

DRAFT

**DRAFT QUESTIONS FOR APAC MEETING
February 10, 2000**

Potency limits for standardized allergen vaccines

Should CBER expand the lot release limits for standardized mite and grass pollen allergen vaccines to 0.5 to 2.0, as described in the *Draft Guidance for Reviewers, Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: a Revised Protocol?*

Allergen standardization

Should CBER implement their proposed algorithm for the standardization of new allergens?

Should cockroach, *Alternaria alternata* and *Aspergillus fumigatus* be selected as standardization targets, given the support of the DHHS asthma initiative?

Allergen Standardization Algorithm
January 2000

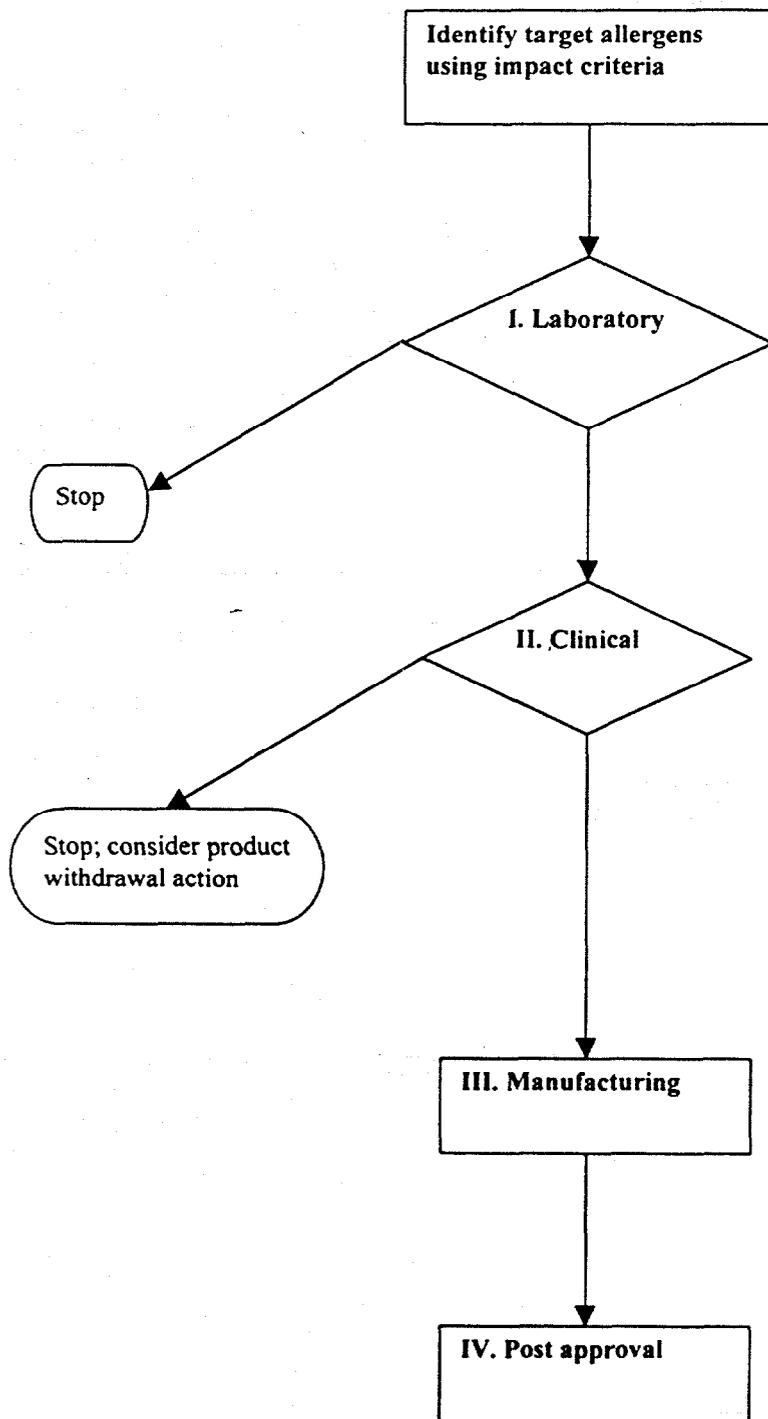
The purpose of this algorithm is to state clearly the criteria by which CBER will select allergens for standardization, and the procedures by which the selected allergens will be standardized. Most of what follows is not new. Rather, it represents an effort to build upon the essential scientific successes of prior standardization activities at CBER. These successes include: the establishment of national reference standards; the recognition of the central role of clinical testing in developing allergen unitage and surrogate potency testing; and the approval of significantly less variable and more stable products. Innovations proposed here include pre-agreed criteria for selecting standardization targets, specified points for discontinuing a particular standardization campaign (or withdrawing the unstandardized product), and a tentative delineation of responsibilities.

The algorithm is meant to help establish priorities and procedures. It is not intended to be exclusionary or inflexible. Thus, for example, an extract produced by only one manufacturer might still be a standardization target if other impact criteria are met. Likewise, CBER might decide to move forward with a little used or difficult to characterize product of great public health importance, the standardization of which might enhance its availability and quality in the U.S.

Most of the details have not been specified (e.g., precise assays, clinical trial protocols, or CBER's exact level of commitment). Different allergens will require different laboratory and clinical approaches; funding initiatives or reductions may expand or contract CBER's role.

Impact criteria:

1. Availability of stable, preferably lyophilized material for use as long-term reference extracts.
2. Consistency of currently marketed product.
3. Widespread use as a diagnostic and/or therapeutic reagent in the U.S.
4. Number of manufacturers producing the product.
5. Potential use in immunotherapy (higher score) or diagnostics (lower score).
6. Public health impact of correct diagnosis and/or adequate treatment.



I

Identify target allergens
Impact, current status

CBER;
APMA,
APAC
input

Obtain three lots from each
manufacturer + other sources

CBER
and
APMA
and
NIAID

Perform SDS-PAGE on each
extract and compare profiles
Position of bands
Number of bands
Relative intensity
Presence of
background
total protein
Initial testing for IgE binding
Assess human IgE antibody
binding (Western blot
analysis)

Yes: re-evaluate
standardization
impact value

Comparable?

Partially: re-evaluate
standardization impact value

CBER
and
APAC

No: proceed with
standardization

Stop

Clinical efficacy measures (skin
tests, BHR, IT trials)

Stop

APMA
or
CBER
or
NIAID
or
AAAAI

II

No clinical
evidence of IgE
binding: re-
evaluate
standardization
impact value

Evidence of
IgE-binding?

Stop; consider product
withdrawal action

CBER
APAC

II

III

IV

Yes: establish unitage, and identify ideal dosing range based on clinical studies

Develop in vitro surrogate for the clinical dosing assessment; select provisional standards

CBER validation

Industry validation

Establish industry-wide criteria for reference selection, reference storage conditions, and release limits; initiate stability studies

Post-approval safety and stability studies

APMA

CBER
with
APMA
and
APAC
input