July 3, 2012

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

Re:  Docket No. FDA–2010–N–0547

To Whom It May Concern:

We are pleased to submit the enclosed comments in response to your request for information about the clinical development and use of sedation products in adult and pediatric age groups. We offer these comments in response to your Federal Register notice of November 3, 2011 (76 FR 68197).

A dental perspective would be invaluable to the development of any clinical development program guidance. Dental surgical/restorative procedures are excellent models for the use of sedation drug products and their evaluation. The procedures are short and recovery is such that end-of-procedure responses can be elicited from the patients. Meaningful safety data come from both healthy patients and those who are more susceptible to respiratory complications, particularly children and adolescents.

Safe and effective sedation products are a critical part of oral health care, especially for patients with special needs and those who suffer from anxiety associated with dental or other medical procedures and conditions. We urge you to include dental representatives on any future panels or workgroups that may aid in drafting of industry guidance on the clinical development and use of sedation products in adult and pediatric age groups.

We appreciate the opportunity to comment on this important topic. Please contact Mr. Robert J. Burns at the American Dental Association if you have any questions or require additional information. Bob can be reached at (202) 789-5176 or burnsr@ada.org.

Sincerely,

American Dental Association
American Academy of Pediatric Dentistry
American Academy of Periodontology
American Association of Oral and Maxillofacial Surgeons
American Society of Dentist Anesthesiologists
This page intentionally left blank.
CLINICAL DEVELOPMENT PROGRAMS FOR SEDATION PRODUCTS

We are pleased to submit these comments in response to your request for information about the clinical development and use of sedation products in adult and pediatric age groups. We offer these comments in response to your Federal Register notice of November 3, 2011 (76 FR 68197).

(1) For clinical trials of sedation drug products, which surgical and diagnostic procedures would provide the most relevant efficacy and safety data, while still allowing for a reasonable level of feasibility and efficiency?

Dental surgical/restorative procedures are excellent models for the use of sedation drug products and their evaluation. The procedures are short and recovery is such that end-of-procedure responses can be elicited from the patients. Early drug studies normally involve reasonably healthy, ambulatory adults that involve high-volume procedures. Dental extractions and certain restorative procedures where bone is involved may be attractive procedural options. The desired patient cohort is also common to nearly all dental office settings. In addition, these dental procedures provide variable levels of stimulation that may involve behavioral and pain responses, which may be desirable in evaluating efficacy.

Other outpatient procedures such as knee arthroscopy, gastroenterology/endoscopic procedures (e.g., colonoscopy), gynecology procedures and urology procedures may also be acceptable options.

Dental diagnostic procedures do not commonly require sedation. However, subpopulations, such as highly anxious or phobic patients (or, for example, autistic patients), may present special needs that should be considered in sedation studies.

Meaningful safety data also come from not only healthy patients, but also those who are representative of higher risk categories, especially those more susceptible to respiratory complications associated with sedation products. These subgroups are also mentioned as part of the response to question 2 below: obese patients, those who have been diagnosed with or are at high risk for obstructive sleep apnea, and the elderly. Children of course require specific trials, according to current regulations for new drugs.

(2) What patient subgroups, other than pediatric, geriatric, and patient with hepatic or renal impairment, would require specific evaluation in clinical trials involving sedation drug products?

Since respiratory depression, elevation of end-tidal carbon dioxide levels, hypoxemia and loss of the patency of the airway are among the most prevalent complications associated with sedation products, patients with chronic obstructive pulmonary disease (emphysema and chronic bronchitis), mild-moderate asthmatic patients and those with obstructive sleep apnea must be included in the design of sedation product clinical evaluations. The relative safety (margin of safety or safe dose range) in these compromised groups versus healthy subjects is an important aspect to consider.

Highly anxious patients are common in the dental office setting, perhaps up to 30% according to some investigators. This subpopulation should be considered. Emotionally/behaviorally
challenged and other patients with special needs may be another group to consider, as is recovering drug abusers/addicts.

(3) What is the most appropriate primary efficacy endpoint to assess in a clinical trial of a sedation drug product? Which measurement scales have been adequately studied and validated for use in assessing the endpoint measure recommended previously? Is there a clinically meaningful effect size that should be considered as a minimal requirement for a determination of efficacy? How do the response to the previous questions differ, if at all, for the pediatric population, in particular, the youngest of these patients who have no or limited communication skills?

Determining the most appropriate endpoint and evaluation method for a sedation product depends on the anticipated level of sedation produced, the attributes of the specific sedation product used and the type of patient sedated (pre-cooperative infant or child, grade school-aged child, adolescent, adult or elderly patient). It may not be possible or even desirable to establish the "most appropriate" efficacy endpoint that would apply to all new sedation products. Continued verbal response from the patient is the most common endpoint.

