ISSUE SUMMARY

Blood Products Advisory Committee
95th Meeting, July 20-21, 2009

Topic I: Scientific Basis for Demonstration of Coral Snake Antivenom Efficacy

Issue: FDA seeks the advice of the Committee on alternative strategies to demonstrate efficacy for Coral Snake Antivenom Products.

Background:

A. Coral Snakes

Coral snakes are brightly colored and identified by their red, yellow/white, and black colored banding. However, several nonvenomous species, including the Scarlet Kingsnake, the Milk Snake, and the Colorado Desert shovel-nosed snake have similar coloration. In some geographical areas, the order of the bands distinguishes between the non-venomous and the venomous coral snakes, inspiring some folk rhymes — "Red and yellow, kill a fellow; red and black, friendly jack." However, this coloring only applies to coral snakes native to North America: *Micrurus fulvius fulvius* (Eastern or common coral snake), *Micrurus tener* (Texas coral snake), *Micruris fulvius barbouri*, and *Micruroides euryxanthus* (Arizona coral snake). Coral snakes found in other parts of the world can have distinctly different patterns, e.g., red bands touching black bands, pink and blue banding, or have no banding at all.

Most species of coral snake are small in size. However, North American species average around 3 feet (91 cm) in length, but specimens of up to 5 feet (150 cm) or slightly larger have been reported.

Image of Coral Snake, Digital Library System, US Fish & Wildlife Service

B. Coral Snake Envenomation

Coral Snake venom consists of alpha neurotoxins that block the post-synaptic neuromuscular junction by competitive binding to the acetyl choline receptor. The venom also contains phospholipases, hyaluronidase, and other enzymes. Coral snakes can typically inject 2-6 mg of venom, but large snakes can yield up to 28 mg (by manual milking of the venom glands) of venom (1). The adult human LD100 of *M. f. fulvius* (Eastern Coral Snake) venom has been estimated to be 4 to 5 mg of dried venom.

Coral snake bites are rare, occurring in an estimated 100 people/year over a large geographic portion of the southern U.S. The bite wound can be unremarkable and asymptomatic or may exhibit swelling; paresthesias and pain at the site and extending up the limb have also been reported. Onset of neurological symptoms and signs varies with a mean time of 170 minutes, but abrupt paralysis has occurred up to 13 hours after exposure (2). When it occurs, major neurological dysfunction usually begins with bulbar paralysis (diplopia, dysarthria/slurred speech, inability to handle secretions) followed by complete loss of motor function requiring intubation and ventilatory support. Once a patient develops neurological symptoms, progression to paralysis is rapid and difficult to reverse with antivenom treatment. Many clinicians prophylactically administer Coral Snake Antivenom (CSAV) if they believe that a coral snake bite was likely, based on the patient's history (2, 3). Mortality among case series published prior to the 1967 licensure and availability of the Wyeth antivenom was estimated to be 10% (4). Mortality is now uncommon with one documented death since 1967 in an untreated patient (5). Morbidities include aspiration pneumonia, consequences and complications of ICU admission, and prolonged time (1-2 months) to complete neurological recovery (2).

The natural history of coral snake envenomation has been described in case reports and small case series published prior to 1967. The case-fatality rate was estimated by Parrish and Khan to be approximately 10%, based on their experience and the published literature (4). Of the publications cited by Parrish and Khan, only the paper by Neill reported cases in detail (6). All of the case series contain a sizeable proportion of patients who never developed systemic symptoms.

Table 1: Coral Snake Envenomation Case-fatality Rate.

Publication	Death	Comments
Parrish et al	1/11 (9%)	8/11 – no symptoms 2/11 – moderate 1/11 - severe
Neill, W.	4/17[1] (24%)	
Total	5/28 (17.9%)	

1 Number of patients in series was 20, but 3 received unspecified antivenom or antisera, and are not included in the denominator.

