjects were screened, 12 subjects were randomized, and 11 subjects completed the study. The EIR did not specify the reasons for subject who discontinued the study. Per sponsor data listings, one subject discontinued due to hospitalization for lumbar spinal stenosis and a herniated disc.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, Ethics Committee/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, subject diaries, spirometry and DLco assessments, concomitant medications, and primary efficacy endpoint data (UPDRS Part 3 motor score). Clinical trial monitoring was performed by (b) (4). Spirometry data collected by clinical sites was reviewed by a central spirometry laboratory, (b) (4)

The FDA field investigator verified the primary efficacy endpoint data, UPDRS Part 3 motor scores, with no discrepancies identified. There was no evidence of under-reporting of adverse events.

As requested by the review division, the FDA field investigator reviewed the spirometry assessments. There was one discrepancy noted in which Subject (b) (6) was unable to complete any of the 8 trials at SV1 (Visit 1) OFF state because "the subject exhaled too slowly at the

start of forced exhalation and did not exhale long enough and/or did not reach a plateau." However, sponsor data listings include spirometry data from this visit. Per inclusion criterion 11 of the protocol, subjects "must be able to perform a spirometry maneuver in the ON and OFF states and must have a screening FEV1 > 50% of predicted, and an FEV1/FVC ratio >60% in the ON state at screening." This subject was unable to perform spirometry at SV1 in the OFF state. This subject did not repeat the spirometry assessments at SV2. This subject, therefore, did not meet this eligibility criterion. Per documentation at the site, the "screen documents pertaining to subject eligibility" were reviewed by (b) (4), and this subject was approved to be enrolled.

Reviewer comments: Subject (b) (6) *appears not to have been eligible for the study since the subject was unable to perform spirometry at SV1 in the OFF state. This was not included as a protocol deviation in the NDA submission. Approval was given to enroll this subject. We recommend that the review division conduct an exploratory analysis removing the data from Subject* (b) (6)

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Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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DNP/Medical Officer/Susanne Goldstein
DNP/Project Manager/Stacy Metz
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OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analyst/Yolanda Patague

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/s/

CARA L ALFARO
07/30/2018

PHILLIP D KRONSTEIN
07/30/2018

KASSA AYALEW
07/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209184

DISCIPLINE REVIEW LETTER

Acorda Therapeutics, Inc.
Attention: Todd F. Baumgartner, MD, MPH
Senior Vice President-Regulatory Affairs
420 Saw Mill River Road
Ardsley, NY 10502

Dear Dr. Baumgartner:

Please refer to your New Drug Application (NDA) dated December 5, 2017, received December 5, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Inbrija (Levodopa Inhalation Powder).

We identified the following deficiencies in your human factors (HF) validation study submitted on December 5, 2017, in support of NDA 209184:

1. Your HF validation study methodology is flawed; thus, the results are ultimately not generalizable to the intended user population. Specifically, the study methodology lacks a representative group of untrained patient users. For the "untrained" patient participants, the study moderator provided the following instruction: "The inhaler uses powder-filled capsules to deliver the medication. A dose is 2 capsules, inhaled with the inhaler one at a time. The powder that you inhale gives a rapid boost of Levodopa, to curb your off state until your next dose of your regular oral medication. The procedure is as follows: You will load one capsule into the inhaler. Exhale. Orally inhale the powder. Hold your breath, then breathe out normally. Then remove the used capsule and repeat with a 2nd capsule. A full dose is 2 capsules".

   We find this overview of how to use the product representative of training, as the study moderator informed participants regarding how to use Inbrija, including the correct route of administration. This method does not reflect the condition of real-world use where untrained users would not receive training prior to first use. Therefore, the data collected for the untrained patient group may not represent the data that would we expect if the study was conducted with untrained patients. We consider that inclusion of a representative untrained patient group is necessary to demonstrate that the device can be used by the intended users safely and effectively, for the intended uses and under the expected use conditions. It is important to note that testing with representative users may identify additional use-related errors.

