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


To Whom It May Concern:

The American Association of Nurse Anesthetists (AANA) welcomes the opportunity to submit comments regarding this request for comments, Clinical Development Programs for Sedation Products (76 Fed. Reg. 68197, November 3, 2011). The AANA had previously submitted comments to this docket in January, 2011 (75 Fed. Reg. 73104, November 29, 2010). These current comments represent information which AANA believes continue to be pertinent to those questions most recently posed by the FDA. The AANA is submitting comments in the following areas:

- **Q1.** 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?
- **Q2.** What patient subgroups, other than pediatric, geriatric, and patients with hepatic or renal impairment, would require specific evaluation in clinical trials involving sedation drug products?
- **Q3.** What is the most appropriate primary efficacy endpoint to assess in a clinical trial of a sedation drug product?
  a. Which measurement scales have been adequately studied and validated for use in assessing the endpoint measure recommended previously.
  c. How do the responses 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.
• Q4. 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?

• Q5. 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?

Background of the AANA and CRNAs
The AANA is the professional association for more than 44,000 Certified Registered Nurse Anesthetists (CRNAs) and student nurse anesthetists representing over 90 percent of the nurse anesthetists in the United States. CRNAs are advanced practice nurses who personally administer about 32 million anesthetics given to patients each year in the United States, according to the 2010 AANA Practice Profile Survey. Nurse anesthetists have provided anesthesia in the U.S. for nearly 150 years, and high quality, cost effective CRNA services continue to be in high demand. CRNAs are Medicare Part B providers and since 1989, have billed Medicare directly for 100 percent of the physician fee schedule amount for services. CRNA services include providing a pre-anesthesia patient assessment, obtaining informed consent for anesthesia administration, developing a plan for anesthesia administration, administering the anesthetic, monitoring and interpreting the patient's vital signs, and managing the patient throughout the surgery. CRNAs also provide acute and chronic pain management services. CRNAs provide anesthesia for a wide variety of surgical cases and in some states are the sole anesthesia providers in nearly 100 percent of rural hospitals, affording these medical facilities obstetrical, surgical, trauma stabilization, and pain management capabilities.

According to a 2007 Government Accountability Office (GAO) study, CRNAs are the predominant anesthesia provider where there are more Medicare beneficiaries and where the gap between Medicare and private pay is less.¹ Nurse anesthesia predominates in Veterans Hospitals and in the U.S. Armed Forces. CRNAs work in every setting in which anesthesia is delivered including hospital surgical suites and obstetrical delivery rooms, ambulatory surgical centers (ASCs), pain management facilities and the offices of dentists, podiatrists, and all types of specialty surgeons.

RESPONSES TO QUESTIONS POSED IN REQUEST FOR COMMENTS

Q1. 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?

The surgical and diagnostic procedures that would provide the most relevant efficacy and safety data are those that frequently require varying levels of consciousness to accomplish a given procedure. For example, procedures that require titration of medication include but are not limited to endoscopic retrograde cholangiopancreatography (ERCP), rigid bronchoscopy, portacath (PAC) placements, and extracorporeal shock wave lithotripsy (ESWL). Any medication or device that is developed to be marketed for use in patient sedation should be thoroughly tested to delineate the clinical practice parameters that will minimize adverse outcomes associated with the sedation product.

Q2. What patient subgroups, other than pediatric, geriatric, and patients with hepatic or renal impairment, would require specific evaluation in clinical trials involving sedation drug products?

We believe that it is critical to determine the effects of sedation products on patients with certain co-morbidities, rather than solely focusing on a single procedure. Such information aids in determining the effectiveness of the sedation product across patient subgroups. In addition to pediatric and geriatric populations, as well as patients with hepatic or renal impairment, other subpopulations for special consideration include but are not limited to patients with morbid obesity with or without metabolic syndrome, and with or without obesity hypoventilation syndrome (also known as Pickwickian syndrome); patients with obstructive sleep apnea; patients who are taking medications for chronic conditions that significantly alter their sensorium; patients with pulmonary or other structural respiratory impairments; patients with coronary artery disease; and patients who have respiratory or cardiovascular derangements due to procedural positioning (e.g., patients in the prone or face-down position).

Q3. What is the most appropriate primary efficacy endpoint to assess in a clinical trial of a sedation drug product?

We recommend that the FDA consider including a mechanism to control for the impact that preexisting co-morbidities, age, anesthesia physical status, and type of procedure may have when designing clinical
trials for efficacy (i.e., Phase II and III trials). The optimal trial design should take into consideration the pharmacokinetic and pharmacodynamic profile of the sedation product to be tested when determining the optimal comparator. An agent with similar profiles would be best suited for comparison and therefore, it is possible that midazolam will rise to the top as being the best agent for comparison in randomized controlled trials of the new agent. Important measurable endpoints that should be assessed by these designs include adequacy of effect of the drug; cardiovascular and respiratory parameters; time to full patient recovery; time to discharge post procedure; adverse events; successful completion of the procedure; and patient and provider satisfaction. Composite endpoints may also be considered when developing a study design and analysis depending on the study drug, procedure, evaluations tools, or patient population.