C. Coral Snake Antivenom Supply

Coral Snake Antivenom was licensed in 1967, by Wyeth Laboratories, Inc. Wyeth is no longer manufacturing CSAV, but sufficient supply of potent licensed product is available through at least October, 2009. Based on the data generated so far, potency and the other quality attributes have been maintained. Wyeth continues to perform periodic potency testing to evaluate the remaining product. There is no alternative U.S.-licensed product.

D. Coral Snake Antivenom Licensure and Product Characteristics

According to a report published in 1985, as part of an efficacy review, an expert Advisory Panel opined that the Wyeth CSAV was safe, effective and not misbranded (7). The product is an intact equine IgG, manufactured from serum of horses that have been immunized with *M. f. fulvius* venom. Potency of each lot of licensed CSAV is demonstrated by prevention of lethality in mice. The potency assay is performed by adding antivenom to a known amount of venom and injecting this mixture into mice. Each vial of CSAV can neutralize 250 mouse $LD_{50,}$ or approximately 2 mg of *M. f. fulvius* venom in mice (8).

E. Efficacy Trials – Challenges

FDA regulations require adequately controlled trials showing safety and efficacy prior to marketing approval. However, there are many challenges to conducting a clinical trial in a short period of time for this rare condition. These challenges include:

- Low number of cases (100/year estimated)
- Geographically widespread cases (see Appendix A)
    - Southeastern states for *M. f. fulvius* – Florida, North Carolina, South Carolina, Missippi, Alabama, Georgia – *most cases occur in Florida*
    - Southwestern states for *M. t. tener* – Texas, Missouri, Arkansas – *most cases occur in Texas*
    - Rate of cases/hospital is low (1-2/hospital per year in “high incidence” areas) (2)
- Unpredictable patient location; patients cannot be pre-identified
- Treatment is needed urgently to prevent neurological deterioration
    - Logistics – getting IND product to patients
- False-positive coral snake identification
    - Confusion with king snakes
    - Patient confusion/anxiety
- Uncertainty of envenomation - Approximately 75% of coral snake bites in untreated patients are estimated to result in neurological symptoms of envenomation (25% of bites have minimal or no envenomation) (2)
- High proportion of inebriated patients (20%) (2) – informed consent may not be possible for these cases

- Perceived cost of clinical trials relative to earnings
  - Enrollment of multiple hospitals/IRBs/investigators
  - 24/7 availability of investigators
  - Urgent shipment of investigational products
  - Cost recovery not guaranteed
  - Product development/cGMP facility
  - Preclinical studies
  - Establishment fees
  - Time to licensure – maintenance of sites and study

F. Alternative pathways to licensure

FDA regulations define alternative licensure pathways for products, however, all licensures require a demonstration of safety and efficacy. Orphan products have been licensed under these requirements but it is challenging to identify a specific strategy that optimizes the time to licensure and economic feasibility. The four frameworks under which products can be licensed are:

Conventional licensure (9)	Safety and efficacy demonstrated in clinical trials
Conventional licensure with a validated surrogate endpoint (10)	Efficacy demonstrated in humans by effect on an endpoint shown to be a marker predictive of clinical benefit (e.g. cholesterol levels as a surrogate for coronary artery disease/angina/myocardial infarction); safety studies in humans.
Accelerated approval (11)	Licensure based on an endpoint that is "reasonably likely" to be a surrogate marker of clinical benefit; safety studies in humans.
Animal efficacy (12)	Licensure based on efficacy in an animal model, and safety studies in humans; ONLY in cases where human studies are "not ethical or feasible," and cannot be used if any other licensure mechanism could be used.

To assure availability in the absence of any licensed product, use of an investigational antivenin under IND can be achieved through expanded treatment use programs (Treatment IND) (13). Since this setting involves an unmet medical need for a life-threatening condition, licensure may be expedited by use of the fast track process and priority review timelines (14).

Discussion:

A. *Demonstration of safety and efficacy for new coral snake antivenoms*

FDA believes that use of the currently licensed antivenom (Wyeth) as a comparator (active control) in a prospective trial to show clinical non-inferiority of a new product is precluded by its limited availability, and the need for large numbers of patients (500 or more depending on assumptions of treatment effect and the non-inferiority margin). A placebo-controlled trial would expose placebo patients to unwarranted risk of morbidity and mortality, and would be considered unethical.