   To address this deficiency, you should perform a supplemental HF validation study using appropriate methodology with 15 representative untrained patient participants. We

recommend that you submit a new HF study protocol for the Agency's review and feedback prior to commencing your HF validation study. In addition, we provide recommendations for your instructions for use and container label below to promote the safe use of your product and recommend they are implemented prior to initiating your HF validation study.

A. Instructions for Use (IFU)
    1. The instruction regarding cleaning the inhaler appears to include conflicting information. The sentences "You do not need to clean the inhaler. You can use a dry cotton swab or tissue to wipe the outside of the inhaler" should be clarified to specify which parts of the inhaler (e.g. inside of the inhaler, outside of the inhaler) should or should not be cleaned.

B. Container label (blister)
    1. The container label (blister) should be revised to include the phrase "For oral inhalation only" on the principal display panel (PDP). We recommend this revision to mitigate the risk of incorrect route of administration errors.

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Gerald D. Podskalny, DO, MPHS
Cross Disciplinary Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

GERALD D PODSKALNY
05/07/2018

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 3, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209184
Product Name and Strength:	Inbrija (levodopa inhalation powder), 42 mg
Product Type:	Single-ingredient Combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Acorda Therapeutics Inc.
Submission Date:	June 27, 2017; December 5, 2017
OSE RCM #:	2017-1271-1; 2017-1514
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Neurology Products (DNP) to review the human factors (HF) validation study results and labels and labeling submitted as part of the Resubmission/After Refusal to File submission for Inbrija (levodopa inhalation powder) (NDA 209184) and to address areas of vulnerability that may lead to medication errors.

1.1 PRODUCT BACKGROUND AND REGULATORY HISTORY

Inbrija (levodopa inhalation powder) is a combination product (e.g. capsule-based dry powder oral inhaler) intended for treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen. The Inbrija user interface consists of an inhaler device and levodopa capsules; the contents of the capsules are orally inhaled using the inhaler device. The Inbrija inhaler is intended for administration by patients, caregivers and healthcare providers (HCPs) in the home or healthcare setting. Currently, there are no approved inhaled medications for treatment of Parkinson's disease. Inbrija is a 505(b)(2) product and the RLD is Sinemet (NDA 17555) oral tablets.

We previously reviewed the sponsor's proposed human factors (HF) validation study protocol under IND 115750; as part of our review, we noted that the proposed inclusion of only trained patient participants is not reflective of real use and recommended that the sponsor provide rationale to justify how training all patient participants is reflective of real use or revise the HF study protocol to include untrained patient participants.[a]

The sponsor submitted NDA 209184 on June 27, 2017. In the NDA submission, the sponsor included the results of training survey as justification for use of an all trained patient user group. However, the sponsor did not submit this justification for Agency concurrence prior to commencing their HF validation study and we noted that the survey results did not confirm that every patient user will consistently receive training. The submission received a Refuse to File action due to CMC deficiencies.[b] The Refuse to File letter also provided HF comments on the HF study methodology, specifically, regarding the lack of untrained patient participants in the human factors validation study and the lack of representative education demographics in the patient participants. The sponsor made changes to the study methodology and conducted the study; however, the revised protocol was not submitted to the Agency for review before the study was conducted. On December 5, 2017, the sponsor resubmitted NDA 209184.

[a] Whaley, E. Human Factors Protocol Review for CVT-301 IND 115750. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 6. RCM No.: 2016-1771.

[b] Bastings, E. Refusal to File for NDA 209184. Silver Spring (MD): FDA, CDER, OND, DNP (US); 2017 AUG 25.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the human factors (HF) validation study results, prescribing information (PI), Instructions for Use (IFU), container label, and carton labeling are as follows:

3.1 HUMAN FACTORS VALIDATION STUDY METHODOLOGY

Fifty-seven representative patients, caregivers, and healthcare providers (HCPs) participated in the HF validation study within the following user groups: untrained patients (n=7), trained patients (n=20), untrained caregivers (n=8), trained caregivers (n=7), and trained HCPs (n=15).