Certain endpoints are subjective and may be difficult to quantify, for example, patient or provider satisfaction. Baseline metrics and expectations would need to be established in order to measure whether these metrics were met. Patient and provider assessments of whether the procedure and sedation occurred successfully may vary between the two groups. For example, patient expectations for the procedure, cultural perceptions, pain tolerance, or recovery expectations may vary. Additionally, any patient questionnaires would need to be designed to discern the patient’s satisfaction with the sedation versus the patient’s satisfaction with the procedure. A structured lexicon, terminology, and implementation process need to be established for identification of adverse events and incidents, assignment of anesthesia physical status, and interpretation of sedation scales. Typically these aspects have a subjective component based on clinical judgment. We also recommend that any measure of provider satisfaction should take into account all types of providers involved in the procedure, not just physicians.

Standardization of protocols and procedures needs to be taken into account when designing studies and selecting appropriate endpoints. Clear definitions and protocols need to be stated regarding the use of concomitant medications, rescue medications, or titration of the study drug. If appropriate, the same concomitant medications should be used in both arms of a study, to minimize any confounding effect which may appear in the efficacy analysis. Titration of a medication may have differing side effects, which would need to be taken into consideration in the analysis. Whether use of a rescue medication is designated as a “failure” study endpoint may also depend on the class of the rescue drug. An intent-to-treat analysis may be considered in this scenario, although it is recommended to consult with an epidemiologist or biostatistician on the appropriate analysis methods for any study.
a. Which measurement scales have been adequately studied and validated for use in assessing the endpoint measure recommended previously.

A measurement scale should be selected for the setting and study population for which it was developed and validated. A commonly employed sedation scale is the Ramsey Sedation Scale, which assesses the level of a patient’s rousability. Despite the scale’s ease of use, variability may exist among clinical practitioners’ because of its subjective nature. Even with advancements in current technology, endpoints such as depth of sedation cannot be accurately measured using instruments such as awareness monitors. Since practitioner behavior may vary, a study protocol should be developed during trial design, which incorporates appropriate training and education to ensure consistency in measurement using any type of grading scale for evaluation.

c. How do the responses 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.

Special consideration should be taken when designing trials or implementing evaluation methods for sedation products in the pediatric population. Certain evaluation methods may require the patient to provide a verbal response or perform a requested task. Because children, particularly very young children, infants, or neonates, may not have the understanding or communication skills required to perform requested tasks or responses, evaluators must create tools or assessment methods which are appropriate for this population. The pediatric population may also require a deeper level of sedation for various procedures, which also needs to be taken into account when designing trials and determining appropriate endpoints.

Q4. 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?

There are many meaningful secondary endpoints that may provide valuable information when assessing a sedation product. We would recommend that the agency consider, at a minimum, anxiolysis, recall, pre- and post-procedure oxygen saturation at room air, pre- and postprocedural cardiovascular measurements,
respiratory status, spontaneous ventilation, end tidal CO₂, positive recovery profile, length of stay, time to discharge, and patient and provider satisfaction as meaningful secondary efficacy endpoints.

**Q5. 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?**

To ensure patient safety, therapeutic dose response ranges should be established to achieve the desired level of sedation. A medication efficacy range should be determined which incorporates any amount of stimulation typically expected for a given procedure. Manufacturers should work with operating practitioners to identify these dose ranges. Depth of sedation is determined by several factors which may include invasiveness of the procedure, degree of stimulation, or expected responsiveness of the patient. Designed protocols should be assessed against these ranges. As indicated previously, certain scales or current technology may not be sensitive to assessing depth of sedation.

We thank you for the opportunity to comment on the request for comments for Clinical Development Programs for Sedation Products. As noted, the AANA had submitted comments to the previous set of questions (75 Fed. Reg. 73104, November 29, 2010). The AANA has valuable input to offer the FDA in addressing this and other issues that affect anesthesia care. We look forward to continuing to serve as a resource to the FDA and we request that the FDA include the AANA in all communication and dialogue with anesthesia professionals on this issue. Please do not hesitate to contact AANA Executive Director Wanda O. Wilson, CRNA, PhD, at (847) 655-1100 or wwilson@aana.com if you have any questions or comments.

Sincerely,

Debra P. Malina, CRNA, DNSc, MBA
AANA President

cc: Wanda O. Wilson, CRNA, PhD, AANA Executive Director
Ewa Greenier, MPH, MBA, AANA Professional Practice Specialist