On the other hand a trial comparing the new product to a modeled historical control with no treatment may be feasible. Using the historical weighted mean mortality rate (15%) as a modeled control, varying numbers of patients would be required depending on different assumptions and statistical considerations (Appendix B). This approach may enable licensure based on a clinical study with a small sample size. Additional patients could be enrolled in a postmarketing study to collect further safety and efficacy data.

While historical survival may not be reflective of current ICU supportive care, progression to intubation may be a modern-day analog of mortality. Thus, a combined endpoint of mortality or intubation could be compared with the historic mortality rate to demonstrate efficacy.

B***. Consideration of efficacy surrogates***

Validated surrogate markers for efficacy of coral snake envenomation treatments have not been described. Consequently, conventional licensure with a validated surrogate endpoint is not possible. Nevertheless, consideration can be given to accelerated approval (conditional licensure) based on a reasonably likely surrogate of clinical benefit. FDA proposes that a reasonably likely efficacy surrogate is decline in venom levels after antivenom treatment in patients, as correlated with lack of onset/lack of progression of neurological symptoms.

Venom levels in animals and humans can be measured by ELISA assays which are sensitive to nanogram levels (15). The cadaveric serum venom level was 47 ng/ml in a deceased untreated patient, but this is the only reported measurement in an *M.f. fulvius* envenomated person (5). Animal studies of sublethal and lethal elapid envenomations further support the potential utility of using an ELISA assay to assess whether or not envenomation has occurred, and the extent of envenomation. Timing of post-treatment venom level testing could be estimated from animal venom level measurements after antivenom injections.

A strategy also will be needed to determine the appropriate dose of a new product for use in clinical studies. FDA proposes that the dose of the new product can be based on a proportional adjustment from the dose of the licensed product (Wyeth) using the relative potency determined by venom neutralization studies in animals.

In vivo determination of relative potency comparing licensed CSAV to a new product can be done by titration of antibody preparations against a defined amount of venom, in animals. Neutralization of *M. f. fulvius* venom by non-U.S. licensed antivenoms has been compared to neutralization by the licensed Wyeth product in several studies, although not all of these studies included titrations of antivenom dosing (Table 2). The products reported in the table below are cross-reactive with venom of *M. f. fulvius*. These non-U.S. licensed antivenoms are licensed in other countries, and are manufactured from serum of horses immunized with venoms of other snake species. All studies were done by mixing venom/antivenom in vitro, followed by injection into mice.

Table 2: Neutralization of *M. f. fulvius* venom by non-U.S. licensed antivenoms

Product	LD_{50} *M.f.f.* venom	Animal model	Efficacy
Coralmyn Mfr: Instituto Bioclon (Mexico) (16)	3	BALB/c 8 mice/group Dose response to Wyeth CSAV and Coralmyn	Wyeth: 1 ml neutralizes 0.239 mg venom Coralmyn: 1 ml neutralizes 0.55 mg venom
Australian Tiger Snake Antivenom Mfr: CSL Limited (Australia) (17)	5	CF-1 7 mice/group CSAV: 0.12 ml/mouse Notechis antivenom: 0.24 ml/mouse	No difference in survival compared to treatment with Wyeth CSAV
Anticoral Instituto Clodomiro Picado (Costa Rica) (18)	4 for i.p. 2 and 5 for i.v.	CD-1 6 mice/group Dose response to Anticoral	Anticoral: 1 ml neutralizes 1.02-1.28 mg venom

Questions to the Committee:

1. Is a clinical trial to assess efficacy of a new coral snake antivenom feasible and practical within a suitable timeframe

    a) using the licensed product as an active control?
    b) using a modeled historical control of no antivenom treatment?

