"Quick" Summary

of the

Allergenic Products Advisory Committee Meeting

March 5, 2001

After a series of updates on the Laboratory of Immunobiochemistry, lot release statistics, guidance documents, research, cockroach allergen standardization and compliance activities, the committee discussed the following three regulatory issues:

I. Sourcing of materials of bovine origin and allergenic products

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

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.

Therefore the APAC committee was asked:

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?

> The committee reached a consensus that rederivation (the process of taking a master mold stock and making several passes of the agent in fresh media) would reduce the risk of transmission of the agent several fold. There were no major objections from any individuals from industry attending the meeting. The process did not seem to be that burdensome on industry and would reduce the theoretical risk of TSE transmission. Therefore the committee recommended that CBER request manufacturers to rederive master stocks of mold strains used for allergenic extracts to reduce the theoretical risk of TSE transmission. This action should not have an impact on the effectiveness of the extract but should reduce even further the associated risk of 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). These recommendations were discussed and the committee was asked:

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

> Committee members made several suggestions. They concurred that studies comparing allergen extracts should be sufficiently powered to make a meaningful determination of equivalence. They were uncertain of how the selection of an appropriately diverse study population would further increase the sample size. While the current test method is a clinical test that provides a good guide for dosing highly sensitive individuals, committee members stated that the current test was cumbersome and difficult to read. The committee recommended that alternative methods, such as *in vitro* systems and other methods of measurements, should be studied in an effort to decrease some of the variation and increase the precision of the test.

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 posed the following question to the committee

Please discuss future areas of investigation which may provide information in ascertaining the effect of precipitates on the administration of allergenic extracts.

> The committee stated that there should be an attempt to collect more data to better understand the precipitate problem. They wanted information on the extent of the problem and quantitative studies to determine the severity of the problem. They wanted information on the effects of temperature, light, detergent, shipping conditions and centrifugation on allergen precipitation. Most importantly, they wanted more data on whether precipitates affect the safety and potency of allergen extracts. They suggested doing animal immunogenicity studies. They stated that this precipitate problem must be addressed, but that a plan needs to be developed in order to properly collect additional meaningful data. A suggestion was made for a questionnaire to be given to physicians at a national meeting or for CBER to ask some regional societies or standards committees for assistance in studying this precipitation issue.