Prior to simulated use testing, the untrained caregiver and patient participants were provided an introduction and self-familiarization period. For the untrained patient participants specifically, we note the study moderator provided an overview of the instructions for use of Inbrija (e.g. “A dose is 2 capsules, inhaled with the inhaler one at a time…The procedure is as follows: You will load one capsule into the inhaler. Exhale. Orally inhale the powder. Hold your breath, then breathe out normally. Then remove the used capsule and repeat with a 2nd capsule. A full dose is 2 capsules.”). We consider the instructions provided by the moderator to be a form of participant training. We find that the overview of the IFU for the untrained patient group is not representative of real-world use; and therefore, the data collected for the untrained patient group may not represent the data that would we expect had the sponsor conducted the study with untrained patients. Despite this methodological deficiency, we evaluated the results of the patient user group to determine if the study identified additional

deficiencies that need to be addressed by the applicant. We provide our recommendation to address this study methodology deficiency in Section 4.2 below.

3.2 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with critical tasks, and our analysis of the HF validation study results. We agree with the identified critical tasks and overall study methodology, with the exception of the methodology for the untrained patient participant user group as noted in Section 3.1.

Table 2 below summarizes and focuses on the results observed with critical tasks, including simulated use tasks, subjective questions, IFU Knowledge Probe, and IFU Reading Comprehension.

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
Attach Mouthpiece and Compress to Puncture Capsule	n = 3 failures	n = 1 close call n = 2 use difficulties	**Failures** 1. **One untrained patient participant** compressed the mouthpiece for the first capsule several times and damaged the capsule. As a result, the capsule did not produce the whirl sound upon inhalation. The participant did not get a new, replacement capsule. In response to a question regarding why they compressed the mouthpiece numerous times, the participant responded "I thought I had the arrows lined up but I just couldn't get it on". The sponsor noted that the participant had severe hand tremors (which were not self-reported during the initial participant screening) and lack of hand strength which made it difficult for the participant to line up arrows on the device and compress the mouthpiece. The sponsor also noted that the patient attempted several different hand position techniques. The sponsor lastly noted that the participant stated they "tend to break the rules" and disregarded the instruction regarding obtaining a new capsule if the first is damaged. The participant successfully completed this task with the second capsule. The sponsor noted that the IFU clearly states to discard a damage capsule and use a new one. 2. **Two untrained patient participants** compressed the mouthpiece multiple times for first of the two capsules. In both cases, the capsule was not damaged and the devices produced the whirl sound. The sponsor noted that the participants unnecessarily compressed the mouthpiece multiple times due to being unsure if the mouthpiece attached correctly. In both cases, the participants did not get a new, replacement capsule.	We reviewed the use-related issues (e.g. failures, close calls and difficulties) associated with the task to attach the mouthpiece and compress to puncture capsule. We note that of the 6 use-related issues, 5 users incorrectly compressed the capsule multiple times prior to inhaling. According to the use-related risk analysis, if the mouthpiece is compressed more than three times, there is potential for underdose if the capsule is damaged. However, the proposed IFU labeling is more restrictive in that it recommends that users compress the mouthpiece no more than once. We note that during the study, the capsule was not damaged with 2 of the use errors and those participants successfully produced the whirl sound. Our review of the instructions for use (IFU) finds the IFU labeling adequately describes how to attach

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
			For the three failures described above, the sponsor noted that the IFU recommends only one compression, which is more restrictive than the actual requirement for successful attachment (less than three compressions). The sponsor did not propose mitigations in response to the failures. **Close call** 1. **One trained participant** failed to attach the mouthpiece in a single compression and replaced the capsule. No further details were provided. The sponsor did not propose mitigations in response to this close call. **Use Difficulties** 1. **One untrained caregiver participant and one trained patient participant** verbalized difficulty with compressing the mouthpiece for the first capsule. The untrained caregiver participant stated that compressing the mouthpiece took more effort than they thought and that it was "a little difficult". The sponsor did not provide additional subjective details regarding the trained patient participant. Both participants successfully attached the mouthpiece. The sponsor noted that they expected some observed difficulty and subjective feedback on this task and that a minority of users may experience or perceive initial difficulty in attaching the mouthpiece, especially until they have practiced and established the proper technique. The sponsor did not propose mitigations in response to these use difficulties.	the mouthpiece and what to do if the mouthpiece is compressed more than once. In addition, the study participants did not attribute the root cause of their use-related issues to the labeling or instructions. However, as previously mentioned, we find the deficiency in the study methodology (e.g. untrained patient group) impacts our ability to determine whether the residual risk associated with failure with this task is acceptable. **We provide a recommendation to address this concern in Section 4.2 below.**