2. If the answers to Questions 1.a) and 1.b) are no, does the committee agree that the following data are reasonably likely to predict clinical efficacy of coral snake antivenom?

    a) Dose Determination

    Determining the relative potency (venom neutralization) of the new product against the Wyeth product to inhibit a lethal challenge in an established animal model; then

    Basing the dose of the new product on a proportional adjustment of the dose of the Wyeth antivenom immune globulin using the relative potency in the animal model

    b) Clinical studies on a small number of envenomated patients treated with the new product (10 or more) showing

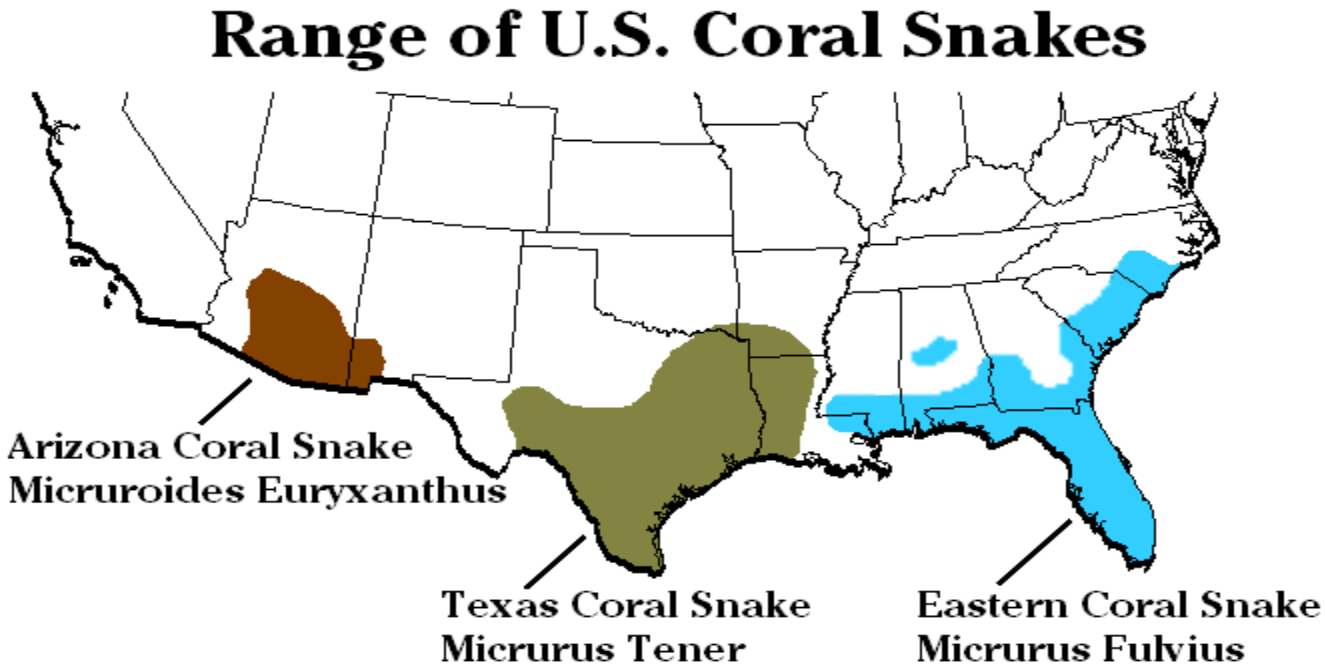
    - a point estimate of improved clinical outcome compared to historical controls with no treatment (i.e. mortality/intubation rate less than a modeled control point estimate of 15% mortality), and
    - a consistent decrease in venom levels after treatment

Note: PK and safety data would be obtained from normal volunteers pre-market and a post-market study would be required to confirm product safety and clinical efficacy. The post-market study would take place as a continuation of the pre-license clinical trial.

