

Pediatric Subcommittee
of the
Anti-Infective Drugs Advisory Committee
Center for Drug Evaluation and Research, Food and Drug Administration
April 24, 2001

Issue: Clinical Development of Products for Drooling in Neurologically Impaired Children

Questions/Discussion Points for the Subcommittee

Because these products will likely reduce salivation at some doses, the questions for the subcommittee are directed to safety, dose titration, and ethical issues as follows:

1. How can adverse events best be assessed in this population?

Patients with neurologic impairment, cognitive impairment, and/or inability to communicate are at a distinct disadvantage with respect to the measurement of anticipated pharmacologically induced adverse events. The development of measures for pain and discomfort in individuals with disabilities has been limited, and there is very little information available in the literature.

Please include in your discussion measurement instruments/approaches and who should perform the assessments.

2. What characteristics are important in developing a pediatric formulation?

Currently, the majority of antimuscarinics are extemporaneously compounded into pediatric formulations using either the IV preparation or crushed tablets. The concentrations of the active ingredients as well as the excipients may vary. This can affect stability and absorption. It also may increase the possibility of dosing errors. Also, there is variation in the way that individual patients respond to medications. There may be some patients who are unable to tolerate even the minimal effective dose because of undesirable side effects. The optimal dosing regimen will need to be individualized. It will require a balance between inhibition of saliva production and adverse events for any given patient.

FDA thinks an optimal dosing regimen should include a formulation which is not extemporaneously compounded and which can be titrated.

3. Since therapies need to be titrated, guidance on dosing is necessary in the product labeling. Please discuss the labeling tools to help caregivers assess the benefits and side effects of these medications.

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Questions/Discussion Points for the Subcommittee (cont.)

4. Are there additional processes or procedures that need to be in place to ensure the safe and ethical conduct of studies in this special needs population?

Patients with disabilities are a unique and vulnerable population. While they are frequently viewed to be similar to pre-communicative children, there are important differences. These patients will have neurologic deficits that affect motor function, but within this population, there are varying degrees of cognitive function and ability to communicate. Communication and sensory disorders may mask a normal intellect.

Please consider in your discussion:

- a. Should the study(ies) be performed only in a subset of these patients that can communicate (e.g., verbally or via keyboard)?
- b. Should IRBs consult individuals or organizations with expertise in this area for protocol review?
- c. Should there be independent assessors who are not the caregivers in these studies?