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
Remove Used Capsule from Inhaler	n = 1 failure	N/A	**One trained healthcare provider participant** did not remove used capsule after the second inhalation and before storing device. The sponsor noted that in the debrief, the participant stated that they did not remove the used capsule from the inhaler because they were not paying attention ("I didn't pay attention. I don't know"). The sponsor determined that the participant was operating from memory and did not reference the IFU. The sponsor also noted that the participant correctly removed the first capsule and only committed a failure with the second capsule. The sponsor noted that the study participant did not attribute the root cause of their error to the device, labeling, or instructions. The sponsor stated that failure on this task is "low risk" with no clinical impact because users would discover the used capsule in the inhaler upon their next dose attempt. The sponsor did not propose mitigations in response to this failure.	According to the use-related risk analysis, there is risk of re-using the same capsule for the second inhalation if users do not correctly identify that a used capsule was left in the inhaler from the first inhalation, which might result in underdose. Our review of the IFU labeling finds that the IFU adequately informs users that the used capsule should be removed from the inhaler. In addition, according to the sponsor, the root cause information does not suggest that the user interface contributed to the failure. The participant subjective feedback does not attribute failure to repeat the procedure with the second capsule to the user interface but instead attributes to inattention. Based on the results from this study, we agree with the sponsor that no mitigations are needed and the residual risks are acceptable. However, as previously mentioned,

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
				we find the deficiency in the study methodology (e.g. untrained patient group) impacts our ability to determine whether additional errors may have occurred in an untrained patient user group.
Repeat Procedure with Second Capsule (for a full dose administration)	n = 1 failure	N/A	**One untrained caregiver participant** did not load and administer the second capsule. The sponsor noted that in the debrief, the participant stated "I forgot to load the second one…Probably because I was just trying to remember everything." The sponsor stated that they believe that the participant assumed they didn't need to demonstrate repeating the dose with a second capsule. The sponsor noted that the study participant did not attribute the root cause of their errors to the device, labeling, or instructions. The sponsor did not propose mitigations in response to this failure.	According to the use-related risk analysis, there is risk of underdose if users do not repeat dose administration steps (e.g. only takes one capsule). Our review of the IFU labeling finds that the IFU clearly indicates that 2 capsules should be orally inhaled to complete the dose. We also note that the container labels note that a full dose is 2 capsules. Furthermore, the submitted root cause information does not suggest that the user interface contributed to the failures. The participant's subjective feedback does not attribute failure to repeat the procedure with the second capsule to the user interface

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
				but instead attributes to memory failure. We agree with the sponsor that no mitigations are needed and the residual risks are acceptable. However, as previously mentioned, we find the deficiency in the study methodology (e.g. untrained patient group) impacts our ability to determine whether additional errors may have occurred in an untrained patient user group.
Identify What to Do if Device Does Not "Whirl"	n = 1 failure	n= 1 close call	**Failure** 1. **One untrained patient participant** did not hear the whirl sound with the second capsule and did not attempt to re-inhale as indicated in the IFU. During the subjective interview, the participant stated "…I skipped it. But it's not through any fault of the instructions. That was just me". The sponsor noted that the participant performed all the preparation steps correctly and inhaled deeply. The sponsor attributed this failure to study artifact due to use of empty capsules in the simulated use scenario. **Close call** 1. **One untrained patient participant** did not hear a whirl sound upon inhalation and correctly re-inhaled.	According to the use-related risk analysis, if users fail to re-inhale if the device does not "whirl" during dose administration, there is risk of underdose. We disagree with the sponsor's determination that the failure occurred due to study artifact because other participants also used empty capsules during the simulated use scenario and were able to produce the whirl sound. Our review of the IFU labeling finds that the IFU adequately informs users that "Important: If you did not