References

1. Fix, J.D. and Minton, S.A. Venom extraction and yields from the North American coral snake, *Micruris fulvius*. Toxicon. 1976; 14: 143-5.
2. Kitchens CS, Van Mierop LH. Envenomation by the Eastern coral snake (*Micrurus fulvius fulvius*). A study of 39 victims. JAMA. 1987;258:1615-8.
3. NIH Coral Snake Antivenom Conference, January 28, 2009 (Bethesda, MD) (discussion communications)
4. Parrish HM, Khan MS. Bites by coral snakes: report of 11 representative cases. Am J Med Sci. 1967;253:561-8.
5. Norris, R.L., Pfalzgraf, R.R., and Laing, G. Death following coral snake bite in the United States- first documented case 9with ELISA confirmation of envenomation) in over 40 years. Toxicon. 2009; 53: 693-7.
6. Neill, W.T. Some misconceptions regarding the Eastern Coral Snake, Micrurus fulvius. Herpetologica. 1957; 13: 111-118.
7. Federal Register 50 (247): 52691-4, December 24, 1985.
8. Wyeth® package insert: Antivenin (Micrurus fulvius) (Equine Origin) North American Coral Snake Antivenin at http://66.102.1.104/scholar?hl=en&lr=&q=cache:Tm087osHb5QJ:www.fda.gov/cber/label/coralsnake0801lb.pdf+related:Tm087osHb5QJ:scholar.google.com/
9. Code of Federal Regulations: 21 CFR Part 314, Subpart D (21 CFR 314.126)
10. Discussed in the Federal Register, volume 57 No. 239, December 11, 1992: 58942-58945
11. Code of Federal Regulations: 21 CFR Part 601, Subpart E
12. Code of Federal Regulations: 21 CFR Part 601, Subpart H
13. Code of Federal Regulations: 21 CFR Part 312, Subpart B, (21 CFR 312.34-35)
14. At http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm (accessed June 30, 2009)
15. Amuy E, Alape-Girón A, Lomonte B, Thelestam M, Gutiérrez JM. Development of immunoassays for determination of circulating venom antigens during envenomations by coral snakes (Micrurus species). Toxicon. 1997;35:1605-16.
16. Sánchez EE, Lopez-Johnston JC, Rodríguez-Acosta A, Pérez JC. Neutralization of two North American coral snake venoms with United States and Mexican antivenoms. Toxicon 2008; 51: 297-303.
17. Wisniewski MS, Hill RE, Havey JM, Bogdan GM, Dart RC. Australian Tiger Snake (*Notechis scutatus*) and Mexican Coral Snake (*Micrurus* species) antivenoms prevent death from United States Coral Snake (*Micrurus fulvius fulvius*) venom in a mouse model. J Toxicol Clin Toxicol. 2003;41:7-10.
18. Arce V, Rojas E, Ownby CL, Rojas G, Gutiérrez JM. Preclinical assessment of the ability of polyvalent (Crotalinae) and anticoral (Elapidae) antivenoms produced in Costa Rica to neutralize the venoms of North American Snakes. Toxicon 2003;41: 851-60.

Appendix A, Coral Snake Range



Appendix B: Statistical Considerations to Determine Sample Size based on Historical Mortality without Treatment

To estimate the overall "historical" mortality rate without treatment from the Parrish and Neill studies cited above (1/11=9% and 4/17=25%), the weighted mean was applied (weight: the inverse of the variance of each study).
The weighted rate equals 15% (0.15085).

Null hypothesis: H0: $p \geq 0.15$
Alternative hypothesis: H1: $p < 0.15$
p: new antivenom treatment mortality rate
0.15: historical control (weighted mean generated by two published studies)

Sample size for testing mortality rate after treatment with a new product, to the fixed historical rate: 15% (80% power and one-sided 0.025, or 0.05 significance levels)

New product mortality rate	Sample size required Alpha = 0.025	Sample size required Alpha = 0.05
0.5%	23	19
1%	34	29
2%	46	30
3%	55	40
4%	66	50
5%	75	67

If we apply the 95% confidence interval approach, the historical mortality becomes 4%. Below is the corresponding table using a 4% historical rate.

Sample size for testing mortality rate after treatment with a new product, to the fixed historical rate: 4% (80% power) and one-sided 0.025 or 0.05 significance level)

New product mortality rate	Sample size required Alpha = 0.025	Sample size required Alpha = 0.05
0.1%	91	74
0.5%	137	117
1%	217	192
2%	583	483
3%	2756	2183
4%	NA	NA