# BRIEFING DOCUMENT

for

# MEETING OF ANTIVIRAL DRUGS ADVISORY COMMITTEE

to discuss

# USE OF SURROGATE MARKERS IN EARLY PRODUCT DEVELOPMENT OF IMMUNE-BASED THERAPIES

to be held

October 16th, 2000.

**Background: Limitations of current regimens**

Worldwide it is estimated that at least 33 million individuals are infected with human immunodeficiency virus type 1 (HIV-1). Although advances have been made in our understanding of the pathophysiology of HIV-1 infection and AIDS, much remains to be learned. There is also a need for new therapeutic agents given the only partial effectiveness and toxicity associated with currently available therapies.

Data from clinical trials indicate that the best way to achieve maximum viral suppression is with highly active antiretroviral therapy (HAART). HAART usually consists of triple therapy including two nucleoside analogues and a protease inhibitor. Drug toxicity, incomplete and/or transient drug responses, emerging viral resistance, poor patient compliance, and high drug costs, etc. have adversely affected the usefulness of HAART

therapy. Toxic side effects, for example, prevent some patients from taking these drugs in combination for extended periods. In addition, continuous combination drug therapy is necessary to maintain viral suppression, and prevent the emergence of drug resistant strains of virus.

Given the need for more efficacious and less toxic therapies, there is intense interest in use of immune-based therapies (IBTs) that are used, in conjunction with HAART to restore or bolster immune function. Examples of IBTs include adoptive autologous immunotherapies, syngeneic and allogeneic cell therapies, xenogeneic transplants, passive immunotherapy, immune and activation and suppression with cytokines and/or gene therapies, etc. Despite their obvious potential as therapeutic moieties, there are many questions about how to develop IBTs. Although IBTs are believed to confer benefits via effects on the immune system, no surrogate markers measuring the function or phenotype of the immune system have been validated as meaningful measures of drug activity or clinical benefit. Use of clinical outcome measures as a demonstration of efficacy is most straightforward, but may be impractical in certain patient populations.

**Use of surrogate markers in early product development**

Although many candidate immunophenotypic and immunofunctional markers have been measured in clinical trials, few are routinely used by sponsors as endpoint for products that are in early stages of drug development. Several explanations for this have been posited, including a) the failure to validate preliminary observations from smaller studies in larger follow-up studies, b) a poor understanding of the relationship of many surrogate

markers to HIV disease pathophysiology, c) technical barriers that prevent assay consistency or widespread use, and d) inherent difficulties associated with assay validation through clinical trials (*Mildvan et al, CID 1997; 24764-774).*

As a first step, and because of the clear and significant difficulties associated with the validation of surrogate markers as measures of bioactivity and efficacy for IBTs for patients with HIV, the agency seeks guidance from the committee on the use of surrogate markers in early IBT product development. A wide variety of biomarkers, including cell surface proteins, functional *in vitro* immunoassays, soluble immune markers, *in vivo* correlates of immune function, and quantitative and dynamic measurements of plasma RNA will be discussed. The committee will discuss questions posed to them regarding the feasibility and scientific merits of different markers and their utility in the early product development.

**Summary**

This advisory committee to the FDA will be convened to discuss which surrogate markers might be developed and validated for use in the early development of immune-based therapies (IBTs).

**Specific questions to the committee regarding the use of surrogate endpoints in the early development of IBTs will be provided in the near future.**