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Inbrija HF Validation Study				
Critical Task Description	**Number of Failures**	**Number of Close Calls and Use Difficulties**	**Participants' Subjective Feedback and Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
			The sponsor noted that the study participants did not attribute the root cause of their use-related issues to the device, labeling, or instructions. The sponsor determined that no design mitigations are needed and finds the residual risk acceptable.	hear or feel the capsule "whirl" while inhaling you may need to take a deeper, longer breath. Start again from the beginning of Step 8 using the same capsule.". We also note the submitted root cause information does not suggest that the user interface contributed to the failures. However, we note the deficiency in study methodology (e.g. untrained patient group) impacts our ability to determine whether the residual risk is acceptable. **We provide a recommendation to address this concern in Section 4.2 below.**

3.3 LABEL AND LABELING

Our review of the proposed Prescribing Information (PI) labeling, Instructions for Use (IFU) labeling, container label and carton labeling identified areas which may be improved to decrease risk of medication error. We note our review of the labels and labeling is limited due to the study methodology concern (e.g. lack of an untrained patient participant group) noted in Section 3.1.

Prescribing Information

1. The route of administration statement in Section 2 Dosage and Administration, 2.1 Usual Dosage lacks prominence and may pose risk of incorrect route of administration errors.
2. Section 16 How Supplied/Storage and Handling, 16.2 Storage and Handling, the storage information does not contain the temperature scale designation (i.e., "°C") after each numerical value and may lead to risk of administration of degraded drug.

Instructions for Use

1. The IFU contains conflicting information regarding cleaning the inhaler.

Container label (blister)

1. The container label (blister) does not include the route of administration.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur.

4 CONCLUSION & RECOMMENDATIONS

Our review of the HF validation study identified a methodological deficiency where the untrained patients were provided an overview of the IFU prior to their simulation. We consider this a form of training. Thus, the results from the untrained patient group are ultimately not generalizable to this intended user population and the data collected for the untrained patient group may not represent the data that would we expect had the sponsor conducted the study with untrained patients. It is important to note that testing with representative users may identify additional use-related errors.

We consider that inclusion of a representative untrained patient group is necessary to demonstrate that the device can be used by the intended users safely and effectively for the intended uses and under the expected use conditions. We recommend the sponsor complete a supplemental human factors validation study in untrained patient participants. We provide recommendations in section 4.2 to address the human factors validation study methodology deficiency.

Additionally, our review of the Prescribing Information, IFU, container label, and carton labeling identified areas that are vulnerable to medication error and we provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. In Section 2 Dosage and Administration, 2.1 Usual Dosage, relocate the sentence "INBRIJA capsules are for oral inhalation only and should be used only with the INBRIJA inhaler" so that it is the first sentence in Section 2. We recommend this revision so that the affirmative language appears first to mitigate the risk of incorrect route of administration errors.
    2. In Section 16 How Supplied/Storage and Handling, 16.2 Storage and Handling, the storage information does not contain the temperature scale designation (i.e., "°C") after each numerical value. We recommend the phrase "excursions permitted to 15–30°C (59–86°F)" is revised to "excursions permitted to 15°–30°C (59°–86°F)". We recommend this revision to mitigate the risk of incorrect storage errors.

4.2 RECOMMENDATIONS FOR ACORDA THERAPEUTICS INC.

We refer to your human factors (HF) validation study submitted on December 5, 2017, in support of NDA 209184.

Your HF validation study methodology is flawed; thus, the results are ultimately not generalizable to the intended user population. Specifically, the study methodology lacks a representative group of untrained patient users. For the "untrained" patient participants, the study moderator provided the following instruction "The inhaler uses powder-filled capsules to deliver the medication. A dose is 2 capsules, inhaled with the inhaler one at a time. The powder that you inhale gives a rapid boost of Levodopa, to curb your off state until your next dose of your regular oral medication. The procedure is as follows: You will load one capsule into the inhaler. Exhale. Orally inhale the powder. Hold your breath, then breathe out normally. Then remove the used capsule and repeat with a 2nd capsule. A full dose is 2 capsules".