In early studies, the number or percentage of patients requiring "rescue" sedation using a marketed product may be necessary to ensure patient comfort and ethical care. “Rescue” sedation refers to secondary drug or drugs which may be used to render care efficiently and effectively in a safe manner when an initial drug or drugs was ineffective. “Rescue” sedation should not be used for the oral route of administration, especially in the pediatric population. Some products such as benzodiazepines are useful for producing amnesia while others are designed to elevate the pain threshold, making them useful when analgesia is needed but amnesia is not. A desired “minimal sedation” endpoint may be appropriate when a drug is designed and dosed to produce a totally cooperative but relaxed patient who’s cardiovascular and respiratory functions are not altered or altered only minimally. An endpoint of either minimal or moderate sedation may relate to the degree of amnesia of various events associated with a procedure. An endpoint of deep sedation might relate to the degree of impairment of unnecessary movement associated with the procedure, the lack of response to a local anesthetic injection or perhaps the degree to which cough or gag reflex are blocked.

There are a variety of sedation scales that are used to evaluate the level of sedation for both children and adults, though validation in specific dental outpatient procedures may not have yet been accomplished. A clinically meaningful effect size depends on adequate study power and the magnitude of effect of the drug(s) used in the individual study (e.g., “90% of patients showed an improvement over the standard regimen”).

Studies involving infants and young children should utilize the same principles as used for adults but the specifics must often be tailored to the age or physical status of the child. The use of three standard self-rating scales (Visual Analog Scale [VAS], Eland Scale, and Faces Scale) and three modified methods (Cube Test, Modified Eland Scale, and Modified Faces Scale) could be utilized for determining pre- or post- sedation effects involving anxiety and/or memory in young children, whereas recording subjective ratings and behavioral expressions, either with videotapes for replay analysis or impromptu impressions, of anxiety during a procedure by a trained observer or parent could be utilized for a non-cooperative or non-verbal children. One concern however is that children under the age of 12 may have variable responses to sedative doses, including delirium, intense anxiety, and hysteria, especially related to dental procedures.
(4) What secondary efficacy endpoints might be considered clinically meaningful (e.g., subjective and objective assessments of memory, recall, anxiety, agitation, or delirium) if appropriately studied?

The clinically meaningful secondary efficacy endpoints in the assessment of memory associated with sedation products, for instance, must involve evaluation of memory of various aspects of a clinical procedure such as a local anesthetic injection, penetration of an orifice with an endoscope or gas inflation of the bowel rather than only memory of generic events such as pictures shown or various words spoken.

Similar endpoints such as anxiety, agitation, or delirium likewise must be evaluated during actual clinical procedures rather than in experimental or artificial non-clinical environments. An assessment of the ease of subject care may be useful (clinician/anesthesiologist or parent/observer assessment) especially for pediatric or special care patients unable to respond to questions about amnesia or anxiety. Additionally, post-operative patient satisfaction level may be considered.

(5) How should responses to rapid changes in procedural stimulation be considered in the evaluation of efficacy (e.g., the time of initial incision or negotiating a colonoscope around the splenic or hepatic flexure)?

Responses of the sedated patient to a rapid change in procedural stimulation are undoubtedly the most critical point and a complex part of the evaluation of sedation products during dental and oral surgery procedures, similar to colonoscopy, etc. Evaluation of sedation may be assessed at specific time points (by the clock) however, for procedural sedation, the “rapid changes in procedural stimulation” must be included as part of the protocol assessment plan, rather than only sequential evaluation intervals.

The intensity/duration of the stimulation may be assessed, with the observed level of sedation before, during (and intensity of subject response) and after stimulation. Effects on the heart rate, blood pressure, oxygen/hemoglobin saturation may be assessed.

Likewise, evaluation during periods of minimal or no stimulation and during postoperative recovery is equally important to accurately characterize a sedation drug product since these periods of sedation without stimulation might unmask significant cardiorespiratory depression that may have been blunted by the stimulation during the procedure.

(6) How do the responses of each of the previous questions differ for evaluation of sedation products used in the operating room, the ICU, the emergency department, and the gastrointestinal suite?

In dental outpatient facilities and other health care settings, the procedures and levels of procedural stimulation may be completely different. Additionally, patients presenting with dental or medical injuries or conditions in the hospital emergency department may have a full stomach or may be hypovolemic or intoxicated. Patients in the operating room are generally intubated and in the intensive care unit, patients may be on a plethora of medications and are physiologically compromised, compared to ambulatory patients. For example, the cardiovascular response to ketamine in a normovolemic patient is elevation of heart rate and
blood pressure whereas the same dose of ketamine produces significant cardiovascular depression in the severely hypovolemic patient whose level of sympathetic activity is already maximized.

Additionally, the level of pharmacology and anesthesia training of the sedationist, their ability to recognize and manage complications of sedative products and the availability of certain monitoring devices and equipment in each of these settings may vary according to level of sedation typically used in each setting and state requirements. Therefore, these potential differences must be considered in the design of studies to evaluate the efficacy, safety and suitability of a sedative product in various settings.

One aspect of sedation product safety not yet addressed is predictable reversibility of the sedative effect, especially in the outpatient setting. Reversing agents that can be given rapidly through multiple routes of administration are desired to provide safe use and predictable recovery in outpatient settings.