Summary for the Allergenic Products Advisory Committee, March 5, 2001

I. Sourcing of materials of bovine origin and allergenic products

The Transmissible Spongiform Encephalopathies (TSEs) are a group of fatal neurodegenerative disorders associated with the presence of infectious proteins called prions. TSE in cattle ("mad cow disease") has been implicated in the appearance of a human TSE – called new variant CJD – in the United Kingdom. Epidemiologic evidence strongly suggests that new variant CJD results from eating certain meat products from infected cattle. To minimize any potential for TSE transmission to humans from biological products, CBER has asked all manufacturers to use only bovine products obtained from bovine TSE-free countries as defined by the US Department of Agriculture.

Last year, CBER requested information from allergenic product manufacturers regarding the sources of materials of bovine origin in the manufacture of allergenic products. Based on the data submitted, CBER has made an assessment of the theoretical risks of TSE transmission associated with allergen immunotherapy.

CBER has concluded:

1. Most allergen extracts are produced without any bovine components other than glycerol. Glycerol may be of plant or animal origin, and most of the glycerol used in allergenic extracts is of plant origin. Because it is distilled, glycerol – even if it is derived from animal sources - is not believed to be associated with any TSE risk.

2. Molds for mold allergen extracts are stored and propagated in culture media, some of which contain bovine components. While most of these bovine components have been certified to be from countries that have not reported cases of bovine TSE, some of the components are of unknown origin.

3. The risks associated with the use of these components appear to be minimal.

Manufacturers have been instructed to assure that the bovine components of the media that they use are certified to be from countries that have not reported cases of bovine TSE. The

following question pertains to mold allergenic extracts for which the master seed stocks are stored in a growth medium that contains bovine components of unknown origin:

In July 2000, TSEAC/VRBPAC suggested that the master seed stocks of bacterial vaccines need not be rederived to reduce the likelihood of TSE transmission. The joint committee came to this conclusion after agreeing that the risk of TSE transmission was remote, and the risks associated with rederivation of the master seed stocks of bacterial vaccines were substantial. In contrast, CBER does not believe that there are any risks to product efficacy or safety associated with the rederivation of the master stocks of mold strains used for allergenic extracts.

Does the Committee agree with CBER that master stocks of mold strains used for allergenic extracts should be rederived to reduce any theoretical risk of TSE transmission?

II. Statistical power of clinical studies comparing allergen extracts

In the past, in vivo bioequivalence studies of allergen extracts have been conducted according to the "Methods of the Allergenic Product Testing Laboratory" (1994). This included the recommendation that at least four study subjects be enrolled per allergen tested. Since 1994, FDA and CBER have reexamined the number of study subjects necessary for a statistically valid demonstration of bioequivalence. The most recent document that discusses this is Statistical principles for clinical trials (ICH E9, at http://www.ifpma.org/pdfifpma/e9.pdf). The specific recommended approach, the two one-side testing protocol, is described in detail in Schuirmann DJ, *J Pharmacokinetics Biopharmaceutics* 15:657 (1987). These recommendations will be discussed and illustrated for the Committee.

CBER requests that the Committee discuss CBER's current approach to clinical bioequivalence studies as it applies to allergen extract studies.

III. Particulates in allergen extracts

Many allergen extracts precipitate over time. FDA inspectors have identified allergen precipitation as one of the leading cited causes of physician complaints and product returns. A review of manufacturer data suggests that precipitation occurs almost exclusively in

unstandardized aqueous allergen extracts. There is no evidence that the precipitates are a result of microbial contamination. The physicochemical composition of the precipitates is uncertain. Preliminary data suggests that the appearance of precipitates is not associated with any consistent changes in PNU or phenol content. Only one standardized extract (aqueous short ragweed) precipitates frequently. Limited data are available regarding the effect of precipitation on the potency of standardized short ragweed extract. CBER is working with industry to gather additional data on the effect of precipitates on allergenic extracts.

CBER has taken the following position regarding allergen precipitates:

1. Manufacturers should not ship final containers exhibiting precipitates
2. Manufacturers should develop in-house quality control programs to identify and describe precipitates
3. Manufacturers must validate any re-processing procedures performed on precipitated extracts
4. Labeling should be modified to address precipitates
5. Biological Product Deviation Reports should be submitted when precipitates are identified.

CBER requests that the Committee discuss precipitates that appear in allergen extracts and possible future areas of investigation to ascertain the effect of precipitates on the safety and efficacy of these products.