We find this overview of how to use the product is representative of training, as the study moderator informed participants regarding how to use Inbrija, including the correct route of administration. This method does not reflect the condition of real-world use where untrained users would not receive training prior to first use. Therefore, the data collected for the untrained patient group may not represent the data that would we expect if the study was conducted with untrained patients. We consider that inclusion of a representative untrained

patient group is necessary to demonstrate that the device can be used by the intended users safely and effectively, for the intended uses and under the expected use conditions. It is important to note that testing with representative users may identify additional use-related errors.

To address this deficiency, perform a supplemental HF validation study using appropriate methodology with 15 representative untrained patient participants. We recommend that you submit a new HF study protocol for the Agency's review and feedback prior to commencing your HF validation study. In addition, we provide recommendations for your instructions for use and container label below to promote the safe use of your product and recommend they are implemented prior to initiating your HF validation study.

A. Instructions for Use (IFU)
    1. The instruction regarding cleaning the inhaler appears to include conflicting information. The sentences "You do not need to clean the inhaler. You can use a dry cotton swab or tissue to wipe the outside of the inhaler" should be clarified to specify which parts of the inhaler (e.g. inside of the inhaler, outside of the inhaler) should or should not be cleaned.
B. Container label (blister)
    1. The container label (blister) should be revised to include the phrase "For oral inhalation only" on the principal display panel (PDP). We recommend this revision to mitigate the risk of incorrect route of administration errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Inbrija that Acorda Therapeutics submitted on December 5, 2017.

Table 2. Relevant Product Information for Inbrija	
Initial Approval Date	N/A
Active Ingredient	levodopa
Indication	the treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen
Route of Administration	oral inhalation
Dosage Form	capsule
Strength	42 mg
Dose and Frequency	The recommended dose is oral inhalation of the contents of two 42 mg capsules (84 mg) as needed for treatment of symptoms of OFF periods, up to 5 times a day. The maximum daily dose of INBRIJA should not exceed 420 mg. Do not take more than one dose (2 capsules) per OFF period.
How Supplied	Inbrija contains foil blister strips of levodopa capsules with two black bands on the body and "A42" in black on the cap, and one Inbrija inhaler. - Carton containing 60 Inbrija capsules (15 blister cards containing 4 capsules each) and 1 INBRIJA inhaler: NDC 10144-342-60 - Carton containing 92 Inbrija capsules (23 blister cards containing 4 capsules each) and 1 INBRIJA inhaler: NDC 10144-342-92 Inbrija inhaler consists of a blue cap, blue handle with "INBRIJA" imprinted on it, and white mouthpiece covering the capsule chamber.
Storage	Store in a dry place at 25°C (77°F), excursions permitted to 15–30°C (59–86°F).
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 26, 2018, we searched DMEPA's previous reviews using the terms, levodopa and Inbrija. Our search identified 3 previous reviews[cde], and we note that our previous recommendations were considered or implemented, with the exception of the methodology for the untrained patient participant user group as noted in Section 3.1.

[c] Whaley, E. Human Factors Protocol Review for CVT-301 IND 115750. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 6. RCM No.: 2016-1771.

[d] Whaley, E. Label and Labeling Memorandum for CVT-301 IND 115750. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 5. RCM No.: 2016-1771-1.

[e] Whaley, E. Human Factors Memorandum for Inbrija NDA 209184. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 8. RCM No.: 2017-1271.

APPENDIX C. HUMAN FACTORS STUDY

Link to the human factors validation study results document:

\\cdsesub1\evsprod\nda209184\0008\m5\53-clin-stud-rep\535-rep-effic-safety-stud\off-periods\5354-other-stud-rep\rpt-2202\rpt-2202-v4-0.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Inbrija labels and labeling submitted by Acorda Therapeutics on June 27, 2017 and December 5, 2017.

- Container label (blister)
- Container label (inhaler)
- Carton labeling
- Instructions for Use (image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

(b) (4)

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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