

**REGULATORY CONSIDERATIONS IN
TUMOR VACCINE DEVELOPMENT:
Clinical Development of Tumor Vaccines**

**Development of Therapeutic Cancer Vaccines
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Clinical Development of Tumor Vaccines

Regulatory background

- Authority derives from the PHS Act
- Regulation of investigational trials set out in 21 CFR 312
- Marketing approval regulated under 21 CFR 601

Clinical Development of Tumor Vaccines

Regulatory background

- Tumor vaccines currently reside in both the Office of Therapeutics and the Office of Tissue, Cell, and Gene Therapy in CBER
- Clinical review for >90% of tumor vaccines performed by oncologists within Div. of Clinical Trials & Analysis (OTRR)

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- Among active INDs, there are
 - 122 in OCTGT coded as “immunotherapy, cancer treatment”
 - 84 in OTRR coded as “immunotherapy, cancer treatment”
 - 19 INDs for which Phase 3 trials are underway or completed.
 - Trials are ongoing in melanoma, NHL, ovarian, breast, colorectal, pancreatic, and renal cell cancer

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Public Health Service Act

- “any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives applicable to the prevention, treatment, or cure of injuries or disease of man”

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How are Biologics different?

- **Infectious risks**

- Derived or arise from human and animal sources
- Manufactured by techniques which can propagate infectious agents (tissue culture, fermentation)
- May not be able to be terminally sterilized

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How are Biologics different?

- **Product characterization**

Many are less well characterized therefore

- 1) require more review and control of manufacturing process and
- 2) cannot be assumed to be unaltered when process changes/site of manufacture based upon final product testing

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How are Biologics different?

- Immunogenicity

- Intended mode of action is to elicit an immune response
- Use may be accompanied by unintentional immune responses as well (e.g., vitiligo and retinopathy observed in some trials of tumor vaccines for melanoma)

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Phase 1 trials (antineoplastic drugs)

- Purpose: determination of dose range appropriate for future studies and toxicity profile
- Generally conducted in patients with cancer
- Considerations:
 - Number of patients to be exposed
 - Monitoring for toxicity
 - Pharmacokinetic & pharmacodynamic data

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Phase 2 studies (antineoplastic drugs)

- **Goals:**

- Initial determination of activity
- Further study of appropriate dose range

- **Generally conducted in patients with measurable disease**

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Phase 2 studies (antineoplastic drugs)

■ Considerations:

- Number of patients exposed
- Efficient determination of activity
- Careful monitoring & characterization of toxicity

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Phase 1/2 Studies (tumor vaccines)

Objectives:

- Identification of a pharmacologically effective dose or optimal biologic dose rather than MTD
- Rationale
 - biologically active doses occur below the MTD
 - technically infeasible to administer volumes necessary to achieve MTD

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Phase 1/2 Studies (tumor vaccines)

Design issues

- **Dose selections should cover broad range to characterize dose-immunologic activity relationship**
- **Dose escalation based on potential for toxicity and for observing differences in immunologic responses**
- **Use of assays able to discriminate between active & optimal immune responses-critical**

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Phase 1/2 Studies (tumor vaccines)

Patient populations

- **Immunocompetent patients necessary**
- **Underlying disease not rapidly progressing**
- **Measurable or evaluable tumor generally not necessary**
- **May require larger cohorts within dose levels to allow comparisons of immunologic activity between doses**

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Phase 1/2 Studies (tumor vaccines)

Analytic Methods

- **Detailed description of the immunologic assay(s), including controls and performance characteristics**
- **Provides the basis for the number of patients per dose level (sample size)**
- **Defines biologically active and optimal biologic doses**

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Phase 2 studies-tumor vaccines

- **Continues exploration of dose, schedule, route of administration**
- **Exploration of combination approaches (e.g., immunoadjuvants, cytokines, multiple antigens)**
- **Exploration of multiple strategies can be compared in contemporaneously**

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Phase 3 Studies (antineoplastic drugs)

Goals:

- Further characterization of safety and effectiveness compared to a control group
- Establish effectiveness
 - Equivalent or superior activity relative to active (efficacious) control
 - Superior to inactive control or no treatment (if none is available)

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Phase 3 Studies of tumor vaccines

- Studies generally conducted in adjuvant setting or in minimal residual disease states
- Studies designed to assess survival, disease-free survival, or time to progression need to be internally controlled (randomized)

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Phase 3 Studies - Efficacy standards

- Adequate and well-controlled clinical trials
- Evidence of net clinical benefit or of an effect on a surrogate reasonably likely to predict clinical benefit

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Phase 3 - Efficacy standards

- Net clinical benefit must be evaluated in:
 - the setting of currently available therapy
 - the natural history of the disease or clinical course following standard therapy for the specific neoplastic subtype and stage of disease

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Phase 3 studies - Efficacy standards

- For initial approval, more than one phase 3 study necessary unless highly significant survival benefit shown
- For supplemental approval, activity in the initial approval may be supportive of activity in the new setting

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Clinical Benefit Endpoints

- **Improved survival or cure**
- **Response rate with beneficial effect on disease-related symptoms and/or patient-reported outcomes**

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Surrogate Endpoints

- Durable complete and partial tumor responses have been accepted surrogate in most cancers
- Time to progression accepted surrogate in adjuvant settings, hormonal therapy of prostate cancer

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Surrogate Endpoints

Effects on:

- serologic tumor associated antigens,
- reduction (below limits of detection) in cells containing gene markers for disease, and
- immunologic responses against tumor antigens

not accepted surrogate endpoints

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Basis for Marketing Approval

- **Replicable demonstration of efficacy with acceptable safety in adequate and well-controlled trials**
- **Ability to write a product label that:**
 - **defines an appropriate patient population for treatment**
 - **provides adequate information to enable safe and effective use of the drug**

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Phase 4 Commitments

- Post-marketing studies to further assess safety and efficacy
- May be required as condition of accelerated approval
- Examples:
 - Obtain further information on sustained or delayed effects
 - Evaluation of PK, safety, efficacy in specific subpopulations (e.g., pediatric patients, impaired renal function)

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Special provisions for serious & life-threatening diseases

- Expedited review “Subpart E”
 - 21 CFR 312.80-88
- Accelerated approval
 - 21 CFR 314.500-560 (Subpart H)
 - 21 CFR 601.40-46 (Subpart E)
- Fast Track (FDA Modernization Act of 1997)

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Expedited Review 21 CFR 312.80-88

- Intended for serious & life-threatening diseases
- Provides procedures to expedite development
- Encourages early & repeated contacts w/ FDA

Clinical Development of Tumor Vaccines

Expedited Review 21 CFR 312.80-88

- Provides potential for marketing approval based on *efficacy* in adequate and well-controlled Phase 2 trials, where clinically appropriate
- Further evaluation in Phase 4 studies as indicated

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Accelerated Approval

21 CFR 314.500-560 & 21 CFR 601.40

- **Intended for serious and life-threatening diseases**
- **Provides meaningful therapeutic benefit over existing therapies**

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Accelerated Approval

21 CFR 314.500-560 & 21 CFR 601.40

- Approval based on:
 - surrogate endpoint or
 - endpoint other than survival or irreversible morbidity
- Approval is conditional & can be withdrawn if PMC's not met
- Approval may carry restrictions to ensure safe use

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FDA Modernization Act of 1997

Fast track designation

- Incorporates provisions of expedited review and accelerated approval
- Also provides for “rolling” application at time of pre-NDA/BLA meeting
- Intended for serious & life-threatening diseases with unmet medical need
- Requires demonstration of potential benefit